

Clinical Pharmacokinetics of Mexiletine

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Abstract

Mexiletine, a class Ib antiarrhythmic agent, is rapidly and completely absorbed following oral administration with a bioavailability of about 90%. Peak plasma concentrations following oral administration occur within 1 to 4 hours and a linear relationship between dose and plasma concentration is observed in the dose range

of 100 to 600mg. Mexiletine is weakly bound to plasma proteins (70%). Its volume of distribution is large and varies from 5 to 9 L/kg in healthy individuals.

Mexiletine is eliminated slowly in humans (with an elimination half-life of 10 hours). It undergoes stereoselective disposition caused by extensive metabolism. Eleven metabolites of mexiletine are presently known, but none of these metabolites possesses any pharmacological activity. The major metabolites are hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine, *m*-hydroxy-mexiletine and *N*-hydroxy-mexiletine. Formation of hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine is genetically determined and cosegregates with polymorphic debrisoquine 4-hydroxylase [cytochrome P450 (CYP) 2D6] activity. On the other hand, CYP1A2 seems to be implicated in the *N*-oxidation of mexiletine.

Various physiological, pathological, pharmacological and environmental factors influence the disposition of mexiletine. Myocardial infarction, opioid analgesics, atropine and antacids slow the rate of absorption, whereas metoclopramide enhances it. Rifampicin (rifampin), phenytoin and cigarette smoking significantly enhance the rate of elimination of mexiletine, whereas ciprofloxacin, propafenone and liver cirrhosis decrease it. Cimetidine, ranitidine, fluconazole and omeprazole do not modify the disposition of mexiletine. Conversely, mexiletine is known to alter the disposition of other drugs, such as caffeine and theophylline. Factors affecting the elimination of mexiletine may be clinically important and dosage adjustments are often necessary.

Mexiletine [1-(2,6-dimethylphenoxy)-2-amino-propane] is a primary amine which was developed originally as an anticonvulsant. It became available in clinical practice as an antiarrhythmic agent following the discovery of its cardiac electrophysiological properties. Indeed, mexiletine is an orally effective class Ib antiarrhythmic agent used in the treatment of ventricular arrhythmias.^[1-3] It blocks the voltage-dependent fast sodium channel, reducing the rate of depolarisation of ventricular cardiac myocytes.^[4]

Mexiletine possesses desirable electrophysiological and haemodynamic properties for combination with other antiarrhythmic agents.^[5-8] This has become a significant asset for the clinical use of mexiletine, since combination therapy is often required with the drug because of a disappointing efficacy when mexiletine is used as monotherapy.^[9,10] One of the most studied combinations is the concomitant administration of mexiletine with quinidine.^[9,11-17] This combination is not only of greater efficacy than either agent alone, but also produces a lower incidence of adverse effects. Pharmacokinetic interactions, as well as electrophysiological

synergistic properties, may explain part of the greater efficacy.^[14,18]

Combination of mexiletine with other antiarrhythmic drugs has also been studied and used. Mexiletine has been combined with class Ia drugs (procainamide and disopyramide), class Ic agents (propafenone), with β -adrenoceptor antagonists or the class III agents (sotalol and amiodarone).^[10,19-28]

Mexiletine has a narrow therapeutic index with effective and minimally toxic concentrations ranging from 0.75 to 2 mg/L.^[2,29] An important correlation exists between its serum concentration and both its antiarrhythmic efficacy and its adverse effects.^[29,30] Large interindividual variations in mexiletine serum concentrations have been observed following administration of the drug.^[29] Several pathological, physiological, pharmacological, environmental and also genetic factors have been reported to explain parts of the high interindividual variability in its disposition.

The disposition of mexiletine has been studied, both in healthy volunteers and patients with different disease states, after both intravenous and oral

administration. Intramuscular administration is rarely used clinically. The pharmacokinetics of mexiletine have nevertheless been studied after intramuscular administration, and are similar to those with intravenous administration.^[31] The area under the plasma concentration-time curve (AUC) in one participant was a linear function of the dose, indicating that first-order kinetics apply in this situation.^[32]

1. Pharmacokinetics of Mexiletine in Healthy Volunteers

1.1 Oral Absorption

Mexiletine is rapidly and completely absorbed from the gastrointestinal tract.^[33] Mexiletine is a weak base (pKa 8.5) and for this reason it is completely ionised in the stomach, where only limited absorption occurs. Gastrointestinal absorption largely takes place in the small intestine where the pH is higher and favours the non-ionised lipophilic form.

Peak drug plasma concentrations (C_{\max}) occur within 1 to 4 hours of the ingestion of the capsule.^[33-36] However, after administration of the sustained release formulation, C_{\max} appears as a plateau after 8.0 to 9.2 hours.^[34,37] The C_{\max} and AUC of mexiletine increased linearly with the dose in 12 volunteers who received 600mg or less of mexiletine hydrochloride orally.^[38] This is in agreement with other studies which demonstrated a linear correlation between plasma concentrations and daily doses of mexiletine in patients.^[29]

Mexiletine is not subjected to extensive first-pass metabolism in the liver. The bioavailability of mexiletine following oral administration in an aqueous solution was 88% in 4 healthy volunteers.^[33] Moreover, the systemic availability of mexiletine for the conventional capsule is about 85%.^[34,39] However, with a sustained release form, a bioavailability of 78.7% was estimated.^[34]

1.2 Distribution

Following intravenous administration, serum concentrations of mexiletine decrease rapidly be-

cause of the extensive drug distribution into tissue. The total volume of distribution (Vd) is large and varies from 5 to 9 L/kg.^[3,33,40] Prescott et al.^[33] proposed that the disposition of mexiletine is consistent with a 3-compartment model, although the tissue into which mexiletine is distributed is not well characterised.

Following a fatal overdose of mexiletine in a 25-year-old male, the tissue distribution of the drug was studied.^[41] The authors measured mexiletine in heart blood (44.8 mg/L), femoral blood (10.0 mg/L), vitreous (8.6 mg/L), liver (171.6 mg/kg) and brain (84.0 mg/kg). Mexiletine penetrates the erythrocytes, and the erythrocyte : serum concentration ratio is 1.26 ± 0.28 after administration of a single oral dose.^[42] Moreover, the concentration of mexiletine in whole blood is about 15% higher than in plasma.^[33]

Mexiletine is lipid-soluble and freely crosses the placental barrier.^[43] Similar mexiletine concentrations (0.3 mg/L) were found in maternal and cord blood.^[44] In another study, maternal serum and fetal cord blood mexiletine values were 0.6 mg/L and 0.4 mg/L, respectively.^[45] The drug is excreted in milk and the milk : plasma drug concentration ratio varies between 0.8 and 1.9.^[46]

Mexiletine is only 70% bound to plasma proteins.^[3] The nature of the serum proteins to which the drug is bound is not well characterised, although binding to albumin and α_1 -acid glycoprotein was suggested.^[47] The amount bound compared with the total amount of drug in the body is quite insignificant. Indeed, following distribution, less than 1% of the total amount of the drug in the body is in plasma.^[4] Therefore, small changes in the fraction of the drug bound to plasma proteins are not expected to be of clinical significance.

1.3 Metabolism

Mexiletine is eliminated slowly in humans with a half-life ($t_{1/2\beta}$) of about 10 hours, although the drug undergoes extensive metabolism.^[33,36] Indeed, mexiletine is metabolised in the liver by oxidation, deamination, reduction and conjugation reactions. Eleven metabolites of mexiletine

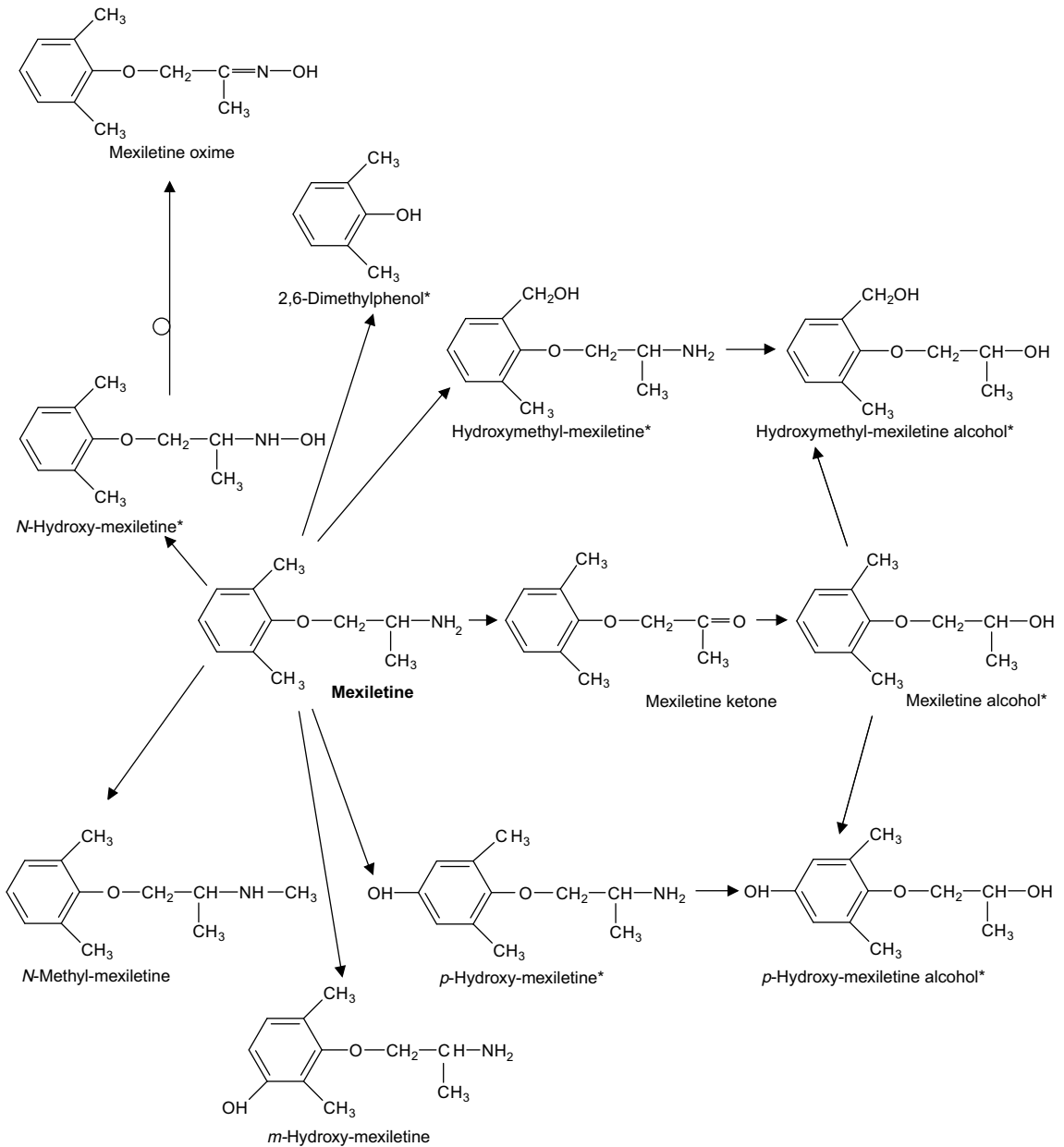


Fig. 1. Metabolic pathways of mexiletine in humans. * indicates metabolites also eliminated as glucuronide conjugates.

(fig. 1), most of which are eliminated as glucuronide conjugates, have been identified but none of these metabolites appears to possess any pharmacological activity.

In 1977, Beckett and Chidomere^[48] identified 9 mexiletine metabolites in the urine of healthy volunteers following oral or intravenous administration of single doses of mexiletine. They found that

p-hydroxy-mexiletine, hydroxymethyl-mexiletine and their corresponding alcohols represent up to 20% of the total elimination of mexiletine in urine. The *N*-glucuronide metabolite of mexiletine, which was further characterised as *N*-hydroxy-mexiletine glucuronide, represents a major metabolic pathway (10% of urinary recovery) in the disposition of mexiletine.^[18,40,49,50] The minor metabolic routes are deamination to the ketone and reduction to the alcohol (up to 4%); *N*-methylation occurs to a very minor extent. More than 10 years later, 2 other metabolites, 2,6-dimethylphenol and *m*-hydroxy-mexiletine, were identified by Grech-Bélanger et al.^[51,52] In humans, *m*-hydroxy-mexiletine accounts for approximately 2% of the urinary recovery of an administered oral dose of mexiletine.^[51]

1.4 Excretion

Under conditions of normal urinary pH, less than 10% of an administered oral dose is recovered unchanged in urine.^[33,34,53] This amount is significantly decreased or increased depending on whether urine is acidified or alkalinised. At the extreme urine pH values of 5 and 8, the percentage of mexiletine excreted unchanged has been reported as 57.5 and 0.6%, respectively.^[54,55] In the same studies, mexiletine $t_{1/2\beta}$ was increased 3-fold by altering the urinary pH from 5 to 8 in 4 volunteers.

