Concurrent administration of donepezil HCl and ketoconazole: assessment of pharmacokinetic changes following single and multiple doses

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Aim The aim of this study was to examine the pharmacokinetics of donepezil HCl and ketoconazole separately, and in combination, following administration of single and multiple oral doses.

Methods This was an open-label, randomized, three-period crossover study in healthy volunteers ($n=21$). During each treatment period, subjects received single daily doses of either donepezil HCl (5 mg), ketoconazole (200 mg), or a combination of both drugs for 7 consecutive days. Pharmacokinetic comparisons were made between treatment groups for the day 1 and day 7 profiles. Each treatment period was followed by a 3-week, drug-free washout period.

Results On both day 1 and day 7, a statistically significant difference was observed between the donepezil and the donepezil + ketoconazole treatment groups in terms of $C_{\max}$ and $AUC_{(0-24)}$ of donepezil. The concurrent administration of both drugs resulted in a 12% greater $C_{\max}$ (9.5 ng ml^{-1} versus 8.4 ng ml^{-1} ; $P=0.01$) and a 12% greater $AUC_{(0-24)}$ ($135.2 \text{ ng h ml}^{-1}$ versus $118.7 \text{ ng h ml}^{-1}$; $P=0.001$) than donepezil alone on day 1, and a 26.8% greater $C_{\max}$ (37.7 ng ml^{-1} versus 27.6 ng ml^{-1} ; $P<0.0001$) and a 26.4% greater $AUC_{(0-24)}$ ($680.9 \text{ ng h ml}^{-1}$ versus $501.0 \text{ ng h ml}^{-1}$; $P<0.0001$) than donepezil alone on day 7.

In contrast, ketoconazole plasma concentrations were unaffected by the concurrent administration of donepezil, and there were no statistically significant differences in ketoconazole pharmacokinetics when ketoconazole administered alone was compared with ketoconazole administered with donepezil.

Conclusions The concurrent administration of ketoconazole and donepezil produces no change in ketoconazole plasma concentrations, but a statistically significant change in donepezil plasma concentrations. These observed changes, which are smaller than those produced by ketoconazole for other agents sharing the CYP-3A4 pathway, are most likely the result of donepezil also being metabolized by CYP-2D6, as well as its slow rate of clearance from plasma.

Keywords: donepezil, ketoconazole, drug–drug interaction, acetylcholinesterase inhibitor

Introduction

Cholinergic deficit is one of the major pathological features of Alzheimer's disease. This deficit has been associated with the loss of cognition and memory, the primary symptoms of this disorder [1]. In an attempt to alleviate these clinical symptoms, therapeutic investigations have focused on enhancing the action of the remaining cholinergic neurones. To date, the most successful approach has been in the development of cholinergic agents, in particular, acetylcholinesterase (AChE) inhibitors [2, 3]. The first of the 'new-generation' AChE inhibitors used in the symptomatic treatment of mild–moderate Alzheimer's disease is donepezil HCl.

Donepezil HCl (also known as E2020 or Aricept®, the registered trademark of Eisai Co. Ltd, Tokyo, Japan) is a distinct, piperidine-based agent that inhibits the enzyme

AChE [4–8]. In pre-clinical investigations, donepezil was found to have a greater specificity for AChE as opposed to butyrylcholinesterase (BuChE) than either physostigmine or tacrine, and a longer duration of action than either of these drugs [9]. In clinical trials, treatment with single daily doses of either 5 or 10 mg of donepezil significantly improved cognition and global function in patients with Alzheimer's disease [10–12]. Treatment with donepezil was well tolerated and was not associated with hepatotoxicity. Adverse events, when present, tended to be mild and transient gastrointestinal disturbances, such as abdominal pain, nausea and vomiting. All of these events are consistent with an increase in cholinergic stimulation and resolved within a few days for most patients, without the need for dose modification [11].

In healthy individuals, the pharmacokinetics of donepezil are characterized by hepatic metabolism and slow plasma clearance ($0.13 \text{ l h}^{-1} \text{ kg}^{-1}$) [13]. Owing to its long half-life (approximately 70 h), donepezil is therapeutically effective using once-daily dosing.

