Concentration-time profile for perhexiline and hydroxyperhexiline in patients at steady state

Terry E. Jones,¹ Raymond G. Morris^{2,3} & John D. Horowitz²

Departments of ¹Pharmacy, ²Clinical Pharmacology and Cardiology, The Queen Elizabeth Hospital and Health Service, Woodville South, South Australia 5011 and ³Department of Clinical and Experimental Pharmacology, University of Adelaide, Adelaide, South Australia 5000

Correspondence

Dr T. E. Jones, Pharmacy Department,
The Queen Elizabeth Hospital, 28
Woodville Road, Woodville South,
South Australia, 5011.

Tel: + 61 8822 26694 or 8222 6753

Facsimile: + 61 8822 26019 or
8822 26033

E-mail: terryej@hotmail.com

Keywords

perhexiline, pharmacokinetics, steady-state, therapeutic drug monitoring, therapeutic range

Received

26 December 2002

Accepted

27 June 2003

Aim

To define inter- and intraday variability in plasma perhexiline concentrations, time-to-maximum plasma perhexiline concentration and variability in the ratio of hydroxyperhexiline to parent perhexiline concentrations over the course of the day in patients at steady state.

Methods

Eight blood samples were taken over a 24-h period from 12 adult patients already taking perhexiline for the treatment of angina pectoris. These patients were assumed to be at steady state, having taken the same dose of perhexiline for more than 4 weeks and having no changes made to other drug therapy that might have affected plasma perhexiline concentrations (especially drugs that interfere with CYP2D6). Perhexiline was assayed by HPLC/FL. The percentage increase over baseline concentration was determined for each patient for both perhexiline and hydroxyperhexiline.

Results

Trough plasma perhexiline concentrations from two patients were below the limit of quantification of the assay (0.05 mg l⁻¹) and thus were excluded from the analysis. The greatest mean percentage increase in plasma perhexiline concentration over the day was 21% (95%CI 9%, 33%, range -19% to 45%) which occurred 6 h postdose. The greatest mean percentage increase in plasma hydroxyperhexiline concentration was 10.8% (95%CI -5.3%, 26.9%, range -13% to 60%) which occurred 4 h postdose. However individual patients demonstrated >60% intraday variability in perhexiline concentrations which was not related to the concomitant use of drugs that affect CYP2D6 activity. Changes in random plasma perhexiline concentration which are attributed to changes in concomitant drug therapy should be supported by additional kinetic data. Inter-day variability in plasma perhexiline concentration as determined by the ratio of C₂₄ : C₀ was small (mean 0.90, 95%CI 0.77, 1.03) which supports C₀ as the best sampling time for perhexiline concentration monitoring. The variability in C₂₄ : C₀ for hydroxyperhexiline concentrations was smaller (mean 0.96, 95%CI 0.81, 1.11). Variability in the ratio of plasma concentrations of hydroxyperhexiline to perhexiline over the day was also small. The ratio of plasma hydroxyperhexiline to perhexiline concentration over the day fell within a narrow range for all subjects with 95% confidence intervals being <15% for eight patients and <25% for the remaining patient. This suggests that formation of the metabolite occurs rapidly and may be presystemic. It also supports the calculation of the hydroxyperhexiline : perhexiline ratio (in patients at steady state) on blood samples taken at any time during the dosing interval.

Conclusions

The within-day variability in plasma perhexiline concentrations was small. While C₀ is probably the best time for therapeutic drug monitoring purposes, it is not unreasonable to use samples drawn at any time during the dosing interval. The therapeutic range used in this hospital (0.15–0.6 mg l⁻¹) was devised from earlier work using 4 h postdose blood sampling which is close to the 'peak' concentration and a mean of 16% higher than C₀ in this study. This increase is probably clinically insignificant and a different C₀ range is therefore not warranted.

Introduction

Perhexiline has been used as an anti-anginal drug since the early 1970s [1] when its mode of action was thought to be via coronary artery vasodilatation mediated by calcium channel antagonism [2]. Its use declined in the mid 1970s [3] because of the occurrence of severe adverse effects during long-term therapy including neuropathy and hepatotoxicity [2–4]. The incidence of these adverse effects was noted to be related to plasma perhexiline concentration and it was observed that adverse effects could be prevented if plasma concentrations were kept below defined values [5, 6].

