Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients

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Aims

To evaluate the pharmacokinetics (PK), pharmacodynamics (PD), tolerability and safety of donepezil HCl 5 mg following oral doses for 1 and 24 days in hepatically impaired patients compared with healthy controls under steady-state, multiple-dose conditions.

Methods

In this single-centre, multiple-dose, open-label study, patients with impaired hepatic function (Child–Pugh grade A or B) and healthy controls (matched by gender, age and weight to the hepatically impaired patients) received a single 5 mg dose of donepezil on day 1 and then donepezil HCl 5 mg once daily from days 6 to 29. PK and PD (determination of erythrocyte acetylcholinesterase inhibition) parameters were evaluated on days 1 and 29. Treatment-emergent adverse events (AEs), vital signs, physical examination and clinical laboratory test parameters were monitored throughout the study.

Results

A total of 35 subjects (18 patients with hepatic impairment and 17 healthy controls) were enrolled and 32 subjects (16 in each group) completed the study. On day 1 (following a single dose) hepatically impaired patients showed a significant decrease in T_{max} , while $t_{1/2}$ and $AUC_{0-\infty}$ were significantly increased compared with the healthy controls. On day 29 (following multiple doses), $AUC_{0-24\text{ h}}$, C_{max} , $t_{1/2}$, C_{SS} and R_A were significantly increased in hepatically impaired patients compared with healthy controls. $AUC_{0-24\text{ h}}$ increased by 47.6% in the patients with hepatic impairment compared with the healthy controls. There were no significant differences in PD between the groups, although at steady state, the mean AChE inhibition was 16.2% higher in the hepatically impaired patients. No serious AEs were reported and no subject withdrew from the study due to AEs. The most common AEs in both groups were headache and diarrhoea. No clinically significant changes from baseline were observed in vital signs, physical examination findings or electrocardiograms. There was a significant difference in the number of hepatically impaired subjects with abnormalities in serum glucose compared with healthy subjects. However, these elevations were not associated with AEs.

Conclusions

The results of this study suggest that patients with AD and mild to moderate hepatic impairment (Child–Pugh grade A or B) can be safely given donepezil 5 mg once daily and that this dose is associated with a nonsignificantly higher AChE inhibition than age-matched volunteers.

Introduction

Patients with Alzheimer's disease (AD) experience a progressive deterioration in cognition and in their ability to perform activities of daily living (ADL), as well as behavioural symptoms and mood changes that cause distress to both patient and caregiver. The gradual loss of cholinergic neurones within the cerebral cortex and subcortical structures is a central feature of AD [1]. Cholinesterase (ChE) inhibitors increase the activity of the remaining cholinergic neurones and are approved for the symptomatic treatment of patients with mild to moderate AD.

Donepezil hydrochloride (Aricept®) is a chemically distinct, reversible and specific inhibitor of AChE with a long elimination half-life (~70 h) that facilitates once-daily administration [2]. Clinical trials have demonstrated that treatment with donepezil (5 or 10 mg day⁻¹) is associated with significant improvements in cognition, and benefits in global function and in ADL vs. placebo [3–5]. Furthermore, two double-blind, placebo-controlled trials have demonstrated that the significant cognitive and functional benefits of donepezil are maintained for at least 1 year [6, 7]. Donepezil has also recently been demonstrated to significantly improve the behavioural symptoms of AD [8], and has consistently shown good tolerability in patients with this condition [3–8].

Donepezil undergoes extensive first-pass metabolism following oral administration [9, 10]. Furthermore, both pre-clinical and clinical studies have demonstrated that donepezil is metabolized principally by the liver [11]. *In vitro* studies using human hepatic microsomes have shown that the P450 isoenzymes CYP 3A4 and CYP 2D6 are primarily responsible for the metabolism of donepezil [12]. The observations that liver volume and hepatic blood flow decline with age [13], and that the liver loses some of its capacity to regenerate in the aged [14], suggest that many patients with AD may also be susceptible to intercurrent hepatic impairment. It is therefore important to assess the impact of hepatic impairment on the pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of donepezil.

An earlier PK study demonstrated that the peak plasma concentration (C_{max}) of donepezil following the administration of a single oral 5 mg dose of donepezil was increased by 37.5% in male patients with stable hepatic impairment compared with age- and weight-matched healthy controls [15]. However, since donepezil is always administered as a long-term therapy, there is a need to assess its safety under steady-state conditions. This study evaluated the PK, PD, safety and tolerability of donepezil in patients with stable hepatic

impairment compared with healthy matched controls under steady-state, once-daily dosing conditions.