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Ketoconazole is an imidazole derivative that is administered as a treatment for superficial and systemic fungal infections [14]. It is a specific, potent inhibitor of the cytochrome P-450 isoenzyme CYP-3A4 via which numerous compounds are metabolized. It has been shown to reduce the metabolism of other drugs sharing the CYP-3A4 pathway, including cyclosporin, warfarin, terfenadine, astemizole and some benzodiazepines [15, 16]. In addition, drug interactions with ketoconazole have also been reported for other medications, including corticosteroids, antihistamines and antacids [17–19].

As donepezil is predominantly metabolized by CYP-3A4, and to a lesser extent by CYP-2D6 (Aricept® US package insert, 1998), concurrent administration of ketoconazole might affect plasma concentrations of donepezil. Therefore, the primary objective of this study was to examine the pharmacokinetics of donepezil and ketoconazole administered separately and in combination, following single and multiple oral doses.

Methods

Subjects

Entry into the study was confined to healthy, non-smoking volunteers between 18 and 45 years of age who were within 20% of ideal body weight based on the Metropolitan Insurance Company Height and Weight Tables (1983). Subjects with evidence of clinically significant hepatic, gastrointestinal, renal, respiratory, endocrine, haematological, neurological, psychiatric or cardiovascular system abnormalities were specifically excluded from the study, as were those who had a known or suspected history of alcohol or drug misuse or a positive urine drug screen. None of the subjects had donated blood or had received investigational or prescription medications within 1 month of commencing trial medication.

The study was conducted in accordance with the principles stated in the Declaration of Helsinki, and the Institutional Review Board for Investigations Involving Human Subjects, Harris Laboratories, Lincoln, Nebraska, USA, approved the protocol. All subjects gave written informed consent prior to participation in the study.

Protocol

This was an open-label, randomized, multiple-dose, three-period crossover study. The three randomized treatments administered in this study were (1) donepezil HCl, 5 mg tablet, (2) ketoconazole, 200 mg tablet (Nizoral®, Janssen), and (3) donepezil, 5 mg + ketoconazole, 200 mg. Each treatment period was 7 days in duration and was followed by a 3-week, drug-free washout period. The dose of donepezil was chosen on the basis of results of clinical efficacy studies conducted in the USA, and the dose of ketoconazole is the recommended therapeutic dose for treatment provided by the Physicians' Desk Reference.

All volunteers were screened by medical history, ECG and laboratory and physical examinations ≤ 2 weeks prior to the start of the study. For each treatment period, subjects were admitted to the study site on the evening of day 0, at

least 12 h prior to drug administration. Subjects were fasted overnight (8 h) prior to receiving their first dose of medication on the morning of day 1. Following drug administration, blood samples for analytical determinations were collected at specified intervals during the next 24 h. Subjects were discharged from the study site the following morning, after providing a 24-h blood sample.

The subjects returned to the clinic as out-patients for the next four mornings (48, 72, 96 and 120 h) to provide trough blood samples for pharmacokinetic analysis and to receive their daily dose of medication. They were re-admitted to the study site on the evening of day 6 and repeated the same schedule of events as on day 0. The subjects were discharged from the study site on the morning of day 8, 24 h after receiving their final dose of medication. They returned to the clinic as out-patients for the next six mornings to provide blood for post-dose pharmacokinetic analyses (to 168 h). During the course of the treatment period, subjects were not allowed to consume caffeine-containing food or drinks, and physical exercise was limited to normal walking.

Sample collection and analysis

Venous blood samples for the determination of donepezil and/or ketoconazole concentrations in plasma were collected 1 h prior to drug administration, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96 and 120 h post-dose on days 1 and 7. Additional samples were taken at 144 and 168 h after the last dose of medication on day 7 of each treatment period.

Immediately after collection, the blood samples were placed on ice and centrifuged for 15 min (2000 g at 4°C). Plasma was then removed and transferred into polypropylene tubes, which were stored upright at -20°C until analysis. Plasma concentrations of donepezil (hydrochloride salt) were determined using a specific high-performance liquid chromatography (HPLC) method with UV detection [20]. Ketoconazole was also analysed using a standard HPLC method with UV detection. The limits of detection for these assays were 2 ng ml^{-1} for donepezil and $0.04\text{ }\mu\text{g ml}^{-1}$ for ketoconazole.

