

Department of Clinical Pharmacology
Department of Anaesthesiology and Intensive Care Medicine
University of Helsinki
Finland

Cytochrome P450-mediated drug interactions affecting lidocaine

Mika Isohanni

ACADEMIC DISSERTATION

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Supervisors:

Professor Klaus Olkkola
Department of Anesthesiology, Intensive Care, Emergency
Care and Pain Medicine
University of Turku
Turku, Finland

Professor Pertti Neuvonen
Department of Clinical Pharmacology
University of Helsinki
Helsinki, Finland

Reviewers:

Docent Markku Salonen
Department of Anesthesiology, Intensive Care, Emergency
Care and Pain Medicine
University of Turku
Turku, Finland

Docent Vesa Kontinen
Department of Anaesthesiology and Intensive Care Medicine
University of Helsinki
Helsinki, Finland

Opponent:

Professor Hannu Kokki
Department of Anesthesiology and Intensive Care
University of Kuopio
Kuopio, Finland

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ABBREVIATIONS

3-OH	3-hydroxy
AAG	α_1 -acid glycoprotein
AhR	aryl hydrocarbon receptor
AMI	acute myocardial infarction
ANOVA	analysis of variance
AUC	area under the concentration-time curve
BRCP	breast cancer resistance protein
CAR	constitutive androstane receptor
CL	clearance
C_{\max}	peak plasma concentration
CNS	central nervous system
CV	coefficient of variation
CYP	cytochrome P450
ERBT	erythromycin breath test
GX	glycinexylidide
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
IVRA	intravenous regional anaesthesia
k_{el}	elimination rate constant
MDR1	multidrug resistance protein 1
MEGX	monoethylglycinexylidide
MI	metabolic intermediate
MRP	multidrug resistance-associated protein
NSAID	non-steroidal anti-inflammatory drug
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OCTN	organic cation/carnitine transporter
PEPT	peptide transporter
PXR	pregnane X receptor
SD	standard deviation
SEM	standard error of mean
SSRI	selective serotonin reuptake inhibitors
$t_{1/2}$	elimination half-life
t_{\max}	time to peak concentration
V_{ss}	steady-state volume of distribution

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:

I Isohanni MH, Neuvonen PJ, Palkama VJ, Olkkola KT: Effect of erythromycin and itraconazole on the pharmacokinetics of intravenous lignocaine. *Eur J Clin Pharmacol* 1998, 54, 561-565.

II Isohanni MH, Neuvonen PJ, Olkkola KT: Effect of erythromycin and itraconazole on the pharmacokinetics of oral lignocaine. *Pharmacol Toxicol* 1999, 84, 143-146.

III Isohanni MH, Neuvonen PJ, Olkkola KT: Effect of itraconazole on the pharmacokinetics of inhaled lidocaine. *Basic Clin Pharmacol Toxicol* 2004, 95, 120-123.

IV Olkkola KT, Isohanni MH, Hamunen K, Neuvonen PJ: The effect of erythromycin and fluvoxamine on the pharmacokinetics of intravenous lidocaine. *Anesth Analg* 2005, 100, 1352–1356.

V Isohanni MH, Neuvonen PJ, Olkkola KT: Effect of fluvoxamine and erythromycin on the pharmacokinetics of oral lidocaine. *Basic Clin Pharmacol Toxicol* 2006, 99, 168-172.

VI Isohanni MH, Ahonen J, Neuvonen PJ, Olkkola KT: Effect of ciprofloxacin on the pharmacokinetics of intravenous lidocaine. *Eur J Anaesthesiol* 2005, 22, 795-799.

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ABSTRACT

Background and aims. Lidocaine is a widely used local anaesthetic agent that also has anti-arrhythmic effects. It is classified as a type Ib anti-arrhythmic agent and is used to treat ventricular tachycardia or ventricular fibrillation. Lidocaine is eliminated mainly by metabolism, and less than 5% is excreted unchanged in urine. Lidocaine is a drug with a medium to high extraction ratio, and its bioavailability is about 30%. Based on *in vitro* studies, the earlier understanding was that CYP3A4 is the major cytochrome P450 (CYP) enzyme involved in the metabolism of lidocaine. When this work was initiated, there was little human data on the effect of inhibitors of CYP enzymes on the pharmacokinetics of lidocaine. Because lidocaine has a low therapeutic index, medications that significantly inhibit lidocaine clearance (CL) could increase the risk of toxicity. These studies investigated the effects of some clinically important CYP1A2 and CYP3A4 inhibitors on the pharmacokinetics of lidocaine administered by different routes.

Methods. All of the studies were randomized, double-blind, placebo-controlled cross-over studies in two or three phases in healthy volunteers. Pretreatment with clinically relevant doses of CYP3A4 inhibitors erythromycin and itraconazole or CYP1A2 inhibitors fluvoxamine and ciprofloxacin was followed by a single dose of lidocaine. Blood samples were collected to determine the pharmacokinetic parameters of lidocaine and its main metabolites monoethylglycinexylidide (MEGX) and 3-hydroxylidocaine (3-OH-lidocaine).

Results. Itraconazole and erythromycin had virtually no effect on the pharmacokinetics of intravenous lidocaine, but erythromycin slightly prolonged the elimination half-life ($t_{1/2}$) of lidocaine (Study I). When lidocaine was taken orally, both erythromycin and itraconazole increased the peak concentration (C_{max}) and the area under the concentration-time curve (AUC) of lidocaine by 40-70% (Study II). Compared with placebo and itraconazole, erythromycin increased the C_{max} and the AUC of MEGX by 40-70% when lidocaine was given intravenously or orally (Studies I and II). The pharmacokinetics of inhaled lidocaine was unaffected by concomitant administration of itraconazole (Study III). Fluvoxamine reduced the CL of intravenous lidocaine by 41% and prolonged the $t_{1/2}$ of lidocaine by 35%. The mean AUC of lidocaine increased 1.7-fold (Study IV). After oral administration of lidocaine, the mean AUC of lidocaine increased 3-fold and the C_{max} 2.2-fold by fluvoxamine (Study V). During the pretreatment with fluvoxamine combined with erythromycin, the CL of intravenous lidocaine was 53% smaller than during placebo and 21% smaller than during fluvoxamine alone. The $t_{1/2}$ of lidocaine was significantly longer during the combination phase than during the placebo or fluvoxamine phase. The mean AUC of intravenous lidocaine increased 2.3-fold and the C_{max} 1.4-fold (Study IV). After oral administration of lidocaine, the mean AUC of lidocaine increased 3.6-fold and the C_{max} 2.5-fold by concomitant fluvoxamine and erythromycin. The $t_{1/2}$ of oral lidocaine was significantly longer during the combination phase than during the placebo (Study V). When lidocaine was given intravenously, the combination of fluvoxamine and erythromycin prolonged the $t_{1/2}$ of MEGX by 59% (Study IV). Compared with placebo,

ciprofloxacin increased the mean C_{max} and AUC of intravenous lidocaine by 12% and 26%, respectively. The mean plasma CL of lidocaine was reduced by 22% and its $t_{1/2}$ prolonged by 7% (Study VI).

Conclusions. These studies clarify the principal role of CYP1A2 and suggest only a modest role of CYP3A4 in the elimination of lidocaine *in vivo*. The inhibition of CYP1A2 by fluvoxamine considerably reduces the elimination of lidocaine. Concomitant use of fluvoxamine and the CYP3A4 inhibitor erythromycin further increases lidocaine concentrations. The clinical implication of this work is that clinicians should be aware of the potentially increased toxicity of lidocaine when used together with inhibitors of CYP1A2 and particularly with the combination of drugs inhibiting both CYP1A2 and CYP3A4 enzymes.

INTRODUCTION

Variability in drug response can be due to either pharmacokinetic or pharmacodynamic factors. The reasons for people differing in pharmacokinetics or pharmacodynamics are manifold, including genetic factors, diseases, age and concomitantly administered drugs. As far as pharmacokinetics is concerned, oxidation reactions are dominant in the metabolism of drugs, and the cytochrome P450 (CYP) enzymes have been recognized as chief contributors (Wilkinson 2005). The primary organ for the biotransformation of drugs is the liver. However, CYP enzymes can be detected in several other organs as well. For example, the wall of the small intestine plays a major role in the presystemic elimination of many drugs, and intestinal drug metabolism can greatly reduce the oral bioavailability of drugs.

Modern anaesthetic techniques involve combinations of drugs to produce synergistic or additive interactions. Furthermore, many patients coming to operations take medications unrelated to surgery. In fact, a pharmacoepidemiological study showed that half of the adult general surgery patients take medicines unrelated to surgery (Kennedy et al. 2000).

Lidocaine is a popular amide-type local anaesthetic that is also widely used intravenously for ventricular arrhythmias. Lidocaine is not solely a local anaesthetic and an anti-arrhythmic drug. Intravenous lidocaine also has analgesic, anti-inflammatory and anti-hyperalgesic properties (Marret et al. 2008). Recently, several potential indications for lidocaine have emerged (Wright et al. 2008). Lidocaine is eliminated mainly by metabolism and less than 5% is excreted unchanged in urine. Lidocaine is a drug with a medium to high extraction ratio, and therefore, its clearance (CL) is significantly dependent on liver blood flow (Tucker and Mather 1979). After oral ingestion, lidocaine has extensive first-pass metabolism, resulting in a bioavailability of about 30%. The principal metabolic pathway of lidocaine is oxidative N-deethylation to monoethylglycinexylidide (MEGX). In human liver microsomes, lidocaine is also metabolized via hydroxylation to 3-hydroxylidocaine (3-OH-lidocaine) (Imaoka et al. 1990). Based on *in vitro* studies, the earlier understanding was that CYP3A4 is mainly responsible for the formation of MEGX, whereas CYP1A2 is responsible for the production of 3-OH-lidocaine (Bargetzi et al. 1989, Imaoka et al. 1990).

CYP-related drug interactions are known to affect the pharmacokinetics of several drugs. Erythromycin and itraconazole are inhibitors of CYP3A4. Itraconazole, for instance, increases the area under the oral midazolam concentration-time curve over 600% and reduces the clearance of midazolam by 70% (Olkola et al. 1996). Fluvoxamine and ciprofloxacin inhibit CYP1A2 (Fuhr et al. 1992, Rasmussen et al. 1995).

When this work was initiated, little human data existed on the effect of inhibitors of CYP enzymes in general on the pharmacokinetics of lidocaine. Because lidocaine has a low therapeutic index, medications that significantly inhibit its clearance, thereby increasing lidocaine plasma concentrations, could increase the risk of toxicity. If inhibiting CYP3A4 affects lidocaine to the same extent with, e.g., itraconazole, as it affects midazolam, it can be predicted that during long-term infusion of lidocaine, the dose would

be reduced by 70-80% or otherwise the targeted therapeutic concentrations would be exceeded 3- to 5-fold resulting in serious toxic reactions.

Previous studies have shown that cimetidine, a non-specific inhibitor of CYP enzymes, reduces the plasma clearance of lidocaine significantly (Feely et al. 1982). Propafenone, an inhibitor of CYP2D6, reduces the clearance of lidocaine negligibly (Ujhelyi et al. 1993). The β -adrenoreceptor antagonist propranolol reduces lidocaine clearance by 20-40% (Ochs et al. 1980), the reduction in lidocaine metabolism being apparently mediated both by enzyme inhibition and by the reduction of liver blood flow (Bax et al. 1985). *In vitro* studies show that propranolol does not affect the formation of MEGX, but inhibits the 3-hydroxylation of lidocaine mediated by CYP1A2 (Imaoka et al. 1990, Suzuki et al. 1993).

The present studies investigated the effects of some clinically important CYP1A2 and CYP3A4 inhibitors on the pharmacokinetics of lidocaine in healthy volunteers.

REVIEW OF THE LITERATURE

1 Pharmacokinetics

Pharmacokinetics refers to the phases and time course of a drug and its metabolites in the body or, more accurately, what the body does to the drug. Pharmacokinetics is often divided into absorption and disposition. Absorption describes the movement of a drug from the site of administration to the circulatory system. The rate of absorption is indirectly described by the peak plasma drug concentration (C_{\max}) and the time at which it occurs (t_{\max}). Disposition consists of distribution and elimination. Distribution involves the transfer of a drug between plasma and tissues. Distribution initially occurs into highly perfused tissues, followed by slower uptake into muscle and fat. Elimination involves the loss of a drug from the body. Disposition, this combined process of distribution and elimination, is generally described by the clearance and the terminal elimination half-life ($t_{1/2}$).

The major mechanism for elimination of drugs from the body is metabolism; only relatively few drugs are eliminated unchanged by the kidneys (Rowland and Tozer 1995). The liver is the major organ for drug biotransformation, but drug-metabolizing enzymes are also present at other sites, such as the gastrointestinal and respiratory tracts, kidney, lung, brain and skin (Krishna and Klotz 1994). As in the liver, orally administered drugs can be subject to significant metabolism in the intestinal wall before they reach the systemic circulation. This phenomenon is referred to as first-pass, or presystemic, metabolism, and it can considerably decrease the oral bioavailability of many drugs.

Most pharmacologically active molecules are lipophilic, which facilitates their passing through biological membranes. Lipophilic compounds need to be biotransformed into more hydrophilic metabolites in order to be excreted into urine or bile. This biotransformation is catalysed in humans by several drug-metabolizing enzymes. Drug metabolism has been traditionally classified into functionalization (phase I) and conjugation (phase II) reactions. The functionalization reactions include dehydrogenation or hydrogenation, oxidation, hydrolysis, reduction and mono-oxygenation (Meyer 1996). Most phase I metabolism reactions are catalysed by CYP enzymes in the endoplasmic reticulum. The enzymes involved in phase II reactions transfer water-soluble chemicals, such as glutathione, glucuronide or sulphate, to other compounds. They are located in both the cytoplasm and the endoplasmic reticulum. Many drugs undergo both phase I and phase II metabolism sequentially, but some can be excreted after either phase I or phase II reactions or even while still unmetabolized. And further, despite the nomenclature, phase II metabolism can occur in some unchanged drugs, and phase I enzymes can also metabolize conjugated drugs (Josephy et al. 2005).

The metabolites produced by phase I and II reactions are usually inactive or less active than the parent drug. However, some metabolites may have enhanced activity (prodrugs) or toxic effects. Thus, changes in the activity of a drug-metabolizing enzyme can have different consequences depending on the properties of the drug. A decrease in enzyme activity leads to increased plasma concentrations of the substrate drug, which usually

means exaggerated effects and toxicity, and vice versa, an increase in enzyme activity leads to decreased plasma concentrations of the substrate, which can result in therapeutic failure due to lack of effect. Alterations in enzyme activity are most relevant in the case of drugs with a narrow therapeutic window.

2 Cytochrome P450 enzymes

In phase I human drug metabolism, CYP enzymes play a major role. The CYP enzymes comprise a superfamily of haem-containing mono-oxygenases. In the presence of carbon monoxide, they have an absorption maximum at a wavelength of 450 nm and are therefore called P450 (Nebert and Russell 2002). Human CYP enzymes are located intracellularly in the endoplasmic reticulum (microsomes). The CYP superfamily has been divided on the basis of structural homology into families (enzymes with >40% amino acid sequence similarity), which are then further classified into subfamilies (enzymes within a family having >55% amino acid similarity). Individual CYP enzymes are named by a number for the family (e.g. CYP3A4), a letter for the subfamily (CYP3A4) and a number for the individual enzyme (CYP3A4). Currently, there are 18 different known CYP families and 44 subfamilies in humans, covering 57 CYP genes and 58 pseudogenes (Lewis 2004, Nelson et al. 2004) (<http://drnelson.utmem.edu/CytochromeP450.html>). Enzymes in families 1-3 have been traditionally thought to function mostly in the metabolism of a wide variety of xenobiotics, while other families are involved mainly in physiological functions such as the biosynthesis of fatty acids, steroid hormones and bile acids (Venkatakrisnan et al. 2001, Nebert and Russell 2002). The metabolism of over 90% of all drugs is estimated to be mediated, at least partially, by CYPs (Pelkonen et al. 2008).

The estimated proportions of the major drug-metabolizing CYP enzymes in the human liver are as follows; CYP3A4/5/7 35%, CYP2C9 17%, CYP2E1 14%, CYP1A2 12%, CYP2A6 8%, CYP2C8 6%, CYP2C19 3%, CYP2B6 3% and CYP2D6 2% (Rostami-Hodjegan and Tucker 2007, Figure 1). However, notable interindividual differences exist in the hepatic proportion of the different CYP enzymes. Furthermore, the hepatic abundance of a CYP enzyme does not correlate with the importance of the enzyme in drug metabolism. A typical feature of drug-metabolizing CYP enzymes is also broad and overlapping substrate specificity. CYP enzymes can be inhibited and induced by various drugs and other xenobiotics (Pelkonen et al. 2008). Examples of substrates, inhibitors and inducers of individual CYP isoenzymes are presented in Table 1.

Table 1. *Examples of substrates, inhibitors and inducers of some drug-metabolizing CYP enzymes.*

CYP1A2	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrates					
Caffeine ¹	Amiodarone ⁹	Celecoxib ¹³	Citalopram ¹⁶	Amitriptyline ¹⁷	Alfentanil ¹
Clozapine ²	Cerivastatin ⁹	Diclofenac ¹³	Diazepam ¹⁶	Codeine ¹⁷	Alprazolam ¹
Melatonin ¹	Ibuprofen ⁹	Fluvastatin ¹³	Lansoprazole ¹⁶	Dextromethorphan ¹⁷	Atorvastatin ¹
Ropivacaine ³	Paclitaxel ⁹	Ibuprofen ¹³	Omeprazole ¹⁶	Fluoxetine ¹⁷	Carbamazepine ¹⁹
Theophylline ¹	Pioglitazone ¹⁰	Losartan ¹³	Phenobarbital ¹⁶	Fluvoxamine ¹⁷	Cyclosporin ¹
Tizanidine ⁴	Repaglinide ¹¹	Naproxen ¹³	Proguanil ¹⁶	Haloperidol ¹⁷	Dexamethasone ¹⁹
	Rosiglitazone ⁹	Phenytoin ¹³	Propranolol ¹⁶	Metoprolol ¹⁷	Diltiazem ¹⁹
		S-warfarin ¹³		Oxycodone ¹⁷	Erythromycin ¹
				Paroxetine ¹⁷	Felodipine ¹
				Propafenone ¹⁷	Lovastatin ¹
				Risperidone ¹⁷	Midazolam ¹
				Tramadol ¹⁸	Nifedipine ¹
					Simvastatin ¹
					Tacrolimus ¹
					Triazolam ¹
					Verapamil ¹⁹
Inhibitors					
Ciprofloxacin ⁵	Gemfibrozil ⁹	Amiodarone ¹⁴	Fluconazole ¹	Fluoxetine ¹	Clarithromycin ¹⁹
Fluvoxamine ⁶	Trimethoprim ⁹	Fluconazole ¹⁴	Fluvoxamine ¹⁶	Paroxetine ¹	Diltiazem ¹⁹
Furafylline ¹		Miconazole ¹⁴	Ketaconazole ¹⁶	Quinidine ¹	Erythromycin ¹⁹
Rofecoxib ⁷		Sulfaphenazole ¹⁴	Omeprazole ¹⁶	Terbinafine ¹	Grapefruit juice ¹
		Voriconazole ¹⁵			HIV protease inhibitors ¹⁹
					Itraconazole ¹
					Ketoconazole ¹
					Voriconazole ¹⁵
Inducers					
Cigarette smoke ¹	Phenobarbital ¹²	Phenobarbital ¹²	Phenobarbital ¹²	Not known	Carbamazepine ¹
Omeprazole ⁸	Rifampicin ¹²	Rifampicin ¹²	Rifampicin ¹²		Dexamethasone ¹
					Phenobarbital ¹
					Phenytoin ¹
					Rifampicin ¹

References: ¹Pelkonen et al. (2008), ²Bertilsson et al. (1994), ³Jokinen et al. (2000), ⁴Granfors et al. (2004), ⁵Fuhr et al. (1992), ⁶Rasmussen et al. (1995), ⁷Backman et al. (2006), ⁸Gunes and Dahl (2008), ⁹Totah and Rettie (2005), ¹⁰Jaakkola et al. (2006a), ¹¹Kajosaari et al. (2005), ¹²Gerbal-Chaloin et al. (2001), ¹³Rettie and Jones (2005), ¹⁴Miners and Birkett (1998), ¹⁵Theuretzbacher et al. (2006), ¹⁶Desta et al. (2002), ¹⁷Zanger et al. (2004), ¹⁸Stamer and Stuber (2007), ¹⁹Dresser et al. (2000).

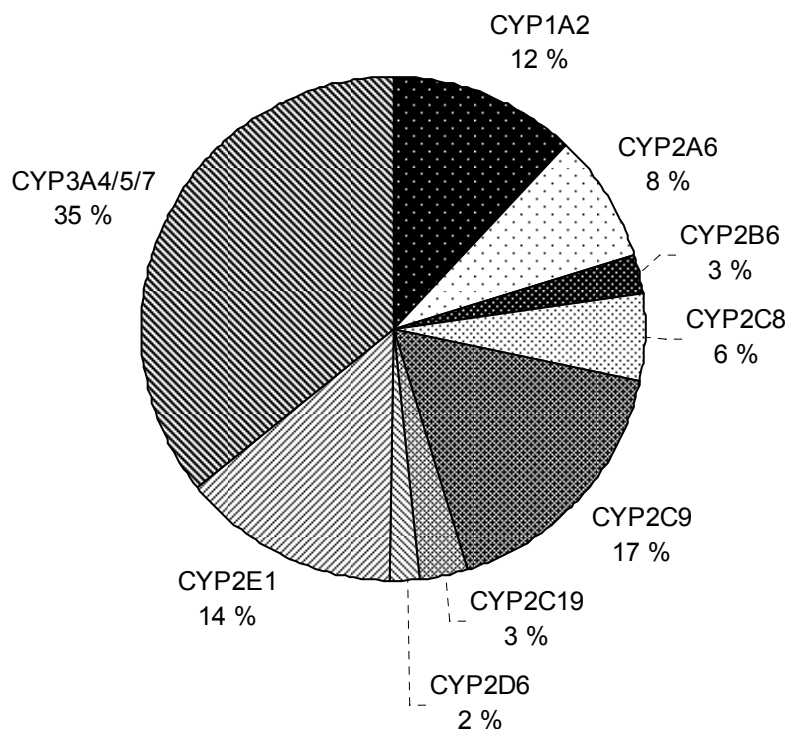


Figure 1 *Relative abundances of CYP enzymes in the human liver.*

2.1 CYP1 family

The CYP1A subfamily consists of two members: CYP1A1 and CYP1A2. CYP1A1 is expressed mainly in extrahepatic tissues such as the lung, skin, larynx and placenta, whereas CYP1A2 is expressed mainly in the liver (Gunes and Dahl 2008). The substrate specificity of CYP1A1 overlaps with that of CYP1A2, but it is of little importance in drug metabolism due to localization.

CYP1A2 is important in the metabolism of several drugs, including caffeine, clozapine, ropivacaine, theophylline and tizanidine (Bertilsson et al. 1994, Jokinen et al. 2000, Granfors et al. 2004, Pelkonen et al. 2008). CYP1A2 is also involved in the biotransformation of some endogenous compounds, e.g. melatonin, and in the elimination of environmental toxins as well as the bioactivation of environmental procarcinogens (Härterter et al. 2001, Faber et al. 2005). Fluvoxamine, ciprofloxacin and rofecoxib are known inhibitors of CYP1A2 (Fuhr et al. 1992, Rasmussen et al. 1995, Backman et al. 2006). CYP1A2 can be induced by environmental factors, such as polycyclic aromatic hydrocarbons found in, for example, cigarette smoke and chargrilled food. Other inducers include dietary agents in, for instance, cruciferous vegetables, and drugs such as omeprazole (Gunes and Dahl 2008). Large interindividual and intraindividual variability of CYP1A2 activity has been found in humans (Faber et al. 2005). CYP1A2 expression varies up to 40-fold, and there is a corresponding variability of enzyme activity and drug metabolism (Gunes and Dahl 2008). Although the CYP1A2 gene shows structural

polymorphism (<http://www.cypalleles.ki.se/cyp1a2.htm>), its importance in explaining variability in CYP1A2 activity is unclear.

2.2 CYP2 family

CYP2A6 is a predominantly hepatic enzyme. Its most specific substrates include coumarin and nicotine. CYP2A6 is inhibited by methoxsalen and induced by phenobarbital (Pelkonen et al. 2008). CYP2A6 is highly polymorphic, and its genotype has been associated with, for example, smoking behaviour (Ingelman-Sundberg et al. 2007).

CYP2B6 has recently been recognized to be a clinically important enzyme in drug metabolism. It is mainly a hepatic enzyme, but is also expressed at lower levels in several extrahepatic tissues, including the brain, lung, nasal mucosa and trachea. It is highly polymorphic (Walsky et al. 2006). CYP2B6 metabolizes bupropion, methadone and propofol (Oda et al. 2001, Walsky et al. 2006, Totah et al. 2008). Clopidogrel and ticlopidine are potent inhibitors of CYP2B6 (Turpeinen et al. 2005). It is inducible by rifampicin (Pelkonen et al. 2008).

The importance of **CYP2C8** in drug metabolism, like that of CYP2B6, has been clarified recently (Ingelman-Sundberg et al. 2007). CYP2C8 is expressed mainly in the liver, where it has a major role in the metabolism of many drugs, including amiodarone, cerivastatin, paclitaxel, repaglinide and rosiglitazone (Rahman et al. 1994, Baldwin et al. 1999, Ohyama et al. 2000, Wang et al. 2002b, Bidstrup et al. 2003). Furthermore, certain endogenous agents, such as arachidonic acid, can be metabolized by CYP2C8 (Rifkind et al. 1995). CYP2C8 inhibitors include gemfibrozil and trimethoprim (Wang et al. 2002b, Wen et al. 2002). Montelukast is a selective and potent inhibitor of CYP2C8 *in vitro*, but due to its low free concentration in plasma, it does not inhibit CYP2C8 *in vivo* (Jaakkola et al. 2006b). CYP2C8 is induced by rifampicin (Gerbai-Chaloin et al. 2001). Several functional CYP2C8 polymorphisms have been published (Dai et al. 2001, Niemi et al. 2003, Martinez et al. 2005, Rodriguez-Antona et al. 2008).

CYP2C9 is the most abundant CYP2C isoform in both the liver and intestine (Läpple et al. 2003). Its substrates include many clinically important drugs, e.g. S-warfarin, losartan, phenytoin and many non-steroidal anti-inflammatory drugs (NSAIDs) (Rettie and Jones 2005). Amiodarone, sulphafenazole and several azole antifungals inhibit CYP2C9, and it is induced by rifampicin and barbiturates (Miners and Birkett 1998, Pelkonen et al. 2008). CYP2C9 polymorphisms have functional consequences for pharmacokinetics as well as for clinical drug response and side-effects (Kirchheiner and Brockmüller 2005).

CYP2C19 participates in the metabolism of many commonly used drugs, e.g. citalopram, diazepam, omeprazole, phenobarbital, proguanil and propranolol (Desta et al. 2002). No selective inhibitors for CYP2C19 have been found, but at least omeprazole and fluconazole inhibit this enzyme (Funck-Brentano et al. 1997, Kang et al. 2002). The inducers of CYP2C19 include rifampicin and artemisinin (Desta et al. 2002). CYP2C19 is also polymorphically expressed. Only 2-5% of Caucasians, but up to 20% of Orientals are

poor metabolizers of CYP2C19 (Ingelman-Sundberg et al. 2007). CYP2C19 genotype has been shown to influence the efficacy of proton pump inhibitor treatment (Klotz et al. 2004).