Methods

This was a single-centre, multiple-dose, open-label, parallel-group study involving patients with stable hepatic impairment, and healthy controls who were matched to hepatically impaired patients by gender, age and weight.

Subjects

Hepatically impaired patients (male or female) were required to be aged 18–65 years, have a body weight no more than 35% above ideal and present evidence of cirrhosis with Child–Pugh [16] grade A or B hepatic impairment [17]. Hepatically impaired patients were not enrolled if they had experienced a hepatic coma, or had severe ascites/oedema, hepato-renal syndrome, extrahepatic bile duct obstruction, grade 3 or 4 hepatic encephalopathy, or acute or chronic hepatitis other than chronic, stable hepatitis B or C. Further reasons for ineligibility included serious, uncontrolled concomitant disease and current interferon therapy, or interferon therapy within 6 months of assessment.

Healthy volunteers were enrolled as controls in the study, and each was matched to a hepatically impaired patient (within 7 years of age and 20% body weight of hepatically impaired patient, and within 20% of his/her ideal body weight). Healthy subjects were excluded if they had evidence of clinically significant gastrointestinal, renal, respiratory, endocrine, haematological, neurological, psychiatric or cardiovascular abnormalities, positive serum hepatitis B surface antigen, antibody to hepatitis C, or HIV screen.

Women were enrolled into either cohort providing that they were not pregnant, or were at least 2 years post-menopausal, surgically sterile, or using a suitable contraceptive method. Exclusion criteria for both cohorts included: history of alcohol or drug abuse and/or positive urine drug screen; and loss/donation of > 450 ml of blood within 1 month of screening, with haemoglobin and haematocrit not within 5% of normal values. Unapproved prior or concomitant medications included medications that were known inhibitors or inducers of CYP 3A4 and CYP 2D6.

Study design

The study period included two phases: a single-dose phase followed by a multiple-dose phase. On day 1, after a 10-h fast, both groups received a single 5 mg dose of donepezil HCl. Blood samples were collected and vital

signs monitored pre-dose and for up to 24 h post-dose. All study participants were discharged from the site on day 2, following a routine physical examination, and returned to the Clinical Research Center daily for the next 4 days (days 3–6) for further measurements of vital signs and collection of blood samples.

After blood sampling on day 6, both the hepatically impaired patients and the healthy controls received the first 5 mg dose of a 24-day, once-daily dosing regimen of donepezil HCl. Thereafter, both groups returned to the site daily, up to day 29, for drug administration. Blood samples were collected pre-dose and for up to 24 h post-dose on day 29 and once daily up to day 37, when a complete physical examination was performed. All subjects were discharged from the study on day 37 provided that they did not show any clinically significant abnormalities in physical characteristics, electrocardiogram (ECG) results, vital signs or laboratory test parameters.

Patients could be removed from treatment in the event of an adverse event (AE) or intercurrent illness that might place the subject at risk, for protocol violation or disruptive behaviour, or for administrative or other reasons.

This study received Institutional Review Board approval, and was conducted in compliance with the US Food and Drug Administration *Code of Federal Regulations*. Written informed consent was required for all patients and subjects, and the study was conducted under the principles of the Declaration of Helsinki and its most recent amendments.

Treatment

All subjects received a single 5 mg dose of donepezil HCl on day 1, followed by a single 5 mg daily dose of donepezil HCl on days 6–29. Medication was administered orally as a 5 mg film-coated tablet of Aricept® (Eisai Inc., Teaneck, NJ, USA) accompanied by 250 ml of tap water. Subjects were allowed to consume a light snack approximately 10 h before the scheduled drug administration. An absolute fast from foods and fluids (except water) was then maintained until after drug administration. A 5 mg dose was selected since this is the clinically effective starting dose approved for the symptomatic treatment of mild to moderate AD [12]. Furthermore, the $C_{\max}$ in hepatically impaired patients following a single 5 mg dose was 37.5% higher than in matched controls [15], and it was therefore expected that the 5 mg dose would not induce plasma concentrations of donepezil above those experienced by subjects without hepatic impairment administered 10 mg day⁻¹, a

dose which has consistently been demonstrated to be well tolerated [3–8].