Pharmacokinetic assessments

Characterization of donepezil and/or ketoconazole pharmacokinetics for each treatment phase was performed by analysing blood samples collected over a 24-h period following initial dose administration, and a 168-h period following final dose administration.

Pharmacokinetic parameters for both drugs were estimated by a non-compartmental method. Peak plasma concentration (C_{max}) and the time at which it occurred (t_{max}) were recorded from the observed values. The terminal disposition phases of both donepezil and ketoconazole were identified by visual inspection of each subject's log concentration–time curve. The terminal disposition rate constant (λ_z) was estimated as -2.303 multiplied by the slope of the best-fit linear regression line of the terminal phase. The terminal half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$, and the area under the plasma concentration–time curve from 0 to 24 h ($\text{AUC}_{(0-24)}$) was estimated using the trapezoidal rule. The

accumulation ratio (R_A) was defined as $AUC_{(0-24)}$ on day 7 divided by $AUC_{(0-24)}$ on day 1.

Statistical analysis

Pharmacokinetic parameters for all three treatment groups were calculated following single-dose administration on day 1 and the final dose on day 7. An analysis of variance model (ANOVA), accounting for the effects of treatment, period, sequence and subject, was used to compare these parameters between days and between treatment periods. The type III sum of squares for all model effects was used to determine statistical significance at the 0.05 level.

Results

Subjects

A total of 21 subjects were enrolled into the trial and 18 successfully completed all three treatment phases. They ranged in age from 20 to 45 years (mean 31.2 years), in height from 158 to 189 cm (mean 174.1 cm), and in body weight from 54.5 to 81.5 kg (mean 72.1 kg). Of the 21 volunteers, 19 were Caucasian, one was Hispanic and one was Asian.

Pharmacokinetics of donepezil

Mean plasma donepezil concentrations were calculated for each time-point for both donepezil treatment groups (donepezil alone, donepezil + ketoconazole). A plasma concentration–time plot of these data is presented in Figure 1.

On day 1, a statistically significant difference was observed between the donepezil and the donepezil + ketoconazole treatment groups in terms of C_{max} ($P=0.01$) and $AUC_{(0-24)}$ of donepezil ($P=0.001$). The combination group had a 12% greater C_{max} (9.5 ng ml^{-1} versus 8.4 ng ml^{-1}) and a 12% greater $AUC_{(0-24)}$ ($135.2 \text{ ng h ml}^{-1}$ versus $118.7 \text{ ng h ml}^{-1}$) compared with the donepezil-only group (Table 1). No significant difference in t_{max} was observed between the groups. No significant sequence effects were observed.

On day 7, a statistically significant difference was again

Figure 1 The effect of concomitant administration of donepezil (5 mg) and ketoconazole (200 mg) once daily for 7 days on the mean ($\pm$ SE) plasma concentration–time profile of donepezil in healthy male volunteers: 24-h profiles were conducted following dose administration on day 1 and day 7.

Table 1 Comparison of donepezil pharmacokinetic parameters on day 1 (mean $\pm$ SE).

	Donepezil	Donepezil + ketoconazole	P-value
C_{max} (ng ml $^{-1}$)	8.4 ± 0.4	9.5 ± 0.5	0.01
t_{max} (h)	3.8 ± 0.2	3.6 ± 0.3	0.50
$AUC_{(0-24)}$ (ng h ml $^{-1}$)	118.7 ± 5.3	135.2 ± 7.5	0.001

Table 2 Comparison of donepezil pharmacokinetic parameters on day 7 (mean $\pm$ SE).