CYP2D6 plays a central role in drug metabolism in humans. It is responsible for the clearance of 25% of the compounds in current clinical use, and its polymorphisms can affect the metabolism of 50% of these drugs (Ingelman-Sundberg et al. 2007). In addition to the liver, CYP2D6 is expressed at lower levels in the gastrointestinal tract and brain. Its substrates comprise many anti-arrhythmics, anti-emetics, antipsychotics, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, beta-blockers and opioids, e.g. dextromethorphan (Zanger et al. 2004). Furthermore, CYP2D6 is important in the bioactivation of the prodrugs codeine and tramadol (Stamer and Stuber 2007). This isoenzyme is inhibited by many drugs, including quinidine and terbinafine (Pelkonen et al. 2008). CYP2D6 is the only CYP enzyme involved in drug metabolism that is not inducible (Ingelman-Sundberg et al. 2007). CYP2D6 exhibits significant polymorphism, ranging from null alleles to multiple copies of active alleles. Individuals can be divided into poor, intermediate, extensive and ultrarapid metabolizers according to the activity of CYP2D6 (Zanger et al. 2004).

CYP2E1 has mainly toxicological relevance since it is involved in the formation of many carcinogens and reactive metabolites, such as the hepatotoxic metabolite of paracetamol. This isoenzyme participates in the metabolism of chlorzoxazone, ethanol, paracetamol and many halogenated anaesthetics, including enflurane, halothane, isoflurane and sevoflurane (Tanaka et al. 2000). Inhibitors of CYP2E1 include disulfiram and pyridine, and it is induced by ethanol and isoniazid (Pelkonen et al. 2008).

2.3 CYP3 family

CYP3A enzymes are the most important oxidative enzymes in drug metabolism. They account for approximately 40% of the total CYP content in the human liver and have been estimated to participate in the metabolism of >50% of all marketed drugs (Liu et al. 2007). The CYP3A subfamily of enzymes consists of four isoforms; CYP3A4, CYP3A5, CYP3A7 and CYP3A43.

CYP3A4 is mainly located in the liver, but it is also the most abundant CYP enzyme in the intestine (Kivistö et al. 1996). In addition, it is expressed in the lung, kidney, brain and prostate (Anttila et al. 1997, Zhou 2008b). The active site of CYP3A4 is large and flexible so that many preferentially lipophilic compounds can bind to it. Its substrates include the opioid alfentanil, the benzodiazepines midazolam and triazolam, several calcium-channel blockers, the HMG-CoA reductase inhibitors atorvastatin and simvastatin, the immunosuppressants cyclosporine and tacrolimus, macrolide antibiotics such as erythromycin, and many others. Relatively low substrate specificity makes CYP3A4 susceptible to inhibition by a broad variety of structurally unrelated substances. On the other hand, drug interactions caused by inhibition of CYP3A4 exhibit substantial substrate dependency (Pelkonen et al. 2008). Its inhibitors include the azole antifungals ketoconazole and itraconazole, the calcium-channel blockers diltiazem and verapamil, the

macrolide antibiotics clarithromycin, erythromycin and troleandomycin, the human immunodeficiency virus (HIV) protease inhibitors and grapefruit juice (Dresser et al. 2000, Pelkonen et al. 2008). Both hepatic and intestinal CYP3A4 can be induced by several drugs such as carbamazepine, dexamethasone, phenobarbital, phenytoin and rifampicin (Luo et al. 2004). There is a high degree of interindividual variability in CYP3A4 activity. Numerous variants of CYP3A4 alleles have been found, but their frequencies are very low, and they are unlikely to explain the variability in CYP3A4 activity (Zanger et al. 2008).

CYP3A5 is found mainly in the liver, but it is also expressed in the intestine. Furthermore, it is the dominant CYP3A form in the kidney and lung (Kivistö et al. 1996, Lamba et al. 2002). The substrate specificity of CYP3A5 is similar, but not identical, to that of CYP3A4. However, the catalytic efficiency of CYP3A5 is usually weaker, and it can be less susceptible to inhibition than CYP3A4. CYP3A5 is genetically polymorphic, and it is significantly expressed in livers of only about 20% of Caucasians. However, in some individuals CYP3A5 can represent up to 50% of total hepatic CYP3A content (Daly 2006). CYP3A5 polymorphism seems to explain the interindividual variability of some CYP3A substrates such as tacrolimus (Zanger et al. 2008).

CYP3A7 is predominantly expressed in the fetal liver, but some adults continue to express this isoenzyme. CYP3A43 is expressed in relatively high levels in the prostate and testes, but its expression in the liver is low, and its function remains unknown (Daly 2006).

2.4 Inhibition and induction of CYP enzymes

CYP enzymes play a central role in the metabolism of drugs, and inhibition or induction of these enzymes can alter the plasma concentrations and effects of their substrate drugs. Inhibition of CYP enzymes has been considered to be the most common cause of harmful drug-drug interactions (Pelkonen et al. 2008). Inhibition of a drug-metabolizing enzyme can lead to decreased clearance and increased plasma concentrations of its substrate compound, thus increasing the likelihood of adverse effects and toxicity. By contrast, in the case of prodrugs, inhibition can reduce the clinical efficacy of the substrate drug. CYP enzyme inhibition usually occurs rapidly, even after a single dose of the inhibitor (Lin and Lu 1998).

Mechanisms of inhibition

The mechanisms of enzyme inhibition can be divided roughly into three categories: reversible, quasi-irreversible and irreversible (Lin and Lu 1998).

Reversible inhibition can be further divided, based on enzyme kinetics, into competitive, non-competitive, uncompetitive and mixed-type inhibition. In competitive inhibition, the inhibitor competes with the substrate for the same binding site within a CYP enzyme. Competitive inhibitors are often but not necessarily substrates for the

enzyme they inhibit. Typical competitive inhibitors of CYP enzymes include the CYP3A4 inhibitor itraconazole and the CYP1A2 inhibitor ciprofloxacin (Pelkonen et al. 2008). In non-competitive inhibition, the active binding sites of the substrate and inhibitor differ from each other, but are located in the same enzyme. In uncompetitive inhibition, the inhibitor binds to the enzyme-substrate complex and makes the complex catalytically inactive. In practice, reversible inhibition often displays elements of both competitive and non-competitive inhibition, and thus, is called mixed-type inhibition (Lin and Lu 1998).

Irreversible inhibition requires metabolic activation by the enzyme and is therefore known as mechanism-based inactivation (Obach et al. 2007). In irreversible inhibition, an inhibitor is metabolically activated by the CYP enzyme, and this inhibitory metabolite then forms a stable metabolic intermediate (MI) complex with the prosthetic haem of CYP, rendering the enzyme functionally inactive. The difference between quasi-irreversible and irreversible inhibition is that in the former this MI complexation can be reversed *in vitro*. Irreversible inhibition is often long-lasting because it is reversed only by a synthesis of new, catalytically active enzymes. Erythromycin is an example of a quasi-irreversible inhibitor of CYP3A (Lin and Lu 1998). Typical mechanism-based inhibitors include the CYP1A2 inhibitor furafylline and the CYP3A4 inhibitor gestodene (Pelkonen et al. 2008).

Induction of CYP enzymes

Induction is an adaptive process in which long-term exposure to drugs or environmental agents produces an upregulation in the amount of drug-metabolizing enzymes. Thus, induction leads to decreased plasma concentrations and often reduced pharmacological activity of the substrate drug. Drugs or environmental agents can induce CYP enzymes by enhancing the rate of their synthesis or by reducing their rate of degradation. Increased synthesis of CYPs is mediated by a group of ligand-activated transcription factors, which include intracellular aryl hydrocarbon receptor (AhR) and nuclear receptors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR). The inducer binds to and activates one or more of these receptors, leading to increased transcription of the respective CYP enzymes. Contrary to CYP inhibition, induction is a slow process and can usually be seen only days or even weeks after exposure to the inducer has begun, and it may require multiple dosing with the inducing compound (Lin 2006). Common inducers of CYP enzymes comprise antiepileptic drugs, polycyclic aromatic hydrocarbons and rifampicin (Pelkonen et al. 2008).

3 Drug transporters

Transporters are increasingly recognized to be essential in drug absorption, distribution and excretion. Therefore, both metabolism by CYP enzymes and transport mechanisms should be considered when predicting *in vivo* pharmacokinetics of a drug. In addition to

drugs, transporters have important roles in transporting endogenous substances such as amino acids, bile acids, glucose, lipids, steroids and hormones (Ho and Kim 2005). Based on the direction of movement, transporters are usually divided into efflux and uptake transporters. The inhibition and induction of drug transporters follow the same principles as seen with drug-metabolizing enzymes. In addition to drug-induced changes in transporter activity, many transporters also exhibit genetic polymorphism (Ho and Kim 2005, Maeda and Sugiyama 2008).

Efflux transporters transport compounds out of the cell. They act to limit the entry of drugs or to assist their removal from the cell. The best-known efflux transporter is P-glycoprotein (MDR1, multidrug resistance protein 1), a member of the ATP-binding cassette transporter protein family. It is a transmembrane protein that mediates the transport of various compounds through cell membranes. High levels of P-glycoprotein have been identified on the luminal surfaces of the small and large intestine, in proximal tubules of the kidneys and on the luminal surface of the biliary tract and hepatocytes. P-glycoprotein is involved in the excretion of substances into urine, intestinal lumen and bile (i.e. reduced absorption) and has an important role in the blood-brain barrier (Fromm 2004). There is overlapping substrate specificity between P-glycoprotein and CYP3A4, and there are also similarities in the inhibitors and inducers of CYP3A4 and P-glycoprotein (Zhang and Benet 2001). Substrate drugs for P-glycoprotein include anticancer drugs, digoxin and HIV protease inhibitors. Itraconazole, erythromycin, verapamil and cyclosporine are inhibitors of P-glycoprotein. An inducer of P-glycoprotein is rifampicin (Zhou 2008a). Other efflux transporters include the multidrug resistance-associated protein (MRP) family and the breast cancer resistance protein (BRCP) (Ho and Kim 2005).

Uptake transporters enhance the entry of drugs into cells. This category of transporters includes the organic anion transporting polypeptide (OATP), organic anion transporter (OAT), organic cation transporter (OCT), organic cation/carnitine transporter (OCTN) and peptide transporter (PEPT) families. The OATPs are expressed in the intestine, liver, kidney and brain (Ho and Kim 2005). These transporters have several clinically important substrates such as bile salts, steroid conjugates, thyroid hormones, digoxin, HMG-CoA reductase inhibitors (statins) and methotrexate. OATPs can be inhibited by cyclosporine, rifampicin, gemfibrozil and macrolides, e.g. erythromycin (Niemi 2007).

4 Lidocaine

Lidocaine is an amide-type local anaesthetic agent with an intermediate duration of action. Lidocaine is also a class Ib anti-arrhythmic agent that can be used intravenously in the acute treatment and prevention of ventricular arrhythmias, especially after myocardial infarction. Lidocaine was synthesized in 1943, being the first amino amide-type local anaesthetic compound used in clinical practice (Covino 1986).

At therapeutic plasma concentrations, 64-70% of lidocaine is bound to plasma proteins (Benowitz and Meister 1978, Tucker and Mather 1979). Less is bound at higher plasma concentrations, e.g. at concentrations of 6-10 µg/ml, only 60%. Lidocaine is mainly bound to the acute phase reactant α_1 -acid glycoprotein (AAG). Plasma concentrations of AAG are increased as a result of various pathophysiological conditions, such as surgery, trauma and certain disease states, with a subsequent rise in plasma protein binding. Thus, the free fraction of lidocaine may vary up to eightfold, being relatively low in, for instance, postoperative and post-myocardial infarction patients (Tucker 1986).

4.2 Pharmacokinetics

Absorption

Lidocaine is readily absorbed from mucous membranes and through damaged skin. Absorption through intact skin is poor (Sweetman 2009). Lidocaine is rapidly absorbed from the upper airway, tracheobronchial tree and alveoli into the bloodstream (DiFazio 1981). It is also well-absorbed from the gastrointestinal tract, but oral bioavailability is only 35% due to extensive first-pass metabolism (Boyes et al. 1971). When injected into tissues, lidocaine is rapidly absorbed. The absorption rate is related to vascularity and the presence of tissue and fat capable of binding lidocaine of the particular tissues. Thus, the absorption rate from the site of injection decreases in the order intercostal > paracervical > lumbal epidural > brachial > spinal > subcutaneous (Tucker and Mather 1979, Tozer and Rowland 2006). The peak plasma concentrations following administration of lidocaine by various routes are presented in Appendix 1. Addition of a vasoconstrictor, e.g. epinephrine, to the solution reduces the rate of absorption by limiting the local blood flow, and therefore, the local anaesthetic effect is prolonged.

Distribution

When lidocaine is administered intravenously, it is rapidly distributed into highly perfused tissues, which achieve fast equilibration, followed by redistribution into skeletal muscle and adipose tissue, which reach equilibration slower. Thus, lidocaine plasma concentrations decline rapidly after an intravenous dose, with an initial half-life of less than 30 min. The elimination half-life ($t_{1/2}$) is 1-2 h. The $t_{1/2}$ may be prolonged if lidocaine is administered with an infusion lasting longer than 24 h, or if hepatic blood flow is reduced. Lidocaine has a steady-state volume of distribution (V_{ss}) in the range of 50-160 litres (Benowitz and Meister 1978).

Elimination

Lidocaine is eliminated mainly metabolically, with less than 5% of the dose excreted unchanged in urine (Tucker and Mather 1979). Like the volume of distribution, the clearance of lidocaine varies markedly in healthy volunteers; estimates for plasma clearance range from 0.54 to 1.44 l/min. Lidocaine is a drug with a medium to high extraction ratio (0.65), and therefore, its clearance is significantly dependent on liver blood flow (Benowitz and Meister 1978). Consequently, an inverse relationship exists between lidocaine levels and estimated hepatic blood flow (Stenson et al. 1971).

The metabolism of lidocaine has been thoroughly investigated since the drug entered the market more than half a century ago. However, the metabolism has been shown to be complex, and different results have been obtained from *in vitro* and *in vivo* studies. The principal metabolic pathway of lidocaine is oxidative N-deethylation to MEGX, which is further de-ethylated to 2,6-xylidine and glycinexylidide (GX). 2,6-xylidine is hydrolysed to 4-hydroxy-xylidine, which is the major metabolite found in urine (Keenaghan and Boyes 1972, Tucker and Mather 1979). Based on *in vitro* studies, this hydroxylation is catalysed by CYP2A6 (Gan et al. 2001). Although 4-hydroxy-xylidine appears to be formed mainly from MEGX, evidence has emerged that some 4-hydroxy-xylidine is formed via direct hydrolysis of lidocaine (Nelson et al. 1974). A minor metabolic pathway of lidocaine is hydroxylation of the aromatic ring to form 3-OH-lidocaine (Hermansson et al. 1980). All hydroxylated metabolites are prone to subsequent phase II conjugation reactions (Falany et al. 1999).

Earlier *in vitro* studies with human liver microsomes suggested that the formation of MEGX and 3-OH-lidocaine is catalysed mainly by CYP3A4 and CYP1A2, respectively (Bargetzi et al. 1989, Imaoka et al. 1990). Therefore, lidocaine was initially considered to be a probe for *in vivo* assessment of CYP3A4 activity (Brockmöller and Roots 1994). In a recent review article, lidocaine is still presented as a model substrate of CYP3A4 (Zhou 2008b). Accordingly, the MEGX test, which measures the formation of MEGX following an intravenous bolus of lidocaine, has been used as a marker to evaluate the *in vivo* activity of hepatic CYP3A4 and as a dynamic test of liver function (Reichel et al. 1998, Sakka 2007). However, recent *in vitro* studies by Wang et al. (1999a, 2000) confirm that both CYP3A4 and CYP1A2 are important in the metabolism of lidocaine, but their relative roles can differ at different lidocaine concentrations. There is also some evidence that CYP2C9 can catalyse the formation of MEGX, but its role seems to be negligible (Wang et al. 2000, Nagashima et al. 2005). CYP1A2 appears to be the major enzyme catalysing the formation of both MEGX and 3-OH-lidocaine at therapeutically relevant plasma lidocaine concentrations.

Some evidence has emerged of extrahepatic formation of MEGX. After lidocaine injection, formation of MEGX was demonstrated in a patient in unhepatic phase waiting for a liver transplant (Sallie et al. 1992).

P-glycoprotein

P-glycoprotein seems to have a negligible role in the transport of lidocaine. In both *in situ* and *in vitro* absorption models, the jejunal permeability of lidocaine was high, but carrier-mediated intestinal efflux apparently did not have a significant role (Berggren et al. 2004). In rats, the P-glycoprotein inhibitor quinidine failed to reduce the plasma concentration threshold for lidocaine-induced convulsions (Funao et al. 2003). However, based on a structure-activity relationship analysis, lidocaine could exhibit some P-glycoprotein inhibitory activity (Wang et al. 2003).

4.3 Drug interactions

At the time that this study commenced, little human data were available on the effect of CYP enzymes in general on the pharmacokinetics of lidocaine. Specifically, there was virtually no data on the effect of effective CYP1A2 or CYP3A4 inhibitors on the pharmacokinetics of lidocaine.

The histamine-2 receptor antagonist cimetidine reduced the plasma clearance and V_{ss} of intravenous lidocaine by 20-25% and 7-21%, respectively, and increased lidocaine C_{max} by 50%, resulting in lidocaine toxicity (Feely et al. 1982, Wing et al. 1984). Cimetidine increased the oral bioavailability of lidocaine by 35% (Wing et al. 1984). When lidocaine was applied to the oropharynx, the area under the concentration-time curve (AUC) of lidocaine was increased by approximately 50% by concomitant cimetidine (Parish et al. 1987). Ranitidine, another histamine-2 receptor antagonist, had only little or no effect on the metabolism of either oral or intravenous lidocaine (Jackson et al. 1985, Robson et al. 1985). Both cimetidine and ranitidine are non-specific inhibitors of CYP enzymes, but cimetidine appears to be stronger (Bertz and Granneman 1997). In addition to enzyme inhibition, cimetidine reduces liver blood flow up to about 30% (Feely et al. 1981). Omeprazole, an inhibitor of the CYP2C19 isoenzyme, had no effect on the disposition of intravenous lidocaine (Noble et al. 1994), and the anti-arrhythmic agent propafenone, an inhibitor of the CYP2D6 isoenzyme, reduced the clearance of lidocaine negligibly (Ujhelyi et al. 1993).

Some earlier studies have investigated the effect of β -adrenoreceptor antagonists on the pharmacokinetics of lidocaine. Although the mechanism of this interaction has been somewhat controversial, the reduction in lidocaine metabolism seems to be mediated by both enzyme inhibition and reduction of liver blood flow (Tucker et al. 1984). β -adrenoreceptor antagonists have a variable effect on lidocaine metabolism *in vitro*, and they can either decrease or have no effect on hepatic blood flow. Atenolol is a β -adrenoreceptor antagonist that has little impact on lidocaine metabolism *in vitro* and does not change hepatic blood flow (Tucker et al. 1984). It also does not affect the pharmacokinetics of either oral or intravenous lidocaine in humans (Miners et al. 1984). Propranolol reduces both the intrinsic clearance of lidocaine and the hepatic blood flow. Thus, it is understandable that propranolol increased the AUC of oral lidocaine by over 100% (Bax et al. 1985) and reduced the clearance of intravenous lidocaine by 40% (Ochs

et al. 1980). In addition, propranolol prolonged the $t_{1/2}$ of lidocaine by over 50% and increased the steady-state plasma concentrations of lidocaine during a 35- to 36-h infusion by 30% (Ochs et al. 1980). However, in a rat model, propranolol increased the threshold for lidocaine-induced convulsions apparently by acting directly on the brain (Nakamura et al. 2008).

Unfortunately, there is little information available on the effects of the β -adrenoreceptor antagonists on individual CYP isoenzymes. *In vitro*, propranolol is a potent CYP2D6 inhibitor and a moderate CYP1A2 inhibitor (Turpeinen et al. 2006). Studies in rat liver microsomes have shown that propranolol competitively inhibits the 3-hydroxylation of lidocaine, but does not affect the formation of MEGX from lidocaine (Suzuki et al. 1993). Propranolol can also decrease the binding of lidocaine in liver tissues (Tesseromatis et al. 2007). In human liver microsomes, propranolol inhibits both the hydroxylation and deethylation of lidocaine (Al-Asady et al. 1989).

There are isolated reports of a pharmacokinetic and pharmacodynamic interaction between lidocaine and amiodarone, another anti-arrhythmic drug (Keidar et al. 1982, Siegmund et al. 1993). In six patients, amiodarone increased the AUC of lidocaine by about 20% and decreased the clearance of lidocaine by about 20% (Ha et al. 1996). This interaction was explained by the inhibition of CYP3A4 by amiodarone and/or its main metabolite desethylamiodarone.

Addition of the α_2 -specific adrenergic agonist clonidine to lidocaine increases the duration of anaesthesia. This effect may be explained by both pharmacodynamic and pharmacokinetic interactions (Kopacz and Bernards 2001, Pratap et al. 2007). However, in an *in vitro* study, microsomal lidocaine de-ethylation was not altered by clonidine (Inomata et al. 2003a).

Mexiletine is an anti-arrhythmic drug with structural similarity to lidocaine. It may increase the toxicity of lidocaine (Geraets et al. 1992, Christie et al. 1993). In a study of rabbits, the concurrent use of mexiletine and lidocaine resulted in a decrease in the clearance of lidocaine and an increase in lidocaine plasma levels. This interaction was interpreted to be due to mexiletine displacing the tissue binding of lidocaine and reducing its distribution (Maeda et al. 2002).

Midazolam is a short-acting hypnotic and anxiolytic agent, which is metabolized substantially by CYP3A4 (Pelkonen et al. 2008). In human liver microsomes, lidocaine metabolism was non-competitively inhibited by midazolam (Nagashima et al. 2005).

Propofol, an intravenous anaesthetic agent, inhibits CYP3A4 and decreases the clearance of, for instance, midazolam (Hamaoka et al. 1999). *In vitro*, propofol has a dose-dependent inhibitory effect on the formation of MEGX from lidocaine (Inomata et al. 2003b). However, in patients, propofol infusion did not alter the metabolism of epidural lidocaine compared with sevoflurane (Nakayama et al. 2004). Accordingly, a bolus dose of propofol had no effect on serum lidocaine concentrations in smokers and chronic alcohol users (Elmas et al. 2003).

Argatroban, a direct thrombin inhibitor, is metabolized by CYP3A4/5. In healthy volunteers, no pharmacokinetic interactions were detected between argatroban and lidocaine (Inglis et al. 2002).

While this study was in progress, two other studies on the interactions of CYP3A4 inhibitor erythromycin and lidocaine were published. Swart et al. (2002) reported that erythromycin 500 mg four times daily for five days had no significant effect on the disposition kinetics of intravenous lidocaine. By contrast, Orlando et al. (2003) reported that a pretreatment with four doses of erythromycin 600 mg decreased the clearance of intravenous lidocaine by about 20%, prolonged the $t_{1/2}$ of lidocaine by 30%, and increased the AUC of MEGX by about 30%. However, in a recent study by Bhise and Dias (2008), erythromycin had no effect on the MEGX test.

Orlando et al. (2004) have recently also investigated the effect of CYP1A2 inhibitor fluvoxamine on the pharmacokinetics of intravenous lidocaine. In healthy volunteers, fluvoxamine decreased the clearance of lidocaine by 60% and prolonged the $t_{1/2}$ by about 30%. The C_{max} and AUC of MEGX were decreased by about 60%. Based on their own studies and the *in vitro* study by Wang et al. (2000), Orlando et al. suggested that CYP1A2 and CYP3A4 are responsible for approximately two-thirds and one-third of lidocaine metabolism, respectively.

Lidocaine itself has also been reported to act as a competitive inhibitor of CYP1A2 as well as a mechanism-based inhibitor of CYP3A4 (Bensoussan et al. 1995, Wei et al. 1999). Potential clinical consequences of these inhibitory effects remain obscure.

4.4 Toxicity

In addition to blocking conduction in nerve cells in the peripheral nervous system, lidocaine can interfere with the function of all organs in which conduction or transmission of impulses occurs. Thus, like all local anaesthetics, it may have an influence on the central nervous system (CNS) and produce direct and indirect cardiovascular effects (Mather and Chang 2001). Unintentional toxic blood levels are possible after intra-arterial, intravenous or peripheral tissue injections of local anaesthetics.

The maximum plasma concentration of lidocaine resulting from an accidental intravascular injection depends on a number of factors. Clearly, it is directly influenced by the total dose of lidocaine injected, the speed and site of injection and whether the injection is administered intravenously or intra-arterially. The lungs are an important repository for local anaesthetic drugs; plasma concentrations of lidocaine will be much higher if the lungs are bypassed (e.g. an accidental intra-arterial injection in the head, face or neck region).

Systemic toxic reactions occur much less frequently when lidocaine is administered to peripheral sites than with intravascular injection. A number of factors influence the degree of absorption that takes place from the periphery to the central circulation. The most important factor is the site of injection, absorption being more rapid in highly vascular tissues and less so in poorly perfused ones. The addition of epinephrine to lidocaine reduces the rate of absorption, but the magnitude of this reduction can depend on the site of injection (Tucker and Mather 1979).

Systemic toxic reactions to lidocaine are manifested by a progressive spectrum of neurological symptoms as blood levels rise. As the plasma concentration of lidocaine

approaches systemic toxicity, a typical progression occurs from effects on the CNS to effects on the cardiovascular system. However, this pattern of symptomatology may not be seen after a rapid intravascular injection. Initial symptoms suggest some form of CNS excitation and are often described as a ringing in the ears, a metallic taste in the mouth or a tickling sensation or numbness of the tongue and perioral tissues. With increasing blood levels of lidocaine, there is progression to motor twitching in the periphery, followed by grand mal seizures. These higher blood levels are associated with coma and eventually respiratory arrest. At extremely high levels, cardiac arrhythmia or hypotension and cardiovascular collapse occur.

In humans, subjective effects from lidocaine are associated with venous plasma concentrations of 3-5 µg/ml. Symptoms of subjective toxicity include light-headedness, euphoria, digital paresthesias, restlessness and drowsiness. Objective toxicity presents with nausea, vomiting, tremors, blurred vision, slurred speech, tinnitus, confusion, excitement, psychosis and muscular fasciculations or twitching. Objective toxic effects occur in conscious subjects at a plasma level higher than 5 µg/ml (at 6-10 µg/ml), but seizures and cardiorespiratory depression do not usually occur until plasma concentrations exceed 10 µg/ml. Above this level, subjects may become comatose, with respiratory arrest and cardiac asystole. Anaesthetized patients do not, however, show signs of toxicity until a level of 10 µg/ml is reached, when circulatory depression becomes obvious (Scott et al. 1972, Tucker and Mather 1979).

4.5 Clinical use

Lidocaine has wide range of clinical applications as a local anaesthetic of intermediate duration. It is used for local anaesthesia by topical application, infiltration, peripheral nerve block and central nerve block. It can also be applied in intravenous regional anaesthesia.