Mitchell et al.^[56] observed that urinary acidification produced a large and consistent increase in the renal clearance (CL_R) of mexiletine, and that CL_R fell greatly following alkalinisation to pH 8. These authors did not observe significant decreases in $t_{1/2\beta}$, AUC or nonrenal clearance (CL_{NR}). However, mean values of mexiletine $t_{1/2\beta}$ as short as 2.8 and 3.9 hours have been described following urinary acidification.^[54,55,57] Moreover, Beckett and Chidomere^[58] have reported a reduction in biological $t_{1/2\beta}$ from mean values of 9 hours in normal urinary pH to between 4 and 5 hours in controlled acidic urine. Both urinary excretion and plasma concentrations of mexiletine are affected by urinary pH.^[58,59] Under conditions of maintained acidic urinary pH, the plasma concentrations of

mexiletine were directly related to the urinary excretion rates.^[58]

Table I summarises the pharmacokinetic parameters of mexiletine in healthy volunteers.

2. Modulators of Mexiletine Pharmacokinetics

2.1 Genetic Polymorphism

Genetically determined patterns of drug metabolism can influence the individuals response to drug therapy as a result of highly variable plasma concentrations of the parent compound or its metabolites. One of the most widely studied polymorphisms in drug oxidation is the metabolism of the antihypertensive agent debrisoquine to its 4-hydroxy metabolite. In fact, in the late 1970s, it was reported that the alicyclic 4-hydroxylation of debrisoquine was bimodally distributed.^[76] On the basis of an 8-hour urinary excretion profile following a single oral dose of debrisoquine 10mg, a metabolic ratio (defined as the percentage dose excreted as debrisoquine divided by the percentage dose excreted as 4-hydroxydebrisoquine) discriminated between 2 distinct phenotypes.^[76] Individuals with a ratio greater than 12.6 were defined as poor metabolisers (PMs) whereas a value less than this anti-mode reflected an ability to extensively metabolise (EMs) the probe drug.^[77,78] Further studies indicated that the biochemical basis of this genetically-determined drug polymorphism was related to the activity of a specific cytochrome P450 (CYP) isozyme, namely CYP2D6.^[79-81]

The disposition of over 30 other pharmacological agents, including mexiletine, cosegregates with the debrisoquine 4-hydroxylase polymorphism. In fact, it was demonstrated that the formation of hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine is genetically determined and cosegregates with CYP2D6 activity.^[18,82] *In vitro* studies performed with human liver microsomes suggested that the formation of hydroxymethyl-mexiletine and *p*-hydroxy-mexiletine was predominantly catalysed by CYP2D6.^[40,82,83] The formations of these 2 metabolites of mexiletine were

Table 1. Pharmacokinetic parameters of mexiletine in healthy volunteers. Values are given as means \pm SD except where indicated (items marked with an asterisk are means \pm SEM)

n and gender	Dose of mexiletine hydrochloride	Phenotype	Smoker	C _{max} (mg/L)	t _{max} (h)	t _{1/2β} (h)	Vd (L)	CL/F (L/h)	CL _R (L/h)	Ae (%)	Reference
Intravenous											
5	Single 1.5 mg/kg				10.2 \pm 0.8		5/kg			5 to 10 ^b	3
4	Single 100mg				10.4 \pm 2.8		663 \pm 238	45.1 \pm 24.8			33
5M	Single 200mg				11.8 \pm 1.5		506 \pm 64	31.0 \pm 4.3			39
6M	Single 200mg				6.3 \pm 1.5		5.5 \pm 0.5/kg	50.7 \pm 14.3		8.6 \pm 5.1 ^b	34
1M	Single 100mg				8.3		6.4/kg ^c	0.53/kg			32
6M	Single 200mg*		2S		9.9 \pm 1.6		5.9 \pm 0.4/kg ^d	0.50 \pm 0.07/kg			60
6M	Single 200mg		NS		9.1 \pm 2.6		5.6 \pm 1.2/kg	0.47 \pm 0.14/kg			31
8M, 7F	Single 250mg	5 rapid EMs	3S/15	1.19 \pm 0.18	11.6 \pm 1.3			27.0 \pm 6.8	1.26 \pm 0.42	4.7 \pm 2.0	61
		5 slow EMs		1.17 \pm 0.41	13.8 \pm 1.5			22.7 \pm 5.1	1.56 \pm 0.3	7.1 \pm 3.1	
		5 PMs		1.76 \pm 0.60	18.5 \pm 3.0			13.0 \pm 4.8	1.26 \pm 0.3	9.3 \pm 4.1	
Intramuscular											
1M	Single 50mg ^e				9.8		10.0/kg ^e	0.70/kg			32
1M	Single 100mg ^f				15.1		11.8/kg ^e	0.54/kg			32
1M	Single 400mg ^g				11.6		11.6/kg ^e	0.7/kg			32
6M	Single 400mg		NS		10.1 \pm 2.6		5.2 \pm 0.6/kg	0.40 \pm 0.09/kg			31
Oral solution											
6	Single 3 mg/kg			0.3-0.4	2 to 3						3
6	Single 3 mg/kg			0.3-0.5	1 to 4	11.5 (8-14) ^h				3 to 15 ^b	62
4	Single 3 mg/kg				9.3 \pm 1.0			40.9 \pm 10.7			33
Oral capsule											
5	Single 400mg			0.87 - 1.55	2 to 4						33
8M	Single 400mg		NS	1.45	1.97	9.5					63
6M	Single 400mg			0.77 \pm 0.13	2.2 \pm 1.2					7.5 \pm 3.1 ^b	34
3M, 3F	Single 400mg		NS	1.00 \pm 0.41	1.7 \pm 1.1	17.2 \pm 5.3					64
5M, 5F	Single 400mg			1.99 \pm 0.46	1.7 \pm 0.7	9.3 \pm 1.9					36
3M, 5 F	Single 400mg*			1.02 \pm 0.13	1.9 \pm 0.4	8.5 \pm 0.8	349 \pm 55 ^c	33.7 \pm 6.4	4.2 \pm 1.7		65
3M, 1F	Single 400mg				3						37
6M	Single 400mg		NS	0.75 \pm 0.05	1.9 \pm 0.8	10.4 \pm 1.5	406 \pm 32	27.3 \pm 3.7			66

4M, 4F	Single 200mg	NS		11.1 ± 3.4	7.2 ± 2.7/kg ^c	0.59 ± 0.25/kg	0.035 ± 0.018/kg	6.4 ± 3.3	49
4M, 2F	Single 200mg	S		7.2 ± 1.8	6.3 ± 1.5/kg ^c	0.79 ± 0.2/kg	0.048 ± 0.017/kg	6.1 ± 1.5	35
3M, 3F	Single 300mg	3S		7.5 ± 1.7	459 ± 65 ^c	48.5 ± 10.1			38
12M	Single 100mg		1.1 ± 0.3	11.3 ± 1.0	707 ± 80	45.9 ± 4.6			38
12M	Single 200mg		1.9 ± 0.2	10.8 ± 1.2	695 ± 91	52.2 ± 9.7			38
12M	Single 300mg		1.8 ± 0.3	7.9 ± 0.6	592 ± 60	57.0 ± 8.2			38
12M	Single 400mg		2.0 ± 0.3	7.9 ± 0.6	580 ± 60	46.7 ± 7.8			38
12M	Single 600mg		2.6 ± 0.6	9.5 ± 0.7	580 ± 60	46.7 ± 7.8			38
11M	Single 600mg		1.8 ± 0.2	10.7 ± 0.8	591 ± 43	40.4 ± 3.8			42
5M, 2F	Single 200mg			7.9 ± 2.2					67
8M	Single 100mg	NS	0.18 ± 0.04	12.3 ± 3.7		0.62 ± 0.32/kg		4.0 ± 2.3	67
7M	Single 100mg	NS	0.16 ± 0.05	14.4 ± 4.5		0.51 ± 0.17/kg		4.3 ± 1.7	68
10M	Single 400mg	NS	0.69 ± 0.11	7.7 ± 1.4	5.4 ± 1.4/kg ^j	0.54 ± 0.08/kg			69
5M	Single 200mg		2.3 ± 1.6	12.4 ± 6.4					18
13M, 1F	Single 200mg	10 EMs		8.9 ± 1.1	461 ± 179	41.4 ± 19.9	2.28 ± 1.92	5.7 ± 3.5	40
13M, 1F	Single 200mg	4 PMS ⁱ		12.6 (8.9-14.8)	304 (255-578)	21 (15.2-32.2)	1.92 (0.60-2.46)	7.0(3.4-12.0)	
7M, 2F	Single 200mg	3S, 4NS						7.3 ± 4.2	
7M, 2F	Single 200mg	7 EMs						16.7 ± 2.7	
7M, 2F	Single 200mg	2 PMS							
7M, 2F	Single 200mg	2 EMs	0.25-0.40	7.0-7.6	4.9/kg	0.51-0.56/kg	0.029-0.058/kg		
7M, 2F	Single 200mg	1 PM	0.61	10.8	4.7/kg	0.33/kg	0.051/kg		
5M, 1F	Single 200mg	3S, 3NS						7.6 ± 4.5	70
6M	Single 200mg		0.46 ± 0.08	7.1 ± 2.7	5.4 ± 1.2/kg	0.55 ± 0.18/kg			71
9M	Single 200mg		0.44 ± 0.10	8.6 ± 2.2	6.9 ± 0.9/kg	0.60 ± 0.18/kg			72
9M	Single 200mg	NS				27.0 ± 11.0	1.38 ± 0.72	5 ± 2	73
8M	Single 200mg	S				46.0 ± 14.0	2.58 ± 0.90	5 ± 2	
Sustained release form									
6M	Single 432mg		0.34 ± 0.12	9.2 ± 1.3				9.2 ± 6.6 ^b	34
6M	Single 360mg	NS	0.44 ± 0.08	4.3 ± 1.1	354 ± 65	28.5 ± 5.9			66
3M, 1F	Single 432mg								37
Chronic oral administration									
8M, 1F	50mg tid × 10 days			10.4 ± 3.2					74
3M, 4F	50mg tid × 10 days	NS		11.4 ± 1.8					75
8M, 2F	50mg tid × 10 days	NS		10.5 ± 3.1					

Continued over page

competitively inhibited by quinidine, several CYP-2D6 substrates and an antiserum containing anti-liver/kidney microsome antibodies type I (anti-LKM1) directed against CYP2D6. These results were confirmed by other *in vivo* studies.^[18,40,61,70]

Turgeon et al.^[18] investigated the role of debrisoquine polymorphism and the effects of low dose quinidine on the disposition of mexiletine in 14 healthy volunteers: 10 EMs and 4 PMs. Each volunteer received a single dose of mexiletine hydrochloride 200mg orally on 2 occasions 1 week apart, one dose alone and the other dose under steady-state conditions for quinidine 50mg 4 times daily. The disposition of mexiletine was different between EMs and PMs after administration of mexiletine alone. Mean plasma concentrations of mexiletine were higher in those with the PM phenotype compared with the EM group. The $t_{1/2\beta}$ was longer in the PM group [median and range: 12.6h (8.9-14.8h)] than in the EM group (mean \pm SD: 8.9 \pm 1.1h). The systemic clearance (CL), CL_{NR} and partial metabolic clearance (CL_{PM}) of mexiletine to hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine or *m*-hydroxy-mexiletine were all decreased in the PM group compared with the EM group.^[18]

Moreover, quinidine treatment selectively altered mexiletine disposition in EMs.^[18] In these individuals, the addition of quinidine increased the mean drug plasma concentrations and $t_{1/2\beta}$ of mexiletine. CYP2D6 inhibition by quinidine also produced a decrease in the CL, CL_{NR} and CL_{PM} of mexiletine to hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine. The administration of quinidine altered the pharmacokinetics of mexiletine to an extent such that differences were no longer observed between the EM and PM groups. In PMs, quinidine did not alter mexiletine plasma concentrations, nor did it significantly change any of the derived pharmacokinetic parameters. These results were confirmed by another study which showed a decreased urinary excretion of hydroxymethyl-mexiletine and *p*-hydroxy-mexiletine in EMs after quinidine administration.^[70] Thus, formation of hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine is

Table I. Contd

n and gender	Dose of mexiletine hydrochloride	Phenotype	Smoker	C _{max} (mg/L)	t _{max} (h)	t _{1/2β} (h)	Vd (L)	CL/F (L/h)	CL _R (L/h)	Ae (%)	Reference
Combination											
2M, 1 F	200mg IM ^k + orally*					8.2 ± 1.9					32
3M, 3F	200mg IM ^l + orally*					7.1 ± 0.6					
a	0 to 5 days.										
b	0 to 72 hours.										
c	Apparent Vd in β-phase.										
d	Volume of distribution at steady-state.										
e	2ml of 25 mg/ml.										
f	2 × 2ml of 25 mg/ml.										
g	4 × 2ml of 25 mg/ml.										
h	Values are reported as the mean and range.										
i	Vd in z-phase.										
j	Values are reported as the median and range.										
k	2 × 4ml of 25 mg/ml.										
l	2ml of 100 mg/ml.										
<p>Ae = urinary excretion of mexiletine in the 48h period following administration, expressed as a percentage of the dose; CL/F = apparent clearance; CL_R = renal clearance; C_{max} = maximum drug plasma concentration; EMS = extensive metabolisers (CYP2D6); F = female; IM = intramuscular; M = male; n = number of participants; NS = nonsmoker; PMS = poor metabolisers (CYP2D6); S = smoker; t_{max} = time to maximum drug plasma concentration; t_{1/2β} = elimination half-life; tid = 3 times daily; Vd = volume of distribution.</p>											

largely mediated by CYP2D6 and is under genetic control.