	Donepezil	Donepezil + ketoconazole	P-value
C_{max} (ng ml $^{-1}$)	27.6 ± 1.7	37.7 ± 2.2	<0.0001
t_{max} (h)	4.2 ± 0.2	3.9 ± 0.2	0.32
$AUC_{(0-24)}$ (ng h ml $^{-1}$)	501.1 ± 38.3	680.9 ± 48.4	<0.0001
$t_{1/2}$ (h)	58.4 ± 2.1	60.0 ± 3.2	0.46
R_A	4.2 ± 0.2	5.0 ± 0.2	<0.0001

observed between the donepezil and the donepezil + ketoconazole groups in terms of C_{max} and $AUC_{(0-24)}$ of donepezil ($P<0.0001$ for both). As shown in Table 2, the donepezil + ketoconazole group had a 26.8% greater C_{max} (37.7 ng ml^{-1} versus 27.6 ng ml^{-1}) and a 26.5% greater $AUC_{(0-24)}$ ($680.9 \text{ ng h ml}^{-1}$ versus $501.1 \text{ ng h ml}^{-1}$) than the donepezil-only group. There was also a significant ($P<0.0001$) increase of 16% in the rate of donepezil accumulation (R_A) for the combination group, compared with the donepezil-only group (Table 2), although this increase is not considered to be clinically relevant. No significant differences in t_{max} and $t_{1/2}$ were observed between the two treatment groups. No significant sequence effects were observed.

Steady-state pharmacokinetics

As this study involved only 7 consecutive days of drug administration during each treatment period and donepezil steady-state concentrations are not attained until 14–21 days, the effect of concomitant administration at steady state was estimated using pharmacokinetic modelling. Projected steady-state plasma concentrations of donepezil during concomitant administration with ketoconazole were calculated by fitting day 1 and day 7 data to both a one-compartment model and a sigmoidal E_{max} model. The mean trough concentration of donepezil at steady state was estimated to be 30.7 ng ml^{-1} and 27.7 ng ml^{-1} for the two models, respectively. Previous phase I studies with donepezil have calculated C_{min} to be 21.4 ng ml^{-1} [21]. Using the one-compartment model, these data suggest that the concurrent administration of ketoconazole will produce a 30% increase in donepezil concentrations at steady state. Using the E_{max} model, a 23% increase in donepezil concentrations at steady state is predicted.

Pharmacokinetics of ketoconazole

Mean plasma ketoconazole concentrations were calculated per time-point for each ketoconazole treatment group

Figure 2 The effect of concomitant administration of donepezil (5 mg) and ketoconazole (200 mg) once daily for 7 days on the mean ($\pm$ SE) plasma concentration–time profile of ketoconazole in healthy male volunteers: 24-h profiles were conducted following dose administration on day 1 and day 7. Concentrations of ketoconazole were below the detectable limit in one or both treatment groups at 18, 24, 48, 192 and 216 h.

(ketoconazole alone, donepezil + ketoconazole). A plasma concentration–time plot of this mean data is presented in Figure 2.

Results of the ketoconazole pharmacokinetic analyses are summarized in Tables 3 and 4. On days 1 and 7, no statistically significant differences in ketoconazole pharmacokinetics were observed when ketoconazole administered alone was compared with ketoconazole administered in combination with donepezil. No significant sequence effects were observed.

Safety

All treatments were well tolerated and no serious or unexpected adverse events occurred during the course of the study. Treatment-emergent signs and symptoms were mild or moderate in severity, and the incidence and severity of symptoms for donepezil and ketoconazole administered

in combination were similar to those for donepezil administered alone.

Discussion

Ketoconazole is a potent inhibitor of the P-450 isoenzyme CYP-3A4. Several reports have demonstrated that concurrent administration of this drug can reduce the metabolism of other drugs [15–19]. As CYP-3A4 is the primary route of donepezil metabolism, it is important to investigate whether co-administration with ketoconazole would produce any changes in donepezil metabolism and/or plasma concentrations.

The concurrent administration of both single and multiple doses of donepezil (5 mg) + ketoconazole (200 mg) resulted in a significant increase in the plasma levels of donepezil compared with the single- and multiple-dose administration of donepezil alone. This change in donepezil plasma concentration was reflected by increases in $C_{\max}$ and $AUC_{(0-24)}$ on both day 1 and day 7. There was no difference in the $t_{\max}$ values of the two groups on either day 1 or 7 and no difference in $t_{1/2}$ on day 7. The rate of donepezil accumulation in plasma (as reflected by the accumulation ratio, R_A) was 16% higher for the donepezil + ketoconazole group after 7 days of drug treatment. Clinical studies have shown that donepezil accumulation continues until steady state is achieved within 14–21 days [10]. As each treatment lasted for 7 days, steady-state donepezil plasma concentrations during concurrent administration of both drugs were estimated using both a sigmoidal $E_{\max}$ model and a one-compartment model. Donepezil concentrations were projected to increase by 23% in the $E_{\max}$ model and by 30% in the one-compartment model.