Lidocaine penetrates intact skin poorly, but absorption through mucous membranes may be rapid. Lidocaine is used for topical anaesthesia in the oropharyngeal region before endoscopic procedures and to treat painful conditions of the mouth and throat. Lidocaine can be delivered to the airways by direct spraying or spraying through an endoscope (“spray-as-you-go”), and may be used as a viscous solution or a jelly. Lidocaine can be inhaled by a nebulizer to reach the lower airways. It can also be injected transtracheally to anaesthetize the vocal cords and trachea (Kundra et al. 2000, Xue et al. 2009). For example, during a bronchoscopy the maximum safe dosage of lidocaine for topical airway anaesthesia has generally been considered to be 4 mg/kg, but even as large a dose as 8.2 mg/kg has been suggested by the British Thoracic Society (British Thoracic Society Bronchoscopy Guidelines Committee, a Subcommittee of Standards of Care Committee of British Thoracic Society 2001). For painful conditions of the mouth, lidocaine solution can be used as a rinse and then ejected; for pharyngeal pain, the solution is gargled and often swallowed. This method is also often used prior to endoscopic procedures before other methods of airway anaesthesia.

An eutectic mixture of lidocaine and prilocaine is applied as a cream to produce surface anaesthesia of the skin or mucous membranes before minor procedures, e.g. venipuncture (Gajraj et al. 1994). Another method of dermal delivery includes a transdermal patch of lidocaine for the treatment of, for instance postherpetic neuralgia (Dworkin et al. 2007). A novel method is an iontophoretic drug delivery system incorporating lidocaine and epinephrine, which produces a rapid local anaesthesia for venipuncture (Rose et al. 2002).

A 2% gel of lidocaine can be used for anaesthesia of mucous membranes, especially in the urinary tract, where a dose of 60-200 mg is typically applied (Sweetman 2009).

The dose of lidocaine used for local anaesthesia depends on the site of injection and the procedure used. For infiltration anaesthesia, a 0.5% to 1% solution of lidocaine in doses varying from 5 to 200 mg (or up to 500 mg with epinephrine) is commonly administered. The duration of infiltration anaesthesia can be more or less doubled by the addition of epinephrine (usually 5 µg/ml). Epinephrine also decreases peak concentrations of lidocaine in blood. For example, in the tumescent technique for liposuction large volumes of very dilute lidocaine (0.05-0.1%) and epinephrine are infiltrated into subcutaneous tissue to achieve widespread local anaesthesia (Kucera et al. 2006). In these procedures, very large lidocaine doses ranging from 35 to 55 mg/kg have been used (Kenkel et al. 2004).

The dosage and concentration of lidocaine in peripheral nerve blocks depend on the route. For a brachial plexus block, for example, 225-300 mg as a 1-2% solution is recommended, but clinicians often use much larger doses of up to 900 mg (Pälve et al. 1995, Sweetman 2009). For an intercostal nerve block, 30 mg is given as a 1% solution, and for a paracervical block a dose of 100 mg on each side as a 1% solution is recommended (Sweetman 2009).

A hyperbaric solution of 5% lidocaine in glucose is available for spinal anaesthesia. Lidocaine, usually at a dose of 50-100 mg, has been used for spinal anaesthesia seemingly successfully for decades. It has been especially popular in outpatient spinal anaesthesia because of its fast onset and short duration of action. However, recently, a number of reports have suggested lidocaine as a possible cause of neurological complications after spinal anaesthesia. The incidence of transient radicular irritation in patients who receive intrathecal lidocaine has been reported to be as high as one in every third patient (Zaric et al. 2005). Accordingly, the use of lidocaine in spinal anaesthesia has decreased lately.

Epidural block is widely used to provide anaesthesia or analgesia for surgical and obstetric procedures. For epidural anaesthesia, 1-1.5 ml of 2% lidocaine solution is needed for each dermatome to be anaesthetized (Sweetman 2009). Following injection of 400 mg of lidocaine into the lumbal epidural space, peak concentrations of lidocaine average 3-4 µg/ml (Scott, et al 1972). Continuous epidural infusion of lidocaine at doses of 0.44-0.98 mg/kg/h for postoperative analgesia produced lidocaine concentrations ranging from approximately 1 to 4 µg/ml (Rygnestad et al. 1999).

A 0.5 % solution of lidocaine in doses of 50-300 mg has been widely used for intravenous regional anaesthesia (IVRA). It provides a relatively reliable anaesthesia for surgery of extremities; however, analgesia after tourniquet release is short-lived (Sweetman 2009). While CNS side-effects can occur with IVRA, after an 80-mg dose of

lidocaine and a total tourniquet inflation time of 72 min, C_{max} of lidocaine was 1.7 $\mu\text{g/ml}$ 3 min after tourniquet release (Atanassoff and Hartmannsgruber 2002).

Lidocaine is commonly used to prevent pain on injection of propofol. It can be administered at a dose of 10-40 mg before propofol injection, with or without a tourniquet, or it can be mixed with propofol (Picard and Tramer 2000).

Lidocaine is classified as a class Ib anti-arrhythmic drug and may be used intravenously in the treatment of ventricular arrhythmias. Lidocaine suppresses activity of depolarized, arrhythmogenic tissues while interfering minimally with the electric activity of normal tissues. It is therefore effective in suppressing arrhythmias associated with depolarization (e.g. ischaemia), but is relatively ineffective against arrhythmias occurring in normally polarized cells (e.g. atrial fibrillation). Lidocaine decreases the duration of the action potential and decreases automaticity. Following a bolus dose (normally 1-1.5 mg/kg), lidocaine has an immediate onset (within minutes) and a brief duration (10-20 min) of action. Thus, a continuous intravenous infusion of lidocaine (1-4 mg/min) is necessary to maintain anti-arrhythmic effects. In emergency situations, lidocaine has also been given for arrhythmias by intramuscular injection at a dose of 300 mg, repeated if necessary after 60-90 min (Sweetman 2009).

Earlier, the prophylactic use of lidocaine to suppress ventricular arrhythmias in acute myocardial infarction (AMI) was considered the standard of care. However, although prophylactic lidocaine reduces the incidence of primarily ventricular fibrillation, it has never been shown to decrease mortality. On the contrary, there are increasing concerns about the safety of prophylactic lidocaine, and it is no longer recommended in the management of patients with AMI (Yadav and Zipes 2004).

Until 2000, lidocaine was considered to be the anti-arrhythmic drug of choice during cardiopulmonary resuscitation. Studies comparing it with amiodarone have displaced it from this position, and lidocaine at a dose of 1 mg/kg is now indicated in refractory ventricular fibrillation or tachycardia only if amiodarone is unavailable (Nolan et al. 2005).

Lidocaine has been shown to be effective in treating peripheral neuropathic pain. Systemic lidocaine relieves the symptoms of neuropathic pain in patients with painful diabetic neuropathy, postherpetic neuralgia and idiopathic trigeminal neuralgia among others (Amir et al. 2006). Topical lidocaine, usually as a transdermal patch of 5% lidocaine, is a first-line medication for patients with localized peripheral neuropathic pain, e.g. postherpetic neuralgia (Dworkin et al. 2007). Systemic lidocaine may also be of benefit in the treatment of central neuropathic pain associated with stroke or spinal cord injury (Attal et al. 2000).

Perioperative systemic lidocaine has preventive effects on postoperative pain and opioid consumption after major abdominal surgery (Groudine et al. 1998, Koppert et al. 2004, Kaba et al. 2007). Continuous intravenous lidocaine infusion accelerates postoperative recovery of bowel function and shortens hospital stay (Marret et al. 2008). Possibly, some of the beneficial effects of epidural administration of local anaesthetics may be caused by anti-inflammatory effects of circulating local anaesthetics (Hollmann and Durieux 2000). Conversely, perioperative systemic lidocaine did not offer any

beneficial effect on postoperative analgesia and functional recovery after total hip arthroplasty (Martin et al. 2008).

Lidocaine is frequently used intravenously or locally to prevent cardiovascular and airway responses during tracheal intubation. Various studies have reviewed the effect of lidocaine to blunt these responses. Lidocaine is commonly agreed to blunt cough reflexes and dysrhythmias and may even diminish the prolongation of the QT interval induced by tracheal intubation (Lev and Rosen 1994, Owczuk et al. 2008). The effects of lidocaine on rises in pulse, blood pressure and intracranial and intraocular pressure following intubation are somewhat controversial (Miller and Warren 1990, Moeini et al. 2006, Salhi and Stettner 2007, Vaillancourt and Kapur 2007).

Lidocaine has been used intravenously and also intratympanically in the treatment of tinnitus (Simpson and Davies 1999). Occasionally, intravenous or intranasal lidocaine has been effective in treating various types of severe headache (Matharu et al. 2004).

Lidocaine has a concentration-dependent effect on seizures. At low concentrations (< 5 µg/ml), it has anticonvulsant properties, while high concentrations (> 15 µg/ml) often result in seizures (DeToledo 2000). Lidocaine has been used to control status epilepticus that does not respond to more conventional treatment, especially in children and neonates (Hamano et al. 2006). The usual dose is a 1.5-2 mg/kg intravenous bolus, followed by a 3-4 mg/kg/h infusion (Sweetman 2009).

Lidocaine, like other local anaesthetics, has potent anti-inflammatory properties. The detailed mechanisms of action are not fully understood, but seem to involve a interaction with membrane proteins and lipids, thus having an effect at almost every level of the inflammatory cascade, including cellular adhesion to the endothelium, transendothelial migration, phagocytosis and release of such inflammatory mediators as histamine and leukotrienes (Hollmann and Durieux 2000, Fischer et al. 2001, Cassuto et al. 2006). Furthermore, lidocaine appears to prevent overactive inflammatory responses without impairing host defence or suppressing normal inflammation (Wright et al. 2008). There is convincing evidence of these effects in experimental *in vitro* and *in vivo* studies, but so far clinical use has been limited to selected inflammatory conditions or diseases. For example, nebulized lidocaine has a glucocorticoid-sparing effect in the treatment of asthma (Hunt et al. 2004). The anti-inflammatory effect of lidocaine seems to be prolonged, continuing after serum levels have decreased.

5 CYP inhibitors evaluated

5.1 Erythromycin

Erythromycin, first introduced in 1952, is a macrolide antibiotic widely used in the treatment of various bacterial infections. It has mainly been used in infections of the upper respiratory tract, skin and soft tissue, especially in patients who are allergic to penicillin. As with other macrolides, erythromycin inhibits RNA-dependent protein synthesis of sensitive microorganisms (Champers 2006). It is usually bacteriostatic, although

administration of labelled erythromycin, which finally generates labelled CO₂, which can be monitored in the exhalation (Watkins 1994). However, it has recently been discovered, that ERBT does not merely reflect CYP activity; hepatic P-glycoprotein might also be an important determinant of ERBT (Kurnik et al. 2006).

Adverse effects

Erythromycin is a safe antibiotic, and most adverse reactions are non-life-threatening. Gastrointestinal symptoms, including nausea, vomiting, abdominal cramps and diarrhoea, are the most common adverse effects (Alvarez-Elcoro and Enzler 1999).

Interactions

Erythromycin inhibits CYP3A4 and is associated with clinically significant drug interactions. It increased the AUC of oral midazolam more than 4-fold and decreased the clearance of intravenously administered midazolam by 50% (Olkola et al. 1993). The AUC of zopiclone, another hypnotic, was increased by 80% by erythromycin (Aranko et al. 1994). Erythromycin decreased the clearance of alfentanil, a short-acting opioid, by 25% and prolonged its $t_{1/2}$ by approximately 60% (Bartkowski et al. 1989). When erythromycin was given together with the histamine-1-antagonist terfenadine, the pharmacokinetics of terfenadine was significantly altered, and also electrocardiographic changes were seen in subjects who accumulated terfenadine (Honig et al. 1992). The AUC values of the anxiolyte buspirone and the cholesterol-lowering drug simvastatin were 6-fold increased after a pretreatment of erythromycin (Kivistö et al. 1997, Kantola et al. 1998). Erythromycin increased the AUC and C_{max} of sildenafil, an oral drug used in the treatment of erectile dysfunction, by 2.8- and 2.6-fold, respectively (Muirhead et al. 2002). The plasma concentrations of warfarin and its anticoagulant effect were increased when it was co-administered with erythromycin (Weibert et al. 1989). Erythromycin had only a minor effect on the pharmacokinetics of intravenous ropivacaine, a long-acting amide-type local anaesthetic (Jokinen et al. 2000).

Recently, the effect of erythromycin on the pharmacokinetics of ximelagatran, an oral direct thrombin inhibitor, was investigated in both healthy volunteers and in an *in vitro* model to investigate the interaction mechanism (Eriksson et al. 2006). Erythromycin increased the AUC and C_{max} of oral ximelagatran by approximately 80% and 70%, respectively, and inhibited the P-glycoprotein-mediated transport of ximelagatran. This inhibition of P-glycoprotein by erythromycin has also been shown earlier and may partly explain the interactions caused by erythromycin (Takano et al. 1998, Schwarz et al. 2000, Zhang and Benet 2001).

5.2 Itraconazole

Itraconazole is a triazole antifungal agent that was synthesized in 1980. It inhibits the growth of fungi by interfering with a fungal CYP enzyme, 14 α -demethylase, thus impairing the synthesis of ergosterol, a vital component of the cell membrane (De Beule and Van Gestel 2001). Itraconazole is a potent antimycotic drug, particularly because its main metabolite, hydroxy-itraconazole, also has clinically significant activity (Isoherranen et al. 2004). Itraconazole has a broad spectrum of activity against fungal pathogens, including *Candida albicans* and *Aspergillus* species (Grant and Clissold 1989). The recommended daily dose of itraconazole is from 100 to 400 mg, and the duration of treatment varies from one day to one year depending on the mycosis treated. It can also be given as a pulse therapy (typically, one week on and three weeks off therapy).

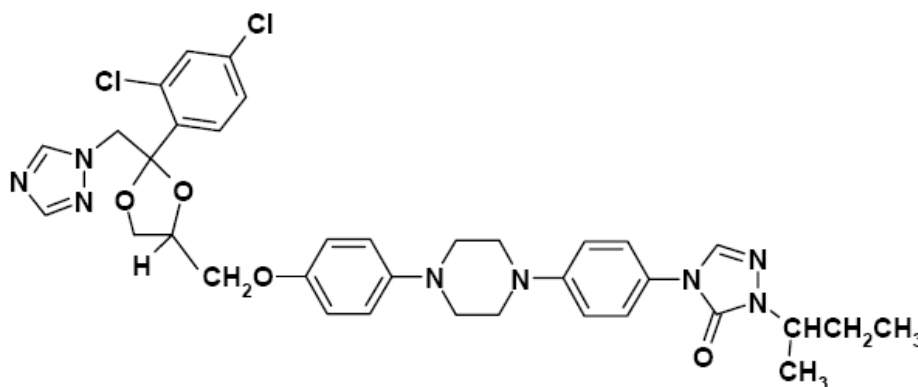


Figure 4 Chemical structure of itraconazole.

Pharmacokinetics

Itraconazole is a highly lipophilic weak base, and gastric acidity is needed for its dissolution and absorption. A capsule formulation of itraconazole, which has been used for many years, is associated with a high degree of variability in absorption. In healthy fasting volunteers, the bioavailability of itraconazole is 40%, and it is improved if the drug is taken with food (Grant and Clissold 1989). This variability in absorption led to the development of an oral solution and intravenous preparation of itraconazole. The oral solution had almost 40% higher bioavailability than the capsule formulation after a single 200-mg dose of itraconazole in healthy volunteers (Willems et al. 2001).

In blood, itraconazole is 94.9% bound to plasma proteins, mainly albumin, and 4.9% is bound to blood cells, leaving only 0.2% in free form. It has a large apparent volume of distribution of 11 l/kg. It accumulates in the kidney, liver, bone, stomach, spleen, the female genital tract, muscle and keratinous tissues (Grant and Clissold 1989).

Itraconazole is extensively metabolized in the liver to produce more than 30 metabolites. Hydroxy-itraconazole, the major metabolite, reaches higher plasma

concentrations than the parent agent. The primary rates of excretion are via bile and urine as metabolites (De Beule and Van Gestel 2001). Elimination of itraconazole is biphasic. The $t_{1/2}$ is approximately 20 h after a single dose, but is prolonged to 30 h during steady state (Grant and Clissold 1989). This indicates that the metabolism of itraconazole is saturated with clinical doses.

Adverse effects

Itraconazole is generally well-tolerated, with most adverse effects being minor and reversible. The most common adverse effects are gastrointestinal disturbances, dizziness, pruritus and headache (Grant and Clissold 1989). A mild asymptomatic elevation in hepatic enzymes is seen in 1-5% of patients using itraconazole continuously, and in 1.7-2% of patients receiving pulse therapy. The increased enzyme levels usually return to normal following discontinuation of therapy or even spontaneously (Gupta et al. 2002).

Interactions

Because itraconazole is a potent inhibitor of CYP3A4 both *in vitro* and *in vivo*, itraconazole co-administration with a CYP3A4 substrate can result in a clinically significant drug interaction (Wang et al. 1999b, Dresser et al. 2000). Furthermore, the metabolites of itraconazole can be as potent inhibitors of CYP3A4 as itraconazole itself (Isoherranen et al. 2004, Templeton et al. 2008). Consequently, itraconazole can greatly increase the plasma concentrations of many drugs, like terfenadine (Honig et al. 1993), midazolam (Olkkola et al. 1994), triazolam (Varhe et al. 1994), felodipine (Jalava et al. 1997b), buspirone (Kivistö et al. 1997), dexamethasone (Varis et al. 2000) and both oral and intravenous methylprednisolone (Varis et al. 1998, Varis et al. 1999). For example, itraconazole increased the C_{max} of oral midazolam over 3-fold and the AUC over 10-fold (Olkkola et al. 1994). The clearance of intravenous midazolam was decreased 69% by concomitant itraconazole (Olkkola et al. 1996). Pretreatment with itraconazole reduced the clearance of both enantiomers of intravenous bupivacaine, an amide-type local anaesthetic, by approximately 20-25% (Palkama et al. 1999). Itraconazole had no significant effect on the pharmacokinetic parameters of intravenous ropivacaine, another amide-type local anaesthetic, although it inhibited the CYP3A4-mediated formation of pipercoloxylidide from ropivacaine (Jokinen et al. 2001). This lack of interaction with ropivacaine suggests that CYP1A2 has a major role in its metabolism. Finally, itraconazole increased the AUC of inhaled glucocorticoid budesonide by about 4-fold, resulting in suppression of cortisol production (Raaska et al. 2002).

Itraconazole is also a potent inhibitor of P-glycoprotein (Wang et al. 2002a). Thus, it can increase plasma concentrations of P-glycoprotein subjects even when they are not significantly metabolized. For example, significant interactions have been reported following co-administration of itraconazole with celiprolol (Lilja et al. 2003), vincristine (Bermúdez et al. 2005) or digoxin (Jalava et al. 1997a). Also the drastic effect of

itraconazole on the pharmacokinetics of the cholesterol-lowering drug lovastatin may be the result of inhibition of both P-glycoprotein and CYP3A4 (Neuvonen and Jalava 1996, Kivistö et al. 1998).

5.3 Fluvoxamine

Fluvoxamine is an antidepressant drug that belongs to the selective serotonin reuptake inhibitor (SSRI) group. It is used widely in the treatment of depression, with daily doses ranging from 50 to 300 mg. Other potential therapeutic indications include obsessive-compulsive disorder, anxiety, panic disorder and social phobia (Perucca et al. 1994, Figgitt and McClellan 2000).

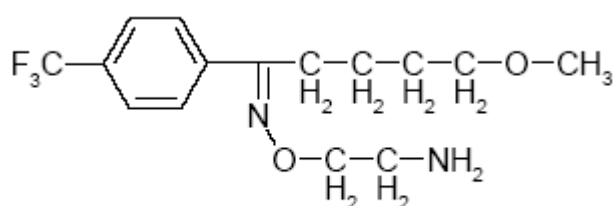


Figure 5 Chemical structure of fluvoxamine.

Pharmacokinetics

Fluvoxamine is almost completely, albeit slowly, absorbed from the gastrointestinal tract, but the oral bioavailability is only ~ 50% (Perucca et al. 1994, van Harten 1995). After repeated therapeutic doses, fluvoxamine exhibits non-linear pharmacokinetics. A C_{max} of about 70 $\mu\text{g/l}$ is reached within 2-8 h when fluvoxamine is administered at a daily dose of 100 mg, with a steady state attained in about 10 days. Fluvoxamine has a volume of distribution of 25 l/kg and is only 77% bound to plasma proteins (Figgitt and McClellan 2000). It is extensively metabolized, primarily by the hepatic CYP enzymes CYP2D6 and CYP1A2, to inactive metabolites (Carrillo et al. 1996, Spigset et al. 2001). Only 3% of orally administered fluvoxamine is excreted unchanged in urine (Figgitt and McClellan 2000). The $t_{1/2}$ of fluvoxamine ranges from 15 to 20 h (Perucca et al. 1994).

Adverse effects

Fluvoxamine is generally well-tolerated and serious adverse effects are rare. The most common adverse effect is nausea; other, less common side-effects include somnolence, asthenia, headache, dry mouth and sleep disorders (Figgitt and McClellan 2000).

Interactions

Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 (Rasmussen et al. 1995, Yao et al. 2003), but it may also inhibit CYP3A4, CYP2C9 and CYP2D6 (von Moltke et al. 1995, Kashuba et al. 1998, Hemeryck et al. 1999). It has the potential, therefore, to modify the pharmacokinetics of many drugs metabolized by these routes. Fluvoxamine considerably increases the plasma concentrations of CYP1A2 substrate drugs such as caffeine (Christensen et al. 2002), theophylline (Yao et al. 2001), tacrine (Larsen et al. 1999), clozapine (Fabrazzo et al. 2000) and the local anaesthetic ropivacaine (Jokinen et al. 2000). Coadministration of fluvoxamine produces moderate increases in the AUC of such CYP3A4 substrates as alprazolam and buspirone (Fleishaker and Hulst 1994, Lamberg et al. 1998). Fluvoxamine also has a moderate impact on the pharmacokinetics of the CYP2C9 substrates tolbutamide and glimepiride (Madsen et al. 2001, Niemi et al. 2001). Fluvoxamine is an effective inhibitor of CYP2C19 and has a marked effect on the pharmacokinetics of omeprazole and (S)-mephenytoin (Christensen et al. 2002, Yao et al. 2003). Recently, fluvoxamine was found to have a mild effect on the pharmacokinetics of the CYP2C8 substrate rosiglitazone (Pedersen et al. 2006).

Fluvoxamine is only an intermediate inhibitor of P-glycoprotein *in vitro*, and in healthy volunteers it had no significant effect on the pharmacokinetics of digoxin (Ochs et al. 1989, Weiss et al. 2003).

5.4 Ciprofloxacin

Ciprofloxacin is a broad-spectrum fluoroquinolone antimicrobial agent showing high activity, especially against Gram-negative bacteria (van Bambeke et al. 2005). The mechanism of action of its rapid bactericidal effect involves interacting with DNA gyrase and topoisomerase IV enzymes, leading to cleavage of bacterial DNA (Hooper 1999). The usual adult oral dose ranges from 250 mg to 750 mg twice daily.

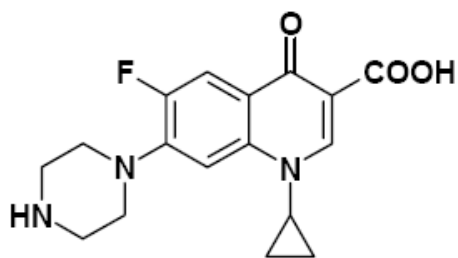


Figure 6 Chemical structure of ciprofloxacin.

Pharmacokinetics

The oral bioavailability of ciprofloxacin is approximately 70%. After single oral doses of 250-750 mg in healthy volunteers, C_{\max} values ranging from 0.8 to 3.9 mg/l are reached within 1-2 h (Davis et al. 1996). Ciprofloxacin has a volume of distribution of 1.7-2.5 l/kg and is only 20-40% bound to plasma proteins. It is widely distributed in the body, and tissue penetration is good in most tissues, with the exception of cerebrospinal fluid. Ciprofloxacin is eliminated mainly in unchanged form, with about one-third of the dose being metabolized. Its $t_{1/2}$ is between 3 and 5 h (Aminimanizani et al. 2001).

Adverse effects

The adverse effects of ciprofloxacin are generally mild and reversible, and most often involve the gastrointestinal tract, CNS or skin. The most common side-effects are gastrointestinal symptoms, particularly nausea, vomiting and diarrhoea. CNS symptoms, including headache, dizziness, tremor and restlessness, are less common. Skin effects, such as phototoxicity, may also be seen (Davis et al. 1996). Because of the risk of chondrotoxicity, ciprofloxacin is not recommended for use in children (van Bambeke et al. 2005). Finally, ciprofloxacin is associated with tendon disorders, especially in elderly patients (van der Linden et al. 2002).

Interactions

Ciprofloxacin is a moderate inhibitor of CYP1A2 (Fuhr et al. 1992, Bertz and Granneman 1997). It inhibits the metabolism of such CYP1A2 substrates as theophylline (Batty et al. 1995), caffeine (Nicolau et al. 1995), clozapine (Raaska and Neuvonen 2000) and ropivacaine (Jokinen et al. 2003).

AIMS OF THE STUDY

Lidocaine is a widely used local anaesthetic agent that is administered by injection or local application. It is also used intravenously in the prevention and treatment of ventricular arrhythmias. Lidocaine is eliminated mainly by metabolism, with only trace amounts being excreted unchanged in urine. One of the major metabolites is MEGX. Lidocaine is also metabolized via hydroxylation to 3-OH-lidocaine. At the time that this study commenced, CYP3A4 was thought to be mainly responsible for the formation of MEGX, and CYP1A2 for the production of 3-OH-lidocaine.

CYP enzyme-related drug interactions affect the pharmacokinetics of many drugs. Erythromycin and itraconazole are known inhibitors of CYP3A4, and ciprofloxacin and fluvoxamine inhibit CYP1A2 (Pelkonen et al. 2008). Previous studies have demonstrated that non-specific inhibitors of CYP enzymes, e.g. cimetidine and ranitidine, have some effect on lidocaine pharmacokinetics, but the effect of specific CYP inhibitors remain obscure.

Specific aims of this study were as follows:

1. To evaluate the effect of strong inhibitors of CYP3A4 on the pharmacokinetics of lidocaine (Studies I-III).
2. To determine the effect of route of administration of lidocaine when CYP3A4 is inhibited (Studies I-III).
3. To investigate the effect of inhibiting both CYP1A2 and CYP3A4 on the pharmacokinetics of lidocaine administered intravenously or orally (Studies IV and V).
4. To elucidate the role of CYP1A2 in the metabolism of lidocaine and to examine the interaction potential of ciprofloxacin with intravenous lidocaine (Study VI).

MATERIALS AND METHODS

1 Subjects

All 34 subjects (17 females, 17 males) were healthy volunteers. Before being accepted into the studies, volunteers were ascertained to be healthy by medical history, clinical examination and a 12-lead electrocardiogram. None of the participants was on continuous medication, except for six female subjects using oral contraceptive steroids. Detailed characteristics of the volunteers are presented in Table 2.

Table 2. *Characteristics of healthy volunteers in Studies I-VI*

Study	Subjects (f/m)	Age, years*	Weight, kg*	No. of women using contraceptives
I	9 (4/5)	22 (18-25)	69 (55-80)	4
II	9 (4/5)	23 (21-25)	72 (61-83)	2
III	10 (5/5)	24 (22-25)	69 (60-80)	3
IV	9 (6/3)	23 (19-27)	68 (58-90)	1
V	8 (3/5)	24 (21-27)	68 (50-83)	1
VI	9 (6/3)	24 (21-29)	72 (45-95)	1

Values indicated with an asterisk are mean (range). f/m = female/male.