Sample collection and analysis

On day 1, blood samples for the determination of plasma donepezil concentrations were collected 1 h prior to, and 1, 2, 3, 4, 6, 8, 12, 18 and 24 h after dosing. Further blood samples were collected daily up to day 6 to allow the elimination phase of the single dose to be evaluated. Blood samples were also collected pre-dose on days 22, 24, 26, 27 and 28 to characterize steady-state conditions. Blood collection on days 29 and 30 followed the same pattern as days 1 and 2. Once-daily samples were again collected on days 31–36 to characterize the elimination phase. Additional blood samples for the estimation of donepezil protein binding during steady-state conditions were collected pre-dose on days 27–29 as well as 4 h post-dose on day 29.

At each sampling point, 7 ml of blood was collected into an evacuated, heparinized tube. At least 2 ml of plasma was transferred into a polypropylene tube and stored at –20 °C and used for the determination of the plasma concentrations of donepezil. The remaining plasma, the buffy coat and the top 3 mm of red blood cells (RBCs) were discarded, and the remaining RBCs transferred to a second polypropylene tube. These cells were used to measure AChE inhibition.

Pharmacokinetic assessments

Pharmacokinetic parameters were derived from measurements of the plasma concentration of donepezil and 6-OH donepezil (the major active metabolite) using a high performance liquid chromatographic system with a triple quadrupole tandem mass spectrometer detector. The lower limit of quantification for both donepezil and 6-OH donepezil was 0.2 ng ml⁻¹.

The following PK parameters were calculated for the single-dose treatment phase: the area under the plasma drug concentration–time curve (AUC) from time 0–24 h ($AUC_{0-24\text{ h}}$), AUC extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration ($C_{\max}$), plasma drug concentration at time of dose ($C_{\min}$), time taken to attain $C_{\max}$ ($t_{\max}$), and $t_{1/2}$, first-order terminal elimination half-life ($t_{1/2} = 0.693 \lambda_z^{-1}$).

The PK parameters calculated for the steady state (SS) were: $AUC_{0-24\text{ h,SS}}$, the mean steady-state concentration ($C_{\text{SS}} = AUC_{0-24\text{ h,SS}}/24\text{ h}$), $C_{\max}$, $C_{\min}$, $t_{\max}$, $t_{1/2}$, the degree of accumulation ($R_A = AUC_{0-24\text{ h,SS}}/AUC_{0-24\text{ h day 1}}$) and terminal or elimination rate constant (λ_z , determined by a linear least squares regression analysis of the terminal phase using the natural logarithm of the plasma drug concentration data).

Pharmacodynamic assessments

Blood samples for the PD analysis were collected following the same schedule as that used for the collection of PK samples. Samples of RBCs were assayed for erythrocyte AChE inhibition using a validated sensitive radioenzyme assay.

The following PD parameters were derived from the AChE inhibition data: the area under the effect–time curve from time 0–24 h ($AUE_{0-24\text{ h}}$), maximum effect (% AChE inhibition; $E_{\max}$), time to maximum effect ($t_{E_{\max}}$) and average effect (% AChE inhibition) during steady-state plasma concentrations (EC_{ss}).

Safety assessments

Safety was assessed using a combination of physical examinations, vital signs, 12-lead ECG, clinical laboratory tests, monitoring of AEs and evaluation of general health and well-being.

Statistical analysis

The study was powered to detect a 40% difference in the mean AUC of donepezil between the hepatically impaired patients and the healthy controls, with 80% power at a 5% significance level. This required the enrolment of at least 12 patients with hepatic impairment and 12 healthy controls.

Baseline data were analysed for all subjects enrolled, i.e. those who received at least one dose of donepezil HCl. Between-group differences were tested using analysis of variance (ANOVA) models for quantitative parameters and Fisher's exact test for categorical parameters.

PK and PD parameters were analysed for all subjects who completed the study. Between-group differences in the mean values of PK and PD parameters were evaluated using a two-tailed ANOVA and a 5% significance level. A similar ANOVA was also used to test for differences in the percentage of free (unbound) donepezil between the two groups. Analyses of the PK parameters was performed on the subjects who completed the study.

Safety parameters were evaluated for all patients and volunteers enrolled. Differences in the incidence of treatment-related AEs by body system, and changes from baseline to last visit values in physical examination, vital signs and clinical laboratory assessments were tested using Fisher's exact test.