Although both the observed and estimated increases in donepezil concentrations were significant, they are smaller than those produced by ketoconazole administered concomitantly with other agents sharing the CYP-3A4 pathway. This is most probably the result of donepezil also being metabolized by CYP-2D6, as well as its slow rate of clearance from plasma.

Conversely, ketoconazole pharmacokinetics were not affected by the concurrent administration of donepezil. The lack of effect on ketoconazole plasma concentrations was expected, and is consistent with the results obtained from *in vitro* studies with donepezil (Aricept® US package insert, 1998). Isoform-selective substrate studies conducted in human hepatic microsomes determined that the donepezil concentrations required for 50% inhibition (IC_{50}) of P-450 isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4 were all greater than 100 μ M. In addition, the mean k_i values for CYP-3A4 and CYP-2D6 were found to be 131 μ M and 47 μ M, respectively. Clinical studies have estimated that the steady-state concentration for the 10 mg dose of donepezil is approximately 164 nM at the level of the hepatocyte. As it is expected that therapeutic concentrations of donepezil are more than 280-fold lower than the lowest k_i obtained for CYP-2D6 and almost 800-fold lower than the k_i observed with CYP-3A4, it is anticipated that donepezil will not inhibit the metabolism of other drugs metabolized via these P-450 isoenzymes.

In summary, the concurrent administration of donepezil

Table 3 Comparison of ketoconazole pharmacokinetic parameters on day 1 (mean $\pm$ SE).

	Ketoconazole	Donepezil + ketoconazole	P-value
$C_{\max}$ (ng ml ⁻¹)	4.0 $\pm$ 0.4	4.1 $\pm$ 0.3	0.94
$t_{\max}$ (h)	1.9 $\pm$ 0.1	2.0 $\pm$ 0.2	0.83
$AUC_{(0-24)}$ (ng h ml ⁻¹)	16.4 $\pm$ 1.7	16.1 $\pm$ 1.5	0.82

Table 4 Comparison of ketoconazole pharmacokinetic parameters on day 7 (mean $\pm$ SE).

	Ketoconazole	Donepezil + ketoconazole	P-value
$C_{\max}$ (ng ml ⁻¹)	4.6 $\pm$ 0.3	4.7 $\pm$ 0.4	0.79
$t_{\max}$ (h)	3.2 $\pm$ 0.3	2.8 $\pm$ 0.2	0.14
$AUC_{(0-24)}$ (ng h ml ⁻¹)	25.1 $\pm$ 1.6	25.1 $\pm$ 2.4	1.00
$t_{1/2}$ (h)	2.7 $\pm$ 0.2	2.7 $\pm$ 0.3	0.82
R_A	2.6 $\pm$ 0.8	1.8 $\pm$ 0.3	0.32

and ketoconazole was found to produce no change in ketoconazole plasma concentrations, but did result in an increase in donepezil plasma concentrations estimated to be 23–30% at steady state. The results of this study support *in vitro* findings (unpublished data) demonstrating that donepezil HCl is primarily metabolized by both CYP-3A4 and CYP-2D6, and that drugs that inhibit the CYP-3A4 pathway will also inhibit donepezil metabolism to some degree. However, it is unclear whether the metabolism of the drug is altered in such a way as to produce a changed pattern of metabolites. As the metabolites of donepezil are essentially clinically inactive (due both to low plasma concentrations as well as an inability to cross the blood–brain barrier), it is unlikely that even a substantial change in the metabolic processing of the drug would result in either a modification of drug effect or an increase in adverse events. Moreover, both the observed and the estimated increases in donepezil plasma concentrations are smaller than those produced by ketoconazole for other agents sharing the CYP-3A4 pathway and are thus unlikely to be clinically relevant. These findings suggest that dose modifications should not be required in patients to whom ketoconazole or another CYP-3A4 inhibitor are administered concurrently with donepezil.