2 Study protocol

2.1 Design

The studies were performed between April 1996 and May 1999 at the Department of Anaesthesiology and Intensive Care Medicine and the Department of Clinical Pharmacology, University of Helsinki. All studies were randomized, double-blinded, placebo-controlled cross-over studies in two or three phases with a 2- to 4-week wash-out interval. The study designs are summarized below and in Table 3.

In Studies I, IV and VI, the volunteers fasted for 1-2 h before the lidocaine infusion. They had standard meals 3 and 6 h after the infusion. In Studies II, III and V, the volunteers fasted for 4 h before lidocaine administration and had standard meals 3 and 6 h

afterwards. Ingestion of alcohol, coffee, tea, cola beverages and grapefruit juice was not allowed on the test days, nor was smoking permitted.

Study I

Nine volunteers were given orally either erythromycin 500 mg three times a day (Erymax, Astra, Sweden), itraconazole 200 mg once daily (Sporanox, Janssen Pharma, Belgium) or placebo three times a day for four days. The dose of 1.5 mg/kg of intravenous lidocaine (Lidokainklorid 4 mg/ml, Kabi-Pharmacia, Sweden) was given on day 4, with the infusion lasting for 60 min. Lidocaine was given 1 h after the administration of erythromycin, itraconazole or placebo.

Study II

As in Study I, the nine volunteers were given orally either erythromycin 500 mg three times a day (Erymax, Astra, Sweden), itraconazole 200 mg once daily (Sporanox, Janssen Pharma, Belgium) or placebo three times a day for four days. On day 4, each subject ingested a single dose of 1 mg/kg of oral lidocaine (Xylocain 5 mg/ml, Astra, Sweden) one hour after the administration of erythromycin, itraconazole or placebo.

Study III

Ten volunteers were given orally, once daily, either itraconazole 200 mg (Sporanox, Janssen Pharma, Belgium) or placebo for four days. The dose of 1.5 mg/kg of lidocaine (Lidocain 40 mg/ml, Orion, Finland) was given on day 4 one hour after the administration of itraconazole or placebo. Lidocaine was administered using a disposable nebulizer (Micro Mist, Hudson RCI, CA, USA) powered by oxygen at a flow of 8 l/min. The subjects breathed the lidocaine aerosol through a mouthpiece until nebulization of the lidocaine solution was complete (10 min). A nasal clip was not used.

Study IV

Nine volunteers were given either fluvoxamine 100 mg (Fevarin, Solvay Duphar, Holland) once a day and placebo thrice daily, or fluvoxamine 100 mg once a day and erythromycin 500 mg (Ery-Max, Astra, Sweden) thrice daily, or the corresponding placebos. Erythromycin was given for six days and fluvoxamine for five days before lidocaine. On day 6, the dose of 1.5 mg/kg of intravenous lidocaine (Lidokainklorid 4 mg/ml, Kabi-Pharmacia, Sweden) was given over 60 min. Lidocaine infusion was started one hour after the administration of erythromycin 500 mg (or placebo) or 9 h after the last 100-mg dose of fluvoxamine (or placebo).

Study V

Eight volunteers were given either fluvoxamine 100 mg (Fevarin, Solvay Duphar, Holland) once a day and placebo thrice daily, or fluvoxamine 100 mg once a day and erythromycin 500 mg (Ery-Max, Astra, Sweden) thrice daily, or the corresponding placebos. Erythromycin was given for six days and fluvoxamine for five days before lidocaine. On day 6, each subject ingested a single dose of 1 mg/kg of oral lidocaine (Xylocain 5 mg/ml, Astra, Sweden). Lidocaine was given one hour after the administration of erythromycin 500 mg (or placebo), or 13 h after the last 100-mg dose of fluvoxamine (or placebo).

Study VI

Nine volunteers were randomized to receive either ciprofloxacin 500 mg (Ciproxin, Bayer, Germany) or placebo twice daily orally for 2.5 days. On day 3, 1.5 mg/kg of lidocaine (Lidocard 20 mg/ml, Orion, Finland) was administered in 60 min. The lidocaine infusion was initiated one hour after the administration of ciprofloxacin or placebo.

Table 3. Study designs (I-VI)

Study	Pretreatment		Lidocaine		Wash-out
	Drug	Duration	Dose	Timing	
I	Erythromycin 500 mg x 3 Itraconazole 200 mg x 1 Placebo	4 days	1.5 mg/kg	60 min i.v. inf day 4 1 h after pre	3 weeks
II	Erythromycin 500 mg x 3 Itraconazole 200 mg x 1 Placebo	4 days	1 mg/kg	p.o. day 4 1 h after pre	3-4 weeks
III	Itraconazole 200 mg x 1 Placebo	4 days	1.5 mg/kg	inhaled day 4 1 h after pre	4 weeks
IV	Fluvoxamine 100 mg x 1 + placebo Fluvoxamine 100 mg x 1 + Erythromycin 500 mg x 3 Placebo	5 days 6 days	1.5 mg/kg	60 min i.v. inf day 6 9 h after fluvo 1 h after erythromycin	2 weeks
V	Fluvoxamine 100 mg x 1 + placebo Fluvoxamine 100 mg x 1 + Erythromycin 500 mg x 3 Placebo	5 days 6 days	1 mg/kg	p.o. day 6 13 h after fluvo 1 h after erythromycin	4 weeks
VI	Ciprofloxacin 500 mg x 2 Placebo	2.5 days	1.5 mg/kg	60 min i.v. inf day 3 1 h after pre	4 weeks

2.2 Blood sampling

On each study day, a cubital vein was cannulated with a plastic cannula and kept patent with an obturator. In Studies I, IV and VI, the samples were taken from the arm contralateral to that used for the administration of intravenous lidocaine. Timed blood samples were drawn into 10-ml EDTA tubes in Studies I, IV and VI just before the

administration of lidocaine and at 30 and 60 min during the 60-min infusion. After the infusion, blood was sampled at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h. In Studies II, III and V, samples were taken just before the administration of lidocaine and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h afterwards. Plasma was separated within 30 min and stored at -40°C until analysis.

2.3 Determination of plasma drug concentrations

Lidocaine

Concentrations of lidocaine were analysed with gas chromatography using etidocaine as an internal standard (Lorec et al. 1994, Demedts et al. 1996). The limit of quantification of the method was 2 ng/ml in Studies I-IV and 0.1 ng/ml in Studies V and VI. The coefficient of variation (CV) for lidocaine was 2.1% at 98.0 ng/ml (n=15) in Studies I and II, 1.5% at 99.8 ng/ml (n=8) in Study III, 2.9% at 98.5 ng/ml (n=7) in Study IV, 1.7% at 75.7 ng/ml (n=7) in Study V and 4.7% at 80.7 ng/ml (n=4) in Study VI.

MEGX

Concentrations of MEGX were analysed with gas chromatography using etidocaine as an internal standard (Lorec et al. 1994, Demedts et al. 1996). The limit of quantification of the method was 2 ng/ml in Studies I-IV, 0.05 ng/ml in Study V and 0.1 ng/ml in Study VI. The CV for MEGX was 4.1% at 95.3 ng/ml (n=15) in Studies I and II, 4.7% at 100.3 ng/ml (n=7) in Study III, 4.0% at 98.9 ng/ml (n=7) in Study IV, 4.3% at 80.1 ng/ml (n=7) in Study V and 5.7% at 84.1 ng/ml (n=7) in Study VI.

3-OH-lidocaine

In Studies V and VI, concentrations of 3-OH-lidocaine were analysed with gas chromatography using etidocaine as an internal standard (Lorec et al. 1994, Demedts et al. 1996). The limit of quantification of the method was 0.03 ng/ml in Study V and 0.05 ng/ml in Study VI. The CV for 3-OH-lidocaine was 4.5% at 0.8 ng/ml (n=7) in Study V and 12.0% at 0.8 ng/ml (n=4) in Study VI.

Erythromycin

Concentrations of erythromycin in Studies I, II, IV and V were measured with high-performance liquid chromatography (HPLC) using roxithromycin as an internal standard

(Laakso et al. 1990). The sensitivity of the method was 0.2 mg/l, and the CV was 3% at 4.97 mg/l (n=9).

Itraconazole

Itraconazole was quantified by HPLC using a method modified from Allenmark et al. (1990). The limit of quantification was 10 ng/ml. The CV was 1.2% at 474 ng/ml (n=9) in Study I, 1.2% at 472 ng/ml (n=9) in Study II and 4.6% at 192 ng/ml (n=12) in Study III.

Fluvoxamine

Fluvoxamine concentrations in Studies IV and V were determined with HPLC using haloperidol as an internal standard (van der Meersch-Mougeot and Diquet 1991). The limit of quantification was 10.0 ng/ml, and the CV was 9.2% at 16.9 ng/ml (n=7) and 4.5% at 85.7 ng/ml (n=7).

Ciprofloxacin

Ciprofloxacin was quantified by liquid chromatography tandem mass spectrometry with electrospray ionization, using ofloxacin as an internal standard (Volmer et al. 1997). The CV was 7.6% at 27.4 ng/ml (n=3) and 3.7% at 794.7 ng/ml (n=3).

2.4 Pharmacokinetic calculations

The peak plasma drug concentrations (C_{max}) and the corresponding times (t_{max}) of lidocaine, MEGX and 3-OH-lidocaine (in Studies V and VI) were taken from the original plasma concentration data. Specifically, t_{max} was obtained for lidocaine in Studies II, III and V, for MEGX in all studies, and for 3-OH-lidocaine in Studies V and VI. In all studies, the terminal log-linear phase of the drug concentration-time curve was visually identified, and the elimination rate constant (k_{el}) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was calculated from $t_{1/2} = \ln 2 / k_{el}$. The areas under the concentration-time curves (AUC) were calculated using the linear trapezoidal rule when successive concentration values increased, and the logarithmic trapezoidal rule when successive concentration values decreased after the peak concentration value. AUC was extrapolated to infinity by using the respective k_{el} value. In Studies I, IV and VI, the values for plasma clearance (CL) and steady-state volume of distribution (V_{ss}) of lidocaine were calculated using non-compartmental methods. The calculations for the V_{ss} of lidocaine were formulated to take into account the time of infusion, i.e.,

$$V_{ss} = (k_0 T \cdot AUMC) / AUC^2 - k_0 T^2 / (2 \cdot AUC),$$

in which k_0 is the infusion rate, T the duration of the infusion and AUMC the area under the first moment of the plasma concentration-time curve.

We also calculated the ratio of AUC of MEGX and 3-OH-lidocaine (Studies V and VI) to that of lidocaine (AUC ratio).

The pharmacokinetic parameters were calculated using the pharmacokinetic program MK-Model, version 5.0 (Biosoft, Cambridge, UK).

2.5 Safety assessment

Studies I, IV and VI were carried out in a postanaesthesia care unit. During the infusion of lidocaine and for 2 h afterwards, a 3-lead ECG of the subjects was monitored continuously.

2.6 Statistical methods

Power analysis was used to determine the number of volunteers needed in each study. Based on previous studies (Tucker and Mather 1979), the sample size was calculated to demonstrate a 25% difference in area under the lidocaine plasma concentration-time curve, and with a chosen power of 0.80 and at a significance level of 0.05.

Balanced Latin square randomization was used to obtain validity and safety in study designs. The assignments for randomization were generated by the Pharmacy of Helsinki University Central Hospital, which arranged for the pretreatment drug and matched placebo capsules in coded envelopes to be delivered to the volunteers.

In Studies I, IV and V, consisting of three phases, analysis of variance (ANOVA) was used to determine the contribution of each treatment to overall variance. A posterior testing was done with Tukey's test. In Study II, because of high standard deviations in AUC values, data were analysed by the Friedman's two-way analysis of variance; a posterior testing was done with the Wilcoxon signed-ranks test. In Studies III and VI, the pharmacokinetic variables between the two phases were compared with Student's t-test for paired data. However, the values for t_{\max} were compared with the Wilcoxon signed-ranks test.

Differences were considered to be significant if $P < 0.05$. Results were generally expressed as means \pm standard deviation (SD); except in some figures, means \pm standard error of the means (SEM) were used for clarity. In Study III, we also calculated the 95% confidence intervals for major differences between the phases, as requested by the editor of *Basic & Clinical Pharmacology & Toxicology*.

Data were analysed with the statistical program Systat for Windows, version 7.0 (SPSS, Chicago, IL, USA).

2.7 Ethical considerations

All study protocols were approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, Helsinki, as well as by the Finnish National Agency for Medicines. All subjects received both oral and written information and gave their written informed consent before entering the studies.

RESULTS

1 Effect of itraconazole on the pharmacokinetics of intravenous and oral lidocaine

A 4-day pretreatment with itraconazole 200 mg once daily had no effect on the pharmacokinetics of intravenous lidocaine. The AUC of lidocaine was 1902 ± 405 ng·h/ml during placebo treatment and 2211 ± 560 ng·h/ml during itraconazole treatment and the C_{\max} of lidocaine was 719 ± 138 and 785 ± 250 ng/ml, respectively. When lidocaine was administered orally, the mean AUC of lidocaine increased by 75% ($P < 0.05$) and the C_{\max} by 55% ($P < 0.05$).

After oral lidocaine, itraconazole prolonged the $t_{1/2}$ of MEGX from 2.3 ± 0.2 h to 2.6 ± 0.4 h ($P < 0.05$) and decreased the ratio of the AUC of MEGX to that of lidocaine by 32% ($P < 0.05$).

At the time of lidocaine administration, the mean concentration of itraconazole was 155 ± 75 ng/ml (332 ± 246 ng/ml at end of lidocaine infusion) in Study I and 170 ± 77 ng/ml (306 ± 167 ng/ml one hour after oral administration) in Study II.

2 Effect of itraconazole on the pharmacokinetics of inhaled lidocaine

Itraconazole 200 mg once daily did not affect the plasma concentrations of inhaled lidocaine or its metabolite MEGX. The AUC of lidocaine was 166 ± 66 ng·h/ml during placebo and 173 ± 60 ng·h/ml during itraconazole and the C_{\max} of lidocaine was 69 ± 24 and 71 ± 24 ng/ml, respectively. The mean concentration of itraconazole at the time of lidocaine administration was 165 ± 72 ng/ml.

3 Effect of erythromycin on the pharmacokinetics of intravenous and oral lidocaine

Compared with placebo, a 4-day pretreatment with erythromycin 500 mg three times daily prolonged the $t_{1/2}$ of intravenous lidocaine from 2.5 ± 0.6 h to 2.9 ± 0.7 h ($P < 0.05$). When lidocaine was administered orally, the mean AUC of lidocaine increased by 50% ($P < 0.05$) and the C_{\max} by 40% ($P < 0.05$). The $t_{1/2}$ of oral lidocaine was longer during erythromycin (2.6 ± 0.5 h) than during itraconazole pretreatment (2.2 ± 0.4 h; $P < 0.05$).

After both intravenous and oral lidocaine, erythromycin increased the C_{\max} ($P < 0.05$) and the AUC ($P < 0.01$) of MEGX, and the AUC_{MEGX} ratio ($P < 0.05$) by 40-70% compared with placebo and itraconazole. After oral administration of lidocaine, the $t_{1/2}$ of MEGX was prolonged from 2.3 ± 0.2 h to 2.6 ± 0.4 h compared with placebo ($P < 0.05$).

The mean concentration of erythromycin at the end of lidocaine infusion was 2.0 ± 1.3 mg/l and one hour after oral administration 2.7 ± 1.6 mg/l. When lidocaine was administered intravenously, a linear correlation ($r=0.89$; $P < 0.01$) existed between the relative changes in MEGX concentrations and the area under the erythromycin concentration-time curve.

4 Effect of fluvoxamine on the pharmacokinetics of intravenous and oral lidocaine

A 5-day pretreatment with fluvoxamine 100 mg once daily reduced the mean CL of intravenous lidocaine by 41% ($P < 0.01$) and prolonged the $t_{1/2}$ of lidocaine from 2.6 ± 0.4 h to 3.5 ± 0.7 h ($P < 0.01$). The mean AUC of lidocaine increased 1.7-fold (range 1.4-2.4; $P < 0.01$). After oral administration of lidocaine, the mean AUC of lidocaine increased 3-fold (range 2.1-7.4; $P < 0.001$) and the C_{max} 2.2-fold (range 1.2-4.8; $P < 0.05$).

Fluvoxamine decreased the C_{max} of MEGX by 65% ($P < 0.001$) and the AUC of MEGX by 54% ($P < 0.001$). The $t_{1/2}$ was prolonged from 3.4 ± 0.8 h to 4.6 ± 1.2 h ($P < 0.05$). The ratio of the AUC of MEGX to that of lidocaine was decreased by 73% ($P < 0.001$) by fluvoxamine. When lidocaine was taken orally, fluvoxamine decreased the C_{max} of MEGX by 47% ($P < 0.001$) and the AUC of MEGX by 26% ($P < 0.05$). The ratio of the AUC of MEGX to that of lidocaine was decreased by 76% ($P < 0.001$).

After oral administration of lidocaine, fluvoxamine prolonged the $t_{1/2}$ of 3-OH-lidocaine from 2.8 ± 0.6 h to 3.7 ± 1.2 h ($P < 0.05$). The ratio of the AUC of 3-OH-lidocaine to that of lidocaine was decreased by 75% ($P < 0.001$).

During the fluvoxamine phase the mean concentration of fluvoxamine immediately before the administration of lidocaine infusion was 56 ± 22 ng/ml and before oral administration 47 ± 24 ng/ml.

5 Effect of the combination of erythromycin and fluvoxamine on the pharmacokinetics of intravenous and oral lidocaine

During pretreatment with fluvoxamine 100 mg once daily for 5 days combined with erythromycin 500 mg three times daily for 6 days, the mean CL of intravenous lidocaine was 53% smaller than during placebo ($P < 0.001$) and 21% smaller than during fluvoxamine alone ($P < 0.05$). The $t_{1/2}$ of lidocaine (4.3 ± 0.8 h) was significantly longer during the combination phase than during the placebo (2.6 ± 0.4 h; $P < 0.001$) or fluvoxamine phase (3.5 ± 0.7 h; $P < 0.01$). The mean AUC of intravenous lidocaine increased 2.3-fold (range 1.8-3.7; $P < 0.01$) and the C_{max} 1.4-fold (range 1.0-2.4; $P < 0.05$). After oral administration of lidocaine, the mean AUC of lidocaine increased 3.6-fold (range 1.7-9.4; $P < 0.001$) and the C_{max} 2.5-fold (range 1.2-5.1; $P < 0.05$). The $t_{1/2}$ of oral lidocaine (3.8 ± 1.2 h) was significantly longer during the combination phase than during the placebo (2.4 ± 0.4 h; $P < 0.001$).

The combination of fluvoxamine and erythromycin decreased the C_{\max} of MEGX by 54% ($P < 0.001$) and the AUC of MEGX by 26% ($P < 0.05$). However, the combination of fluvoxamine and erythromycin decreased the AUC of MEGX less than fluvoxamine alone ($P < 0.05$). The $t_{1/2}$ was prolonged from 3.4 ± 0.8 h to 5.4 ± 2.2 h ($P < 0.01$). The ratio of the AUC of MEGX to that of lidocaine was decreased by 68% ($P < 0.001$) by fluvoxamine and erythromycin. When lidocaine was taken orally, the combination of fluvoxamine and erythromycin decreased the C_{\max} of MEGX by 29% ($P < 0.01$). The ratio of the AUC of MEGX to that of lidocaine was decreased by 65% ($P < 0.01$).

After oral administration of lidocaine, the combination of fluvoxamine and erythromycin prolonged the $t_{1/2}$ of 3-OH-lidocaine from 2.8 ± 0.6 h to 3.8 ± 0.6 h ($P < 0.01$). The ratio of the AUC of 3-OH-lidocaine to that of lidocaine was decreased by 75% ($P < 0.001$).

When lidocaine was administered intravenously, the mean plasma fluvoxamine concentration just before the administration of lidocaine infusion was 56 ± 22 ng/ml during fluvoxamine treatment and 51 ± 28 ng/ml during the combined treatment with erythromycin and fluvoxamine. The corresponding concentration of erythromycin was 1.6 ± 0.6 mg/l during the combined treatment. When lidocaine was given orally, the mean plasma concentration of fluvoxamine before lidocaine administration was 47 ± 24 ng/ml during the fluvoxamine phase and 34 ± 20 ng/ml during the combination of fluvoxamine and erythromycin. The mean plasma concentration of erythromycin at 0.5 h after the ingestion of lidocaine was 1.8 ± 1.6 mg/l.

When lidocaine was administered intravenously, the multiple linear regression model, which included fluvoxamine and erythromycin concentrations as independent variables, was able to predict the observed change in the AUC of lidocaine ($r=0.471$; $P < 0.05$).

6 Effect of ciprofloxacin on the pharmacokinetics of intravenous lidocaine

Compared with placebo, a 2.5-day pretreatment with ciprofloxacin 500 mg twice daily increased the mean C_{\max} and AUC of lidocaine by 12% ($P < 0.05$) and 26% ($P < 0.01$), respectively. The mean plasma CL of lidocaine was reduced by 22% ($P < 0.01$) and its $t_{1/2}$ prolonged by 7% ($P < 0.01$) by ciprofloxacin.

Ciprofloxacin decreased the C_{\max} of MEGX by 40% ($P < 0.01$). The AUC of MEGX was decreased by 21% ($P < 0.01$), and the $t_{1/2}$ was prolonged by 34% ($P < 0.05$). The ratio of the AUC of MEGX to that of lidocaine was decreased by 40% ($P < 0.001$) by ciprofloxacin.

Ciprofloxacin decreased the C_{\max} of 3-OH-lidocaine by 22% ($P < 0.05$) and its AUC by 14% ($P < 0.01$). The t_{\max} and $t_{1/2}$ of 3-OH-lidocaine were not significantly affected. However, the ratio of the AUC of 3-OH-lidocaine to that of lidocaine was decreased by 35% ($P < 0.001$) by ciprofloxacin.

The mean ciprofloxacin plasma concentration was 655 ng/ml before the administration of lidocaine and 288 ng/ml at 10 h after the infusion.

7 Summary of results

The results of the CYP1A2 and CYP3A4 inhibitor-induced changes in the pharmacokinetics of lidocaine are summarized in Figures 7-11 and Table 4. All of the results summarized below are statistically significant.

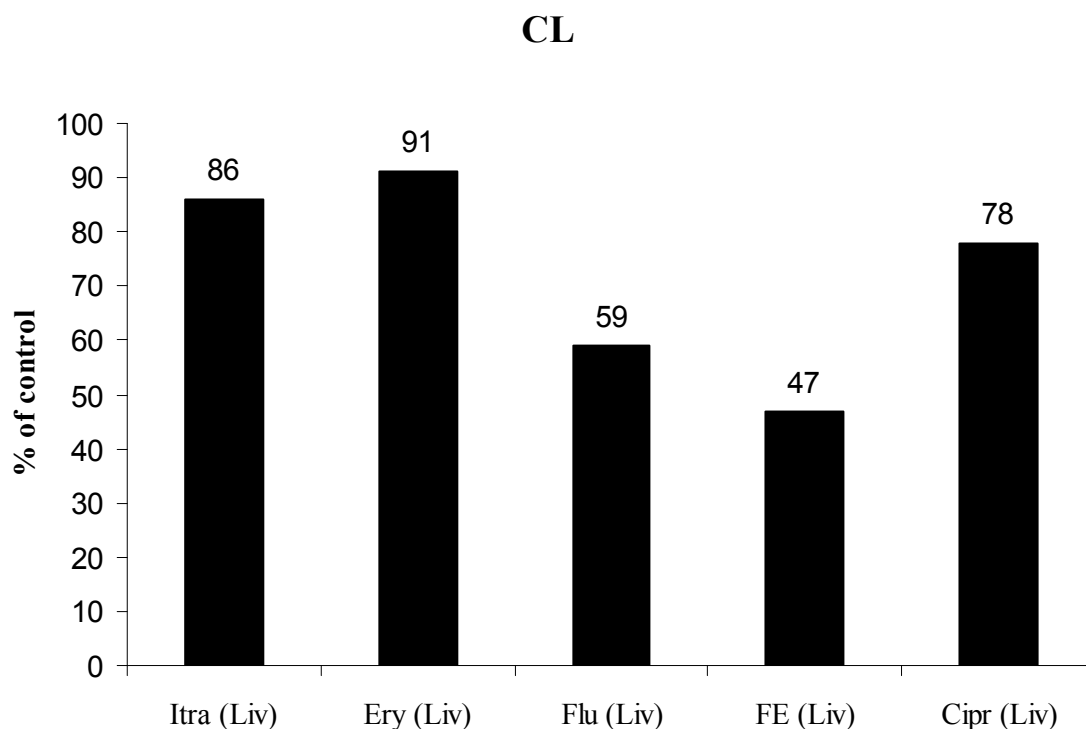


Figure 7 Mean clearance (CL) of intravenous lidocaine (Liv) after pretreatment with itraconazole (Itra), erythromycin (Ery), fluvoxamine (Flu), fluvoxamine plus erythromycin (FE) and ciprofloxacin (Cipr) presented as percentages of the corresponding values during the placebo phase.

7.1 Effect of CYP3A4 inhibitors

Itraconazole and erythromycin did not affect the pharmacokinetics of intravenous lidocaine, but erythromycin increased the C_{\max} and the AUC of MEGX, and the AUC ratio of MEGX by 40-70% compared with placebo and itraconazole. Erythromycin also slightly prolonged the $t_{1/2}$ of lidocaine. Moreover a linear correlation existed between the relative changes in MEGX concentrations and the area under the erythromycin concentration-time curve.

When lidocaine was taken orally, both erythromycin and itraconazole increased the C_{\max} and the AUC of lidocaine by 40-70%. Compared with placebo and itraconazole, erythromycin increased the C_{\max} and the AUC of MEGX by 40-60%. Both CYP3A4 inhibitors slightly prolonged the $t_{1/2}$ of MEGX.

The pharmacokinetics of inhaled lidocaine was unaffected by concomitant administration of itraconazole.

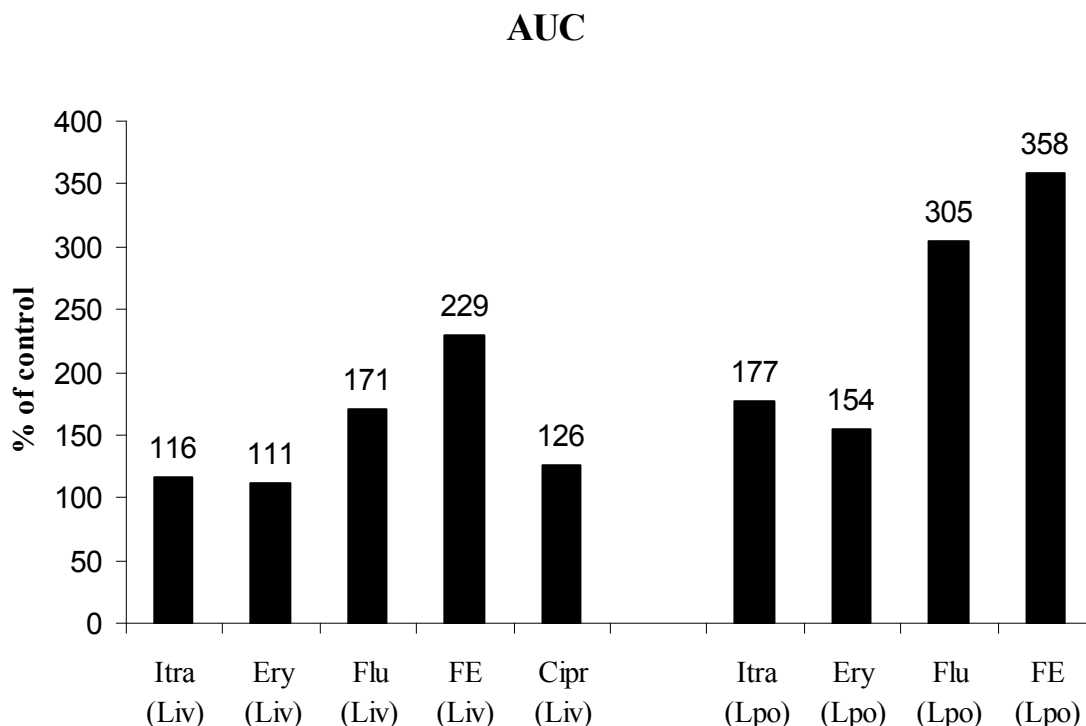


Figure 8 Mean areas under the concentration-time curves (AUC) of either intravenous lidocaine (Liv) or oral lidocaine (Lpo) after pretreatment with itraconazole (Itra), erythromycin (Ery), fluvoxamine (Flu), fluvoxamine plus erythromycin (FE) and ciprofloxacin (Cipr) presented as percentages of the corresponding values during the placebo phase.