Other CYP isozymes also contribute to the formation of hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine. In fact, formation of these metabolites was impaired but not prevented in PMs and partially abolished by quinidine coadministration in EMs.^[18] Moreover, *in vitro* studies using human liver microsomes provided biochemical evidence that CYP2D6 is the predominant, but not sole, enzyme responsible for the formation of hydroxymethyl-mexiletine and *p*-hydroxy-mexiletine.^[82,83] The formation of these 2 metabolites was strongly reduced, but not completely abolished, by several CYP2D6 substrates, by quinidine and by an antibody directed against CYP2D6.

The selective induction by cigarette smoking (a well known inducer of CYP1A2)^[84] of formation of hydroxymethyl-mexiletine, but not *p*-hydroxy-mexiletine, also suggests that different CYP isozymes besides CYP2D6 are responsible, at least in part, for the formation of these metabolites.^[49] Nakajima et al.^[85] recently reported that mexiletine *p*- and methyl-hydroxylations are catalysed partially by CYP1A2 in human liver microsomes and by recombinant human cytochromes. The contribution of CYP1A2 to these 2 hydroxylation pathways of mexiletine is relatively low.

Although CYP2D6 is clearly involved in the formation of hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine, the *N*-oxidation of mexiletine is not mediated by this CYP isozyme. In fact, the CL_{PM} of mexiletine to *N*-hydroxy-mexiletine was not different between PMs and EMs with mexiletine alone and not altered in EMs during quinidine coadministration.^[18] Evidence has accumulated to suggest the role of CYP1A2 in the metabolism of mexiletine and formation of *N*-hydroxy-mexiletine in humans. First, studies have shown that cigarette smoking alters the kinetics of mexiletine in humans and increases the formation rate of a *N*-glucuronide metabolite (characterised as *N*-hydroxy-mexiletine glucuronide).^[49,50] Secondly, *in vitro* studies performed

with microsomes from yeast cells expressing high levels of specific CYP activity showed that the formation rate of *N*-hydroxy-mexiletine by CYP1A2 was more than 50 times greater than that observed with microsomes expressing low CYP activity.^[86] Moreover, the formation rate of *N*-hydroxy-mexiletine measured in human liver microsomes correlated well with 7-ethoxyresorufin deethylase activity, and furafylline (40 µmol/L), a potent and selective inhibitor of CYP1A2,^[87] decreased the formation rate of *N*-hydroxy-mexiletine by 60%.^[86]

2.2 Stereoselectivity

Mexiletine is administered as a racemic mixture of equal parts of the *R*(-)- and *S*(+)-enantiomers. Mexiletine undergoes stereoselective disposition in humans^[53] and the enantiomers possess different antiarrhythmic potency.^[88] The *R*(-)-enantiomer exhibits greater antiarrhythmic properties than the *S*(+)-enantiomer, while neither of the optical isomers significantly affected electrocardiographic intervals and refractory periods.^[88] Moreover, increased binding to cardiac sodium channels has been described for *R*(-)-mexiletine.^[89,90]

The absorption of mexiletine enantiomers is not stereoselective in humans.^[91] Neither the absorption rate constants (K_a), C_{max} or time to C_{max} (t_{max}) differed significantly between mexiletine enantiomers. However, Kwok et al.^[47] reported a significantly higher C_{max} for *R*(-)-mexiletine.

The binding of mexiletine enantiomers to human serum proteins is stereoselective.^[92] The free fraction of *R*(-)-mexiletine is approximately 30% less than that of *S*(+)-mexiletine (19.8 vs 28.3%). This contradicts another report which demonstrated that the serum protein binding of mexiletine was similar between the 2 enantiomers with comparable serum free fractions and *R/S* ratios approaching unity at physiological serum pH.^[47] A pH-dependent serum protein binding of mexiletine enantiomers has been described and may result from changes in the conformation of proteins.

It has been suggested that the protein binding of enantiomers influences their distribution and elimination from the body for drugs with a low extrac-

tion ratio such as mexiletine.^[92] Igwemezie et al.^[91] found an apparent volume of distribution in the β -phase (V_{β}/F) higher for *S*-(+)-mexiletine than *R*-(-)-mexiletine (7.3 ± 2.4 L/kg vs 6.6 ± 2.6 L/kg), whereas other authors did not show any significant differences in the V_{β}/F between the 2 enantiomers of mexiletine.^[47,93] Finally, it was demonstrated that the distribution rate constants for mexiletine enantiomers were similar.^[53]

Following oral administration of mexiletine racemic mixture in healthy volunteers, the AUC of *S*-(+)-mexiletine was higher than that of *R*-(-)-enantiomer, indicating that the pharmacokinetics are stereoselective.^[53] An overall mean saliva *R/S* ratio of 0.89 over 48 hours suggested a stereoselective disposition of mexiletine enantiomers in saliva.^[47] On the other hand, the distribution of mexiletine enantiomers into red blood cells seems to be non-stereoselective.

During the absorption phase, plasma concentrations of *S*-(+)-mexiletine are lower compared with those of *R*-(-)-mexiletine.^[91,93] Igwemezie et al.^[91] explained this phenomenon by a greater V_d for the *S*-(+)-enantiomer. However, plasma concentrations of *S*-(+)-mexiletine become greater than those of *R*-(-)-mexiletine during the elimination phase.^[91,93]

The apparent oral clearance (CL/F) of mexiletine enantiomers were not significantly different.^[47,91,93] However, Igwemezie et al.^[91] demonstrated that the $t_{1/2\beta}$ of *S*-(+)-mexiletine was greater relative to the *R*-(-)-mexiletine (11.0 ± 3.8 h vs 9.1 ± 2.9 h). Differences in estimated $t_{1/2\beta}$ between enantiomers were caused by a greater V_{β}/F for *S*-(+)-mexiletine since the enantiomers did not show any significant differences in CL/F . These authors have also noted that *S*-(+)-mexiletine had a significantly greater CL_R than *R*-(-)-mexiletine. Others did not observe any differences in the $t_{1/2\beta}$ and CL_R between mexiletine enantiomers.^[47,53,94]

Abolfathi et al.^[93] studied the role of CYP2D6 polymorphism in the stereoselective disposition of mexiletine in humans. Following oral administration of mexiletine, the AUC of both *R*-(-)- and *S*-(+)-mexiletine was greater in the plasma of PMs than in EMs. The *R/S* ratio of mexiletine plasma

concentrations was similar in PMs and EMs. Coadministration of quinidine did not alter the plasma concentrations of either *R*-(-)- or *S*-(+)-mexiletine in individuals with the PM phenotype. In contrast, the mean plasma concentrations of both enantiomers were increased by quinidine in EMs. However, quinidine increased the plasma concentrations of *R*-(-)- and *S*-(+)-mexiletine to a similar extent, so that the *R/S* ratio of mexiletine plasma concentrations was not modified. Moreover, the *R/S* ratio of the CL and CL_{NR} of mexiletine and that of the urinary recovery of both enantiomers were similar in EMs and PMs. These ratios were unaltered by quinidine administration.

Formation of *N*-hydroxy-mexiletine is highly stereoselective. Grech-Bélanger et al.^[53] reported that the urinary recovery of mexiletine *N*-glucuronide was more than 10 times greater for the *R*-(-)-enantiomer. Similarly, the CL_{PM} of mexiletine enantiomers to *N*-hydroxy-mexiletine was found to be highly stereoselective; the *R/S* ratio was 11.3 ± 3.4 .^[93] This ratio was similar in EMs and PMs and unaltered by quinidine coadministration. Data obtained in this study indicate that CYP2D6 is not responsible for the stereoselective disposition of mexiletine in humans.

Labbé et al.^[94] suggested that CYP1A2 may be involved in the stereoselective formation of this metabolite. In fact, coadministration of caffeine selectively decreased the CL_{PM} of *R*-(-)-mexiletine to its *N*-hydroxylated metabolite.^[94] Caffeine also reduced the urinary recovery of *N*-hydroxy-mexiletine but only for the *R*-(-)-enantiomer. Consequently, the *R/S* ratio for urinary recovery and the CL_{PM} of mexiletine to *N*-hydroxy-mexiletine were 28% lower following coadministration of caffeine.^[94]

On the other hand, Lanchote et al.^[95,96] studied the stereoselective disposition of mexiletine and its metabolites in 8 Chagasic women with ventricular arrhythmias. The AUC was reduced for *R*-(-)-mexiletine compared with *S*-(+)-mexiletine, whereas the CL/F for *R*-(-)-mexiletine was higher than that of *S*-(+)-enantiomer.^[96] In addition, stereoselective conjugation of *R*-(-)-*N*-hydroxy-mexiletine was

Table II. Pharmacokinetic parameters of mexiletine enantiomers in healthy volunteers who are extensive (EM) or poor (PM) metabolisers by cytochrome P450 (CYP) 2D6. Each study involved a single oral capsule of mexiletine hydrochloride 200mg

n and phenotype	$t_{1/2\beta}$ (h)	V_{β} (L)	CL/F (L/h)	CL _R (L/h)	CL _{NR} (L/h)	CL _{PM NOH} (L/h)	Reference
R(-)-mexiletine							
10 EMs ^a	9.1 ± 3.2	355 ± 125	33.0 ± 16.3	1.7 ± 0.7	28.0 ± 14.4	7.44 ± 3.12	93
10 EMs ^a	9.2 ± 3.0		30.7 ± 13.0	2.0 ± 0.8	25.5 ± 11.3	7.56 ± 2.88	94
4 PMs ^b	14.0 (11.1-20.6)	280 (200-405)	15.5 (13.9-16.9)	1.3 (1.0-1.6)	12.7 (11.5-13.8)	6.00 (5.04-6.66)	93
4 PMs ^b	12.1 (10.4-17.5)		16.4 (13.0-30.4)	1.4 (0.9-2.4)	13.5 (10.7-24.9)	9.18 (4.38-11.76)	94
S-(+)-mexiletine							
10 EMs ^a	9.6 ± 2.9	362 ± 132	31.7 ± 15.6	1.7 ± 0.8	26.8 ± 13.9	0.72 ± 0.36	93
10 EMs ^a	9.7 ± 2.9		28.1 ± 12.1	1.9 ± 0.8	23.3 ± 10.8	0.66 ± 0.36	94
4 PMs ^b	12.8 (12.0-25.7)	299 (229-439)	14.2 (13.1-14.6)	1.3 (1.1-1.6)	11.6 (10.2-12.1)	0.48 (0.42-0.54)	93
4 PMs ^b	14.0 (10.0-18.9)		14.5 (11.0-23.0)	1.1 (0.7-1.8)	11.9 (9.2-18.9)	0.54 (0.30-0.78)	94

a Values are reported as means ± SD.

b Values are reported as the median and range.

CL/F = apparent clearance; CL_R = renal clearance; CL_{NR} = nonrenal clearance; CL_{PM NOH} = partial metabolic clearance of mexiletine to *N*-hydroxy-mexiletine; EMs = extensive metabolisers (CYP2D6); n = number of participants; PMs = poor metabolisers (CYP2D6); $t_{1/2\beta}$ = elimination half-life; tid = 3 times daily; V_{β} = volume of distribution in the β -phase.

observed in these patients.^[95] Studying the same patients, Lanchote et al.^[96] also demonstrated that aliphatic hydroxylation (to hydroxymethyl-mexiletine) of the *R*(-)-enantiomer is also favoured.

In another study,^[97] the same favoured metabolism of the *R*(-)-enantiomer was observed for the aromatic hydroxylation of mexiletine (to *p*-hydroxy-mexiletine) in a patient treated with multiple doses of the antiarrhythmic drug. *In vitro* studies performed with human liver microsomes are in partial agreement with these observations.^[98] It was demonstrated that aliphatic hydroxylation is predominant for *R*(-)-mexiletine, whereas aromatic hydroxylation is favoured for the *S*(+)-enantiomer.^[98] Data also suggest that the metabolic conversion to hydroxylated metabolites is enantioselective as is the glucuronidation of these compounds.^[99]

Table II summarises the effect of genetic polymorphism on the pharmacokinetics of mexiletine enantiomers.