The metabolism of perhexiline has been shown to be highly variable within the Caucasian population and poor metabolizers are more likely to experience serious toxicity [7]. Poor metabolizers of debrisoquine have also been shown to be at greater risk of perhexiline-induced neuropathy [8] and hepatotoxicity [9] and poor metabolizers of perhexiline are also poor metabolizers of debrisoquine [10]. This suggests that perhexiline is metabolized by the same enzyme as debrisoquine, namely cytochrome P450 2D6 (CYP2D6). Perhexiline has also been shown to inhibit CYP2D6 [11]. Large interpatient differences in CYP2D6 activity have been observed in the Caucasian population where 8–9% have been shown to be poor metabolizers [12]. Furthermore, perhexiline hydroxylation via CYP2D6 is saturable within the usual range of dosages employed and hence plasma perhexiline concentrations are nonlinear with respect to daily dosage [13, 14]. These pharmacokinetic properties explain the wide interpatient variability in daily perhexiline dosages needed to maintain therapeutic perhexiline concentrations first noted >15 years ago [5]. The net result of this is that therapeutic drug monitoring is essential if perhexiline is to be used safely and effectively [3–6, 13, 15, 16].

Many patients continue to experience anginal symptoms despite using maximal dosages of alternative prophylactic anti-anginal agents. Other patients are unable to tolerate alternative anti-anginal agents because of pre-existing comorbidities. Such comorbidities include reversible airways limitation and peripheral vascular

disease which frequently restrict β -adrenoceptor blocker use, and cardiac failure which frequently restricts calcium channel blocker use. Perhexiline is relatively free of negative inotropic effects and does not increase airways resistance and is therefore not contraindicated in such situations. Perhexiline has been shown to be superior to β -adrenoceptor blockers [1] in its ability to reduce the frequency of anginal attacks and in addition, because it has a different mode of action, it provides additional anti-anginal benefit when added to existing agents [15, 17, 18].

Perhexiline is now thought to exert its anti-anginal action primarily by inhibiting the enzyme carnitine palmitoyltransferase [19]. This inhibition reduces fatty acid metabolism in favour of carbohydrate metabolism which increases available energy for the same amount of oxygen. It has also been postulated that reduction in fatty acid oxidation might result in phospholipidosis which is responsible for the hepatotoxicity and neurotoxicity seen in long-term usage [3, 19] at elevated plasma concentrations.

Earlier work which defined the therapeutic range for plasma perhexiline concentrations used at this hospital was conducted using 4 h postdose blood sampling (C₄) [5] and we are not aware of analogous data using 'trough' (*viz* C₀ or predose) concentration monitoring. Because perhexiline has a long half-life, it has been assumed that its concentration in plasma would be stable throughout the entire dosing interval and that timing of blood sampling is unimportant [20]. This assumption ignores the possible effect of distribution half-life on its concentration in plasma, an effect that is of considerable importance in the disposition of another cardiac drug, digoxin [12].

The ratio of plasma concentrations of hydroxyperhexiline to perhexiline can be used as a guide to the capacity of patients to metabolize perhexiline. It has been suggested that this ratio can be used to identify poor metabolizers shortly after commencing perhexiline therapy and hence avoid unnecessary drug exposure that results from prescribing 'standard' doses [7, 20]. Because the half-life of hydroxyperhexiline is also long,

it has been assumed that this ratio can be determined from blood samples taken at any time during the dosing interval. This assumes that plasma concentrations of both perhexiline and hydroxyperhexiline fluctuate in parallel over the day, which might occur if metabolism of perhexiline to its hydroxy metabolite is rapid and/or occurs presystemically. This assumption may also not be accurate.

A few cases of drug interactions with perhexiline have been reported in the literature [21–23] but unfortunately these provide very limited data, especially on timing of blood samples. If the concentration-time profile is not stable across the dosing interval, these supposed ‘interactions’ might be equally well explained by variation in the timing of blood samples.