7.2 Effect of CYP1A2 inhibitors

Fluvoxamine reduced the mean CL of intravenous lidocaine by 41% and prolonged the $t_{1/2}$ of lidocaine by 35%. The mean AUC of lidocaine increased 1.7-fold. After oral administration of lidocaine, the mean AUC of lidocaine increased 3-fold and the C_{max} 2.2-fold.

Fluvoxamine decreased the C_{max} of MEGX by 65% and the AUC of MEGX by 54%. The $t_{1/2}$ was prolonged by 35%. The ratio of the AUC of MEGX to that of lidocaine was decreased by 73% by fluvoxamine. When lidocaine was taken orally, fluvoxamine decreased the C_{max} and the AUC of MEGX by 47% and 26%, respectively. The ratio of the AUC of MEGX to that of lidocaine was decreased by 76%.

After oral administration of lidocaine, the $t_{1/2}$ of 3-OH-lidocaine was prolonged by 32% and the ratio of the AUC of 3-OH-lidocaine to that of lidocaine was decreased by 75% by fluvoxamine.

Compared with placebo, ciprofloxacin increased the mean C_{max} and AUC of lidocaine by 12% and 26%, respectively. The mean plasma CL of lidocaine was reduced by 22% and its $t_{1/2}$ prolonged by 7%.

Ciprofloxacin decreased the C_{max} and the AUC of MEGX by 40% and 21%, respectively. The $t_{1/2}$ was prolonged by 34%, and the ratio of the AUC of MEGX to that of lidocaine was decreased by 40% by ciprofloxacin.

Ciprofloxacin decreased the C_{max} and the AUC of 3-OH-lidocaine by 22% and 14%, respectively. The ratio of the AUC of 3-OH-lidocaine to that of lidocaine was decreased by 35% by ciprofloxacin.

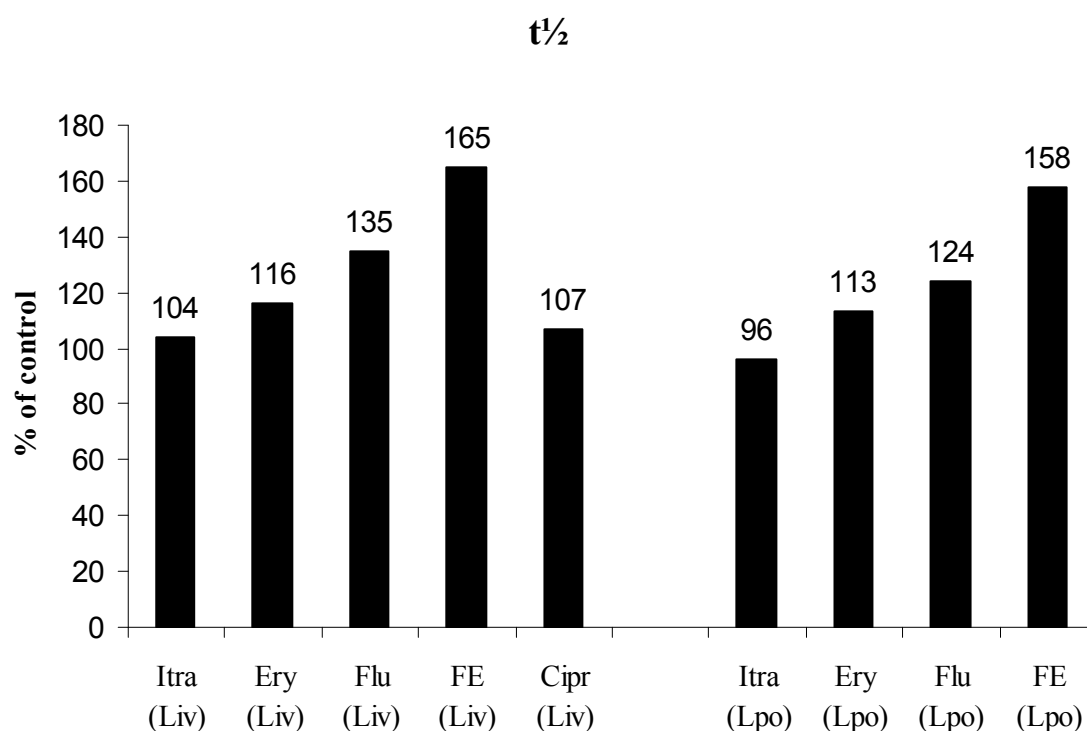


Figure 9 Mean elimination half-lives ($t_{1/2}$) of either intravenous lidocaine (Liv) or oral lidocaine (Lpo) after pretreatment with itraconazole (Itra), erythromycin (Ery), fluvoxamine (Flu), fluvoxamine plus erythromycin (FE) and ciprofloxacin (Cipr) presented as percentages of the corresponding values during the placebo phase.

7.3 Combined effect of CYP3A4 and CYP1A2 inhibitors

During pretreatment with fluvoxamine combined with erythromycin, the mean CL of intravenous lidocaine was 53% smaller than during placebo and 21% smaller than during fluvoxamine alone. The $t_{1/2}$ of lidocaine was significantly longer during the combination phase than during the placebo or fluvoxamine phase. The mean AUC of intravenous lidocaine increased 2.3-fold and the C_{max} 1.4-fold. After oral administration of lidocaine,

the mean AUC of lidocaine increased 3.6-fold and the C_{max} 2.5-fold. The $t_{1/2}$ of oral lidocaine was significantly longer during the combination phase than during the placebo.

The combination of fluvoxamine and erythromycin decreased the C_{max} and the AUC of MEGX by 54% and 26%, respectively. However, this combination decreased the AUC of MEGX less than fluvoxamine alone. The $t_{1/2}$ was prolonged by 59%, and the ratio of the AUC of MEGX to that of lidocaine was decreased by 68% by fluvoxamine and erythromycin. When lidocaine was taken orally, the combination decreased the C_{max} of MEGX by 29% and the ratio of the AUC of MEGX to that of lidocaine by 65%.

After oral administration of lidocaine, the combination of fluvoxamine and erythromycin prolonged the $t_{1/2}$ of 3-OH-lidocaine by 36% and decreased the ratio of the AUC of 3-OH-lidocaine to that of lidocaine by 75%.

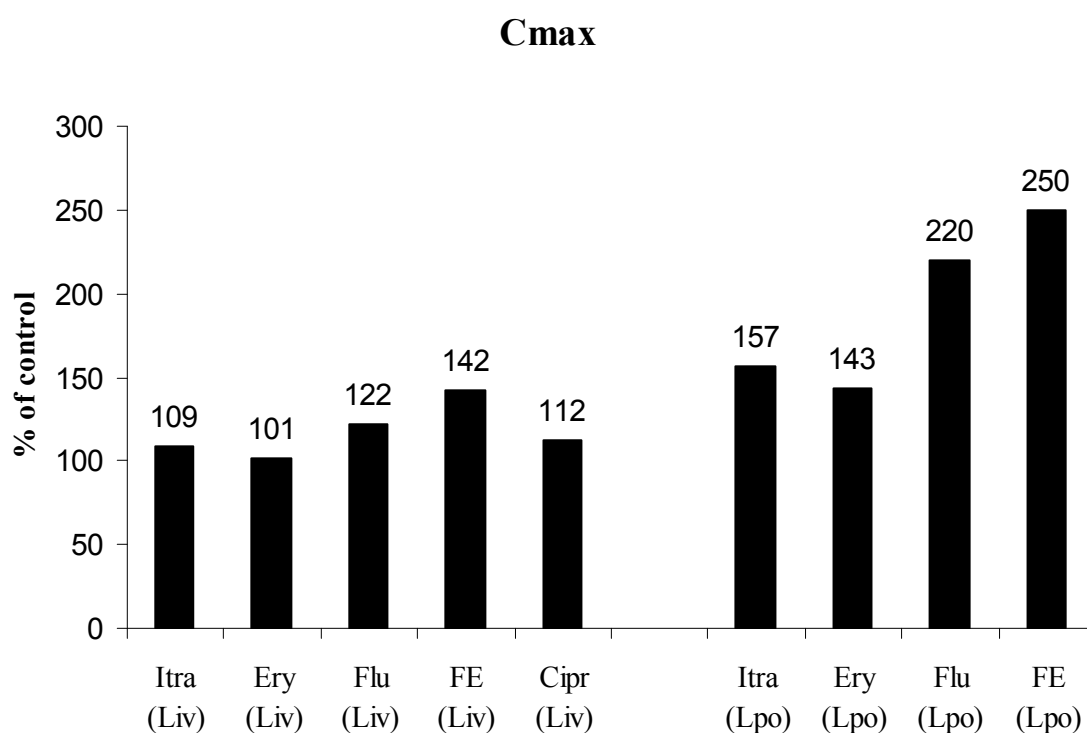


Figure 10 Mean peak plasma concentrations (C_{max}) of either intravenous lidocaine (Liv) or oral lidocaine (Lpo) after pretreatment with itraconazole (Itra), erythromycin (Ery), fluvoxamine (Flu), fluvoxamine plus erythromycin (FE) and ciprofloxacin (Cipr) presented as percentages of the corresponding values during the placebo phase.

AUC ratio MEGX / Lidocaine

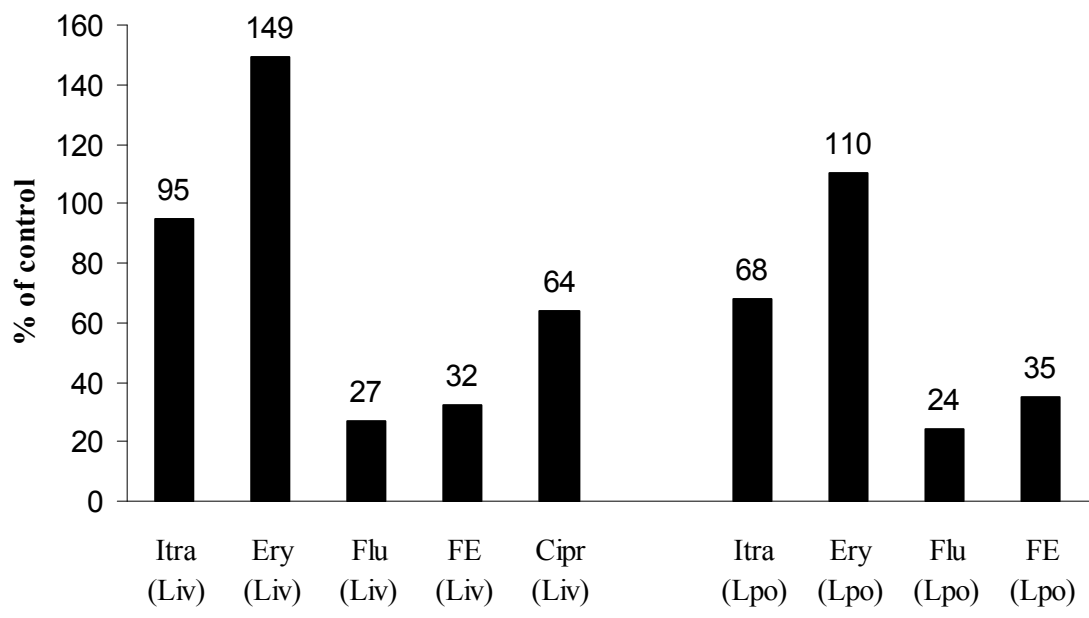


Figure 11 Mean ratio of the areas under the concentration-time curves (AUC) of MEGX to that of either intravenous lidocaine (Liv) or oral lidocaine (Lpo) after pretreatment with itraconazole (Itra), erythromycin (Ery), fluvoxamine (Flu), fluvoxamine plus erythromycin (FE) and ciprofloxacin (Cipr) presented as percentages of the corresponding values during the placebo phase.

Table 4. Summary of the changes in the pharmacokinetics of a single dose of either 1.5 mg/kg of intravenous (i.v.) lidocaine or 1 mg/kg of oral (p.o.) lidocaine after different pretreatments.

Pretreatment	Lidocaine				MEGX		
	Route	C _{max}	AUC	t _{1/2}	C _{max}	AUC	t _{1/2}
Erythromycin 500 mg x 3 for 4 days	i.v.	↔	↔	↑	↑	↑↑	↔
	p.o.	↑	↑↑	↑	↑	↑	↑
Itraconazole 200 mg x 1 for 4 days	i.v.	↔	↔	↔	↔	↔	↔
	p.o.	↑↑	↑↑	↔	↔	↔	↑
Fluvoxamine 100 mg x 1 for 5 days	i.v.	↔	↑↑	↑	↓↓	↓↓	↑
	p.o.	↑↑↑	↑↑↑	↔	↓	↓	↔
Fluvoxamine 100 mg x 1 for 5 days + Erythromycin 500 mg x 3 for 6 days	i.v.	↑	↑↑↑	↑↑	↓↓	↓	↑↑
	p.o.	↑↑↑	↑↑↑	↑↑	↓	↔	↑↑
Ciprofloxacin 500 mg x 2 for 2.5 days	i.v.	↑	↑	↑	↓	↓	↑

Changes (increase or decrease) are indicated as follows: ↑/↓ a 10-50% change, ↑↑/↓↓ a 51-100% change, ↑↑↑/↓↓↓ a > 100% change, ↔ no significant change

DISCUSSION

1 Methodological considerations

A randomized, double-blinded, placebo-controlled cross-over study design was used in all studies. In this design, the subjects serve as their own controls, minimizing the effect of interindividual variation and reducing the number of subjects needed. Based on previous studies, 8-10 subjects in each study was estimated to be sufficient to demonstrate a 25% difference in lidocaine AUC with a $P < 0.05$. Thus, the number of subjects exposed to the drugs was minimized. Balanced randomization and adequate wash-out periods (2-4 weeks) were used to minimize the risk of possible period effects or carry-over effects. As physiological changes during the menstrual cycle seem to have only minor effects on the elimination of drugs (Kashuba and Nafziger 1998), we did not deem it necessary to have the wash-out period equal the average menstrual cycle of 4 weeks.

The pretreatment period in the studies was between 2.5 and 6 days, and all CYP inhibitors were given at clinically relevant dosages. The steady-state concentrations of itraconazole and fluvoxamine were most probably not reached within this period. However, significant inhibition of CYP enzymes occurs even after a single dose of an inhibitor, and the pretreatments were similar to the ones previously involved in clinically significant drug-drug interactions (Neuvonen and Jalava 1996, Backman et al. 1998). In all studies, the dose of lidocaine was, for safety reasons, rather small relative to clinically used doses. The dose and rate of infusion of intravenous lidocaine were kept low to minimize the risks of toxicity. Thus, no lidocaine-related side-effects, except for mild cough irritation during lidocaine inhalation in Study III, were observed in any of the studies. As lidocaine has linear pharmacokinetics and the analysis methods applied were sensitive and specific, our results are likely to be valid also for the higher concentrations typically seen in clinical settings.

To monitor compliance, the plasma concentrations of the pretreatment drugs were measured during the study days. These concentrations were at therapeutic levels, except for one subject in Study I, in whom no erythromycin was detected in plasma during the erythromycin phase of the study. In this subject, no erythromycin-associated changes in MEGX concentrations were observed.

All subjects in the studies were young, healthy volunteers. Although the activities of CYP1A2 and CYP3A4 are quite constant during adulthood, the pharmacokinetics of lidocaine can change with increasing age and concomitant illnesses (Tucker 1986, Tanaka 1998). Care must therefore be taken when extrapolating the results to elderly subjects. Variations in drug interaction may be greater in actual patient populations than in our healthy subjects.

The studies were not balanced with respect to subjects' gender. Many drugs metabolized by CYP3A4 show higher clearance in women than in men, and men have been described to have a higher CYP1A2 activity (Wolbold et al. 2003, Anderson 2005). In a recent review, Greenblatt and von Moltke (2008) postulated that gender has a small, most likely clinically negligible, influence on CYP3A phenotype for substrates not

transported by P-glycoprotein. Some of the female volunteers were using oral contraceptive steroids, which can significantly inhibit CYP1A2 and moderately inhibit CYP3A4 (Palovaara et al. 2000, Granfors et al. 2005). However, no balance with respect to gender or oral contraceptive use was considered necessary because the volunteers served as their own controls. Furthermore, due to the relatively small number of subjects in each study, we could not assess the effects of gender on the pharmacokinetics of lidocaine.

Country of residence and ethnic origin can influence CYP1A2 and CYP3A4 activity (Yu et al. 2001, Ingelman-Sundberg et al. 2007, Gunes and Dahl 2008). All subjects in the studies were Finnish residents of Caucasian origin. Furthermore, they served as their own controls to minimize interindividual variability, and no CYP genotyping of the subjects was considered necessary.

Stimulation of hepatic blood flow by food intake has been shown to influence lidocaine pharmacokinetics. A high-protein meal can increase the CL of intravenously administered lidocaine by 20% and decrease its AUC by 20% (Elvin et al. 1981). Thus, the possible effect of food on the pharmacokinetics of lidocaine was controlled by using a standard fasting period before lidocaine intake and by serving standard meals after the intake.

Venous blood samples were used in this work, as this was considered to be less harmful for the study volunteers. However, after intravenous administration, arterial plasma concentrations increase faster than venous concentrations and would have provided more exact data on the distribution phase of lidocaine. Nevertheless, since the study was more directed at examining the elimination phase, venous blood sampling was chosen. The first plasma sample was taken at 30 min following the end of the lidocaine administration, and venous samples were collected for up to 10 h. This timing largely ignored the distribution phase, but can be regarded as sufficient for characterization of the elimination phase.

The plasma concentrations of lidocaine, MEGX and 3-OH-lidocaine (Studies V and VI) were measured with gas chromatography. The between-day CVs were low in all studies. The quantification limits and CVs for the methods of determining the plasma concentrations of erythromycin, itraconazole, fluvoxamine and ciprofloxacin were also satisfactory.

2 Effect of inhibition of CYP3A4 on lidocaine pharmacokinetics

The plasma concentrations of intravenously administered lidocaine were virtually unaffected by the concomitant administration of the CYP3A4 inhibitors erythromycin and itraconazole (causing an insignificant 9% and 14% reduction in CL). Although the mean elimination half-life of lidocaine was marginally prolonged after erythromycin, this obviously had no clinical consequences. However, when lidocaine was taken orally, both erythromycin and itraconazole increased lidocaine AUC and lidocaine peak concentrations by 40–70%.

Both erythromycin and itraconazole are potent inhibitors of CYP3A4 *in vitro* and in humans (Back and Tjia 1991, Gascon and Dayer 1991, Olkkola et al. 1993, Olkkola et al. 1994). Because they do not appear to change liver blood flow, they are ideal model substances for the study of drug interactions at the level of inhibition of individual isoenzymes. Lidocaine is a drug with a medium to high extraction ratio, and therefore, its CL is significantly dependent on liver blood flow (Tucker and Mather 1979). The “well-stirred model” of hepatic elimination (Rowland and Tozer 1995) enables estimation of the contribution of the changed intrinsic CL and liver blood flow on lidocaine CL (see Appendix 2). If the liver blood flow remains unchanged, a decrease of approximately 75% in the intrinsic CL of lidocaine is necessary to reduce lidocaine blood CL by 50%. The statistically insignificant 14% numerical decrease in lidocaine plasma CL by itraconazole is thus fully consistent with a possible 35-40% decrease in intrinsic CL. Unfortunately, we would have had to include 22 subjects to be able to demonstrate a statistically significant 14% decrease in lidocaine CL.

Recently, Yang et al. (2007) criticized the misuse of the “well-stirred model” and emphasized the importance of not mixing either plasma free fraction and hepatic blood flow or plasma and whole-blood clearance when using this model. In their opinion, one should take into account not only the free fraction in plasma but also the blood to plasma drug concentration ratio when using the model to estimate plasma and not blood clearance. In our estimation in Study I, this was done (see Appendix 2).

Both erythromycin and itraconazole increase the bioavailability and concentrations of orally administered substrates of CYP3A4 such as buspirone (Kivistö et al. 1997), midazolam (Olkkola et al. 1993) and triazolam (Varhe et al. 1994). Considering that the oral bioavailability of lidocaine is only about 30% due to extensive first-pass metabolism (Tucker and Mather 1979), much greater effects on the pharmacokinetics of orally administered lidocaine would have been anticipated if lidocaine were metabolized primarily by CYP3A4. This suggests that in humans CYP3A4 has a lesser significance than previously assumed in the elimination of lidocaine or lidocaine has alternative routes of elimination. This finding is supported by earlier studies with propranolol, showing that it reduces lidocaine CL and increases the AUC of oral lidocaine by over 100% (Ochs et al. 1980, Bax et al. 1985). This reduction in lidocaine metabolism is apparently mediated by both enzyme inhibition and reduction of liver blood flow (Tucker et al. 1984). Because propranolol does not affect the formation of MEGX, but inhibits the 3-hydroxylation of lidocaine mediated by CYP1A2 (Imaoka et al. 1990, Suzuki et al. 1993), it is logical to assume that also 3-hydroxylation is important in lidocaine metabolism in humans.

Erythromycin increased the concentrations of MEGX markedly regardless of the route of lidocaine administration. The reason for this is unknown, but since MEGX is further metabolized, it is possible that erythromycin inhibits the metabolism of MEGX. Orlando et al. (2003) found a similar effect of erythromycin on MEGX concentrations and their conclusion was that erythromycin inhibits the de-ethylation of MEGX to GX, although GX concentrations were not significantly lower after erythromycin co-administration. MEGX has 33-83% of the anti-arrhythmic activity of lidocaine, and it can also cause convulsions (Burney et al. 1974). Unfortunately, our data do not justify any far-reaching conclusions about the clinical significance of the observed increase in MEGX

concentrations. From a theoretical point of view, during prolonged infusions, the accumulation of MEGX potentially could increase the toxicity of lidocaine. This increase in toxicity could be further strengthened by the fact that during prolonged infusion lidocaine clearance is also reduced, probably by the accumulation of MEGX (Thomson et al. 1987). Clearly, a pharmacodynamic study following lidocaine infusion to steady state would provide more information on this erythromycin-lidocaine interaction.

In a later study, Swart et al. (2002) showed a similar insignificant effect of erythromycin on the pharmacokinetics of intravenous lidocaine (9% reduction in CL). The MEGX test was unaffected by erythromycin, but unfortunately the effect on the AUC of MEGX was not reported. In contrast, in the study by Orlando et al. (2003), erythromycin decreased lidocaine CL by 18%, and a greater increase in $t_{1/2}$ (30% compared with 16% in Study I) was observed.

The pharmacokinetics of inhaled lidocaine was unaffected by concomitant administration of itraconazole. This suggests that basically all lidocaine was absorbed from the airways and not from the gastrointestinal tract. For example, in local anaesthesia of the pharynx, a significant amount of lidocaine aerosol can be swallowed and be subjected to first-pass metabolism in the gastrointestinal tract. The pharmacokinetics of an inhaled drug is interesting. Most likely the fraction of the inhaled drug absorbed through the lung has the same disposition characteristics as an intravenous dose, and the swallowed fraction has a similar disposition as an orally administered dose (Taburet and Schmit 1994). Theoretically, inhaled lidocaine could be metabolized as it passes through the pulmonary epithelium during absorption. Studies in experimental animals have shown that the lung tissue of rabbits has enzymatic activity that is capable of metabolizing lidocaine (Le et al. 1996). In humans, substantial variation seems to exist in the pulmonary expression of CYP3A4 between individuals. In the human lung, CYP3A5 is the major CYP3A enzyme, and CYP3A4 is expressed in only about 20% of individuals (Anttila et al. 1997). CYP3A5 appears to be less susceptible to inhibition than CYP3A4 (Isoherranen et al. 2008). On the other hand, very little is known about the presence of CYP3A isoenzymes in the nasal cavity, pharynx, larynx and trachea (Raunio et al. 2005). Although CYP3A4 is poorly expressed in lungs, inhaled CYP3A4 substrates may be susceptible to interactions with the inhibitors of CYP3A4. In a study by Raaska et al. (2002), itraconazole considerably increased the plasma concentrations and delayed the elimination of inhaled CYP3A4 substrate budesonide.

3 Effect of inhibition of CYP1A2 on lidocaine pharmacokinetics

Fluvoxamine, a strong CYP1A2 inhibitor, markedly affected the elimination kinetics of intravenous lidocaine by reducing mean plasma CL by 41%. When lidocaine was given orally, fluvoxamine increased its C_{max} and AUC 2.2- to 3-fold. Ciprofloxacin, a less potent CYP1A2 inhibitor, affected the elimination of intravenous lidocaine by moderately reducing its plasma CL and increasing its C_{max} and AUC.

Our studies and that of Orlando et al. (2004), nevertheless, demonstrate that the inhibition of CYP1A2 alone has a major effect on lidocaine pharmacokinetics.

Fluvoxamine is a potent inhibitor of CYP1A2 and also a moderate inhibitor of CYP3A4. Ciprofloxacin seems to be a less potent inhibitor of CYP1A2 than fluvoxamine (Bertz and Granneman 1997). Therefore, the observed 22% decrease in lidocaine CL caused by ciprofloxacin (41% reduction by fluvoxamine in Study IV) in Study VI is in good agreement with previous reports that ciprofloxacin is a moderately potent inhibitor of CYP1A2. However, in four of the nine subjects in Study VI, ciprofloxacin decreased the lidocaine CL by about 30–40%. As lidocaine has linear pharmacokinetics, this finding means that during a continuous epidural infusion of lidocaine its plasma concentrations could be increased up to 70% in these subjects. Clinically, ciprofloxacin can be administered in higher doses (up to 750 mg twice daily) than in our study. Thus, the plasma concentrations of ciprofloxacin can be higher and the (concentration-dependent) inhibition of CYP1A2 stronger than seen in our healthy volunteers. Furthermore, in patients, one could expect larger individual changes than in this small and rather homogeneous group. Consequently, the possibility of systemic toxicity cannot be excluded during the concomitant use of ciprofloxacin with lidocaine.

Fluvoxamine considerably reduced the C_{max} and AUC of MEGX and the ratio of AUC of MEGX to that of lidocaine and prolonged the $t_{1/2}$ of MEGX. Ciprofloxacin also reduced the C_{max} and AUC of the metabolites MEGX and 3-OH-lidocaine. The reduction of formation of both MEGX and 3-OH-lidocaine by ciprofloxacin demonstrates that CYP1A2 is important also in the formation of MEGX, a reaction earlier thought to be mainly mediated by CYP3A4.