2.3 Age

The effects of age on the pharmacokinetics of mexiletine during long term oral administration were studied in 7 young (23 to 30 years) and 10 elderly (50 to 77 years) healthy individuals.^[75]

Each individual received an oral dose of mexiletine 50mg 3 times daily for 10 days. At steady state, the plasma concentrations and $t_{1/2\beta}$ of mexiletine were not statistically different between the young and elderly individuals. Plasma concentrations were 0.12 ± 0.03 mg/L in the young volunteers but 0.14 ± 0.15 mg/L in the older individuals. The $t_{1/2\beta}$ was 11.4 ± 1.8 hours and 10.5 ± 3.1 hours in young and elderly groups, respectively. There was no correlation between $t_{1/2\beta}$ and age ($r = 0.09$; $p > 0.1$). Similarly, plasma concentrations at steady state were not related to age ($r = 0.16$; $p > 0.1$).

Grech-Bélanger et al.^[67] also compared the kinetics of an oral dose of mexiletine 100mg between 2 groups: a young group (19 to 37 years) and an elderly group (65 to 79 years). No age-related differences in lag-time were noted but the K_a was significantly higher in the younger group. In this group, the C_{max} and t_{max} tended to be higher and shorter, respectively. Neither the $t_{1/2\beta}$ nor CL/F were significantly different between the 2 groups.

On the other hand, Ueno et al.^[100] evaluated the effects of age on mexiletine clearance in 90 inpatients treated with mexiletine for premature ventricular contractions. They found that the CL/F was reduced by about 20% in patients in their 70s and 80s compared with patients in their 40s. In agree-

ment with these results, others obtained a linear decrease of apparent CL/F with age.^[101]

The decrease in mexiletine clearance in elderly patients was explained by factors similar to those affecting resting metabolic rate.^[100] Indeed, resting metabolic rate in elderly men (mean age 75 years) is about 20% lower than in young men (mean age 21 years).^[102] In the study by Ueno et al.,^[100] serum mexiletine concentrations were linearly correlated with dose, leading the authors to conclude that age is not a major determinant in the clearance of mexiletine. Accordingly there is little reason to adjust the dose of mexiletine because of age alone.

In conclusion, studies indicated that there is no pharmacokinetic basis to modify the dosage of mexiletine in elderly patients. However, because aging is known to alter sensitivity to certain drugs, it may be advisable to administer lower dosages when initiating therapy in elderly patients.

2.4 Cigarette Smoking

The effects of cigarette smoking, a CYP1A2 inducer,^[84] on the pharmacokinetics of a single oral dose of mexiletine 200mg were studied in 2 groups of young volunteers: 6 smokers and 8 nonsmokers.^[49] Cigarette smoking had no effects on the absorption and distribution of mexiletine. However, the $t_{1/2\beta}$ was significantly shorter in the smoking group (7.2 ± 1.8 h vs 11.1 ± 3.4 h). The effects of cigarette smoking on the CL of mexiletine were also apparent, with the mean value in nonsmokers 25% less than that found in the smoker groups.

Measurement of the urinary excretion of 3 metabolites of mexiletine showed that the formation rates of hydroxymethyl-mexiletine and mexiletine *N*-glucuronide conjugate were significantly higher in smokers compared with nonsmokers. However, there were no differences in the formation rate of *p*-hydroxy-mexiletine. In contrast, Broly et al.^[40] did not report an increase in formation rate of hydroxymethyl-mexiletine in smokers.

2.5 Liver Disease

Cirrhosis of the liver markedly alters the pharmacokinetics of mexiletine.^[60,103,104] The steady-

state serum concentration of mexiletine is significantly higher in patients with cirrhosis of the liver compared with patients without liver disease.^[103] Following administration of a single intravenous dose of mexiletine hydrochloride 200mg to patients with cirrhosis or healthy controls, the CL and elimination rate constant were significantly lower in patients with cirrhosis compared with the control group.^[60] Indeed, the mean $t_{1/2\beta}$ of mexiletine in patients with cirrhosis was 2.9 times that found in the control group. The rate of distribution, V_d at steady state (V_{ss}) and V_d of the central compartment (V_c) remained unchanged.

The modification of the pharmacokinetics of mexiletine in patients with cirrhosis has definite clinical implications. Loading doses of mexiletine in these patients need no modification, but maintenance dosages should be reduced to a quarter or one-third of the usual dose.

2.6 Renal Disease

The effects of renal failure on the pharmacokinetics of mexiletine were evaluated by El Allaf et al.^[74] Mexiletine 50mg was administered orally 3 times daily for 10 days to 15 patients with chronic renal failure [creatinine clearance (CL_{CR}) lower than 1.8 L/h] and to 9 control individuals. When CL_{CR} was above 0.6 L/h, the pharmacokinetic parameters of mexiletine were not significantly modified by chronic renal failure. However, the plasma concentrations at steady state and $t_{1/2\beta}$ of mexiletine were increased when CL_{CR} was below 0.6 L/h.^[74] Other studies have reported no correlation between the degree of renal failure and CL/F or $t_{1/2\beta}$ of mexiletine in a group of patients with CL_{CR} in the ranges of 0 to 4.13 L/h, 0.12 to 2.4 L/h or 0.3 to 0.9 L/h.^[105-107] No differences in plasma concentrations were noted between control patients with normal renal function and patients with renal insufficiency ($CL_{CR} < 4.5$ L/h) receiving mexiletine 200mg 3 times daily.^[104]

There was no significant removal of mexiletine from plasma during haemodialysis, haemofiltration, peritoneal dialysis or plasmapheresis in 20 dialysis patients.^[108] In 5 individuals requiring long

term haemodialysis, no differences were observed between AUCs during dialysis and during the day on which the patients did not receive dialysis.^[105] Similarly, 2 case reports found no significant changes in the rate of removal of mexiletine following peritoneal dialysis.^[109,110]

These results indicate that the usual dosage regimen of mexiletine can be given without any modification to patients with chronic renal insufficiency having a CL_{CR} above 0.6 L/h. However, it is important to monitor the plasma concentrations of mexiletine in patients with renal failure when CL_{CR} is below 0.6 L/h. Supplemental doses are not likely to be required after dialysis.

2.7 Myocardial Infarction

The influence of acute myocardial infarction on the pharmacokinetics of mexiletine has been evaluated in several studies. Pentikäinen et al.^[111,112] performed 2 studies to investigate the kinetics of mexiletine following single doses of the drug during the acute and recovery phases of myocardial infarction. In these studies, a 400mg oral dose or 200mg intravenous dose of mexiletine hydrochloride were administered to patients (oxycodone was coadministered to most patients: see section 3.3). Both studies performed included 2 phases: the acute phase, within 24 hours of the onset of pain, and the recovery phase, 7 to 14 days following myocardial infarction. The C_{max} of mexiletine were significantly lower during the acute phase than the recovery phase following oral administration.^[112] This was explained by the slower and delayed gastrointestinal absorption of mexiletine in the acute phase study. The t_{max} and absorption $t_{1/2}$ tended to be higher during the acute compared with recovery phase; however, there were no significant differences in these parameters because of the wide interindividual variability, especially in the acute phase study. In addition, the extent of absorption remained unchanged.

Others have confirmed these changes in patients admitted to coronary care units early after the onset of myocardial infarction. Pottage et al.^[113] showed that 3 hours after the first dose of mexiletine

(600mg on arrival and 200mg 2 hours later), mean concentrations of the drug were significantly lower in patients with myocardial infarction than in those without. However, Prescott et al.^[33] found that absorption was delayed and incomplete in patients with acute myocardial infarction, particularly in patients who had received opioid analgesics.

Pentikäinen et al.^[111,112] showed a prolongation of mexiletine $t_{1/2\beta}$ in the acute phase of myocardial infarction. This prolongation of $t_{1/2\beta}$ was explained by an increase in the V_{ss} and the V_d during the γ -phase (V_γ) of the drug. Following intravenous administration of mexiletine, the CL was similar in the acute and recovery phases, while V_{ss} and V_γ were significantly higher (about 30%) in the acute phase. The increased V_{ss} and V_γ could also explain the lower plasma mexiletine concentrations found in the acute phase of myocardial infarction. The CL_R of mexiletine was not changed during the acute and recovery phases of myocardial infarction.^[111,112]

Lévy-Prades et al.^[114] reported an increase in the $t_{1/2\beta}$ of mexiletine in the acute phase of myocardial infarction in 6 patients, while CL and V_{ss} tended to be lower and higher, respectively, during the acute phase.

The loading dose of mexiletine must be increased about one-third in the acute phase of myocardial infarction because of the observed increase in the V_d . On the other hand, the maintenance dosage does not need to be adjusted.

2.8 Cardiac Failure

Leahey et al.^[115] investigated the kinetics of mexiletine in 14 patients with decreased left ventricular function (New York Heart Association functional class III or IV) and in healthy individuals who were free of hepatic or renal diseases. They showed that the $t_{1/2\beta}$ of mexiletine in these patients was 15.4 ± 5.8 hours compared with 8.1 ± 1.8 hours in healthy volunteers. No information was given on the absorption rate, V_d or CL of mexiletine in this study.

Since the elimination rate of mexiletine was slower in patients with heart failure, Leahey et

al.^[115] suggested that the dosage requirements of mexiletine should be lower in these patients. However, Campbell et al.^[29] did not observe any significant prolongation of the $t_{1/2\beta}$ in 6 patients with clinical evidence of congestive heart failure.

In a study including 43 patients with myocardial infarction and taking opioid analgesics, the mean plasma concentrations of mexiletine tended to be lower in patients with heart failure.^[113] In contrast, Nitsch et al.^[104] did not observe any difference in mexiletine concentrations in patients with congestive heart failure. No significant effects of congestive heart failure on the V_{β}/F or CL/F of orally administered mexiletine was also found.^[116] This is predictable, since CL/F reflects intrinsic clearance of the drug and is independent of liver blood flow.

2.9 Ventricular Arrhythmias

The pharmacokinetics of mexiletine are unchanged in patients with ventricular arrhythmias. Ohashi et al.^[117] studied the pharmacokinetics of mexiletine in patients with chronic premature ventricular contractions after single intravenous, single oral and repeated oral doses of the drug (150mg in each group). A diagnosis of primary myocardial disease was made in 3 cases, old myocardial infarction in one and idiopathic ventricular arrhythmia in 6 others. The mean C_{\max} of 0.44 ± 0.05 mg/L was measured 2.6 \pm 0.3 hours after oral administration and relative bioavailability was $83 \pm 9\%$. Steady-state was obtained after 4 to 5 days with no accumulation following repeated administration. The mean $t_{1/2\beta}$ of mexiletine for oral and intravenous administrations were almost the same: 10.5 ± 1.1 and 10.2 ± 1.2 hours, respectively. V_{β}/F and CL were 2.1 ± 0.5 L/kg and 0.36 ± 0.036 L/h/kg.^[117] During refractory ventricular arrhythmias, the mean plasma concentrations and AUC of mexiletine were directly proportional to the administered dose, suggesting first order elimination kinetics as observed in healthy volunteers.^[118,119]

Table III summarises the pharmacokinetics of mexiletine in patients with various pathologies.

3. Drug-Drug Interactions

3.1 Antacids

Administration of a commercially available antacid preparation containing magnesium-aluminium-silicate hydrate 1 hour prior to a single 400mg oral dose of mexiletine to 10 volunteers resulted in a prolongation of the t_{\max} (1.7 ± 0.7 h to 2.9 ± 1.0 h).^[36] Other pharmacokinetic parameters of mexiletine (C_{\max} , AUC and absorption $t_{1/2}$) were unaffected. The authors concluded that the prolongation in t_{\max} might be explained by a delay in gastric emptying.

3.2 Atropine and Metoclopramide

Effects of pretreatment with intravenous metoclopramide 10mg and atropine 0.6mg, both separately and combined, on the absorption rate and relative oral bioavailability of mexiletine 400mg were investigated in 8 healthy volunteers.^[63] The t_{\max} was increased by atropine (1.97 to 3.32h) and reduced by metoclopramide (1.97 to 1.03h). No significant changes in t_{\max} were noted when atropine and metoclopramide were administered together. Atropine pretreatment was also associated with a significant reduction in the C_{\max} of mexiletine (1.45 to 1.17 mg/L). No alteration in this concentration was observed following administration of either metoclopramide or the combined drugs. The $t_{1/2\beta}$ was reduced only with atropine pretreatment (9.49 to 8.02h). Neither of the drugs had an effect on the AUC of mexiletine, which indicates that the bioavailability of this antiarrhythmic agent was not affected.

Changes in mexiletine absorption produced by atropine and metoclopramide may be of particular importance at the beginning of oral mexiletine therapy. On the other hand, alteration in antiarrhythmic effects is unlikely during coadministration of atropine and/or metoclopramide with long term administration of mexiletine, since steady-state plasma concentrations during long term administration depend on the extent, rather than the rate, of absorption.