We therefore undertook this study to define the steady-state concentration-time profile of perhexiline and hydroxyperhexiline in patients taking perhexiline for anginal prophylaxis.

Methods

Adult (>18 years) patients were eligible for the study if they had been taking perhexiline for more than 4 weeks. The study was approved by the hospital’s Ethics of Human Research Committee. Patients were ineligible if they had recently started, stopped or had dosage changes to any drug known to affect the metabolism of perhexiline or to affect CYP2D6 activity. Provided dosages remained stable before and during the conduct of the study, drugs thought to affect CYP2D6 activity were not excluded.

Eight blood samples (5 ml) were taken from an indwelling catheter at times 0 (i.e. predose), and 1, 2, 3, 4, 6, 12 and 24 h following the patient’s usual perhexiline dose. Patency of the venous catheter was maintained by instilling 1.5 ml heparinized saline (15 units heparin) into the catheter after each sample was withdrawn. To prevent contamination of the sample, the first 1.5 ml of blood withdrawn was discarded. Blood samples were immediately stored in a refrigerator (2–8°C) until plasma was separated and the plasma fraction stored similarly until assayed, within 3 days. Perhexiline is stable in plasma under these conditions for more than 4 weeks (personal communication B. Sallustio). Perhexiline and *cis*-hydroxy-perhexiline were assayed using a previously published HPLC/FL assay [20] used for routine therapeutic monitoring. Using this method in our laboratory, intra-assay coefficients of variation (CV%) for perhexiline were 1.6% at 3 mg l⁻¹ and 6.1% at 0.05 mg l⁻¹; and for hydroxyperhexiline, the intra-assay CV% were 4.4% and 7.3% at these same concentrations. Interassay CV% for perhexiline was 0.6% at

3 mg l⁻¹ and 10.7% at 0.05 mg l⁻¹; and for hydroxyperhexiline, the interassay CV% was 3.4% and 12.3%, respectively.

Seven patients were taking twice daily perhexiline regimens and in these, the second dose was taken after the 12 h blood sample.

Results

Between May and July 2002, 12 patients agreed to participate in the study. Patients were identified by their caring doctors, nurses or the laboratory where routine perhexiline assays were performed. Patient details and concurrent drug therapy are shown in Table 1.

Data presented in Figures 1–4 are expressed as percentage increase over baseline (*viz* C₀) for both perhexiline and hydroxyperhexiline. Two patients (numbers 1 and 4) had C₀ perhexiline concentrations that were below the lower limit of quantification of the assay (0.05 mg l⁻¹). Since C₀ was used as the comparator for all other concentrations, data from these patients were excluded from the analysis. These data for perhexiline in the remaining 10 patients are given in Figures 1 and 3. One patient (patient 5) was a poor metabolizer of perhexiline, requiring only 10 mg perhexiline day⁻¹ (administered as 100 mg every 10th day) and producing no detectable concentrations of hydroxyperhexiline. Data for hydroxyperhexiline concentrations for the remaining nine patients are given in Figures 2 and 4. These data show that group mean *t*_{max} for both perhexiline and hydroxyperhexiline was 6 and 4 h, respectively. The group mean *C*_{max} was an increase over baseline of 21.3% (95%CI 9%, 33%, range –19%–45%) for perhexiline and 10.8% (95%CI –5.3%, 26.9%, range –13%–60%) for hydroxyperhexiline.

Mean interday variability in trough plasma perhexiline concentration as determined by the ratio of C₂₄ : C₀ was 0.90 (95%CI 0.77, 1.03, range 0.57–1.2) while the mean interday variability in hydroxyperhexiline trough concentrations was 0.96 (95%CI 0.81, 1.18, range 0.56–1.32).

Maximum intraday variability in plasma perhexiline concentration as expressed by the ratio of *C*_{max} : *C*_{min} for each patient showed four patients (patients 5, 8, 10 and 11) who exceeded values of 1.6 and one (patient 11) whose ratio exceeded 2.0.

Perhexiline and hydroxyperhexiline concentrations varied in parallel over the day. This can be seen in Table 2 where the ratio of plasma hydroxyperhexiline to perhexiline concentrations which fell within a narrow range for all subjects with 95% confidence intervals being <15% for eight of the subjects and <25% in the ninth.