The mean reduction of the CL of lidocaine by ciprofloxacin or fluvoxamine was smaller than previously observed for another amide-type local anaesthetic ropivacaine (Jokinen et al. 2000, Jokinen et al. 2003). Knowing the dissimilar extraction ratios of these two drugs, this is not surprising. Ropivacaine has an extraction ratio of 0.4–0.5, which makes its plasma CL more dependent on the enzymatic capacity of the liver than in the case of lidocaine. Lidocaine is a drug with a high extraction ratio (Benowitz and Meister 1978). Its CL is directly proportional to the liver blood flow, and even a major reduction in CYP1A2 activity does not challenge lidocaine CL as much as ropivacaine CL.

4 Effect of combined inhibition of CYP1A2 and CYP3A4 on lidocaine pharmacokinetics

The pharmacokinetics of lidocaine was affected more strongly when lidocaine was administered after combined pretreatment with fluvoxamine and the CYP3A4 inhibitor erythromycin. The large reduction of lidocaine CL was associated with prolongation of $t_{1/2}$ and significantly increased AUC. The concomitant inhibition of CYP1A2 and CYP3A4 affected the pharmacokinetics of intravenous lidocaine clearly more than the inhibition of either enzyme alone. When lidocaine was given orally, the use of erythromycin together with fluvoxamine had only an insignificant further effect (of 10–20%) on the C_{max} and AUC of lidocaine, compared with the effect of fluvoxamine alone.

In vitro, the results of enzyme kinetic, chemical inhibition, immunoinhibition and recombinant enzyme studies indicate that both CYP3A4 and CYP1A2 enzymes are

important in the metabolism of lidocaine, but their roles seem to be different at different lidocaine concentrations (Wang et al. 1999a, Wang et al. 2000). This phenomenon explains the apparent discrepancy between our results and those of Bargetzi et al. (1989), who previously suggested that CYP3A4 is the enzyme principally responsible for the metabolic clearance of lidocaine. At therapeutically relevant plasma lidocaine concentrations, CYP1A2 is the major enzyme catalysing the formation of both MEGX and 3-OH-lidocaine (Wang et al. 2000). As stated earlier, Orlando et al. (2004) proposed that CYP1A2 and CYP3A4 are responsible for approximately two-thirds and one-third of lidocaine metabolism, respectively.

The tissue distribution of these isoenzymes is different; CYP3A4 is extensively expressed in the gastrointestinal wall and liver, whereas CYP1A2 is mainly located in the liver (Shimada et al. 1994, Kivistö et al. 1996). Accordingly, the relative roles of CYP3A4 and CYP1A2 in lidocaine metabolism can also depend on the route of its administration.

Our work is in good agreement with that of Orlando et al. (2004). In their study, in healthy volunteers, fluvoxamine decreased the clearance of lidocaine by 60% and prolonged the $t_{1/2}$ by about 30%. The C_{max} and AUC of MEGX were decreased by about 60%.

Although in Study I erythromycin alone caused a 9% non-significant decrease in lidocaine CL, in the Study IV the same dose of erythromycin decreased lidocaine CL by 21% once CYP1A2 was inhibited. This is consistent with the effect of fluvoxamine and erythromycin on the pharmacokinetics of ropivacaine (Jokinen et al. 2000). In the condition of an uninhibited CYP1A2, this enzyme can compensate for the role of CYP3A4 in the metabolism of lidocaine and ropivacaine when the latter enzyme is inhibited by erythromycin or other CYP3A4 inhibitors.

Continuous epidural infusion of lidocaine at doses of 0.44–0.98 mg/kg/h for postoperative analgesia produced lidocaine concentrations ranging from approximately 1 to 4 µg/ml (Rygnestad et al. 1999). This is also the concentration range shown to be effective in the treatment of ventricular arrhythmias (Gianelly et al. 1967). Lidocaine results in subjective toxic symptoms already at plasma concentrations of 3–5 µg/ml and objective signs appear at 6–10 µg/ml (Benowitz and Meister 1978). Because fluvoxamine reduced the mean lidocaine CL by 41% and the combination of fluvoxamine with erythromycin by 53%, lidocaine concentrations during continuous epidural infusion can be calculated to increase on average by 70% and 110%, respectively. This means that both the interaction between lidocaine and fluvoxamine and the interaction between lidocaine and the combination of fluvoxamine with erythromycin can result in lidocaine-induced toxicity. Accordingly, Orlando et al. (2004) postulated that the lidocaine infusion rate should be greatly reduced (by 50%–80%) in patients taking fluvoxamine or other potent inhibitors of CYP1A2.

When lidocaine was administered orally in Study V, the C_{max} of lidocaine after placebo ranged from approximately 50 to 220 ng/ml, and after fluvoxamine alone and together with erythromycin from 110 to 900 ng/ml. The highest individual rise in the C_{max} of unchanged lidocaine was about 5-fold. In our studies, the dose of lidocaine was, for safety reasons, rather small relative to the clinically used doses. A usual oral dose prior to gastroscopy is 300 mg in adults, i.e. six times the dose administered to the smallest of our

volunteers in Study V (Sweetman 2009). Because lidocaine has linear pharmacokinetics, following an oral dose of 300 mg, peak plasma concentrations might be expected to attain level of 4-5 µg/ml in individuals using CYP1A2 and CYP3A4 inhibitors. During bronchoscopy, even greater doses of lidocaine (up to 8.2 mg/kg) are used, yielding peak lidocaine concentrations of up to 5.3 µg/ml (Milman et al. 1998, Langmack et al. 2000). In patients using CYP1A2 and CYP3A4 inhibitors or in those with compromised cardiac and liver function, even higher levels might be attained.

Both fluvoxamine and concomitant erythromycin and fluvoxamine affected the pharmacokinetics of MEGX in Studies IV and V. However, erythromycin partially prevented the decrease in the AUC of MEGX caused by fluvoxamine. This opposite effect of erythromycin on the AUC of MEGX can be explained by the inhibition of other CYP3A4-mediated metabolic pathways of lidocaine by erythromycin or by inhibition of further metabolism of MEGX. This finding is in good agreement with Studies I and II, which demonstrated that after intravenous or oral administration of lidocaine, erythromycin increases the AUC of MEGX by 60-70%. Like lidocaine, MEGX has considerable anti-arrhythmic activity and can also cause toxic symptoms (Burney et al. 1974). However, when lidocaine is administered together with fluvoxamine or with a combination of erythromycin and fluvoxamine, the plasma concentrations of MEGX are not higher than usual, and MEGX does not contribute to the toxicity of lidocaine. Similarly, erythromycin also partially reversed the modest, but statistically insignificant effect of fluvoxamine on the formation of 3-OH-lidocaine.

The effect of the concomitant inhibition of CYP3A4 and CYP1A2 on the pharmacokinetics of lidocaine was less than that on the pharmacokinetics of ropivacaine. This is in line with the effect of inhibiting CYP1A2 alone, which is discussed above.

5 General discussion

The use of intravenous lidocaine as an anti-arrhythmic agent has diminished during the last years, but there are several new indications for its systemic use, including postoperative and neuropathic pain and some inflammatory conditions. Lidocaine has a narrow therapeutic window when it is used intravenously. High peak concentrations of lidocaine can also be seen following its administration by various routes (see Appendix I). Lidocaine is not for oral use, but is applied for topical anaesthesia in the oropharyngeal region, and in this indication it is also intentionally swallowed. There are several cases of lidocaine toxicity after accidental oral ingestion of lidocaine for topical anaesthesia (Hess and Walson 1988, Dawling et al. 1989, Gonzalez del Rey et al. 1994, Zuberi et al. 2000).

In the present studies, a small dose of lidocaine was given intravenously, orally or inhaled without any intention to evaluate its pharmacodynamic effects or absorption following infiltration or conduction anaesthesia. These issues are, however, also important in clinical work. In addition to the dose, lidocaine absorption, and thus, the plasma concentrations, depend upon the rate of administration, dilution, vascularity of the area injected and co-administration of a vasoconstrictor (e.g. epinephrine). Duration of a neural blockade depends on absorption of the local anaesthetic from the site of administration. In

other words, absorption of local anaesthetics following a neural blockade is primarily and directly related to local blood flow and inversely related to local tissue binding (Tucker 1986).

From a theoretical point of view, it does not seem probable that erythromycin, itraconazole, fluvoxamine or ciprofloxacin would have a clinically significant effect on the absorption or the pharmacodynamics of lidocaine. Thus, it is not likely that these drugs would influence the duration or intensity of a single neural blockade produced by lidocaine, even if some of them affected the elimination of lidocaine.

The systemic toxicity of lidocaine is related to its free plasma concentration, thus depending on both the absorption and the disposition of the drug (Tucker 1986). A reduction in V_{ss} would lead to an increased C_{max} , but the V_{ss} of lidocaine was not altered by any of the drug interactions evaluated.

Because lidocaine is metabolized by CYP1A2 and CYP3A4, we expected that drugs known to inhibit these enzymes would affect the pharmacokinetics of lidocaine. This proved to be true for CYP1A2 inhibitors, for combined use of CYP1A2 and CYP3A4 inhibitors and also for CYP3A4 inhibitors when lidocaine was given orally. It is not uncommon that patients concomitantly use drugs that inhibit both CYP1A2 and CYP3A4, and then need lidocaine, for instance, for topical anaesthesia of the upper gastrointestinal tract.

6 Clinical implications

Itraconazole and erythromycin, given alone, had no significant effect on lidocaine CL. Inhibiting CYP3A4 alone therefore would not likely have a clinically significant effect on the pharmacokinetics of intravenous lidocaine.

Itraconazole does not affect the plasma concentrations of inhaled lidocaine or its metabolite MEGX. Seemingly, no dosage adjustments are necessary if lidocaine is used to prepare the airway prior to endoscopic procedures or intubation in patients concomitant given CYP3A4 inhibitor. However, accidental ingestion of lidocaine may result in higher lidocaine concentrations than expected in these patients.

The inhibition of CYP1A2 by fluvoxamine considerably reduces the elimination of lidocaine. A concomitant use of fluvoxamine and the CYP3A4 inhibitor erythromycin further increases lidocaine concentration by decreasing its CL. Thus, clinicians should be aware of the potentially increased toxicity of lidocaine when used together with the inhibitors of CYP1A2, particularly with the combination of drugs inhibiting both CYP1A2 and CYP3A4 enzymes. Because the volume of distribution of lidocaine remains unchanged, the interaction is likely to have significant consequences only during continuous intravenous administration of lidocaine.

When lidocaine is ingested, the inhibition of CYP1A2 by fluvoxamine considerably reduces the presystemic metabolism of lidocaine. The concomitant use of fluvoxamine and the CYP3A4 inhibitor erythromycin may further increase the exposure to oral lidocaine. Clinicians should be aware of the potentially increased toxicity of lidocaine applied to the upper respiratory or gastrointestinal tract when it is used together with the inhibitors of

CYP1A2, and, particularly, with the combination of drugs inhibiting both CYP1A2 and CYP3A4 enzymes.

The inhibition of CYP1A2 by ciprofloxacin modestly reduces the elimination of lidocaine. Interindividual variation in the extent of this interaction exists, and, in some individuals, the interaction between lidocaine and ciprofloxacin may result in lidocaine toxicity.

The influence of CYP interactions on toxicity of local anaesthetics is theoretical concerning single-dose nerve blocks. The changes in lidocaine elimination after a single intravenous dose are usually not of major clinical significance. On the other hand, during continuous infusions, the decreased CL of lidocaine by the CYP1A2 inhibitors may play a role in increasing the risk of systemic toxicity. In particular, fluvoxamine is a risky drug in this respect because, in addition to its major inhibition of CYP1A2, it also causes some inhibition of CYP3A4. In patients using fluvoxamine, clinicians should consider reducing the dose in repeated administrations of large amounts of lidocaine within a short time or in long-term continuous regional anaesthetic blocks or intravenous infusions. This can be even more important in patients with compromised cardiac and liver function.

In conclusion, inhibitors of CYP1A2 and CYP3A4 are unlikely to affect the safety of a single injection of lidocaine. Clinicians should, however, be aware that in patients receiving a continuous lidocaine infusion or large doses of lidocaine in the oropharynx and concomitantly using potent inhibitors of both CYP1A2 and CYP3A4 high lidocaine concentrations can result.

CONCLUSIONS

The following conclusions can be drawn on the basis of the results of Studies I-VI:

Study I. Inhibition of CYP3A4 by erythromycin or itraconazole has only a minor effect on the pharmacokinetics of intravenous lidocaine.

Study II. Erythromycin and itraconazole increase exposure to oral lidocaine by 40-70%.

Study III. Itraconazole has no effect on the pharmacokinetics of inhaled lidocaine.

Study IV. Inhibition of CYP1A2 by fluvoxamine reduces the elimination of intravenous lidocaine. The concomitant use of fluvoxamine and the CYP3A4 inhibitor erythromycin further increases lidocaine concentration by decreasing its CL.

Study V. Fluvoxamine reduces the first-pass metabolism of ingested lidocaine. The concomitant use of fluvoxamine and erythromycin may further increase the exposure to oral lidocaine.

Study VI. Inhibition of CYP1A2 by ciprofloxacin reduces the elimination of lidocaine.

General. These findings underline the importance of studying drug interactions in humans to confirm or disprove predictions based on *in vitro* data. This work clarifies the role of CYP1A2, not CYP3A4 as previously thought, as the enzyme principally responsible for the metabolic clearance of lidocaine. Consequently, contrary to current beliefs, lidocaine and its primary metabolite MEGX cannot be considered as probes of CYP3A4 activity. Rather, they mainly reflect CYP1A2 activity.

APPENDIX 1. Pharmacokinetic variables for lidocaine following various routes of administration

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
CL (ml/min/kg)										
	6.1	4.6	9.4	epidural	6 mg/kg (mean)	20	Caesarean section	10		(Downing et al. 1997)
	6.4	4.8	10.7	i.v. 60 s	1 mg/kg		Healthy (21-26)	8	minor	(Swart et al. 2002)
	7.9	4.9	9.9	i.v. 120 s	1 mg/kg	10	Cardiac patients (30-74)	6		(Ha et al. 1996)
	8.5			i.v. inf. 36 h	100 mg bolus + 2 mg/min		Healthy (21-25)	7	minor	(Ochs et al. 1980)
	9.8			i.v. 30 s	1 mg/kg		Patients (18-51)	8	GA	(Finholt et al. 1986)
	9.8			i.v. 60 s	1 mg/kg		Healthy (53±12)	10	minor	(Orlando et al. 2003)
	10.3			i.v. inf. 22 h	2 mg/kg/h		Healthy (22-40)	11	minor	(Ujhelyi et al. 1993)
	11.1			i.v. 30 s	1 mg/kg		Children (0.5-3)	10	GA	(Finholt et al. 1986)
	12.0			i.v. 150 s	100	20	Healthy (19-36)	6	minor	(Perucca and Richens 1979)
	12.1			i.v. 60 s	1 mg/kg		Healthy (52±14)	10	minor	(Orlando et al. 2004)
	12.2*			perineal	400	20	Women in labour	23		(Cavalli et al. 2004)
	14.0	12.0	17.0	i.v. 2.5 min	100	20	Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
C_{max} (µg/ml)	0.14			intranasal	100		Healthy (50-65)	6		(Scavone et al. 1989)
	0.15	0.08		topical patch 18 h	2800	50	Healthy (50-79)	20	no	(Gammaitoni and Davis 2002)
	0.16			nebulized (ultrasonic)	400	40	Healthy (25-32)	5	no	(Chinn et al. 1977)
	0.19	0.12		topical patch 72 h	2800/24 h	50	Healthy (56-79)	10	no	(Gammaitoni et al. 2002)
	0.23	0.17		topical patch 72 h	2800/12 h	50	Healthy (56-79)	10	no	(Gammaitoni et al. 2002)

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
C_{max} ($\mu\text{g/ml}$)	0.29		0.45	nebulized via face mask	6 mg/kg	10	Healthy	10	no	(Parkes et al. 1997)
	0.32			spinal	75	50	Patient (54±6)	10	no	(Giasi et al. 1979)
	0.37	0.1	1.4	pharyngeal spray	120	100	Healthy (23-35)	8	minor	(Parish et al. 1987)
	0.42			epidural	75	20	Patients (44±7)	10	no	(Giasi et al. 1979)
	0.50	0.32	0.61	oral	200		Healthy (26-34)	6		(Bax et al. 1985)
	0.53			spinal	100	50	Patients (35±11)	10		(Burm et al. 1987)
	0.89	0.7	1.1	intercostal	60	10	Patients (28-72)	10		(Yokoyama et al. 1998)
		0.6	1.1	oral	500		Healthy (27-43)	5	minor	(Boyes et al. 1971)
	0.94	0.39	2.2	oral	750		Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
	1.4	1.1	2.2	subcutis	22 mg/kg w/e (mean)	3	Patients (47-68)	6	no	(Ramon et al. 2007)
	1.5	0.6	3.3	nebulized + spray-as-you-go	230-364	40 and 20	Patients (28-77)	19	no	(Jones et al. 1982)
	1.5		3.1	breast tissue	18 mg/kg (mean)	20 and 50	Patients (24-37)	10	no	(Rygnestad and Samdal 2000)
	1.6	0.6	3.5	i.m.	300	100	Patients	25	no	(Ryden et al. 1973)
	1.7	1.3	2.0	stellate	60	10	Patients (38-71)	10		(Yokoyama et al. 1998)
	1.8	1.6	2.1	tumescent technique	22 mg/kg w/e (mean)		Patients (29-40)	5	no	(Kenkel et al. 2004)
	2.0			i.v. 10 min	1 mg/kg		Healthy (20-43)	6	minor	(Feely et al. 1982)
	2.1	0.9	4.2	oropharynx + tracheobronchially	622 (mean)	20	Patients (57±3)	12	no	(Loukides et al. 2000)
	2.2			i.m.	4.5 mg/kg		Patients	21	no	(Koster and Dunning 1985)
	2.3	1.3	3.6	oral	750		Healthy (19-36)	6	minor	(Perucca and Richens 1979)

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
C_{max} ($\mu\text{g/ml}$)	2.4	1.5	5.1	brachial plexus	6.2 mg/kg (mean) w/e	15	Patients (22-43)	7	no	(Mazze and Dunbar 1966)
	2.9		9.6	bronchoscopy	9.3 mg/kg (mean)	10, 20 and 40	Patients	41	no	(Effhimiou et al. 1982)
	3.0			epidural	400 w/e	20	Patients	15		(Scott et al. 1972)
	3.0			i.v. inf. 36 h	100 mg bolus + 2 mg/min		Healthy (21-25)	7	minor	(Ochs et al. 1980)
	3.2*			perineal	400	20	Women in labour	23		(Cavalli et al. 2004)
	3.5	2.0	5.6	endotracheal	200	40	Patients	6	GA	(Chu et al. 1975)
	3.6			brachial plexus	450 w/e	20	Patients	5		(Wildsmith et al. 1977)
	3.7	2.4	6.3	i.v. 30 s	1 mg/kg		Children (0.5-3)	10	GA	(Finholt et al. 1986)
	3.8	0.7	10.0	endotracheal	6.2 mg/kg (mean)		Patients (23-71)	12	GA	(Bromage and Robson 1961)
	3.8			epidural (cervical)	200	20	Patients (41±13)	10	no	(Mayumi et al. 1983)
	4.1			epidural (thoracal)	200	20	Patients (41±7)	10	no	(Mayumi et al. 1983)
	4.3			epidural	400	20	Patients	23		(Scott et al. 1972)
	4.4			epidural inf. 5 h	200 mg/h w/e	20	Patients (52±3)	10	no	(Takasaki and Kajitani 1990)
	4.5			brachial plexus	450	20	Patients	5		(Wildsmith et al. 1977)
	4.8			epidural inf. 5 h	200 mg/h	20	Patients (56±3)	10	no	(Takasaki and Kajitani 1990)
	5.3			intercostal	400 w/e	20	Patients	12	GA	(Scott et al. 1972)
	5.8	2.9	9.5	epidural inf. 7 h (mean)	240 mg/h (mean)	20	Patients (75±8)	10	no	(Sprung et al. 2000)
	6.4	4.5	10.4	epidural	6 mg/kg (mean)	20	Caesarean section	10		(Downing et al. 1997)
	7.4			epidural	700	20	Patients	9	GA	(Braid and Scott 1966)
	6.5			intercostal	400	20	Patients	11	GA	(Scott et al. 1972)

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
$t_{1/2}$ (h)	58 min			i.v. 30 s	1 mg/kg		Children (0.5-3)	10	GA	(Finholt et al. 1986)
	70	49	115	i.v. 2.5 min	100	20	Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
	74	48	97	i.v. 2.5 min	100	20	Healthy (19-36)	6	minor	(Perucca and Richens 1979)
	77	53	107	oral	750		Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
	80	59	106	oral	750		Healthy (19-36)	6	minor	(Perucca and Richens 1979)
	1.6			intranasal	100		Healthy (50-65)	6		(Scavone et al. 1989)
	1.7			oral	200		Healthy (20-34)	7		(Miners et al. 1984)
	1.8			i.v. 10 min	1 mg/kg		Healthy (20-43)	6	minor	(Feely et al. 1982)
	114 min	89	156	epidural	6 mg/kg (mean)	20	Caesarean section	10		(Downing et al. 1997)
	1.9	1.4	2.3	i.v. 2 min	120		Healthy (23-37)	8	minor	(Thomson et al. 1987)
	2.1	1.2	3.7	i.v. 60 s	1 mg/kg		Healthy (21-26)	8	minor	(Swart et al. 2002)
	130 min	111	155	i.v. 120 s	1 mg/kg	10	Cardiac patients (30-74)	6		(Ha et al. 1996)
	131 min			spinal	100	50	Patients (35±11)	10		(Burm et al. 1987)
	2.2			i.v. 60 s	1 mg/kg		Healthy (52±14)	10	minor	(Orlando et al. 2004)
	2.2			i.v. 60 s	1 mg/kg		Healthy (53±12)	10	minor	(Orlando et al. 2003)
	3.0*			perineal	400	20	Women in labour	23		(Cavalli et al. 2004)
	6.2	4.5	7.8	subcutis	22 mg/kg w/e (mean)	3	Patients (47-68)	6	no	(Ramon et al. 2007)
t_{max} (min)	3.4	2	5	stellate	60	10	Patients (38-71)	10		(Yokoyama et al. 1998)
	6.9	6	8	epidural	60	10	Patients (38-79)	10		(Yokoyama et al. 1998)
	7.9	5	10	intercostal	60	10	Patients (28-72)	10		(Yokoyama et al. 1998)
	10			im	4.5 mg/kg		Patients	21	no	(Koster and Dunning 1985)
	10			epidural (cervical)	200	20	Patients (41±13)	10	no	(Mayumi et al. 1983)

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
t_{max} (min)	10			epidural (thoracal)	200	20	Patients (41±7)	10	no	(Mayumi et al. 1983)
	13	5	25	endotracheal	6.2 mg/kg (mean)		Patients (23-71)	12	GA	(Bromage and Robson 1961)
	15			brachial plexus	450	20	Patients	5		(Wildsmith et al. 1977)
	15*			perineal	400	20	Women in labour	23		(Cavalli et al. 2004)
	20			brachial plexus	450 w/e	20	Patients	5		(Wildsmith et al. 1977)
	20			epidural	400	20	Patients	23		(Scott et al. 1972)
	20	15	20	endotracheal	200	40	Patients	6	GA	(Chu et al. 1975)
	24	5	60	pharynx spray	120	100	Healthy (23-35)	8	minor	(Parish et al. 1987)
	30			i.m.	300	100	Patients	25	no	(Ryden et al. 1973)
	31	15	40	epidural	6 mg/kg (mean)	20	Caesarean section	10		(Downing et al. 1997)
	33	20	50	oral	200		Healthy (26-34)	6		(Bax et al. 1985)
	45	30	90	oral	750		Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
	47	30	90	oral	750		Healthy (19-36)	6	minor	(Perucca and Richens 1979)
	0.9 h			intranasal	100		Healthy (50-65)	6		(Scavone et al. 1989)
	71			spinal	100	50	Patients (35±11)	10		(Burm et al. 1987)
	6 h	1 h	10 h	topical patch 72 h	2800/12 h	50	Healthy (56-79)	10	no	(Gammaioni et al. 2002)
	7.3 h	4 h	12 h	breast tissue	18 mg/kg (mean)	20 and 50	Patients (24-37)	10	no	(Rygnestad and Samdal 2000)
	9.3 h	6 h	10 h	subcutis	22 mg/kg w/e (mean)	3	Patients (47-68)	6	no	(Ramon et al. 2007)
	10 h	6 h	15 h	topical patch 72 h	2800/24 h	50	Healthy (56-79)	10	no	(Gammaioni et al. 2002)
	12.8 h	8 h	16 h	tumescent technique	22 mg/kg w/e (mean)		Patients (29-40)	5	no	(Kenkel et al. 2004)
	18 h*	9 h	22 h	topical patch 18 h	2800	50	Healthy (50-79)	20	no	(Gammaioni and Davis 2002)

Variable	Mean	Lowest	Highest	Route, injection time	Dose (mg)	Concentration (mg/ml)	Subjects (age in years)	N	Toxicity reported	Reference
V_{ss} (l/kg)	1.2	0.9	1.6	i.v. 120 s	1 mg/kg	10	Cardiac patients (30-74)	6		(Ha et al. 1996)
	1.3	0.8	1.8	i.v. 2.5 min	100	20	Healthy (19-36)	6	minor	(Perucca and Richens 1979)
	1.5			i.v. 60 s	1 mg/kg		Healthy (53±12)	10	minor	(Orlando et al. 2003)
	1.5	1.0	3.0	i.v. 2.5 min	100	20	Epileptic patients (22-37)	6	minor	(Perucca and Richens 1979)
	1.9			i.v. 60 s	1 mg/kg		Healthy (52±14)	10	minor	(Orlando et al. 2004)

Values indicated with an asterisk are median values. CL = systemic plasma clearance, C_{max} = peak plasma concentration, GA = patients under general anaesthesia, $t_{1/2}$ = elimination half-life, t_{max} = time to peak concentration, V_{ss} = steady-state volume of distribution, w/e = with epinephrine.

APPENDIX 2. The “well-stirred” model

The “well-stirred” model states that

$$CL_{b,H} = \frac{Q_H \cdot CL_{int} \cdot fu_b}{Q_H + CL_{int} \cdot fu_b}$$

, where $CL_{b,H}$ is the hepatic clearance from blood, Q_H the hepatic blood flow, CL_{int} the intrinsic clearance and fu_b the fraction unbound in blood (Rowland and Tozer 1995). Thus, if we assume that normal hepatic blood flow is 1.6 l/min, that the free unbound fraction of lidocaine in blood is 0.36 and that the blood to plasma concentration ratio is 0.8 (Tucker and Mather 1979) and then use the value of lidocaine CL calculated in Study I (mean value 0.9 l/min), we can determine how the change in CL_{int} affects the $CL_{b,H}$ (Table 5). All other pharmacokinetic variables are assumed to remain unchanged by erythromycin or itraconazole.