3.3 Opioid Analgesics

No study has been designed to evaluate the effects of opioid analgesics on the pharmacokinetics of mexiletine. However, it was reported that the mean concentrations measured 3 hours following the first mexiletine dose were significantly lower in patients taking morphine and diamorphine.^[113,127] An intravenous dose of metoclopramide was administered before the first dose of mexiletine in a group of patients treated with diamorphine.^[127] The mean plasma concentrations of mexiletine in this group were increased compared with a group of patients who received only diamorphine, indicating partial reversal of the reduction of mean 3-hour plasma mexiletine concentrations by diamorphine. Furthermore, administration of opioid analgesics reduced the AUC measured up to 8 hours.^[113]

Since opioid analgesics are known to inhibit gastric emptying,^[128] the slower absorption of mexiletine and lower plasma concentrations could be explained by this mechanism. However, it is difficult to determine if opioid analgesics affect the extent of mexiletine absorption, as the AUC were only measured during a short period of time.^[113]

3.4 Caffeine

Joeres et al.^[129] studied the effects of mexiletine on caffeine elimination in 5 healthy volunteers and in 7 patients with cardiac arrhythmias. Volunteers received 366mg of caffeine on 2 occasions: once alone and once with mexiletine 200mg given orally. In the second part of their study, a dose of caffeine was given to patients receiving long term treatment with mexiletine 200mg 3 times daily. Administration of caffeine was repeated at least 3 days after the termination of antiarrhythmic treatment in these patients. Following the coadministration of mexiletine in volunteers, the CL/F of caffeine was reduced from 7.56 ± 0.90 to 3.24 ± 0.24 L/h and $t_{1/2\beta}$ increased from 246 ± 25 to 419 ± 28 minutes (all values are means \pm SEM).

During mexiletine treatment in the patient group, the CL/F of caffeine was only 2.22 ± 0.96 L/h with an $t_{1/2\beta}$ of 878 ± 137 minutes. After the termination

of mexiletine therapy, the CL/F of caffeine increased to 4.26 ± 0.72 L/h with an $t_{1/2\beta}$ of 330 ± 46 minutes.

Labbé et al.^[94] has also studied the effects of caffeine on the stereoselective disposition by CYP2D6 of mexiletine in 14 healthy young volunteers: 10 EMs and 4 PMs. A single oral dose of mexiletine hydrochloride 200mg was administered on 2 occasions; one alone and one during the concomitant administration of caffeine 100mg 4 times daily starting 2 days before and up to 2 days after the administration of mexiletine. Coadministration of caffeine did not alter the CL of mexiletine enantiomers in either EMs or PMs. Although the urinary recovery of unchanged mexiletine for each enantiomer was not modified by caffeine treatment in both phenotypes, a stereoselective decrease (16% in EMs and 14% in PMs) in the urinary recovery of *N*-hydroxy-mexiletine from the R(-)-enantiomer was observed. Also, the CL_{PM} of R(-)-mexiletine to *N*-hydroxy-mexiletine glucuronide was reduced from 7.56 ± 2.88 L/h to 6.36 ± 1.92 L/h and from 9.18 (4.38-11.76) to 6.54 (4.62-7.62) L/h in EMs and PMs, respectively. These results suggest that CYP1A2 is involved in the formation of *N*-hydroxy-mexiletine.

The data obtained indicate that the coadministration of caffeine, a substrate of CYP1A2,^[130,131] does not lead to clinically significant changes in mexiletine plasma concentrations. However, increased plasma concentrations of caffeine caused by the coadministration of mexiletine may still be of concern in patients presenting with cardiac arrhythmias.

3.5 Theophylline

Several studies have documented a pharmacokinetic interaction between mexiletine and theophylline (a CYP1A2 substrate).^[132-142] In patients, theophylline serum concentrations increased about 2-fold following the administration of mexiletine;^[133,134,138,139,141] however, mexiletine serum concentrations did not change. In young volunteers, the administration of mexiletine decreased the CL/F of theophylline by more than 40% and

Table III. Pharmacokinetic parameters of mexiletine in patients with various pathologies. Values are given as means \pm SD except where indicated (items marked with an asterisk are means \pm SEM)

n and gender	Formulation	Dose of mexiletine hydrochloride	C _{max} (mg/L)	t _{max} (h)	t _{1/2β} (h)	Vd (L)	CL/F (L/h)	CLR (L/h)	Ae (%)	Reference
Liver disease (cirrhosis)										
6M	Intravenous	Single 200mg*			28.7 \pm 4.0	5.2 \pm 0.7/kg ^a	0.14 \pm 0.02/kg			60
Renal disease										
5F	Orally	Single 300mg	0.79 \pm 0.31	3.2 \pm 1.8	9.5 \pm 1.0					106
3M, 5F	Orally	50mg tid \times 10 days			15.7 \pm 5.0					74
4M, 3F	Orally	50mg tid \times 10 days			13.8 \pm 3.8					74
14M	Oral capsule	Single 200mg	0.26 - 0.56	2 to 4	18.9 \pm 7.4		22.7 \pm 6.5	4.0 \pm 3.2		105
13M	Oral capsule	Single 200mg	0.30 \pm 0.06	3.5 \pm 1.2	7.8 \pm 1.7					120
Myocardial infarction										
7 ^c	Oral capsule	Single 400mg	0.65 \pm 0.05	4.7 \pm 2.0	15.0 \pm 0.6			2.69 \pm 0.89	8.8 \pm 1.6 ^d	112
4 ^c	Intravenous	Single 200mg			14.5 \pm 2.2	612 \pm 578 ^e	29.2 \pm 5.3	4.0 \pm 0.7	12.1 \pm 2.2 ^d	111
7 ^c	Intravenous	Single 200mg			14.7 \pm 3.4	664 \pm 111 ^e	34.5 \pm 5.4	2.8 \pm 0.6	8.7 \pm 0.7 ^d	114
6M ^c	Intravenous ^f				28.4 \pm 12.1	7.9 \pm 1.4/kg ^a	0.22 \pm 0.09/kg			114
Recovery phase										
7 ^b	Oral capsule	Single 400mg	1.08 \pm 0.11	1.5 \pm 0.2	11.8 \pm 0.8			1.60 \pm 0.42	7.0 \pm 1.1 ^d	112
7 ^b	Intravenous	Single 200mg			11.3 \pm 2.4	458 \pm 52 ^e	31.6 \pm 4.6	3.0 \pm 0.7	9.6 \pm 2.5 ^d	111
6M ^h	SR form	bid \times 5 days			14.1 \pm 4.5	6.3 \pm 3.2/kg ^a	0.38 \pm 0.10/kg			114
6M ⁱ	SR form	Single 360mg				5.4 \pm 1.3/kg ^j	0.37 \pm 0.17/kg			121
Seizures										
2M	Oral capsule	Single 100mg			2.7 and 4.6					122
2M	Oral capsule	Single 200mg			2.7 and 5.1					122
2M	Oral capsule	Single 300mg			5.6 and 5.1					
2M	Oral capsule	Single 400mg			4.8 and 7.2					
2M	Oral capsule	50mg qid \times 7days			5.3 and 3.6					123
2M	Oral capsule	100mg qid \times 7 days			7.8 and 3.5					
2M	Oral capsule	150mg qid \times 7 days			5.9 and 4.5					
2M	Oral capsule	200mg qid \times 7 days			6.7 and 4.9					
Ventricular dysrhythmias										
6	Intravenous	Single 100mg			0.9-2.8					124
1	Orally	Single 7 mg/kg		3	2.67					
11	Orally	Single 600mg	1.6-2.8	3						62

Landacpe table III cont.

prolonged its $t_{1/2\beta}$ (74 to 103%).^[136,137,140] Interactions between theophylline and mexiletine are mostly explained by inhibition of theophylline metabolism because of competitive inhibition of CYP1A2 by mexiletine.^[135,136,140] The inhibitory effects of mexiletine on theophylline biotransformation are independent of gender.^[136] In patients receiving concomitant administration of mexiletine and theophylline, lower dosages of theophylline (approximately 50%) may be required to minimise potential theophylline toxicity. Moreover, plasma theophylline concentrations and the clinical signs of theophylline toxicity should be monitored carefully.

3.6 Ciprofloxacin

The influence of ciprofloxacin, a CYP1A2 inhibitor,^[143,144] on the pharmacokinetics of mexiletine was evaluated in 17 healthy volunteers (smokers and nonsmokers).^[73] Each volunteer received a single 200mg dose of mexiletine hydrochloride orally on 2 occasions (1 week apart), one alone and one with ciprofloxacin 750mg twice daily at steady state. In the mexiletine alone study arm, the CL/F and CL_{NR} of mexiletine were increased in smokers compared with nonsmokers. Coadministration of ciprofloxacin reduced the CL/F of mexiletine in nonsmokers (14.7%) and smokers (10.7%). The CL_{NR} of mexiletine was also decreased 17.3% in nonsmokers and 12.3% in smokers following the administration of ciprofloxacin.

3.7 Phenytoin

Following anecdotal observations suggesting that plasma concentrations of mexiletine were abnormally low in 3 patients treated concomitantly with mexiletine and phenytoin, Begg et al.^[64] studied the effects of phenytoin administration on the pharmacokinetics of mexiletine in 6 healthy volunteers. Each volunteers received a single 400mg oral dose of mexiletine before and after a 7-day pretreatment with phenytoin 300mg daily under conditions of controlled urinary pH. Phenytoin administration caused a significant decrease in AUC (17.7 ± 6.2 to 8.0 ± 3.6 mg/L · h) and $t_{1/2\beta}$ ($17.2 \pm$

5	CI	60 mg/h × 24h			11.7 ± 1.3	469 ± 95	27.9 ± 5.5	125
10	Intravenous	Single 200mg*			13.2 ± 1.7	6.6 ± 0.9/kg ^b	0.39 ± 0.07/kg	29
5M, 2F	Orally	300 or 400mg q8h ^l			12.6(10.0-14.4)	5.6 (3.9-9.0)/kg	24.2 (14.8-41.3)	119
5M, 7F	Oral capsule	200mg q8h × 2 weeks	1.17 ± 0.44	2.0 ± 1.8				126
5M, 7F	SR form	360mg q12h × 2 weeks	1.20 ± 0.45	4.0 ± 1.6				
4M, 4F	Intravenous	Single 150mg			10.2 ± 1.2	2.1 ± 0.5/kg ^b	0.36 ± 0.04/kg	117
5M, 2F	Orally	Single 150mg	0.44 ± 0.05	2.6 ± 0.3	10.5 ± 1.1			

a Vd at steady-state.
b Including 5 individuals who required maintenance dialysis.
c Within 24 hours of the onset of pain.
d 0 to 72 hours.
e Vd in γ-phase.
f Loading dose of 250mg given over 15 minutes followed by a continuous infusion of 1250mg from 1 to 48 hours.
g 7 to 14 days after the onset of pain.
h 7 to 8 days after the onset of pain.
i 8 to 21 days after acute myocardial infarction.
j Vd of the central compartment.
k Vd in β-phase.
l Values are reported as the mean and range.
Ae = urinary excretion of mexiletine in the 48h period following administration, expressed as a percentage of the dose; **bid** = twice daily; **CI** = continuous infusion; **CL/F** = apparent clearance; **CL_R** = renal clearance; **C_{max}** = maximum drug plasma concentration; **F** = female; **M** = male; **n** = number of participants; **qid** = 4 times daily; **q8h** = every 8 hours; **q12h** = every 12 hours; **SR** = sustained release; **t_{max}** = time to maximum drug plasma concentration; **t_{1/2β}** = elimination half-life; **tid** = 3 times daily; **Vd** = volume of distribution.

5.3 to 8.4 ± 4.2 h). However, the C_{\max} and t_{\max} of mexiletine were not modified following phenytoin administration. These authors suggested that the effects of phenytoin on mexiletine kinetics are mainly caused by induction of hepatic mixed-function oxidases.

3.8 Rifampicin (Rifampin)

Pentikäinen et al.^[65] studied the effects of pre-treatment with the CYP3A4 inducer rifampicin 300mg twice daily for 10 days on the kinetics of a single oral dose of mexiletine hydrochloride 400mg administered to 8 healthy volunteers. No effects on absorption and distribution of mexiletine were noted following rifampicin administration, as indicated by a nonsignificant modification in lag-time, absorption $t_{1/2}$, C_{\max} , t_{\max} and V_{β}/F . However, the elimination rate of mexiletine was significantly enhanced by rifampicin, as shown by a reduction in the mean $t_{1/2\beta}$ (8.5 ± 0.8 to 5.0 ± 0.4 h) and an increase in the CL (30.3 ± 5.7 to 45.78 ± 7.08 L/h). The increase in CL was because of significant changes in CL_{NR} (26.1 ± 4.08 to 42.66 ± 6.18 L/h), whereas the CL_R was not affected by rifampicin.