Table 1

Patient demographics and concurrent drug therapy. Drugs known or thought to be metabolized by, or to affect CYP2D6 activity are shown in *italics*

Patient	Gender/Age (years)	Perhexiline dosage	Other drugs taken
1	F/69	100 mg am	Perindopril, insulin, simvastatin, carvedilol, frusemide, aspirin, digoxin, sorbide nitrate, roxithromycin, Coamoxiclav, fluticasone, salmeterol
2	F/82	100 mg am, 50 mg pm	Prochlorperazine, insulin, aspirin, pancrease, sorbide nitrate, enoxaparin, <i>metoprolol</i> , diltiazem
3	M/63	150 mg am, 150 mg pm	Sorbide nitrate, diltiazem, aspirin, trandolopril, thyroxine, roxithromycin, simvastatin, allopurinol, omeprazole, prednisolone, Coamoxiclav, paracetamol, frusemide, fluticasone, salmeterol
4	M/63	100 mg pm	Nicotine, digoxin, nystatin, bromhexine, enoxaparin, prednisolone, alprazolam, fluticasone, salmeterol
5	F/57	100 mg every 10th day	Aspirin, clopidogrel, diltiazem, sorbide nitrate, calcium carbonate, salmeterol, simvastatin, theophylline, prednisolone, <i>morphine</i> , oestrogens, paracetamol/ <i>codeine</i>
6	F/84	100 mg am, 100 mg pm	Simvastatin, iron, aspirin, frusemide, <i>metoprolol</i> , glyceryl trinitrate, flucloxacillin, colchicine, omeprazole, levodopa/carbidopa
7	M/88	100 mg am	Coamoxiclav, paracetamol, <i>dextropropoxyphene</i> , frusemide, captopril, sorbide nitrate, digoxin, temazepam, omeprazole, warfarin, senna
8	M/84	200 mg am	Amlodipine, atenolol, sorbide nitrate, spironolactone, thyroxine, simvastatin, frusemide, omeprazole
9	M/47	200 mg am, 200 mg pm	Enalapril, sorbide nitrate, warfarin, omeprazole, simvastatin, digoxin, metformin, sotalol
10	M/76	100 mg am, 100 mg pm	Digoxin, perindopril, carvedilol, pergolide, warfarin, latanoprost, beclomethasone, ranitidine, colchicine, frusemide, thiamine
11	F/74	100 mg am, 100 mg pm	Iron, <i>amitriptyline</i> , alprazolam, salbutamol, ipratropium, <i>dextropropoxyphene</i> , paracetamol, thyroxine, frusemide, simvastatin, calcitriol, pantoprazole, roxithromycin, <i>codeine</i> , prednisolone, senna
12	F/87	100 mg am, 100 mg pm	Isosorbide mononitrate, aspirin, frusemide, perindopril, ranitidine, allopurinol, senna, amlodipine, spironolactone, Coamoxiclav, fluticasone, salmeterol, enoxaparin

Figure 1

Change from baseline perhexiline concentration over 24 h postdose in 10 patients receiving routine perhexiline for angina prophylaxis. Pt2 (■), Pt3 (▲), Pt5 (—■—), Pt6 (●), Pt7 (◆), Pt8 (✕), Pt9 (□), Pt10 (○), Pt11 (△) and Pt12 (◆)

Figure 2

Change from baseline hydroxyperhexiline concentration over 24 h postdose in nine patients receiving routine perhexiline for angina prophylaxis. Pt2 (■), Pt3 (▲), Pt6 (●), Pt7 (◆), Pt8 (✕), Pt9 (□), Pt10 (○), Pt11 (△) and Pt12 (◆)

Figure 3

Mean change (95% CI) from baseline perhexiline concentration over 24 h postdose in 10 patients receiving routine perhexiline for angina prophylaxis

Figure 4

Mean change (95% CI) from baseline hydroxyperhexiline concentration over 24 h postdose in nine patients receiving routine perhexiline for angina prophylaxis