Results

Baseline characteristics

A total of 35 volunteers (18 hepatically impaired and 17 healthy) were enrolled and received at least one dose

of donepezil HCl. Fifteen of the 18 hepatically impaired patients were categorized as Child–Pugh grade A and three as grade B. All but one of the hepatically impaired patients (17/18) were negative for hepatitis B surface antigen, whereas 14 out of 18 had a positive anti-hepatitis C virus screen. The hepatic impairment group consisted of 11 men and seven women, whereas the control group was made up of 10 men and seven women. The mean age in the hepatically impaired cohort was 49.9 years (range 41.0–65.0) compared with 49.4 years (42.0–67.0) in the healthy control group. The patients in the hepatically impaired group had a mean weight of 82.8 kg (range 53.7–107.2) compared with 74.8 kg (62.3–95.0) in the healthy control group.

Sixteen out of 18 hepatically impaired patients and 16/17 healthy controls completed the study. Two hepatically impaired patients and one healthy control discontinued the study at the request of the subject or investigator (for reasons of disruptive behaviour, intercurrent illness and administration of a disallowed medication, and loss to follow-up, respectively).

The mean rate of compliance (number of tablets taken/number of days the subject should have taken the medication) with donepezil HCl dosing among those who completed treatment was 100% (range 96–104%) for hepatically impaired patients and 101% (100–104%) for healthy controls. Fifteen out of 18 hepatically impaired patients and 10/17 healthy controls received approved concomitant medications before (within 21 days of first dose of donepezil HCl) or during the study period.

Pharmacokinetics

Single-dose pharmacokinetics. Following a single 5 mg dose of donepezil, at most sampling points, mean plasma donepezil concentrations were slightly higher in hepatically impaired patients than in healthy controls (Figure 1). Compared with healthy controls, a significant reduction in $t_{\max}$ and significant increases in $t_{1/2}$ and $AUC_{0-\infty}$ were observed in hepatically impaired patients. There were no significant differences in $AUC_{0-24\text{ h}}$ or $C_{\max}$ between the two cohorts (Table 1).

Steady-state pharmacokinetics. Values of plasma donepezil concentrations leading up to the PK assessment on day 29 demonstrated that steady-state conditions had indeed been attained. The mean plasma concentrations of donepezil during the multiple-dosing phase (following administration on day 29) were consistently higher in hepatically impaired patients than in healthy controls (Figure 2). Mean plasma donepezil concentrations were approximately four to five-fold

higher following multiple dosing compared with the concentrations observed after a single dose in both groups. The $AUC_{0-24hSS}$, C_{max} , $t_{1/2}$, C_{SS} and R_A were all significantly increased in the hepatically impaired patients compared with the healthy controls, while there was a significant decrease in λ_z (Table 2). There was no significant difference in t_{max} between groups. Small increases in the mean proportion of free donepezil in the

hepatically impaired patients compared with the healthy controls were observed at all sampling points. These increases were significant at day 27 (mean $\pm$ s.e.: hepatically impaired patients [$n = 15$], $24.8 \pm 1.1\%$; healthy controls [$n = 16$], $21.4 \pm 1.2\%$; $P = 0.046$) and when the means of data from each subject from all sample points were compared ($24.8 \pm 0.9\%$ [$n = 16$] vs. $22.0 \pm 0.8\%$ [$n = 16$], respectively, $P = 0.023$).

Figure 1

Mean plasma concentrations of donepezil following administration of a single 5 mg dose of donepezil HCl in hepatically impaired patients and healthy controls. Hepatically impaired patients ($n = 16$) (○—○), healthy controls ($n = 16$) (●—●)

Figure 2

Mean plasma concentrations of donepezil following administration of donepezil HCl 5 mg day⁻¹ for 24 days in hepatically impaired patients and healthy controls. Hepatically impaired patients ($n = 16$) (○—○), healthy controls ($n = 16$) (●—●)

Table 1

Pharmacokinetic parameters of donepezil in hepatically impaired patients and healthy controls following a single oral 5 mg dose of donepezil HCl

	Hepatically impaired ($n = 16$)	Healthy ($n = 16$)	Inter-group difference (%)	<i>P</i> -value
$AUC_{0-24\text{ h}}$ (ng·h ml ⁻¹)				
Mean $\pm$ s.e.	78.8 ± 3.6	75.3 ± 4.7	4.7	0.558
Range	57.6–107.7	46.2–109.3		
C_{max} (ng ml ⁻¹)				
Mean $\pm$ s.e.	5.6 ± 0.3	6.2 ± 0.9	-10.2	0.509
Range	3.5–7.5	2.9–17.6		
t_{max} (h)				
Mean $\pm$ s.e.	3.0 ± 0.3	4.6 ± 0.6	-35.1	0.013
Range	1.0–4.0	2.0–8.0		
$t_{1/2}$ (h)				
Mean $\pm$ s.e.	81.9 ± 6.9	60.5 ± 3.7	35.3	0.010
Range	51.5–142.8	42.8–95.2		
$AUC_{0-\infty}$ (ng·h ml ⁻¹)				
Mean $\pm$ s.e.	377.4 ± 32.3	286.6 ± 25.1	31.7	0.034
Range	251.9–720.1	138.3–581.0		

s.e., standard error.