Interactions between mexiletine and either phenytoin or rifampicin are clinically important because the increased elimination of mexiletine results in abnormally low steady-state serum concentrations of the antiarrhythmic agent.

3.9 Cimetidine and Ranitidine

Klein et al.^[35] studied the pharmacokinetics of an oral dose of mexiletine hydrochloride 300mg in 6 healthy individuals before and after 1 week of treatment with cimetidine 300mg 4 times daily. Cimetidine had significant effects on the absorption of mexiletine, resulting in a prolongation of the mean absorption $t_{1/2}$ (0.20 ± 0.14 to 0.61 ± 0.35 h), decrease in C_{\max} (0.74 ± 0.19 to 0.59 ± 0.15 mg/L) and longer t_{\max} (1.13 ± 0.31 to 1.88 ± 0.83 h) of mexiletine. Cimetidine did not alter the distribution and elimination of mexiletine, as demonstrated by the similar AUC, V_{β}/F , CL and $t_{1/2\beta}$ before and after cimetidine administration. These authors concluded that the modifications of gastrointestinal

absorption caused by cimetidine are minor and not of any clinical importance.

The effects of cimetidine and ranitidine on the pharmacokinetics of mexiletine were also studied in 6 healthy volunteers after a single 100mg oral dose and 15-minute intravenous infusions of 3 mg/kg of the antiarrhythmic agent.^[145] Neither H_2 receptor antagonist modified the distribution and elimination of mexiletine, nor did they alter its overall pharmacokinetic parameters or excretion of metabolites.

3.10 Omeprazole

The effects of omeprazole on the pharmacokinetics of a single oral dose of mexiletine 200mg were studied in 9 male Japanese volunteers.^[72] In this study, the concentrations and CL/F of mexiletine were not altered after 7 days of administration of omeprazole 40mg daily. Moreover, no measurable differences were noted in the C_{\max} , K_a , V_d , $t_{1/2\beta}$ and AUC. In brief, the pharmacokinetics of mexiletine were not altered during the concomitant administration of omeprazole.

3.11 Fluconazole

The effects of fluconazole on the pharmacokinetics of a single oral dose of mexiletine 200mg were evaluated in 6 male Japanese volunteers.^[71] The CL/F of mexiletine was not modified after 7 days of fluconazole treatment at a dose of 200mg daily or after an additional 7 days administration of fluconazole at a dose of 400mg daily. Other pharmacokinetic parameters studied (C_{\max} , K_a , V_d and AUC) were not changed. These results suggest that fluconazole does not inhibit the metabolism of mexiletine.

3.12 Digoxin

No clinically significant interactions between mexiletine and digoxin have been reported. The effects of mexiletine on digoxin concentrations were studied in patients and healthy volunteers.^[146,147] Steady-state concentrations of digoxin were not altered by the addition of mexiletine.

Table IV. Pharmacokinetic interactions with mexiletine in healthy volunteers. Values are given as means \pm SD except where indicated (items marked with an asterisk are means \pm SEM). Mexiletine was administered as an oral capsule

n and gender	Dose of mexiletine hydrochloride	Phenotype	C _{max} (mg/L)	t _{max} (h)	t _{1/2β} (h)	Vd (L)	CL/F (L/h)	CLR (L/h)	Ae (%)	Reference
Antacid (1.87g magnesium-aluminium-silicate hydrate)										
5M, 5F	Single 400mg 1h after		1.92 \pm 0.53	2.9 \pm 1.0	9.6 \pm 2.0					36
Atropine 0.6mg IV										
8M	Single 400mg 5 min after		1.17	3.3	8.0					63
Metoclopramide 10mg IV										
8M	Single 400mg 5 min after		1.79	1.0	8.9					63
Atropine 0.6mg IV + metoclopramide 10mg IV										
8M	Single 400mg 5 min after		1.36	1.7	8.5					63
Caffeine 366mg base										
5	Single 200mg*				7.5 \pm 0.6	562 \pm 78	53.1 \pm 8.58			129
Cimetidine 300mg qid \times 7 days										
3M, 3F	Single 300mg on day 7		0.59 \pm 0.15	1.9 \pm 0.8	8.3 \pm 1.7	490 \pm 128 ^a	45.6 \pm 9.24			35
Ciprofloxacin 750mg bid \times 5 days										
17M	Single 200mg on day 3									73
Fluconazole 200mg od \times 7 days										
6M	Single 200mg on day 7		0.45 \pm 0.01		8.0 \pm 2.3	5.6 \pm 1.3/kg	0.47 \pm 0.13/kg			71
Fluconazole 400mg od \times 7 days										
2M	Single 200mg on day 7				11.7, 6.4	5.3, 5.9/kg	0.31, 0.59/kg		7 \pm 3	71
Ornithine 400mg od \times 8 days										
9M	Single 200mg on day 8		0.41 \pm 0.10		8.9 \pm 2.1	7.1 \pm 1.1/kg	0.58 \pm 0.18/kg			72
Phenylephrine 300mg at night \times 7 days										
3M, 3F	Single 400mg on day 8		0.81 \pm 0.28	1.5 \pm 0.7	8.4 \pm 4.2					64
Quinidine (single oral dose of 41.5mg quinidine base)										
5M, 1F	Single 200mg 1h after	EMs								70
Quinidine 50mg od \times 4 days										
13M, 1F	Single 200mg on day 3	10 EMs 4 PMS ^b			10.6 \pm 1.6	420 \pm 132 ^a	31.4 \pm 14.3	4.0 \pm 2.8	9.3 \pm 5.0	18
Rifampicin 300 od \times 10 days										
3M, 5F	Single 400mg on day 10*		0.93 \pm 0.11	2.0 \pm 0.3	5.0 \pm 0.4	313 \pm 36 ^a	50.9 \pm 7.9	3.1 \pm 1.1	12.7 \pm 11.4	65

a Apparent volume of distribution in the β -phase.

b Values are reported as the median and range.

Ae = urinary excretion of mexiletine in the 48h period following administration, expressed as a percentage of the dose; **bid** = twice daily; **CL/F** = apparent clearance; **CL_R** = renal clearance; **C_{max}** = maximum drug plasma concentration; **CYP** = cytochrome P450; **EMs** = extensive metabolisers (CYP2D6); **F** = female; **IV** = intravenous; **M** = male; **n** = number of participants; **od** = once daily; **PMS** = poor metabolisers (CYP2D6); **qid** = 4 times daily; **t_{max}** = time to maximum drug plasma concentration; **t_{1/2β}** = elimination half-life; **Vd** = volume of distribution.

Table IV summarises our knowledge of the pharmacokinetic interactions with mexiletine obtained in studies with healthy volunteers.

3.13 Propafenone

Since mexiletine and propafenone are metabolised by the same isozymes (CYP2D6, 1A2 and probably 3A4), we studied the potential pharmacokinetic interaction between these 2 antiarrhythmic agents.^[148] 15 healthy volunteers, 8 EM and 7 PM (CYP2D6) received oral doses of mexiletine 100mg twice daily from days 1 to 8 and oral doses of propafenone 150mg twice daily from days 5 to 12. Interdose studies were performed at steady state on mexiletine alone (day 4), mexiletine and propafenone (day 8) and propafenone (day 12). Oral clearances of mexiletine and propafenone were 1.5- and 7.9-fold higher, respectively, in EMs compared with PMs ($p < 0.05$) when both drugs were administered alone. In EMs, coadministration of propafenone decreased oral clearances of *R*-(-)-mexiletine (from 41 ± 11 to 28 ± 7 L/h) and *S*-(+)-mexiletine (from 43 ± 15 to 29 ± 11 L/h) to an extent such that these values were no longer different between EMs and PMs. In EMs, partial metabolic clearances of mexiletine to hydroxymethyl-mexiletine, *p*-hydroxy-mexiletine and *m*-hydroxy-mexiletine were decreased by propafenone administration whereas partial metabolic clearance to *N*-hydroxy-mexiletine was unaffected. Propafenone did not alter the kinetics of mexiletine enantiomers in PMs.

On the other hand, no pharmacokinetic parameters of propafenone were modified during the concomitant administration of mexiletine in individuals with either phenotype. We concluded that administration of propafenone is associated with the potent inhibition of CYP2D6 which may lead to increased plasma concentrations of substrate with lower affinity for the enzyme, such as mexiletine.

4. Conclusion

The absorption of mexiletine takes place in the small intestine. Therefore, any factors affecting the rate of gastric emptying modify the rate of drug

absorption, resulting in alterations in C_{max} and t_{max} . Myocardial infarction, opioid analgesics, atropine and antacids slow down the rate of mexiletine absorption, whereas metoclopramide enhances it. None of the interactions affecting the absorption of mexiletine appear, so far, to be of major clinical importance, except perhaps at the beginning of therapy where the serum concentrations of mexiletine will be lower than expected.

Mexiletine is extensively metabolised and formation of its metabolites is mainly mediated by the mixed-function oxidase system (CYP). Patients with cirrhosis of the liver present a decrease in the elimination of mexiletine. Drug-drug interactions significantly affecting the metabolism of mexiletine are largely attributable to the effects on CYP2D6 (quinidine and propafenone), CYP1A2 (ciprofloxacin and cigarette smoking) and CYP3A4 (rifampicin and phenytoin). Any substrates, inducers or inhibitors of these isoenzymes may significantly alter the elimination of mexiletine. On the other hand, mexiletine produces clinically significant changes in the elimination of substrates of these enzymes, as reported with caffeine and theophylline.

The pharmacokinetic interactions reported involving the elimination of mexiletine, unlike those affecting its absorption, are clinically significant, as they result in changes in the steady-state serum concentrations of this drug which possesses a narrow therapeutic index. Monitoring of plasma concentrations should be undertaken if coadministration of interacting drugs is unavoidable.

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References

1. Campbell NPS, Kelly JG, Shanks RG, et al. Mexiletine (Kö 1173) in the management of ventricular dysrhythmias. *Lancet* 1973; II: 404-7
2. Campbell RWF, Dolder MA, Prescott LF, et al. Comparison of procainamide and mexiletine in prevention of ventricular ar-