Table 2

Ratio of hydroxyperhexiline : perhexiline plasma concentrations for nine patients at each sampling time

Time (h) postdose	Patient								
	2	3	6	7	8	9	10	11	12
0	2.38	1.08	5.95	1.95	4.40	4.97	8.15	4.43	13.63
1	2.04	1.54	5.79	1.86	4.33	6.29	7.69	4.97	13.75
2	2.19	1.18	6.17	1.95	4.51	3.96	8.02	4.00	16.11
3	2.01	1.26	5.85	2.02	4.51	5.63	7.63	3.49	12.41
4	2.17	1.17	6.04	1.95	4.00	6.48	7.80	3.05	10.44
6	2.23	1.37	5.42	1.78	3.45	6.00	8.64	3.23	8.33
12		1.43	4.95	1.95	4.13	6.25	17.52	3.98	15.18
24	2.81	1.31	5.4	1.83	4.34	6.95	13.73	4.41	11.64
Mean	2.26	1.29	5.70	1.91	4.21	5.82	9.90	3.94	12.69
95% CI	0.18	0.10	0.27	0.05	0.23	0.62	2.41	0.43	1.66

Variability in plasma perhexiline concentration (as measured by $C_{\max} : C_{\min}$) was not related to capacity to metabolize perhexiline (as measured by hydroxyperhexiline : perhexiline ratio) ($r^2 = 0.0002$).

Discussion

Perhexiline is widely prescribed at this hospital where therapeutic drug monitoring is considered essential for its safe, long-term use. Two patients in this study were prescribed perhexiline for angina prophylaxis despite plasma perhexiline concentrations being below the lower end of the therapeutic range ($0.15\text{--}0.6\text{ mg l}^{-1}$) and indeed, below the limit of quantification of the assay (0.05 mg l^{-1}) both on routine therapeutic monitoring prior to the study and during this study. Although this study did not address the issue of clinical efficacy, it is

possible that these patients were deriving clinical benefit from perhexiline since the lower limit of the therapeutic range has not been validated to the same extent as the upper limit (which was established using long-term toxicity data). Benefit from 'subtherapeutic' perhexiline concentrations has been reported earlier [5, 6].

As noted earlier, the therapeutic range developed by Horowitz *et al.* more than 15 years ago [5] for perhexiline was developed from C_4 concentrations which are close to the maximum concentration achieved during each dosing interval. In the present study, C_4 concentrations averaged 16% higher than C_0 suggesting a corresponding C_0 range of $0.13\text{--}0.5\text{ mg l}^{-1}$. In the earlier work [5] from which the current therapeutic range was developed, the lowest C_4 plasma perhexiline concentration associated with adverse effects was 0.72 mg l^{-1}

which would correlate with a C_0 value of 0.62 mg l^{-1} in the present study. Thus there would not appear to be any reason to change the upper value of the therapeutic range (0.6 mg l^{-1}) when C_0 samples are taken.

The concentration-time profiles for perhexiline and hydroxyperhexiline were relatively stable for the study group over the course of the day. This has been reported earlier by one group [4, 6] but no data were presented. The only sampling time that was repeated on the next day in this study was C_0 and these values were in close agreement (mean $C_{24} : C_0 = 0.9$). This supports the use of C_0 as the preferred sampling time for perhexiline concentration monitoring. Variability in plasma perhexiline concentration at other times of the day was not large (mean maximum increase over $C_0 = 21\%$) and this suggests that it is acceptable to take blood samples for therapeutic drug monitoring at other times during the dosing interval. Additionally, the small fluctuations observed were very similar with regard to extent and timing for both perhexiline and hydroxyperhexiline. This supports the calculation of the ratio of hydroxyperhexiline to perhexiline concentrations from samples drawn at any time during the dosing interval. However, in the present study patients were at steady state, but one of the proposed uses of the ratio of hydroxyperhexiline to perhexiline is to allow estimates of steady state dosage requirements from data collected in the first few days of therapy (*viz* before steady state has occurred). Stability in this ratio over the course of the day should be verified before steady state is achieved if these data are to be used in this manner or alternatively, a specified sampling time should be used.