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References

- Bartus RT, Dean RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science* 1982; **217**: 408–417.
- Giacobini E. Pharmacotherapy of Alzheimer's disease: new drugs and novel strategies. *Prog Brain Res* 1993; **98**: 447–454.
- Doraiswamy PM. Current cholinergic therapy for symptoms of Alzheimer's disease. *Primary Psychiatry* 1996; **3**: 56–68.
- Yamanishi Y, Ogura H, Kosasa T, Araki S, Sawa Y, Yamatsu K. Inhibitory action of donepezil, a novel acetylcholinesterase inhibitor, on cholinesterase. Comparison with other inhibitors. In *Basic, Clinical, and Therapeutic Aspects of Alzheimer's and Parkinson's Diseases*, Volume 2, eds Nagatsu T, Fisher A, Yoshida M. New York: Plenum Press, 1990: 409–413.
- Cardozo MG, Iimura Y, Sugimoto H, Yamanishi Y, Hopfinger AJ. QSAR analysis of the substituted indanone and benzylpiperidine rings of a series of indanone-benzylpiperidine inhibitors of acetylcholinesterase. *J Med Chem* 1992; **35**: 584–589.
- Sugimoto H, Iimura Y, Yamanishi Y, Yamatsu K. Synthesis and anti-acetylcholinesterase activity of 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine hydrochloride (E2020) and related compounds. *Biorg Med Chem Lett* 1992; **2**: 871–876.
- Pang YP, Kozikowski AP. Prediction of the binding site of 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine in acetylcholinesterase by docking studies with the SYSDOC program. *J Comput Aided Mol Design* 1994; **8**: 683–693.
- Nochi S, Asakawa N, Sato T. Kinetic study on the inhibition of acetylcholinesterase by 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (E2020). *Biol Pharm* 1995; **18**: 1145–1147.
- Rogers SL, Yamanishi Y, Yamatsu K. E2020—the pharmacology of a piperidine cholinesterase inhibitor. In *Cholinergic Basis for Alzheimer Therapy*, eds Becker R, Giacobini E. Boston: Birkhäuser, 1991: 314–320.
- Rogers SL, Friedhoff LT, the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter, randomized, double-blind, placebo-controlled trial. *Dementia* 1996; **7**: 293–303.
- Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, the Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50**: 136–145.
- Rogers SL, Doody RS, Mohs R, Friedhoff LT, the Donepezil Study Group. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med* 1998; **158**: 1021–1031.
- Mihara M, Ohnishi A, Tomono Y et al. Pharmacokinetics of E2020—a new compound for Alzheimer's disease, in healthy male volunteers. *Int J Clin Pharmacol Ther Toxicol* 1993; **31**: 223–229.
- Reynolds JEF (ed). *Martindale, The Extra Pharmacopoeia*, 31st edn. London: The Pharmaceutical Press, 1996: 410–411.
- Bennett JE. Antimicrobial agents: antifungal agents. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Ninth Edition, eds Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. New York: McGraw-Hill, 1996: 1175–1190.
- Babe KS, Serafin WE. Histamine, bradykinin, and their antagonists. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th edn, eds Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. New York: McGraw-Hill, 1996: 581–600.
- Khosla S, Wolfson JS, Demerjian Z, Godine JE. Adrenal crisis in the setting of high-dose ketoconazole therapy. *Arch Intern Med* 1989; **149**: 802–804.
- Ament PW, Paterson A. Drug interactions with the non-sedating antihistamines. *Am Fam Physician* 1997; **56**: 223–231.
- Sadowski DC. Drug interactions with antacids. Mechanisms and clinical significance. *Drug Saf* 1994; **11**: 395–407.
- Lee JW, Rogers SL, Friedhoff LT, Stiles MR, Cooper NM. Validation and application of an HPLC method for the determination of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine HCl (E2020) in human plasma. *Pharm Res* 1992; **9**: S350.
- Tiseo PJ, Rogers SL, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following evening administration. *Br J Clin Pharmacol* 1998; **46** (Suppl. 1): 13–18.