- rhythmias after acute myocardial infarction. *Lancet* 1975; 1: 1257-9
3. Talbot RG, Nimmo J, Julian DG, et al. Treatment of ventricular arrhythmias with mexiletine (Kö 1173). *Lancet* 1973; II: 399-403
 4. Chew CYC, Collett J, Singh BN. Mexiletine: a review of its pharmacological properties and therapeutic efficacy in arrhythmias. *Drugs* 1979; 17: 161-81
 5. Akiyama M, Sugimoto T, Uraoka T, et al. Electrophysiological effects of mexiletine in man. *Jpn Heart J* 1982; 23: 237-9
 6. Sami M, Lisbona R. Mexiletine: long-term efficacy and hemodynamic actions in patients with ventricular arrhythmia. *Can J Cardiol* 1985; 1: 251-8
 7. Stein J, Podrid P, Lown B. Effects of oral mexiletine on left and right ventricular function. *Am J Cardiol* 1984; 54: 575-8
 8. Sheldon RS, Duff HJ, Mitchell LB, et al. Effect of oral combination therapy with mexiletine and quinidine on left and right ventricular function. *Am Heart J* 1988; 115: 1030-6
 9. Duff HJ, Roden D, Primm RK, et al. Mexiletine in the treatment of resistant ventricular arrhythmias: enhancement of efficacy and reduction of dose-related side effects by combination with quinidine. *Circulation* 1983; 67: 1124-8
 10. Leahy Jr EB, Heissenbuttel RH, Giardina EGV, et al. Combined mexiletine and propranolol treatment of refractory ventricular tachycardia. *BMJ* 1980; 281: 357-8
 11. Valenzuela C, Sanchez-Chapula J. Electrophysiologic interactions between mexiletine-quinidine and mexiletine-ropitoin in guinea pig papillary muscle. *J Cardiovasc Pharmacol* 1989; 14: 783-9
 12. Costard-Jaeckle A, Liem BL, Franz MR. Frequency-dependent effect of quinidine, mexiletine and their combination of postrepolarization refractoriness *in vivo*. *J Cardiovasc Pharmacol* 1989; 14: 810-7
 13. Duff HJ, Cannon NJ, Sheldon RS. Mexiletine-quinidine in isolated hearts: an interaction involving the sodium channel. *Cardiovasc Res* 1989; 23: 584-92
 14. Duff HJ, Kolodgie FD, Roden DM, et al. Electropharmacologic synergism with mexiletine and quinidine. *J Cardiovasc Pharmacol* 1986; 8: 840-6
 15. Duff HJ. Mexiletine-quinidine combination: enhanced antiarrhythmic and electrophysiologic activity in the dog. *J Pharmacol Exp Ther* 1989; 249: 617-22
 16. Roden DM, Iansmith DHS, Woosley RL. Frequency-dependent interactions of mexiletine and quinidine on depolarization and repolarization in canine Purkinje fibers. *J Pharmacol Exp Ther* 1987; 243: 1218-24
 17. Duff HJ, Rahmberg M, Sheldon RS. Role of quinidine in the mexiletine-quinidine interaction: electrophysiologic correlates of enhanced antiarrhythmic efficacy. *J Cardiovasc Pharmacol* 1990; 16: 685-92
 18. Turgeon J, Fiset C, Giguère R, et al. Influence of debrisoquine phenotype and of quinidine on mexiletine disposition in man. *J Pharmacol Exp Ther* 1991; 259: 789-98
 19. Yeung-Lai-Wah JA, Murdock CJ, Boone J, et al. Propafenone-mexiletine combination for the treatment of sustained ventricular tachycardia. *J Am Coll Cardiol* 1992; 20: 547-51
 20. Valenzuela C, Delpón E, Tamargo J. Electrophysiologic interactions between mexiletine and propafenone in guinea pig papillary muscles. *J Cardiovasc Pharmacol* 1989; 14: 351-7
 21. Breithardt G, Seipel I, Abendroth RR. Comparison of the antiarrhythmic efficacy of disopyramide and mexiletine against stimulus-induced ventricular tachycardia. *J Cardiovasc Pharmacol* 1981; 3: 1026-37
 22. Lüderitz B, Mletzko R, Jung W, et al. Combination of antiarrhythmic drugs. *J Cardiovasc Pharmacol* 1991; 17 Suppl. 6: S48-52
 23. Wagner WL, Manz M, Luderitz B. Combination of sotalol with the class IB substances mexiletine or tocainide in complex ventricular extrasystole. *Z Kardiol* 1987; 76: 296-302
 24. Greenspan AM, Spielman SR, Webb CR, et al. Efficacy of combination therapy with mexiletine and a type IA agent for inducible ventricular tachyarrhythmias secondary to coronary artery disease. *Am J Cardiol* 1985; 56: 277-84
 25. Tanabe T, Takahashi K, Yoshioka K, et al. Evaluation of disopyramide and mexiletine used alone and in combination for ventricular arrhythmias in patients with and without overt heart disease. *Int J Cardiol* 1991; 32: 303-12
 26. Toivonen L, Kadish A, Morady F. A prospective comparison of class IA, B, and C antiarrhythmic agents in combination with amiodarone in patients with inducible, sustained ventricular tachycardia. *Circulation* 1991; 84: 101-8
 27. Hoffmann A, Follath F, Burckhardt D. Safe treatment of resistant ventricular arrhythmias with combination of amiodarone and quinidine or mexiletine. *Lancet* 1983; I: 704-5
 28. Waleffe A, Mary-Rabine L, Legrand V, et al. Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia. *Am Heart J* 1980; 100: 788-93
 29. Campbell NPS, Kelly JG, Adgey AAJ, et al. The clinical pharmacology of mexiletine. *Br J Clin Pharmacol* 1978; 6: 103-8
 30. Peyrieux JC, Boissel JP, Leizorovicz A, et al. Relationship between plasma mexiletine levels at steady-state. Presence of ventricular arrhythmias and side effects. *Fundam Clin Pharmacol* 1987; 1: 45-57
 31. Lévy-Prades R, Philip F, Danays T, et al. Pharmacocinétique de la mexilétine et de son métabolite hydroxyméthyle après administration intramusculaire et intraveineuse de mexilétine chez le sujet sain. *Thérapie* 1987; 42: 3-7
 32. Bradbrook ID, Feldschreiber P, Morrison PJ, et al. Plasma mexiletine concentrations following combined oral and intramuscular administration. *Eur J Clin Pharmacol* 1981; 19: 301-4
 33. Prescott LF, Pottage A, Clements JA. Absorption, distribution and elimination of mexiletine. *Postgrad Med J* 1977; 53 Suppl. 1: 50-5
 34. Häselbarth V, Doevendans JE, Wolf M. Kinetics and bioavailability of mexiletine in healthy subjects. *Clin Pharmacol Ther* 1981; 29: 729-36
 35. Klein A, Sami M, Selinger K. Mexiletine kinetics in healthy subjects taking cimetidine. *Clin Pharmacol Ther* 1985; 37: 669-73
 36. Herzog P, Holtermüller KH, Kasper W, et al. Absorption of mexiletine after treatment with gastric antacids. *Br J Clin Pharmacol* 1982; 14: 746-7
 37. Holt DW, Chadwick DE, Campbell RWF. Absorption and antiarrhythmic efficacy of sustained-release mexiletine. *Clin Ther* 1983; 5: 268-78
 38. Pringle T, Fox J, McNeill JA, et al. Dose independent pharmacokinetics of mexiletine in healthy volunteers. *Br J Clin Pharmacol* 1986; 21: 319-21
 39. Campbell NPS, Kelly JG, Adgey AAJ, et al. Mexiletine in normal volunteers. *Br J Clin Pharmacol* 1978; 6: 372-3
 40. Broly F, Vandamme N, Libersa C, et al. The metabolism of mexiletine in relation to the debrisoquine/sparteine-type polymorphism of drug oxidation. *Br J Clin Pharmacol* 1991; 32: 459-66
 41. Rohrig TP, Harty LE. Postmortem distribution of mexiletine in a fatal overdose. *J Anal Toxicol* 1994; 18: 354-5

42. Turgeon J, Grech-Bélanger O, Gilbert M. Erythrocyte and serum distribution of mexiletine in man. *Biopharm Drug Dispos* 1987; 8: 571-6
43. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; 157: 446-7
44. Timmis AD, Jackson G, Holt DW. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; II: 647-8
45. Gregg AR, Tomich PG. Mexiletine use in pregnancy. *J Perinatol* 1988; 8: 33-5
46. Lewis AM, Patel L, Johnston A, et al. Mexiletine in human blood and breast milk. *Postgrad Med J* 1981; 57: 546-7
47. Kwok DW, Kerr CR, McErlane KM. Pharmacokinetics of mexiletine enantiomers in healthy human subjects. A study of the *in vivo* serum protein binding, salivary excretion and red blood cell distribution of the enantiomers. *Xenobiotica* 1995; 25: 1127-42
48. Beckett AH, Chidomere EC. The identification and analysis of mexiletine and its metabolic products in man. *J Pharm Pharmacol* 1977; 29: 281-5
49. Grech-Bélanger O, Gilbert M, Turgeon J, et al. Effect of cigarette smoking on mexiletine kinetics. *Clin Pharmacol Ther* 1985; 37: 638-43
50. Turgeon J, Paré JRJ, Lalande M, et al. Isolation and structural characterization by spectroscopic methods of two glucuronide metabolites of mexiletine after N-oxidation and deamination. *Drug Metab Dispos* 1992; 20: 762-9
51. Grech-Bélanger O, Turgeon J, Lalande M, et al. Methoxyhydroxymexiletine, a new metabolite of mexiletine. Isolation, characterization, and species differences in its formation. *Drug Metab Dispos* 1991; 19: 458-61
52. Grech-Bélanger O, Turgeon J, Lalande M. 2,6-Dimethylphenol: a new metabolite of mexiletine. *Res Commun Chem Pathol Pharmacol* 1987; 58: 53-62
53. Grech-Bélanger O, Turgeon J, Gilbert M. Stereoselective disposition of mexiletine in man. *Br J Clin Pharmacol* 1986; 21: 481-7
54. Kiddie MA, Kaye CM, Turner P, et al. The influence of urinary pH on the elimination of mexiletine. *Br J Clin Pharmacol* 1974; 1: 229-32
55. Kaye CM, Kiddie MA, Turner P. Variable pharmacokinetics of mexiletine. *Postgrad Med J* 1977; 53 Suppl. 1: 56-8
56. Mitchell BG, Clements JA, Pottage A, et al. Mexiletine disposition: individual variation in response to urine acidification and alkalinisation. *Br J Clin Pharmacol* 1983; 16: 281-4
57. Johnston A, Burgess CD, Henry JA, et al. Mexiletine elimination: influence of urinary pH and volume. *Br J Pharmacol* 1981; 72: 135P
58. Beckett AH, Chidomere EC. The distribution, metabolism and excretion of mexiletine in man. *Postgrad Med J* 1977; 53 Suppl. 1: 60-6
59. Johnston A, Burgess CD, Warrington SJ, et al. The effect of spontaneous changes in urinary pH on mexiletine plasma concentrations and excretion during chronic administration to healthy volunteers. *Br J Clin Pharmacol* 1979; 8: 349-52
60. Pentikäinen PJ, Hietakorpi S, Halinen MO, et al. Cirrhosis of the liver markedly impairs the elimination of mexiletine. *Eur J Clin Pharmacol* 1986; 30: 83-8
61. Lledó P, Abrams SML, Johnston A, et al. Influence of debrisoquine hydroxylation phenotype on the pharmacokinetics of mexiletine. *Eur J Clin Pharmacol* 1993; 44: 63-7
62. Clark RA, Julian DG, Nimmo J, et al. Clinical pharmacological studies of Kö 1173: a new antiarrhythmic agent. *Proc Br Pharmacol Soc* 1973; 47: 622P-3P
63. Wing LMH, Meffin PJ, Grygiel JJ, et al. The effect of metoclopramide and atropine on the absorption of orally administered mexiletine. *Br J Clin Pharmacol* 1980; 9: 505-9
64. Begg EJ, Chinwah PM, Webb C, et al. Enhanced metabolism of mexiletine after phenytoin administration. *Br J Clin Pharmacol* 1982; 14: 219-23
65. Pentikäinen PJ, Koivula IH, Hiltunen HA. Effect of rifampicin treatment on the kinetics of mexiletine. *Eur J Clin Pharmacol* 1982; 23: 261-6
66. Santoni Y, Bruno R, Fornaris M, et al. Pharmacocinétique et biodisponibilité relative chez le sujet sain d'une nouvelle forme orale de mexilétine à libération continue. *Therapie* 1983; 38: 341-4
67. Grech-Bélanger O, Barbeau G, Kishka P, et al. Pharmacokinetics of mexiletine in the elderly. *J Clin Pharmacol* 1989; 29: 311-5
68. Paczkowski D, Sadowski Z, Filipek M, et al. Pharmacokinetics of mexiletine and its metabolites, hydroxymethylmexiletine and p-hydroxymexiletine, after single oral administration in healthy subjects. *Pol J Pharmacol Pharm* 1990; 42: 365-76
69. Katagiri Y, Nagasaki S, Hayashibara M, et al. Salivary excretion of mexiletine in normal healthy volunteers. *J Pharm Pharmacol* 1991; 43: 513-5
70. Broly F, Vandamme N, Caron J, et al. Single-dose quinidine treatment inhibits mexiletine oxidation in extensive metabolizers of debrisoquine. *Life Sci* 1991; 48: PL-123-8
71. Ueno K, Yamaguchi R, Tanaka K, et al. Lack of a kinetic interaction between fluconazole and mexiletine. *Eur J Clin Pharmacol* 1996; 50: 129-31
72. Kusumoto M, Ueno K, Tanaka K, et al. Lack of pharmacokinetic interaction between mexiletine and omeprazole. *Ann Pharmacother* 1998; 32: 182-4
73. Labbé L. Rôle du CYP1A2 dans la pharmacocinétique de la mexilétine chez l'human [thesis]. Quebec City (Quebec): Laval University, 1995
74. El Allaf D, Henrard L, Crochelet L, et al. Pharmacokinetics of mexiletine in renal insufficiency. *Br J Clin Pharmacol* 1982; 14: 431-5
75. El Allaf D, Carlier J, Dressé A. Effects of age on the pharmacokinetics of mexiletine. *Int J Clin Pharmacol Res* 1986; 6: 303-7
76. Mahgoub A, Idle JR, Dring LG, et al. Polymorphic hydroxylation of debrisoquine in man. *Lancet* 1977; 2: 584-6
77. Steiner E, Bertilsson L, Sawe J, et al. Polymorphic debrisoquin hydroxylation in 757 Swedish subjects. *Clin Pharmacol Ther* 1988; 44: 431-5
78. Price Evans DA, Mahgoub A, Sloan TP, et al. A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J Med Genet* 1980; 17: 102-5
79. Zanger UM, Vilbois F, Hardwick JP, et al. Absence of hepatic cytochrome P450bufl causes genetically deficient debrisoquine oxidation in man. *Biochemistry* 1988; 27: 5447-54
80. Dayer P, Kronbach T, Eichelbaum M, et al. Enzymatic basis of the debrisoquine/sparteine-type genetic polymorphism of drug oxidation. Characterization of bufuralol 1'-hydroxylation in liver microsomes of *in vivo* phenotyped carriers of the genetic deficiency. *Biochem Pharmacol* 1987; 36: 4145-52
81. Kagimoto M, Heim M, Kagimoto K, et al. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. *J Biol Chem* 1990; 265: 17209-14
82. Broly F, Libersa C, Lhermitte M. Mexiletine metabolism *in vitro* by human liver. *Drug Metab Dispos* 1990; 18: 362-8