While group data showed limited variation in perhexiline and hydroxyperhexiline concentrations over the day, individual patients exhibited clinically significant variation. Maximum intraday variability in plasma perhexiline concentration for individual patients showed that 4 of the 10 patients (patients 5, 8, 10 and 11) exhibited ratios of $C_{\max} : C_{\min}$ that exceeded 1.6 and in one (patient 11), the ratio exceeded 2.2. Two of these patients [5, 11] were also taking drugs that are known to affect CYP2D6 activity [24]. However another patient (pt 7) who exhibited minimal intraday variability (ratio of $C_{\max} : C_{\min} = 1.15$) was also taking a drug thought to affect CYP2D6 without apparent interference. Whilst limited, these data suggest that intraday variability in plasma perhexiline concentrations is no greater in patients taking drugs affecting CYP2D6 than in those not taking such drugs. This is to be expected since drugs that inhibit CYP2D6 activity would be expected to prolong the elimination half-life and hence reduce peak to trough variability at steady state.

Given the inpatient variability in concentration over the course of the day, changes in random plasma perhexiline concentration attributed to changes in concomitant drug therapy should be supported by additional kinetic data (e.g. metabolite : parent ratio).

There was no relationship between fluctuation over the dosing interval in plasma perhexiline concentration (measured by $C_{\max} : C_{\min}$) and the capacity to metabolize perhexiline (measured by the ratio of hydroxyperhexiline to perhexiline concentrations). This suggests that factors other than metabolic activity (including absorption) determine the extent of fluctuation in plasma perhexiline concentrations.

It was of interest that most patients (7/12) in this study were prescribed a twice daily regimen for perhexiline, a drug with a prolonged half-life. Perhexiline is not noted for gastrointestinal toxicity even when large doses are administered as they were in a recent loading dose study conducted by our group [25]. The modest increase over baseline concentration in the present study, combined with minimal gastrointestinal toxicity suggests that perhexiline need not be administered more frequently than once daily.

Apparent $t_{\max}$ for hydroxyperhexiline was shorter than apparent $t_{\max}$ for perhexiline for four subjects, the same for four and longer in only one of the nine subjects. In a previous single-dose volunteer study [26], the opposite was found where apparent $t_{\max}$ for hydroxyperhexiline occurred later in three out of eight subjects and in the remaining five subjects it coincided with $t_{\max}$ for perhexiline. The reason for this difference may be due to the single-dose nature of the earlier study and/or the infrequent sampling times (2 hourly). Our data suggest that the formation of hydroxyperhexiline occurs rapidly and possibly occurs presystemically which was also suggested by this earlier study.

In conclusion, blood samples for routine perhexiline monitoring are best drawn at C_0 , but samples drawn at later times can be used if interpreted appropriately.

We are indebted to Mr Ian Westley for his invaluable analytical work.

References

- 1 Armstrong ML, Brand D, Emmett AJ, Hodge JLR, Kelleway GSM, Mesitz P, Refman M, Wallace DC. A multicentre trial of perhexiline maleate, beta-blocker and placebo in angina pectoris. *Med J Aust* 1974; 2: 389–93.
- 2 Opie LH. Calcium antagonists. *Lancet* 1980; i: 806–9.
- 3 Horowitz JD, Button IK, Wing L. Is perhexiline essential for the