	Hepatically impaired (n = 16)	Healthy (n = 16)	Inter-group difference (%)	P-value
AUC _{0–24 h,SS} (ng·h ml ⁻¹)				
Mean ± s.e.	496.9 ± 43.8	336.7 ± 32.4	47.6	0.006
Range	273.6–844.7	91.5–568.4		
C _{max} (ng ml ⁻¹)				
Mean ± s.e.	28.0 ± 2.5	20.1 ± 1.4	39.1	0.009
Range	15.0–48.9	8.9–31.1		
t _{max} (h)				
Mean ± s.e.	2.9 ± 0.3	3.6 ± 0.3	–17.5	0.140
Range	1.0–4.0	0.0–6.0		
t _{1/2} (h)				
Mean ± s.e.	97.6 ± 11.5	63.3 ± 2.4	54.2	0.007
Range	55.7–243.6	51.1–86.0		
C _{ss} (ng ml ⁻¹)				
Mean ± s.e.	20.7 ± 1.8	14.0 ± 1.4	47.6	0.006
Range	11.4–35.2	3.8–23.7		
R _A				
Mean ± s.e.	6.4 ± 0.6	4.4 ± 0.3	45.3	0.006
Range	3.7–11.7	2.0–6.5		
λ _z (h ⁻¹)				
Mean ± s.e.	0.008 ± 0.001	0.011 ± 0.000	–27.0	< 0.001
Range	0.003–0.012	0.008–0.014		

s.e., standard error.

Table 2

Pharmacokinetic parameters of donepezil in hepatically impaired patients and healthy controls following 24 daily doses of 5 mg donepezil HCl

Pharmacodynamics

There were no significant differences between the two groups in any of the PD parameters evaluated (Table 3). The mean inhibition of AChE activity was greater at day 29 than at day 1 in both groups. At day 1, the AChE activity (as measured by AUE_{0–24 h} or $E_{\max}$) was lower in hepatically impaired patients than in healthy controls. At day 29, the inhibition of AChE (as measured by AUE_{0–24 h}, $E_{\max}$ or EC_{SS}) was greater in hepatically impaired patients than in healthy control volunteers (Table 3).

Safety

Twelve of the 18 patients with hepatic impairment experienced one or more AEs (all causalities) compared with 8/17 healthy controls; this difference was not significant ($P = 0.315$; Table 4). None of the subjects in either cohort discontinued due to AEs. The most frequently reported AEs in the hepatically impaired patients were headache and diarrhoea, which were reported in five and four patients, respectively. Most AEs were considered to be mild in intensity and transient in nature. Only one severe AE was reported during the study: a severe case of dry mouth in a hepatically impaired patient, which

was judged to be possibly related to the study drug, although this AE is the reverse of what might be expected for a ChE inhibitor. No serious AEs were reported.

Treatment-emergent abnormal laboratory values occurred more frequently in hepatically impaired patients than in healthy controls. With the exception of plasma glucose concentration, there was no significant difference between the two cohorts in the incidence of abnormal clinical laboratory parameters. In the case of plasma glucose concentration, 7/18 hepatically impaired patients reported abnormal values compared with no healthy controls ($P = 0.0076$). The elevated glucose levels ranged from 163 to 384 mg dl⁻¹ (the normal range is 117–125 mg dl⁻¹; conversion factor to SI units = 0.0551). These elevations were not associated with AEs.

No clinically significant changes from baseline in vital signs or physical examination findings were observed in either cohort during the study. Eight hepatically impaired patients and three healthy control volunteers had abnormal ECGs at the time of discharge from the study, but none of these changes was considered to be clinically significant. Examples of these abnormalities included sinus bradycardia and left ventricular hypertrophy.