83. Broly F, Libersa C, Lhermitte M, et al. Inhibitory studies of mexiletine and dextromethorphan oxidation in human liver microsomes. *Biochem Pharmacol* 1990; 39: 1045-53
84. Sesardic D, Boobis AR, Edwards RJ, et al. A form of cytochrome P450 in man, orthologous to form d in the rat, catalyses the O-deethylation of phenacetin and is inducible by cigarette smoking. *Br J Clin Pharmacol* 1988; 26: 363-72
85. Nakajima M, Kobayashi K, Shimada N, et al. Involvement of CYP1A2 in mexiletine metabolism. *Br J Clin Pharmacol* 1998; 46: 55-62
86. Abolfathi Z, Pakdel H, Beaune P, et al. CYP1A2 is the major enzyme involved in the N-oxidation of mexiletine in man [abstract]. *Clin Pharmacol Ther* 1995; 57: 215
87. Sesardic D, Boobis AR, Murray BP, et al. Furafylline is a potent and selective inhibitor of cytochrome P450IA2 in man. *Br J Clin Pharmacol* 1990; 29: 651-63
88. Turgeon J, Uprichard ACG, Bélanger PM, et al. Resolution and electrophysiological effects of mexiletine enantiomers. *J Pharm Pharmacol* 1991; 43: 630-5
89. Hill RJ, Duff HJ, Sheldon RS. Determinants of stereospecific binding of type I antiarrhythmic drugs to cardiac sodium channels. *Mol Pharmacol* 1988; 34: 659-63
90. De Luca A, Natuzzi F, Lentini G, et al. Stereoselective effects of mexiletine enantiomers on sodium currents and excitability characteristics of adult skeletal muscle fibers. *Naunyn Schmiedeberg's Arch Pharmacol* 1995; 352: 653-61
91. Igwezie L, Kerr CR, McErlane KM. The pharmacokinetics of the enantiomers of mexiletine in humans. *Xenobiotica* 1989; 19: 677-82
92. McErlane KM, Igwezie L, Kerr CR. Stereoselective serum protein binding of mexiletine enantiomers in man. *Res Commun Chem Pathol Pharmacol* 1987; 56: 141-4
93. Abolfathi Z, Fiset C, Gilbert M, et al. Role of polymorphic debrisoquin 4-hydroxylase activity in the stereoselective disposition of mexiletine in humans. *J Pharmacol Exp Ther* 1993; 266: 1196-201
94. Labbé L, Abolfathi Z, Robitaille NM, et al. Stereoselective disposition of the antiarrhythmic agent mexiletine during the concomitant administration of caffeine. *Ther Drug Monit* 1999; 21: 191-9
95. Lanchote VL, Cesarino EJ, Santos VJ, et al. Enantioselectivity in the metabolism of mexiletine by conjugation in female patients with the arrhythmic form of chronic Chagas' heart disease. *Chirality* 1999; 11: 29-32
96. Lanchote VL, Cesarino EJ, Santos VJ, et al. Stereoselective metabolism of mexiletine in Chagasic women with ventricular arrhythmias. *Eur J Drug Metab Pharmacokinet* 1998; 23: 259-66
97. Lanchote VL, Bonato PS, Cesarino EJ, et al. HPLC determination of the enantiomeric metabolites of mexiletine in human plasma. *Chirality* 1997; 9: 722-6
98. Vandamme N, Broly F, Libersa C, et al. Stereoselective hydroxylation of mexiletine in human liver microsomes: implication of P450IID6. A preliminary report. *J Cardiovasc Pharmacol* 1993; 21: 77-83
99. Knoche B, Gehrcke B, König WA, et al. Determination of the enantiomeric composition of mexiletine and its four hydroxylated metabolites in urine by enantioselective capillary gas chromatography. *Chirality* 1996; 8: 30-4
100. Ueno K, Kawaguchi Y, Tanaka K. Pharmacokinetics of mexiletine in middle-aged and elderly patients. *Clin Pharmacokinet* 1993; 12: 768-70
101. Uenaka K, Koue T, Iwai T, et al. Population pharmacokinetic analysis of mexiletine in adult arrhythmic patients in Japanese population. *Biol Pharm Bull* 1998; 21: 844-6
102. Fukagawa NF, Bandini LG, Young JB. Effect of age on body composition and resting metabolic rate. *Am J Physiol* 1990; 259: E233-8
103. Nitsch J, Steinbeck G, Lüderitz B. Effect of kidney, liver or heart insufficiency on blood mexiletine levels. *Internist* 1982; 23: 291-3
104. Nitsch J, Steinbeck G, Lüderitz B. Increase of mexiletine plasma levels due to delayed hepatic metabolism in patients with chronic liver disease. *Eur Heart J* 1983; 4: 810-4
105. Wang T, Wuellner D, Woosley RL, et al. Pharmacokinetics and nondialyzability of mexiletine in renal failure. *Clin Pharmacol Ther* 1985; 37: 649-53
106. Herbinger W, Kramar R, Fridrik M, et al. Pharmakokinetische untersuchungen mit mexiletin bei patienten mit niereninsuffizienz. *Adv Clin Pharmacol* 1978; 16: 17-27
107. Baudinet G, Henrad L, Quinaux N, et al. Pharmacokinetics of mexiletine in renal insufficiency. *Acta Cardiol* 1980; 25: 55-65
108. Evers J, Messer W, Aboudan F, et al. Mexiletine in terminal renal failure and various dialysis procedures. *Klin Wochenschr* 1989; 67: 995-8
109. Jones TE, Reece PA, Fisher GC. Mexiletine removal by peritoneal dialysis. *Eur J Clin Pharmacol* 1983; 25: 839-40
110. Guay DRP, Meatherall RC, Ferguson I, et al. Mexiletine clearance during peritoneal dialysis. *Br J Clin Pharmacol* 1985; 19: 857-8
111. Pentikäinen PJ, Halinen MO, Helin MJ. Pharmacokinetics of intravenous mexiletine in patients with acute myocardial infarction. *J Cardiovasc Pharmacol* 1984; 6: 1-6
112. Pentikäinen PJ, Halinen MO, Helin MJ. Pharmacokinetics of oral mexiletine in patients with acute myocardial infarction. *Eur J Clin Pharmacol* 1983; 25: 773-7
113. Pottage A, Campbell RWF, Achuff SC, et al. The absorption of oral mexiletine in coronary care patients. *Eur J Clin Pharmacol* 1978; 13: 393-9
114. Lévy-Prades R, Philip F, Danays T, et al. Mexiletine in acute myocardial infarction. Simulation of a theoretical protocol and validation in six patients. *Drug Res* 1989; 39: 903-8
115. Leahy Jr EB, Giardina EGV, Bigger Jr JT. Effect of ventricular failure on steady state kinetics of mexiletine [abstract]. *Clin Res* 1980; 28: 239A
116. Vozeh S, Katz G, Steiner V, et al. Population pharmacokinetic parameters in patients treated with oral mexiletine. *Eur J Clin Pharmacol* 1982; 23: 445-51
117. Ohashi K, Ebihara A, Hashimoto T, et al. Pharmacokinetics and the antiarrhythmic effect of mexiletine in patients with chronic ventricular arrhythmias. *Drug Res* 1984; 34: 503-7
118. Nattel S, Heger JJ, Rinkenberger RL, et al. The pharmacokinetics of mexiletine in patients with refractory ventricular arrhythmias [abstract]. *Clin Res* 1979; 27: 445A
119. Heger JJ, Nattel S, Rinkenberger RL, et al. Mexiletine therapy in 15 patients with drug-resistant ventricular tachycardia. *Am J Cardiol* 1980; 45: 627-32
120. Hutt V, Pabst G, Salama Z, et al. Untersuchungen zur pharmakokinetik und bioverfügbarkeit einer neuen mexiletin-zubereitung an gesunden freiwilligen. *Drug Res* 1995; 45: 254-7
121. Bruno R, Santoni Y, Iliadis A, et al. Simultaneous modelling of mexiletine and hydroxy-methyl-mexiletine data after single- and multiple-dose administration of a sustained-release mexiletine formulation. *Biopharm Drug Disp* 1992; 13: 481-93

122. Cereghino JJ, Wilder BJ, Kupferberg HJ, et al. A single-dose study of mexiletine (Kö 1173). *Epilepsia* 1975; 16: 665-72
123. Cereghino JJ, Brock JT, Van Meter JC, et al. A multiple-dose study of mexiletine (Kö 1173). *Epilepsia* 1975; 16: 673-7
124. Kiddie MA, Royds RB, Shaw TRD. Preliminary studies on the pharmacology of an antidysrhythmic, Kö 1173, in man. *Proc Br Pharmacol Soc* 1973; 47: 674-5P
125. Paalman ACA, Roos JC, Siebelink J, et al. Development of a dosage scheme for simultaneous intravenous and oral administration of mexiletine. *Postgrad Med J* 1977; 53 Suppl. 1: 128-32
126. Upward JW, Holt DW, Jackson G. A study to compare the efficacy, plasma concentration profile and tolerability of conventional mexiletine and slow-release mexiletine. *Eur Heart J* 1984; 5: 247-52
127. Smyllie HC, Doar JWH, Head CD, et al. A trial of intravenous and oral mexiletine in acute myocardial infarction. *Eur J Clin Pharmacol* 1984; 26: 537-42
128. Nimmo WS, Heading RC, Wilson J, et al. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol* 1975; 2: 509-13
129. Joeres R, Klinker H, Heusler H, et al. Influence of mexiletine on caffeine elimination. *Pharmacol Ther* 1987; 33: 163-9
130. Butler MA, Iwasaki M, Guengerich FP, et al. Human cytochrome P-450_{PA} (P-450IA2), the phenacetin *O*-deethylase, is primarily responsible for the hepatic 3-demethylation of caffeine and N-oxidation of carcinogenic arylamines. *Proc Natl Acad Sci USA* 1989; 86: 7696-700
131. Berthou F, Flinois JP, Ratanasavanh D, et al. Evidence for the involvement of several cytochromes P-450 in the first steps of caffeine metabolism by human liver microsomes. *Drug Metab Dispos* 1991; 19: 561-7
132. Ha HR, Chen J, Freiburghaus AU, et al. Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; 39: 321-6
133. Ueno K, Miyai K, Seki T, et al. Interaction between theophylline and mexiletine. *Ann Pharmacother* 1990; 24: 471-2
134. Stanley R, Comer T, Taylor JL, et al. Mexiletine-theophylline interaction. *Am J Med* 1989; 86: 733-4
135. Ueno K, Miyai K, Kato M, et al. Mechanism of interaction between theophylline and mexiletine. *Ann Pharmacother* 1991; 25: 727-30
136. Loi CM, Wei X, Vestal RE. Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. *Clin Pharmacol Ther* 1991; 49: 571-80
137. Stoysich AM, Mohiuddin SM, Destache CJ, et al. Influence of mexiletine on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 1991; 31: 354-7
138. Katz A, Buskila D, Sukenik S. Oral mexiletine-theophylline interaction. *Int J Cardiol* 1987; 17: 227-8
139. Kendall JD, Chrymko MM, Cooper BE. Theophylline-mexiletine interaction: a case report. *Pharmacotherapy* 1992; 12: 416-8
140. Hurwitz A, Vacek JL, Botteron GW, et al. Mexiletine effects on theophylline disposition. *Clin Pharmacol Ther* 1991; 50: 299-307
141. Inafuku M, Suzuki T, Ohtsu F, et al. The effect of mexiletine on theophylline pharmacokinetics in patients with bronchial asthma. *J Cardiol* 1992; 22: 227-33
142. Kessler KM, Interian Jr A, Cox M, et al. Proarrhythmia related to a kinetic and dynamic interaction of mexiletine and theophylline. *Am Heart J* 1989; 117: 964-6
143. Fuhr U, Strobl G, Manaut F, et al. Quinolone antibacterial agents: relationship between structure and *in vitro* inhibition of the human cytochrome P450 isoform CYP1A2. *Mol Pharmacol* 1993; 43: 191-9
144. Healy DP, Polk RE, Kanawati L, et al. Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; 33: 474-8
145. Brockmeyer NH, Breithaupt H, Ferdinand W, et al. Kinetics of oral and intravenous mexiletine: lack of effect of cimetidine and ranitidine. *Eur J Clin Pharmacol* 1989; 36: 375-8
146. Leahey Jr EB, Reiffel JA, Giardina EGV, et al. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. *Ann Intern Med* 1980; 92: 605-8
147. Saris SD, Lowenthal DT, Affrime MB. Steady-state digoxin concentration during oral mexiletine administration. *Curr Ther Res* 1983; 34: 662-6
148. Labbé L. Metabolisme de la mexiletine chez l'humain: rôle de CYP1A2 et interaction avec la propafenone [thesis]. Québec City (Québec): Laval University, 1999

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