- optimal management of angina pectoris? *Aust NZ J Med* 1995; 25: 111–13.
- 4 Cooper JDH, Turnell DC, Pilcher J, Lockhart D. Therapeutic monitoring of the antianginal drug perhexiline maleate. *Ann Clin Biochem* 1985; 22: 614–17.
 - 5 Horowitz JD, Pia STB, Macdonald PS, Goble AJ, Louis WJ. Perhexiline maleate treatment for severe angina pectoris – correlations with pharmacokinetics. *Int J Cardiol* 1986; 13: 219–29.
 - 6 Pilcher J, Cooper DH, Turnell DC, Matenga J, Paul R, Lockhart JDF. Investigations of long-term treatment with perhexiline maleate using therapeutic monitoring and electromyography. *Ther Drug Monit* 1985; 7: 54–60.
 - 7 Singlas E, Goujet MA, Simon P. Pharmacokinetics of perhexiline maleate in anginal patients with and without peripheral neuropathy. *Eur J Clin Pharmacol* 1978; 14: 195–201.
 - 8 Shah RR, Oates NS, Idle JR, Smith RL, Lockhart JDF. Impaired oxidation of debrisoquine in patients with perhexiline neuropathy. *Br Med J* 1982; 284: 295–9.
 - 9 Morgan MY, Reshef R, Shah RR, Oates NS, Smith RL, Sherlock S. Impaired oxidation of debrisoquine in patients with perhexiline liver injury. *Gut* 1984; 25: 1057–64.
 - 10 Cooper RG, Evans DAP, Whibley EJ. Polymorphic hydroxylation of perhexiline maleate in man. *J Med Genet* 1984; 21: 27–33.
 - 11 Kerry NL, Somogyi AA, Bochner F, Mikus G. The role of CYP2D6 in primary and secondary oxidative metabolism of dextromethorphan: in vitro studies using human liver microsomes. *Br J Clin Pharmacol* 1994; 38: 243–8.
 - 12 Birkett DJ. *Pharmacokinetics Made Easy*. Roseville NSW, Australia, McGraw-Hill Publishers 1998, ISBN 0 07 470 609, 8.
 - 13 Wing LH, Meffin PJ, Grgurinovich N, Harrington BJ, Sheppard JM. Dose-dependent disposition of perhexiline. *Aust NZ J Med* 1982; 12: 318.
 - 14 Horowitz JD, Morris PM, Drummer OH, Goble AJ, Louis WJ. High-performance liquid chromatographic assay of perhexiline maleate in plasma. *J Pharm Sci* 1981; 70: 320–2.
 - 15 Cole PL, Beamer AD, McGowan N, Cantillon CO, Benfell K, Kelly RA, Hartley LH, Smith TW, Antman EM. Efficacy and safety of perhexiline maleate in refractory angina. *Circulation* 1990; 81: 1260–70.
 - 16 Horowitz JD, Morris PM, Drummer O, Goble AJ, Louis WJ. Saturable metabolism of perhexiline maleate: correlations with long-term toxicity. *Am J Cardiol* 1981; 47: 399.
 - 17 Stewart S, Voss DW, Northey DL, Horowitz JD. Relationship between plasma perhexiline concentration and symptomatic status during short-term perhexiline therapy. *Ther Drug Monit* 1996; 18: 635–9.
 - 18 White HD, Lowe JB. Antianginal efficacy of perhexiline maleate in patients refractory to beta-adrenoreceptor blockade. *Int J Cardiol* 1983; 3: 145–55.
 - 19 Kennedy JA, Unger SA, Horowitz JD. Inhibition of carnitine palmitoyltransferase-1 in rat heart and liver by perhexiline and amiodarone. *Biochem Pharmacol* 1996; 52: 273–80.
 - 20 Sallustio BC, Westley IS, Morris RG. Pharmacokinetics of the antianginal agent perhexiline: relationship between metabolic ratio and steady state dose. *Br J Clin Pharmacol* 2002; 54: 1–13.
 - 21 Nyfort-Hansen K. Perhexiline toxicity related to citalopram use. *Med J Aust* 2002; 176: 560–1.
 - 22 Alderman CP. Perhexiline–paroxetine drug interaction. *Aust J Hosp Pharm* 1998; 28: 254–5.
 - 23 Alderman CP, Hundertmark JD, Soetratma TW. Interaction of serotonin re-uptake inhibitors with perhexiline. *Aust NZ J Psych* 1997; 31: 601–3.
 - 24 Michaelts EL. Update: Clinically significant cytochrome P–450 drug interactions. *Pharmacotherapy* 1998; 18: 84–112.
 - 25 Philpott A, Chandi S, Morris R, Horowitz JD. Development of a regimen for rapid initiation of perhexiline therapy in acute coronary syndromes. (in press).
 - 26 Amoah AGB, Lockhart JDF. Further studies on the pharmacokinetics of perhexiline maleate in humans. *Xenobiotica* 1986; 16: 63–8.