Table 5. *Theoretical decrease in lidocaine blood clearance ($CL_{b,H}$) after the decrease in intrinsic lidocaine clearance (CL_{int}), as might be produced by the concomitant administration of erythromycin or itraconazole.*

% decrease in CL_{int}	% decrease in $CL_{b,H}$
5	1.5
10	3.2
25	9.0
50	22.9
75	47.1
90	72.8
95	84.9

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REFERENCES

- Al-Asady SA, Black GL, Lennard MS, Tucker GT, Woods HF.** Inhibition of lignocaine metabolism by beta-adrenoceptor antagonists in rat and human-liver microsomes. *Xenobiotica* 1989; 19: 929-44.
- Allenmark S, Edebo A, Lindgren K.** Determination of itraconazole in serum with high-performance liquid-chromatography and fluorescence detection. *J Chromatogr A* 1990; 532: 203-6.
- Alvarez-Elcoro S, Enzler MJ.** The macrolides: Erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; 74: 613-34.
- Aminimanizani A, Beringer P, Jelliffe R.** Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001; 40: 169-87.
- Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, Gold MS, Porreca F, Strichartz GR.** The role of sodium channels in chronic inflammatory and neuropathic pain. *J Pain* 2006; 7: S1-29.
- Anderson GD.** Sex and racial differences in pharmacological response: Where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J Womens Health* 2005; 14: 19-29.
- Anttila S, Hukkanen J, Hakkola J, Stjernvall T, Beaune P, Edwards RJ, Boobis AR, Pelkonen O, Raunio H.** Expression and localization of CYP3A4 and CYP3A5 in human lung. *Am J Respir Cell Mol Biol* 1997; 16: 242-9.
- Aranko K, Luurila H, Backman JT, Neuvonen PJ, Olkkola KT.** The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; 38: 363-7.
- Atanassoff PG, Hartmannsgruber MW.** Central nervous system side effects are less important after iv regional anesthesia with ropivacaine 0.2% compared to lidocaine 0.5% in volunteers. *Can J Anaesth* 2002; 49: 169-72.
- Attal N, Gaude V, Brasseur L, Dupuy M, Guirimand F, Parker F, Bouhassira D.** Intravenous lidocaine in central pain: A double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; 54: 564-74.
- Back DJ, Tjia JF.** Comparative effects of the antimycotic drugs ketoconazole, fluconazole, itraconazole and terbinafine on the metabolism of cyclosporine by human liver-microsomes. *Br J Clin Pharmacol* 1991; 32: 624-6.

- Backman JT, Kivistö KT, Olkkola KT, Neuvonen PJ.** The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol* 1998; 54: 53-8.
- Backman JT, Karjalainen MJ, Neuvonen M, Laitila J, Neuvonen PJ.** Rofecoxib is a potent inhibitor of cytochrome P450 1A2: Studies with tizanidine and caffeine in healthy subjects. *Br J Clin Pharmacol* 2006; 62: 345-57.
- Baldwin SJ, Clarke SE, Chenery RJ.** Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 1999; 48: 424-32.
- Bargetzi MJ, Aoyama T, Gonzalez FJ, Meyer UA.** Lidocaine metabolism in human-liver microsomes by cytochrome-P450III A4. *Clin Pharmacol Ther* 1989; 46: 521-7.
- Bartkowski RR, Goldberg ME, Larijani GE, Boerner T.** Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; 46: 99-102.
- Batty KT, Davis TME, Ilett KF, Duce LJ, Langton SR.** The effect of ciprofloxacin on theophylline pharmacokinetics in healthy-subjects. *Br J Clin Pharmacol* 1995; 39: 305-11.
- Bax NDS, Tucker GT, Lennard MS, Woods HF.** The impairment of lignocaine clearance by propranolol - major contribution from enzyme-inhibition. *Br J Clin Pharmacol* 1985; 19: 597-603.
- Benowitz NL, Meister W.** Clinical pharmacokinetics of lignocaine. *Clin Pharmacokinet* 1978; 3: 177-201.
- Bensoussan C, Delaforge M, Mansuy D.** Particular ability of cytochromes P450 3A to form inhibitory P450-iron-metabolite complexes upon metabolic oxidation of aminodrugs. *Biochem Pharmacol* 1995; 49: 591-602.
- Berggren S, Hoogstraate J, Fagerholm U, Lennernas H.** Characterization of jejunal absorption and apical efflux of ropivacaine, lidocaine and bupivacaine in the rat using in situ and in vitro absorption models. *Eur J Pharm Sci* 2004; 21: 553-60.
- Bermúdez M, Fuster JL, Llinares E, Galera A, Gonzalez C.** Itraconazole-related increased vincristine neurotoxicity: Case report and review of literature. *J Pediatr Hematol Oncol* 2005; 27: 389-92.
- Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, Lindström L, Rodríguez de la Rubia I, Ramos S, Benitez J.** Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol* 1994; 38: 471-3.
- Bertz RJ, Granneman GR.** Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet* 1997; 32: 210-58.

- Bhise S, Dias R.** Effect of erythromycin and rifampicin on monoethylglycinexylidide test. *Indian J Pharmacol* 2008; 40: 84-6.
- Bidstrup TB, Bjørnsdottir I, Sidelmann UG, Thomsen MS, Hansen KT.** CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; 56: 305-14.
- Boyes RN, Scott DB, Jebson PJ, Godman MJ, Julian DG.** Pharmacokinetics of lidocaine in man. *Clin Pharmacol Ther* 1971; 12: 105-16.
- Braid DP, Scott DB.** Dosage of lignocaine in epidural block in relation to toxicity. *Br J Anaesth* 1966; 38: 596-602.
- British Thoracic Society Bronchoscopy Guidelines Committee, a Subcommittee of Standards of Care Committee of British Thoracic Society.** British thoracic society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001; 56: 1-21.
- Brockmüller J, Roots I.** Assessment of liver metabolic function. Clinical implications. *Clin Pharmacokinet* 1994; 27: 216-48.
- Bromage PR, Robson JG.** Concentrations of lignocaine in the blood after intravenous, intramuscular epidural and endotracheal administration. *Anaesthesia* 1961; 16: 461-78.
- Burm AG, van Kleef JW, Gladines MP, van Duinen M, Spierdijk J.** Spinal anesthesia with hyperbaric lidocaine and bupivacaine: Effects of epinephrine on the plasma concentration profiles. *Anesth Analg* 1987; 66: 1104-8.
- Burney RG, Difazio CA, Peach MJ, Petrie KA, Silvester MJ.** Anti-arrhythmic effects of lidocaine metabolites. *Am Heart J* 1974; 88: 765-9.
- Carrillo JA, Dahl ML, Svensson JO, Alm C, Rodriguez I, Bertilsson L.** Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin Pharmacol Ther* 1996; 60: 183-90.
- Cassuto J, Sinclair R, Bonderovic M.** Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand* 2006; 50: 265-82.
- Cavalli RD, Lanchote VL, Duarte G, Dantas ECM, de Prado MFM, de Duarte LB, da Cunha SP.** Pharmacokinetics and transplacental transfer of lidocaine and its metabolite for perineal analgesic assistance to pregnant women. *Eur J Clin Pharmacol* 2004; 60: 569-74.
- Champers HF.** Protein synthesis inhibitors and miscellaneous antibacterial agents. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. USA: McGraw-Hill; 2006. p. 1173-202.

- Chinn WM, Zavala DC, Ambre J.** Plasma levels of lidocaine following nebulized aerosol administration. *Chest* 1977; 71: 346-8.
- Christensen M, Tybring G, Mihara K, Yasui-Furokori N, Carrillo JA, Ramos SI, Andersson K, Dahl ML, Bertilsson L.** Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). *Clin Pharmacol Ther* 2002; 71: 141-52.
- Christie JM, Valdes C, Markowsky SJ.** Neurotoxicity of lidocaine combined with mexiletine. *Anesth Analg* 1993; 77: 1291-4.
- Chu SS, Rah KH, Brannan MD, Cohen JL.** Plasma concentration of lidocaine after endotracheal spray. *Anesth Analg* 1975; 54: 438-41.
- Covino BG.** Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; 58: 701-16.
- Dai D, Zeldin DC, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI, Goldstein JA.** Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. *Pharmacogenetics* 2001; 11: 597-607.
- Daly AK.** Significance of the minor cytochrome P450 3A isoforms. *Clin pharmacokinet* 2006; 45: 13-31.
- Davis R, Markham A, Balfour JA.** Ciprofloxacin - an updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; 51: 1019-74.
- Dawling S, Flanagan RJ, Widdop B.** Fatal lignocaine poisoning - report of two cases and review of the literature. *Hum Toxicol* 1989; 8: 389-92.
- De Beule K, Van Gestel J.** Pharmacology of itraconazole. *Drugs* 2001; 61: 27-37.
- Demedts P, Wauters A, Franck F, Neels H.** Simultaneous determination of lidocaine, bupivacaine, and their two main metabolites using gas chromatography and a nitrogen-phosphorus detector: Selection of stationary phase and chromatographic conditions. *Ther Drug Monit* 1996; 18: 208-9.
- Desta Z, Zhao X, Shin JG, Flockhart DA.** Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* 2002; 41: 913-58.
- DeToledo JC.** Lidocaine and seizures. *Ther Drug Monit* 2000; 22: 320-2.
- DiFazio CA.** Local anesthetics: Action, metabolism, and toxicity. *Otolaryngol Clin North Am* 1981; 14: 515-9.
- Downing JW, Johnson HV, Gonzalez HF, Arney TL, Herman NL, Johnson RF.** The pharmacokinetics of epidural lidocaine and bupivacaine during cesarean section. *Anesth Analg* 1997; 84: 527-32.

Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000; 38: 41-57.

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; 132: 237-51.

Efthimiou J, Higenbottam T, Holt D, Cochrane GM. Plasma concentrations of lignocaine during fibreoptic bronchoscopy. *Thorax* 1982; 37: 68-71.

Elmas T, Mavioglu O, Oztekin S, Elar Z, Guven H. The effect of propofol (anesthetic and inhibitor of CYP3A4) on serum lidocaine concentrations in smokers and chronic alcohol consumers. *Int J Clin Pharmacol Ther* 2003; 41: 182-4.

Elvin AT, Cole AF, Pieper JA, Rolbin SH, Lalka D. Effect of food on lidocaine kinetics: Mechanism of food-related alteration in high intrinsic clearance drug elimination. *Clin Pharmacol Ther* 1981; 30: 455-60.

Eriksson UG, Dorani H, Karlsson J, Fritsch H, Hoffmann KJ, Olsson L, Sarich TC, Wall U, Schützer KM. Influence of erythromycin on the pharmacokinetics of ximelagatran may involve inhibition of P-glycoprotein-mediated excretion. *Drug Metab Dispos* 2006; 34: 775-82.

Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: Why, how, and when? *Basic Clin Pharmacol Toxicol* 2005; 97: 125-34.

Fabrazzo M, La Pia S, Monteleone P, Mennella R, Esposito G, Pinto A, Maj M. Fluvoxamine increases plasma and urinary levels of clozapine and its major metabolites in a time- and dose-dependent manner. *J Clin Psychopharmacol* 2000; 20: 708-10.

Falany CN, Falany JL, Wang J, Hedström J, von Euler Chelpin H, Swedmark S. Studies on sulfation of synthesized metabolites from the local anesthetics ropivacaine and lidocaine using human cloned sulfotransferases. *Drug Metab Dispos* 1999; 27: 1057-63.

Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. *N Engl J Med* 1981; 304: 692-5.

Feely J, Wilkinson GR, McAllister CB, Wood AJ. Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 1982; 96: 592-4.

Figgitt DP, McClellan KJ. Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders. *Drugs* 2000; 60: 925-54.

Finholt DA, Stirt JA, DiFazio CA, Moscicki JC. Lidocaine pharmacokinetics in children during general anesthesia. *Anesth Analg* 1986; 65: 279-82.

Fischer LG, Bremer M, Coleman EJ, Conrad B, Krumm B, Gross A, Hollmann MW, Mandell G, Durieux ME. Local anesthetics attenuate lysophosphatidic acid-induced priming in human neutrophils. *Anesth Analg* 2001; 92: 1041-7.

Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; 46: 35-9.

Fromm MF. Importance of P-glycoprotein at blood-tissue barriers. *Trends Pharmacol Sci* 2004; 25: 423-9.

Fuhr U, Anders EM, Mahr G, Sorgel F, Staib AH. Inhibitory potency of quinolone antibacterial agents against cytochrome-P450ia2 activity invivo and invitro. *Antimicrobial Agents Chemother* 1992; 36: 942-8.

Funao T, Oda Y, Tanaka K, Asada A. The P-glycoprotein inhibitor quinidine decreases the threshold for bupivacaine-induced, but not lidocaine-induced, convulsions in rats. *Can J Anaesth* 2003; 50: 805-11.

Funck-Brentano C, Becquemont L, Lenevu A, Roux A, Jaillon P, Beaune P. Inhibition by omeprazole of proguanil metabolism: Mechanism of the interaction in vitro and prediction of in vivo results from the in vitro experiments. *J Pharmacol Exp Ther* 1997; 280: 730-8.

Gajraj NM, Pennant JH, Watcha MF. Eutectic mixture of local anesthetics (EMLA) cream. *Anesth Analg* 1994; 78: 574-83.

Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother* 2002; 36: 236-40.

Gammaitoni AR, Alvarez NA, Galer BS. Pharmacokinetics and safety of continuously applied lidocaine patches 5%. *Am J Health-Syst Pharm* 2002; 59: 2215-20.

Gan J, Skipper PL, Tannenbaum SR. Oxidation of 2,6-dimethylaniline by recombinant human cytochrome P450s and human liver microsomes. *Chem Res Toxicol* 2001; 14: 672-7.

Gascon MP, Dayer P. In vitro forecasting of drugs which may interfere with the biotransformation of midazolam. *Eur J Clin Pharmacol* 1991; 41: 573-8.

Geraets DR, Scott SD, Ballew KA. Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; 26: 1380-1.

Gerbal-Chaloin S, Pascussi JM, Pichard-Garcia L, Daujat M, Waechter F, Fabre JM, Carrere N, Maurel P. Induction of CYP2C genes in human hepatocytes in primary culture. *Drug Metab Dispos* 2001; 29: 242-51.

Gianelly R, von der Groeben JO, Spivack AP, Harrison DC. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *N Engl J Med* 1967; 277: 1215-9.

Giasi RM, D'Agostino E, Covino BG. Absorption of lidocaine following subarachnoid and epidural administration. *Anesth Analg* 1979; 58: 360-3.

Gonzalez del Rey J, Wason S, Druckenbrod RW. Lidocaine overdose: Another preventable case? *Pediatr Emerg Care* 1994; 10: 344-6.

Granfors MT, Backman JT, Laitila J, Neuvonen PJ. Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* 2005; 78: 400-11.

Granfors MT, Backman JT, Laitila J, Neuvonen PJ. Tizanidine is mainly metabolized by cytochrome P450 1A2 in vitro. *Br J Clin Pharmacol* 2004; 57: 349-53.

Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; 37: 310-44.

Greenblatt DJ, von Moltke LL. Gender has a small but statistically significant effect on clearance of CYP3A substrate drugs. *J Clin Pharmacol* 2008; 48: 1350-5.

Groudine SB, Fisher HA, Kaufman RP, Jr, Patel MK, Wilkins LJ, Mehta SA, Lumb PD. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998; 86: 235-9.

Gunes A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: Influence of environmental factors and genetic polymorphisms. *Pharmacogenomics* 2008; 9: 625-37.

Gupta AK, Chwetzoff E, Del Rosso J, Baran R. Hepatic safety of itraconazole. *J Cutan Med Surg* 2002; 6: 210-3.

Ha HR, Candinas R, Stieger B, Meyer UA, Follath F. Interaction between amiodarone and lidocaine. *J Cardiovasc Pharmacol* 1996; 28: 533-9.

Hamano S, Sugiyama N, Yamashita S, Tanaka M, Hayakawa M, Minamitani M, Yoshinari S, Eto Y. Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; 48: 220-2.

Hamaoka N, Oda Y, Hase I, Mizutani K, Nakamoto T, Ishizaki T, Asada A. Propofol decreases the clearance of midazolam by inhibiting CYP3A4: An in vivo and in vitro study. *Clin Pharmacol Ther* 1999; 66: 110-7.

Hemeryck A, De Vriendt C, Belpaire FM. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors: In vitro studies with tolbutamide and (S)-warfarin using human liver microsomes. *Eur J Clin Pharmacol* 1999; 54: 947-51.

Hermansson J, Glaumann H, Karlen B, von Bahr C. Metabolism of lidocaine in human liver in vitro. *Acta Pharmacol Toxicol* 1980; 47: 49-52.

Hess GP, Walson PD. Seizures secondary to oral viscous lidocaine. *Ann Emerg Med* 1988; 17: 725-7.

Ho RH, Kim RB. Transporters and drug therapy: Implications for drug disposition and disease. *Clin Pharmacol Ther* 2005; 78: 260-77.

Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: A new therapeutic indication? *Anesthesiology* 2000; 93: 858-75.

Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR, Jr. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; 52: 231-8.

Honig PK, Wortham DC, Hull R, Zamani K, Smith JE, Cantilena LR. Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. *J Clin Pharmacol* 1993; 33: 1201-6.

Hooper DC. Mode of action of fluoroquinolones. *Drugs* 1999; 58: 6-10.

Hunt LW, Frigas E, Butterfield JH, Kita H, Blomgren J, Dunnette SL, Offord KP, Gleich GJ. Treatment of asthma with nebulized lidocaine: A randomized, placebo-controlled study. *J Allergy Clin Immunol* 2004; 113: 853-9.

Härtter S, Ursing C, Morita S, Tybring G, von Bahr C, Christensen M, Rojdmarm S, Bertilsson L. Orally given melatonin may serve as a probe drug for cytochrome P450 1A2 activity in vivo: A pilot study. *Clin Pharmacol Ther* 2001; 70: 10-6.

Imaoka S, Enomoto K, Oda Y, Asada A, Fujimori M, Shimada T, Fujita S, Guengerich FP, Funae Y. Lidocaine metabolism by human cytochrome-P-450s purified from hepatic microsomes - comparison of those with rat hepatic cytochrome-P-450s. *J Pharmacol Exp Ther* 1990; 255: 1385-91.

Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoeconomic and clinical aspects. *Pharmacol Ther* 2007; 116: 496-526.

Inglis AM, Sheth SB, Hursting MJ, Tenero DM, Graham AM, DiCicco RA. Investigation of the interaction between argatroban and acetaminophen, lidocaine, or digoxin. *Am J Health-Syst Pharm* 2002; 59: 1258-66.

Inomata S, Nagashima A, Osaka Y, Tanaka E, Toyooka H. Effects of clonidine on lidocaine metabolism in human or rat liver microsomes. *J Anesth* 2003a; 17: 281-3.

Inomata S, Nagashima A, Osaka Y, Kazama T, Tanaka E, Sato S, Toyooka H. Propofol inhibits lidocaine metabolism in human and rat liver microsomes. *J Anesth* 2003b; 17: 246-50.

Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE. Role of itraconazole metabolites in CYP3A4 inhibition. *Drug Metab Dispos* 2004; 32: 1121-31.

Isoherranen N, Ludington SR, Givens RC, Lamba JK, Pusek SN, Dees EC, Blough DK, Iwanaga K, Hawke RL, Schuetz EG, Watkins PB, Thummel KE, Paine MF. The influence of CYP3A5 expression on the extent of hepatic CYP3A inhibition is substrate-dependent: An in vitro-in vivo evaluation. *Drug Metab Dispos* 2008; 36: 146-54.

Jaakkola T, Laitila J, Neuvonen PJ, Backman JT. Pioglitazone is metabolised by CYP2C8 and CYP3A4 in vitro: Potential for interactions with CYP2C8 inhibitors. *Basic Clin Pharmacol Toxicol* 2006a; 99: 44-51.

Jaakkola T, Backman JT, Neuvonen M, Niemi M, Neuvonen PJ. Montelukast and zafirlukast do not affect the pharmacokinetics of the CYP2C8 substrate pioglitazone. *Eur J Clin Pharmacol* 2006b; 62: 503-9.

Jackson JE, Bentley JB, Glass SJ, Fukui T, Gandolfi AJ, Plachetka JR. Effects of histamine-2 receptor blockade on lidocaine kinetics. *Clin Pharmacol Ther* 1985; 37: 544-8.

Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. *Ther Drug Monit* 1997a; 19: 609-13.

Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. *Clin Pharmacol Ther* 1997b; 61: 410-5.

Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. *Eur J Clin Pharmacol* 2003; 58: 653-7.

Jokinen MJ, Ahonen J, Neuvonen PJ, Olkkola KT. Effect of clarithromycin and itraconazole on the pharmacokinetics of ropivacaine. *Pharmacol Toxicol* 2001; 88: 187-91.

Jokinen MJ, Ahonen J, Neuvonen PJ, Olkkola KT. The effect of erythromycin, fluvoxamine, and their combination on the pharmacokinetics of ropivacaine. *Anesth Analg* 2000; 91: 1207-12.

Jones DA, McBurney A, Stanley PJ, Tovey C, Ward JW. Plasma concentrations of lignocaine and its metabolites during fibreoptic bronchoscopy. *Br J Anaesth* 1982; 54: 853-7.

Joseph PD, Guengerich FP, Miners JO. "Phase I and phase II" drug metabolism: Terminology that we should phase out? *Drug metab rev* 2005; 37: 575-80.

Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, Joris JL. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; 106: 11-8.

- Kajosaari LI, Laitila J, Neuvonen PJ, Backman JT.** Metabolism of repaglinide by CYP2C8 and CYP3A4 in vitro: Effect of fibrates and rifampicin. *Basic Clin Pharmacol Toxicol* 2005; 97: 249-56.
- Kang BC, Yang CQ, Cho HK, Suh OK, Shin WG.** Influence of fluconazole on the pharmacokinetics of omeprazole in healthy volunteers. *Biopharm Drug Dispos* 2002; 23: 77-81.
- Kantola T, Kivistö KT, Neuvonen PJ.** Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; 64: 177-82.
- Kashuba AD, Nafziger AN.** Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. *Clin Pharmacokinet* 1998; 34: 203-18.
- Kashuba AD, Nafziger AN, Kearns GL, Leeder JS, Gotschall R, Rocci ML, Jr, Kulawy RW, Beck DJ, Bertino JS, Jr.** Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. *Clin Pharmacol Ther* 1998; 64: 257-68.
- Keenaghan JB, Boyes RN.** The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. *J Pharmacol Exp Ther* 1972; 180: 454-63.
- Keidar S, Grenadier E, Palant A.** Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* 1982; 104: 1384-5.
- Kenkel JM, Lipschitz AH, Shepherd G, Armstrong VW, Streit F, Oellerich M, Luby M, Rohrich RJ, Brown SA.** Pharmacokinetics and safety of lidocaine and monoethylglycinexylidide in liposuction: A microdialysis study. *Plast Reconstr Surg* 2004; 114: 516-24.
- Kennedy JM, van Rij AM, Spears GF, Pettigrew RA, Tucker IG.** Polypharmacy in a general surgical unit and consequences of drug withdrawal. *Br J Clin Pharmacol* 2000; 49: 353-62.
- Kirchheiner J, Brockmüller J.** Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin Pharmacol Ther* 2005; 77: 1-16.
- Kivistö KT, Kantola T, Neuvonen PJ.** Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998; 46: 49-53.
- Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ.** Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; 62: 348-54.
- Kivistö KT, Bookjans G, Fromm MF, Griese EU, Munzel P, Kroemer HK.** Expression of CYP3A4, CYP3A5 and CYP3A7 in human duodenal tissue. *Br J Clin Pharmacol* 1996; 42: 387-9.
- Klotz U, Schwab M, Treiber G.** CYP2C19 polymorphism and proton pump inhibitors. *Basic Clin Pharmacol Toxicol* 2004; 95: 2-8.
- Kopacz DJ, Bernards CM.** Effect of clonidine on lidocaine clearance in vivo: A microdialysis study in humans. *Anesthesiology* 2001; 95: 1371-6.

- Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M, Hering W.** Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth Analg* 2004; 98: 1050-5.
- Koster RW, Dunning AJ.** Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; 313: 1105-10.
- Krishna DR, Klotz U.** Extrahepatic metabolism of drugs in humans. *Clin Pharmacokinet* 1994; 26: 144-60.
- Kucera IJ, Lambert TJ, Klein JA, Watkins RG, Hoover JM, Kaye AD.** Liposuction: Contemporary issues for the anesthesiologist. *J Clin Anesth* 2006; 18: 379-87.
- Kundra P, Kutralam S, Ravishankar M.** Local anaesthesia for awake fiberoptic nasotracheal intubation. *Acta Anaesthesiol Scand* 2000; 44: 511-6.
- Kurnik D, Wood AJ, Wilkinson GR.** The erythromycin breath test reflects P-glycoprotein function independently of cytochrome P450 3A activity. *Clin Pharmacol Ther* 2006; 80: 228-34.
- Laakso S, Scheinin M, Anttila M.** Determination of erythromycin base and 2'-acetylerythromycin in human plasma using high-performance liquid chromatography with electrochemical detection. *J Chromatogr A* 1990; 526: 475-86.
- Lamba JK, Lin YS, Schuetz EG, Thummel KE.** Genetic contribution to variable human CYP3A-mediated metabolism. *Adv Drug Deliv Rev* 2002; 54: 1271-94.
- Lamberg TS, Kivistö KT, Laitila J, Mårtensson K, Neuvonen PJ.** The effect of fluvoxamine on the pharmacokinetics and pharmacodynamics of buspirone. *Eur J Clin Pharmacol* 1998; 54: 761-6.
- Langmack EL, Martin RJ, Pak J, Kraft M.** Serum lidocaine concentrations in asthmatics undergoing research bronchoscopy. *Chest* 2000; 117: 1055-60.
- Larsen JT, Hansen LL, Spigset O, Brøsen K.** Fluvoxamine is a potent inhibitor of tacrine metabolism in vivo. *Eur J Clin Pharmacol* 1999; 55: 375-82.
- Le KT, Maurice H, du Souich P.** First-pass metabolism of lidocaine in the anesthetized rabbit - contribution of the small intestine. *Drug Metab Disposition* 1996; 24: 711-6.
- Lev R, Rosen P.** Prophylactic lidocaine use preintubation: A review. *J Emerg Med* 1994; 12: 499-506.
- Lewis DF.** 57 varieties: The human cytochromes P450. *Pharmacogenomics* 2004; 5: 305-18.
- Lilja JJ, Backman JT, Laitila J, Luurila H, Neuvonen PJ.** Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther* 2003; 73: 192-8.

- Lin JH.** CYP induction-mediated drug interactions: In vitro assessment and clinical implications. *Pharm Res* 2006; 23: 1089-116.
- Lin JH, Lu AY.** Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998; 35: 361-90.
- Liu YT, Hao HP, Liu CX, Wang GJ, Xie HG.** Drugs as CYP3A probes, inducers, and inhibitors. *Drug Metab Rev* 2007; 39: 699-721.
- Lorec AM, Bruguerolle B, Attolini L, Roucoules X.** Rapid simultaneous determination of lidocaine, bupivacaine, and their 2 main metabolites using capillary gas-liquid-chromatography with nitrogen phosphorus detector. *Ther Drug Monit* 1994; 16: 592-5.
- Loukides S, Katsoulis K, Tsarpalis K, Panagou P, Kalogeropoulos N.** Serum concentrations of lignocaine before, during and after fiberoptic bronchoscopy. *Respiration* 2000; 67: 13-7.
- Luo G, Guenther T, Gan L-, Humphreys WG.** CYP3A4 induction by xenobiotics: Biochemistry, experimental methods and impact on drug discovery and development. *Curr drug metab* 2004; 5: 483-505.
- Läpple F, von Richter O, Fromm MF, Richter T, Thon KP, Wisser H, Griese EU, Eichelbaum M, Kivistö KT.** Differential expression and function of CYP2C isoforms in human intestine and liver. *Pharmacogenetics* 2003; 13: 565-75.
- Madsen H, Enggaard TP, Hansen LL, Klitgaard NA, Brøsen K.** Fluvoxamine inhibits the CYP2C9 catalyzed biotransformation of tolbutamide. *Clin Pharmacol Ther* 2001; 69: 41-7.
- Maeda K, Sugiyama Y.** Impact of genetic polymorphisms of transporters on the pharmacokinetic, pharmacodynamic and toxicological properties of anionic drugs. *Drug metab pharmacokinet* 2008; 23: 223-35.
- Maeda Y, Funakoshi S, Nakamura M, Fukuzawa M, Kugaya Y, Yamasaki M, Tsukiai S, Murakami T, Takano M.** Possible mechanism for pharmacokinetic interaction between lidocaine and mexiletine. *Clin Pharmacol Ther* 2002; 71: 389-97.
- Marret E, Rolin M, Beaussier M, Bonnet F.** Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* 2008; 95: 1331-8.
- Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, Mazoit JX, Chauvin M, Bouhassira D, Fletcher D.** Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology* 2008; 109: 118-23.

- Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM, Agundez JA.** The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. *Br J Clin Pharmacol* 2005; 59: 62-9.
- Matharu MS, Cohen AS, Goadsby PJ.** SUNCT syndrome responsive to intravenous lidocaine. *Cephalalgia* 2004; 24: 985-92.
- Mather LE, Chang DH.** Cardiotoxicity with modern local anaesthetics: Is there a safer choice? *Drugs* 2001; 61: 333-42.
- Mayumi T, Dohi S, Takahashi T.** Plasma concentrations of lidocaine associated with cervical, thoracic, and lumbar epidural anesthesia. *Anesth Analg* 1983; 62: 578-80.
- Mazze RI, Dunbar RW.** Plasma lidocaine concentrations after caudal, lumbar epidural, axillary block, and intravenous regional anesthesia. *Anesthesiology* 1966; 27: 574-9.
- Meyer UA.** Overview of enzymes of drug metabolism. *J pharmacokinet biopharm* 1996; 24: 449.
- Miller CD, Warren SJ.** I.v. lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. *Br J Anaesth* 1990; 65: 216-9.
- Milman N, Laub M, Munch EP, Angelo HR.** Serum concentrations of lignocaine and its metabolite monoethylglycinexylidide during fibre-optic bronchoscopy in local anaesthesia. *Respir Med* 1998; 92: 40-3.
- Miners JO, Birkett DJ.** Cytochrome P4502C9: An enzyme of major importance in human drug metabolism. *Br J Clin Pharmacol* 1998; 45: 525-38.
- Miners JO, Wing LMH, Lillywhite KJ, Smith KJ.** Failure of therapeutic doses of beta-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine. *Br J Clin Pharmacol* 1984; 18: 853-60.
- Moeini HA, Soltani HA, Gholami AR, Masoudpour H.** The effect of lidocaine and sufentanil in preventing intraocular pressure increase due to succinylcholine and endotracheal intubation. *Eur J Anaesthesiol* 2006; 23: 739-42.
- Muirhead GJ, Faulkner S, Harness JA, Taubel J.** The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br J Clin Pharmacol* 2002; 53: 37S-43S.
- Nagashima A, Tanaka E, Inomata S, Honda K, Misawa S.** A study of the in vitro interaction between lidocaine and premedications using human liver microsomes. *J Clin Pharm Ther* 2005; 30: 185-8.

- Nakamura T, Oda Y, Takahashi R, Tanaka K, Hase I, Asada A.** Propranolol increases the threshold for lidocaine-induced convulsions in awake rats: A direct effect on the brain. *Anesth Analg* 2008; 106: 1450-5.
- Nakayama S, Miyabe M, Kakiuchi Y, Inomata S, Osaka Y, Fukuda T, Kohda Y, Toyooka H.** Propofol does not inhibit lidocaine metabolism during epidural anesthesia. *Anesth Analg* 2004; 99: 1131-5.
- Nebert DW, Russell DW.** Clinical importance of the cytochromes P450. *Lancet* 2002; 360: 1155-62.
- Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM, Nebert DW.** Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics* 2004; 14: 1-18.
- Nelson SD, Garland WA, Trager WF.** Lack of evidence for formation of N-hydroxyamide metabolites of lidocaine in man. *Res Commun Chem Pathol Pharmacol* 1974; 8: 45-54.
- Neuvonen PJ, Jalava KM.** Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996; 60: 54-61.
- Nicolau DP, Nightingale CH, Tessier PR, Fu Q, Xuan DW, Esguerra EM, Quintiliani R.** The effect of fleroxacin and ciprofloxacin on the pharmacokinetics of multiple dose caffeine. *Drugs* 1995; 49: 357-9.
- Niemi M.** Role of OATP transporters in the disposition of drugs. *Pharmacogenomics* 2007; 8: 787-802.
- Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, Neuvonen PJ.** Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2003; 74: 380-7.
- Niemi M, Backman JT, Neuvonen M, Laitila J, Neuvonen PJ, Kivistö KT.** Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 2001; 69: 194-200.
- Noble DW, Bannister J, Lamont M, Andersson T, Scott DB.** The effect of oral omeprazole on the disposition of lignocaine. *Anaesthesia* 1994; 49: 497-500.
- Nolan JP, Deakin CD, Soar J, Böttiger BW, Smith G.** European resuscitation council guidelines for resuscitation 2005. Section 4. Adult advanced life support. *Resuscitation* 2005; 67S1: S39-S86.

- Obach RS, Walsky RL, Venkatakrishnan K.** Mechanism-based inactivation of human cytochrome p450 enzymes and the prediction of drug-drug interactions. *Drug Metab Dispos* 2007; 35: 246-55.
- Ochs HR, Carstens G, Greenblatt DJ.** Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 1980; 303: 373-7.
- Ochs HR, Greenblatt DJ, Verburg-Ochs B, Labedski L.** Chronic treatment with fluvoxamine, clovoxamine, and placebo: Interaction with digoxin and effects on sleep and alertness. *J Clin Pharmacol* 1989; 29: 91-5.
- Oda Y, Hamaoka N, Hiroi T, Imaoka S, Hase I, Tanaka K, Funae Y, Ishizaki T, Asada A.** Involvement of human liver cytochrome P4502B6 in the metabolism of propofol. *Br J Clin Pharmacol* 2001; 51: 281-5.
- Ohyama K, Nakajima M, Nakamura S, Shimada N, Yamazaki H, Yokoi T.** A significant role of human cytochrome P450 2C8 in amiodarone N-deethylation: An approach to predict the contribution with relative activity factor. *Drug Metab Dispos* 2000; 28: 1303-10.
- Olkkola KT, Ahonen J, Neuvonen PJ.** The effect of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg* 1996; 82: 511-6.
- Olkkola KT, Backman JT, Neuvonen PJ.** Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; 55: 481-5.
- Olkkola KT, Aranko K, Luurila H, Hiller A, Saarnivaara L, Himberg JJ, Neuvonen PJ.** A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; 53: 298-305.
- Orlando R, Piccoli P, De Martin S, Padrini R, Palatini P.** Effect of the CYP3A4 inhibitor erythromycin on the pharmacokinetics of lignocaine and its pharmacologically active metabolites in subjects with normal and impaired liver function. *Br J Clin Pharmacol* 2003; 55: 86-93.
- Orlando R, Piccoli P, De Martin S, Padrini R, Floreani M, Palatini P.** Cytochrome P450 1A2 is a major determinant of lidocaine metabolism in vivo: Effects of liver function. *Clin Pharmacol Ther* 2004; 75: 80-8.
- Owczuk R, Wujtewicz MA, Sawicka W, Piankowski A, Polak-Krzeminska A, Morzuch E, Wujtewicz M.** The effect of intravenous lidocaine on QT changes during tracheal intubation. *Anaesthesia* 2008; 63: 924-31.
- Palkama VJ, Neuvonen PJ, Olkkola KT.** Effect of itraconazole on the pharmacokinetics of bupivacaine enantiomers in healthy volunteers. *Br J Anaesth* 1999; 83: 659-61.

- Palovaara S, Kivistö KT, Tapanainen P, Manninen P, Neuvonen PJ, Laine K.** Effect of an oral contraceptive preparation containing ethinylestradiol and gestodene on CYP3A4 activity as measured by midazolam 1'-hydroxylation. *Br J Clin Pharmacol* 2000; 50: 333-7.
- Parish RC, Gotz VP, Lopez LM, Mehta JL, Curry SH.** Serum lidocaine concentrations following application to the oropharynx: Effects of cimetidine. *Ther Drug Monit* 1987; 9: 292-7.
- Parkes SB, Butler CS, Muller R.** Plasma lignocaine concentration following nebulization for awake intubation. *Anaesth Intensive Care* 1997; 25: 369-71.
- Pedersen RS, Damkier P, Brøsen K.** The effects of human CYP2C8 genotype and fluvoxamine on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2006; 62: 682-9.
- Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H.** Inhibition and induction of human cytochrome P450 enzymes: Current status. *Arch Toxicol* 2008; 82: 667-715.
- Perucca E, Richens A.** Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* 1979; 8: 21-31.
- Perucca E, Gatti G, Spina E.** Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1994; 27: 175-90.
- Picard P, Tramer MR.** Prevention of pain on injection with propofol: A quantitative systematic review. *Anesth Analg* 2000; 90: 963-9.
- Pratap JN, Shankar RK, Goroszeniuk T.** Co-injection of clonidine prolongs the anesthetic effect of lidocaine skin infiltration by a peripheral action. *Anesth Analg* 2007; 104: 982-3.
- Pälve H, Kirvelä O, Olin H, Syvälahti E, Kanto J.** Maximum recommended doses of lignocaine are not toxic. *Br J Anaesth* 1995; 74: 704-5.
- Raaska K, Neuvonen PJ.** Ciprofloxacin increases serum clozapine and N-desmethyloclozapine: A study in patients with schizophrenia. *Eur J Clin Pharmacol* 2000; 56: 585-9.
- Raaska K, Niemi MC, Neuvonen M, Neuvonen PJ, Kivistö KT.** Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002; 72: 362-9.
- Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW.** Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8. *Cancer Res* 1994; 54: 5543-6.
- Ramon Y, Barak Y, Ullmann Y, Hoffer E, Yarhi D, Bentur Y.** Pharmacokinetics of high-dose diluted lidocaine in local anesthesia for facelift procedures. *Ther Drug Monit* 2007; 29: 644-7.

- Rasmussen BB, Mäenpää J, Pelkonen O, Loft S, Poulsen HE, Lykkesfeldt J, Brøsen K.** Selective serotonin reuptake inhibitors and theophylline metabolism in human liver-microsomes - potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; 39: 151-9.
- Raunio H, Hakkola J, Pelkonen O.** Regulation of CYP3A genes in the human respiratory tract. *Chem Biol Interact* 2005; 151: 53-62.
- Reichel C, Skodra T, Nacke A, Spengler U, Sauerbruch T.** The lignocaine metabolite (MEGX) liver function test and P-450 induction in humans. *Br J Clin Pharmacol* 1998; 46: 535-9.
- Rettie AE, Jones JP.** Clinical and toxicological relevance of CYP2C9: Drug-drug interactions and pharmacogenetics. *Annu Rev Pharmacol Toxicol* 2005; 45: 477-94.
- Rifkind AB, Lee C, Chang TK, Waxman DJ.** Arachidonic acid metabolism by human cytochrome P450s 2C8, 2C9, 2E1, and 1A2: Regioselective oxygenation and evidence for a role for CYP2C enzymes in arachidonic acid epoxyoxygenation in human liver microsomes. *Arch Biochem Biophys* 1995; 320: 380-9.
- Robson RA, Wing LMH, Miners JO, Lillywhite KJ, Birkett DJ.** The effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1985; 20: 170-3.
- Rodriguez-Antona C, Niemi M, Backman JT, Kajosaari LI, Neuvonen PJ, Robledo M, Ingelman-Sundberg M.** Characterization of novel CYP2C8 haplotypes and their contribution to paclitaxel and repaglinide metabolism. *Pharmacogenomics J* 2008; 8: 268-77.
- Rose JB, Galinkin JL, Jantzen EC, Chiavacci RM.** A study of lidocaine iontophoresis for pediatric venipuncture. *Anesth Analg* 2002; 94: 867-71.
- Rostami-Hodjegan A, Tucker GT.** Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. *Nat Rev Drug Discov* 2007; 6: 140-8.
- Rowland M, Tozer TN.** Elimination. In: Clinical pharmacokinetics: concepts and applications. Baltimore: Williams & Wilkins; 1995. p. 156-83.
- Ryden L, Waldenström A, Ehn L, Holmberg S, Husaini M.** Comparison between effectiveness of intramuscular and intravenous lignocaine on ventricular arrhythmia complicating acute myocardial infarction. *Br Heart J* 1973; 35: 1124-31.
- Rygnestad T, Samdal F.** Plasma concentrations of monoethylglycinexylidide during and after breast augmentation. *Plast Reconstr Surg* 2000; 106: 728-31.
- Rygnestad T, Zahlens K, Bergslien O, Dale O.** Focus on mobilisation after lower abdominal surgery. A double-blind randomized comparison of epidural bupivacaine with morphine vs. lidocaine with morphine for postoperative analgesia. *Acta Anaesthesiol Scand* 1999; 43: 380-7.
- Sakka SG.** Assessing liver function. *Curr Opin Crit Care* 2007; 13: 207-14.

- Salhi B, Stettner E.** In defense of the use of lidocaine in rapid sequence intubation. *Ann Emerg Med* 2007; 49: 84-6.
- Sallie RW, Tredger JM, Williams R.** Extrahepatic production of the lignocaine metabolite monoethylglycinexylidide (MEGX). *Biopharm Drug Dispos* 1992; 13: 555-8.
- Scavone JM, Greenblatt DJ, Fraser DG.** The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol* 1989; 28: 722-4.
- Schwarz UI, Gramatte T, Krappweis J, Oertel R, Kirch W.** P-glycoprotein inhibitor erythromycin increases oral bioavailability of talinolol in humans. *Int J Clin Pharmacol Ther* 2000; 38: 161-7.
- Scott DB, Jebson PJ, Braid DP, Ortengren B, Frisch P.** Factors affecting plasma levels of lignocaine and prilocaine. *Br J Anaesth* 1972; 44: 1040-9.
- Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP.** Interindividual variations in human liver cytochrome-P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic-chemicals - studies with liver-microsomes of 30 japanese and 30 caucasians. *J Pharmacol Exp Ther* 1994; 270: 414-23.
- Siegmund JB, Wilson JH, Imhoff TE.** Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* 1993; 21: 513-5.
- Simpson JJ, Davies WE.** Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999; 20: 12-8.
- Spigset O, Axelsson S, Norström A, Hägg S, Dahlqvist R.** The major fluvoxamine metabolite in urine is formed by CYP2D6. *Eur J Clin Pharmacol* 2001; 57: 653-8.
- Sprung J, Bourke DL, Schoenwald PK, Whalley D, Gottlieb A, Mascha EJ, Kapural L.** Small-dose dopamine increases epidural lidocaine requirements during peripheral vascular surgery in elderly patients. *Anesth Analg* 2000; 90: 388-92.
- Stamer UM, Stuber F.** Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* 2007; 20: 478-84.
- Stenson RE, Constantino RT, Harrison DC.** Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. *Circulation* 1971; 43: 205-11.
- Suzuki T, Ishida R, Matsui S, Masubuchi Y, Narimatsu S.** Kinetic-analysis of mutual metabolic inhibition of lidocaine and propranolol in rat-liver microsomes. *Biochem Pharmacol* 1993; 45: 1528-30.

- Swart EL, van der Hoven B, Groeneveld ABJ, Touw DJ, Danhof M.** Correlation between midazolam and lignocaine pharmacokinetics and MEGX formation in healthy volunteers. *Br J Clin Pharmacol* 2002; 53: 133-9.
- Sweetman SC.** Local anaesthetics. In: Martindale: the complete drug reference. London: Pharmaceutical Press; 2009. p. 1850-72.
- Taburet AM, Schmit B.** Pharmacokinetic optimization of asthma-treatment. *Clin Pharmacokinet* 1994; 26: 396-418.
- Takano M, Hasegawa R, Fukuda T, Yumoto R, Nagai J, Murakami T.** Interaction with P-glycoprotein and transport of erythromycin, midazolam and ketoconazole in caco-2 cells. *Eur J Pharmacol* 1998; 358: 289-94.
- Takasaki M, Kajitani H.** Plasma lidocaine concentrations during continuous epidural infusion of lidocaine with and without epinephrine. *Can J Anesth* 1990; 37: 166-9.
- Tanaka E.** In vivo age-related changes in hepatic drug-oxidizing capacity in humans. *J Clin Pharm Ther* 1998; 23: 247-55.
- Tanaka E, Terada M, Misawa S.** Cytochrome P450 2E1: Its clinical and toxicological role. *J Clin Pharm Ther* 2000; 25: 165-75.
- Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL, Isoherranen N.** Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. *Clin Pharmacol Ther* 2008; 83: 77-85.
- Tesseromatis C, Kotsiou A, Tsagataki M, Tigka E, Vovou J, Alevizou A, Perisanidis C, Saranteas T, Karakitsos D, Karabinis A, Kostopanagiotou G.** In vitro binding of lidocaine to liver tissue under the influence of propranolol: Another mechanism of interaction?. *Eur J Drug Metab Pharmacokinet* 2007; 32: 213-7.
- Theuretzbacher U, Ihle F, Derendorf H.** Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; 45: 649-63.
- Thomson AH, Elliott HL, Kelman AW, Meredith PA, Whiting B.** The pharmacokinetics and pharmacodynamics of lignocaine and MEGX in healthy subjects. *J Pharmacokinet Biopharm* 1987; 15: 101-15.
- Total RA, Rettie AE.** Cytochrome P450 2C8: Substrates, inhibitors, pharmacogenetics, and clinical relevance. *Clin Pharmacol Ther* 2005; 77: 341-52.
- Total RA, Sheffels P, Roberts T, Whittington D, Thummel K, Kharasch ED.** Role of CYP2B6 in stereoselective human methadone metabolism. *Anesthesiology* 2008; 108: 363-74.

Tozer TN, Rowland M. Exposure and response after a single dose. In: Introduction to pharmacokinetics and pharmacodynamics: the quantitative basis of drug therapy. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 43-153.

Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; 58: 717-31.

Tucker GT, Mather LE. Clinical pharmacokinetics of local-anesthetics. *Clin Pharmacokinet* 1979; 4: 241-78.

Tucker GT, Bax NDS, Lennard MS, Alasady S, Bharaj HS, Woods HF. Effects of beta-adrenoceptor antagonists on the pharmacokinetics of lignocaine. *Br J Clin Pharmacol* 1984; 17: S21-8.

Turpeinen M, Tolonen A, Uusitalo J, Jalonen J, Pelkonen O, Laine K. Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; 77: 553-9.

Turpeinen M, Korhonen LE, Tolonen A, Uusitalo J, Juvonen R, Raunio H, Pelkonen O. Cytochrome P450 (CYP) inhibition screening: Comparison of three tests. *Eur J Pharm Sci* 2006; 29: 130-8.

Ujhelyi MR, Orangers EA, Fan C, Kluger J, Pharand C, Chow MSS. The pharmacokinetic and pharmacodynamic interaction between propafenone and lidocaine. *Clin Pharmacol Ther* 1993; 53: 38-48.

Vaillancourt C, Kapur AK. Opposition to the use of lidocaine in rapid sequence intubation. *Ann Emerg Med* 2007; 49: 86-7.

van Bambeke F, Michot JM, van Eldere J, Tulkens PM. Quinolones in 2005: An update. *Clin Microbiol Infect* 2005; 11: 256-80.

van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of achilles tendon disorders: Case-control study. *BMJ* 2002; 324: 1306-7.

van der Meersch-Mougeot V, Diquet B. Sensitive one-step extraction procedure for column liquid-chromatographic determination of fluvoxamine in human and rat plasma. *J Chromatogr A* 1991; 567: 441-9.

van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1995; 29: 1-9.

Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; 56: 601-7.

Varis T, Kivistö KT, Backman JT, Neuvonen PJ. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; 68: 487-94.

Varis T, Kivistö KT, Backman JT, Neuvonen PJ. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. *Pharmacol Toxicol* 1999; 85: 29-32.

Varis T, Kaukonen KM, Kivistö KT, Neuvonen PJ. Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; 64: 363-8.

Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Human drug metabolism and the cytochromes P450: Application and relevance of in vitro models. *J Clin Pharmacol* 2001; 41: 1149-79.

Volmer DA, Mansoori B, Locke SJ. Study of 4-quinolone antibiotics in biological samples by short-column liquid chromatography coupled with electrospray ionization tandem mass spectrometry. *Anal Chem* 1997; 69: 4143-55.

von Moltke LL, Greenblatt DJ, Court MH, Duan SX, Harmatz JS, Shader RI. Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and fluvoxamine: Comparison with other selective serotonin reuptake inhibitor antidepressants. *J Clin Psychopharmacol* 1995; 15: 125-31.

Walsky RL, Astuccio AV, Obach RS. Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. *J Clin Pharmacol* 2006; 46: 1426-38.

Wang EJ, Lew K, Casciano CN, Clement RP, Johnson WW. Interaction of common azole antifungals with P glycoprotein. *Antimicrob Agents Chemother* 2002a; 46: 160-5.

Wang JS, Neuvonen M, Wen X, Backman JT, Neuvonen PJ. Gemfibrozil inhibits CYP2C8-mediated cerivastatin metabolism in human liver microsomes. *Drug Metab Dispos* 2002b; 30: 1352-6.

Wang JS, Backman JT, Taavitsainen P, Neuvonen PJ, Kivistö KT. Involvement of CYP1A2 and CYP3A4 in lidocaine N-deethylation and 3-hydroxylation in humans. *Drug Metab Dispos* 2000; 28: 959-65.

Wang JS, Backman JT, Wen X, Taavitsainen P, Neuvonen PJ, Kivistö KT. Fluvoxamine is a more potent inhibitor of lidocaine metabolism than ketoconazole and erythromycin in vitro. *Pharmacol Toxicol* 1999a; 85: 201-5.

- Wang JS, Wen X, Backman JT, Taavitsainen P, Neuvonen PJ, Kivistö KT.** Midazolam alpha-hydroxylation by human liver microsomes in vitro: Inhibition by calcium channel blockers, itraconazole and ketoconazole. *Pharmacol Toxicol* 1999b; 85: 157-61.
- Wang RB, Kuo CL, Lien LL, Lien EJ.** Structure-activity relationship: Analyses of p-glycoprotein substrates and inhibitors. *J Clin Pharm Ther* 2003; 28: 203-28.
- Watkins PB.** Noninvasive tests of CYP3A enzymes. *Pharmacogenetics* 1994; 4: 171-84.
- Wei X, Dai R, Zhai S, Thummel KE, Friedman FK, Vestal RE.** Inhibition of human liver cytochrome P-450 1A2 by the class IB antiarrhythmics mexiletine, lidocaine, and tocainide. *J Pharmacol Exp Ther* 1999; 289: 853-8.
- Weibert RT, Lorentz SM, Townsend RJ, Cook CE, Klauber MR, Jagger PI.** Effect of erythromycin in patients receiving long-term warfarin therapy. *Clin Pharm* 1989; 8: 210-4.
- Weiss J, Dormann SM, Martin-Facklam M, Kerpen CJ, Ketabi-Kiyanvash N, Haefeli WE.** Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther* 2003; 305: 197-204.
- Wen X, Wang JS, Backman JT, Laitila J, Neuvonen PJ.** Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. *Drug Metab Dispos* 2002; 30: 631-5.
- Wildsmith JA, Tucker GT, Cooper S, Scott DB, Covino BG.** Plasma concentrations of local anaesthetics after interscalene brachial plexus block. *Br J Anaesth* 1977; 49: 461-6.
- Wilkinson GR.** Drug metabolism and variability among patients in drug response. *N Engl J Med* 2005; 352: 2211-21.
- Willems L, van der Geest R, de Beule K.** Itraconazole oral solution and intravenous formulations: A review of pharmacokinetics and pharmacodynamics. *J Clin Pharm Ther* 2001; 26: 159-69.
- Wing LM, Miners JO, Birkett DJ, Foenander T, Lillywhite K, Wanwimolruk S.** Lidocaine disposition--sex differences and effects of cimetidine. *Clin Pharmacol Ther* 1984; 35: 695-701.
- Wolbold R, Klein K, Burk O, Nussler AK, Neuhaus P, Eichelbaum M, Schwab M, Zanger UM.** Sex is a major determinant of CYP3A4 expression in human liver. *Hepatology* 2003; 38: 978-88.
- Wright JL, Durieux ME, Groves DS.** A brief review of innovative uses for local anesthetics. *Curr Opin Anaesthesiol* 2008; 21: 651-6.
- Xue FS, Liu HP, He N, Xu YC, Yang QY, Liao X, Xu XZ, Guo XL, Zhang YM.** Spray-as-you-go airway topical anesthesia in patients with a difficult airway: A randomized, double-blind comparison of 2% and 4% lidocaine. *Anesth Analg* 2009; 108: 536-43.

- Yadav AV, Zipes DP.** Prophylactic lidocaine in acute myocardial infarction: Resurface or reburial? *Am J Cardiol* 2004; 94: 606-8.
- Yang J, Jamei M, Yeo KR, Rostami-Hodjegan A, Tucker GT.** Misuse of the well-stirred model of hepatic drug clearance. *Drug Metab Dispos* 2007; 35: 501-2.
- Yao C, Kunze KL, Trager WF, Kharasch ED, Levy RH.** Comparison of in vitro and in vivo inhibition potencies of fluvoxamine toward CYP2C19. *Drug Metab Dispos* 2003; 31: 565-71.
- Yao C, Kunze KL, Kharasch ED, Wang Y, Trager WF, Ragueneau I, Levy RH.** Fluvoxamine-theophylline interaction: Gap between in vitro and in vivo inhibition constants toward cytochrome P4501A2. *Clin Pharmacol Ther* 2001; 70: 415-24.
- Yokoyama M, Mizobuchi S, Nakatsuka H, Hirakawa M.** Comparison of plasma lidocaine concentrations after injection of a fixed small volume in the stellate ganglion, the lumbar epidural space, or a single intercostal nerve. *Anesth Analg* 1998; 87: 112-5.
- Yu KS, Cho JY, Shon JH, Bae KS, Yi SY, Lim HS, Jang IJ, Shin SG.** Ethnic differences and relationships in the oral pharmacokinetics of nifedipine and erythromycin. *Clin Pharmacol Ther* 2001; 70: 228-36.
- Zanger UM, Raimundo S, Eichelbaum M.** Cytochrome P450 2D6: Overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004; 369: 23-37.
- Zanger UM, Turpeinen M, Klein K, Schwab M.** Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* 2008; 392: 1093-108.
- Zaric D, Christiansen C, Pace NL, Punjasawadwong Y.** Transient neurologic symptoms after spinal anesthesia with lidocaine versus other local anesthetics: A systematic review of randomized, controlled trials. *Anesth Analg* 2005; 100: 1811-6.
- Zhang Y, Benet LZ.** The gut as a barrier to drug absorption: Combined role of cytochrome P450 3A and P-glycoprotein. *Clin Pharmacokinet* 2001; 40: 159-68.
- Zhou SF.** Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica* 2008a; 38: 802-32.
- Zhou SF.** Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr Drug Metab* 2008b; 9: 310-22.
- Zuberi BF, Shaikh MR, Jatoi NUN, Shaikh WM.** Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. *Gut* 2000; 46: 435.

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