Table 3

Pharmacodynamic parameters in hepatically impaired patients and healthy controls following a single dose or multiple once-daily dosing of donepezil HCl 5 mg

	Hepatically impaired	Healthy	Inter-group difference (%)	P-value
Single dose	(n = 13)	(n = 12)		
AUE _{0–24 h} (h·% inhibition)				
Mean ± s.e.	498.4 ± 47.4	506.7 ± 81.0	–1.6	0.929
Range	337.5–895.5	178.0–1163		
E _{max} (% inhibition)				
Mean ± s.e.	38.0 ± 1.5	42.4 ± 5.2	–10.6	0.403
Range	30.9–49.2	12.9–74.7		
t _{E_{max}} (h)				
Mean ± s.e.	5.1 ± 0.9	7.3 ± 1.7	–30.8	0.235
Range	1.0–12.0	1.0–18.0		
Multiple dose (24 days)	(n = 14)	(n = 16)		
AUE _{0–24 h} (h·% inhibition)				
Mean ± s.e.	1463 ± 51.2	1260 ± 81.7	16.2	0.051
Range	1185–1712	758.5–1803		
E _{max} (% inhibition)				
Mean ± s.e.	72.0 ± 1.9	67.4 ± 3.0	6.9	0.222
Range	61.6–79.8	46.7–91.2		
t _{E_{max}} (h)				
Mean ± s.e.	4.5 ± 0.9	8.2 ± 2.0	–45.0	0.119
Range	1.0–12.0	0.0–24.0		
EC ₅₅ (% inhibition)				
Mean ± s.e.	61.0 ± 2.1	52.5 ± 3.4	16.2	0.051
Range	49.4–71.3	31.6–75.1		

Table 4

Treatment-emergent adverse events

	Hepatically impaired (n = 18)	Healthy (n = 17)	P-value
Subjects with ≥ 1 AE (all causalities)	12	8	0.315
Subjects with AE (all causalities)*			
Body as a whole			
Abdominal pain	2	0	0.486
Back pain	2	1	1.000
Headache	5	4	1.000
Pain	2	0	0.486
Digestive system			
Diarrhoea	4	3	1.000
Flatulence	2	1	1.000
Nausea	2	2	1.000
Nervous system			
Dizziness	2	1	1.000
Respiratory system			
Rhinitis	0	2	0.229
Skin and appendages			
Abrasion	2	0	0.486
Urogenital system			
Urinary tract infection	3	1	0.603

*Observed in >10% of subjects in either group.

Discussion

The PK of a single 5 mg dose of donepezil HCl have previously been investigated in male patients with hepatic impairment due to alcoholic cirrhosis [15]. The present study featured a number of modifications from this earlier study that were intended to increase the relevance of its findings to the clinical setting. The present study enrolled both male and female patients with stable hepatic impairment due to any causes, more closely representing the hepatically impaired population encountered in the clinic. In addition, 24 daily doses of 5 mg donepezil HCl were chosen for this study rather than the single dose used in the earlier study. This dose was selected because of its demonstrated efficacy in clinical trials [3–5], leading to its approved use for the treatment of mild to moderate AD [12], and the likelihood that it would be well tolerated by hepatically impaired patients [15]. The use of this dose also avoided exposing subjects to unnecessary levels of AChE inhibition.

The present study featured two treatment phases. The single-dose phase was included to confirm consistency of results with those from the earlier hepatic impairment study [15], and to provide a benchmark for the multiple-dose phase. Results from the single-dose phase indicated a significant decrease in $T_{\max}$ and significant increases in $t_{1/2}$ and $AUC_{0-\infty}$ in hepatically impaired patients compared with healthy controls. A slight decrease in $C_{\max}$ was also observed, which is in contrast with the findings of the earlier study in which hepatically impaired patients demonstrated an increase of approximately 37% in the $C_{\max}$ of donepezil compared with healthy subjects. The reasons for this are uncertain. However, there were differences in the patients enrolled in these two studies, which may explain this disparity. For example, in the earlier study only men with hepatic impairment due to cirrhosis were enrolled, whereas in this study both men and women were included. However, in both studies the mean age of the patients with hepatic impairment was 47–50 years. Unfortunately, few elderly patients with hepatic impairment (who might more closely resemble AD patients) volunteered for these studies, and those who did were frequently ineligible.

A central element of the design of this study was the evaluation of donepezil PK and PD parameters under steady-state conditions. Based on the findings of earlier studies, which have demonstrated that steady-state conditions are reached after 14–21 days [18], the administration of donepezil HCl once daily for 24 days was estimated to be sufficient to establish a steady state, before measurements on day 29, and plasma donepezil

concentrations confirmed this. This would presumably be analogous to the conditions encountered when AD patients are administered donepezil HCl at 5 mg day⁻¹ during routine clinical practice.

Plasma concentrations of donepezil were approximately four to fivefold higher at steady state than following a single dose in both cohorts. Values of R_A confirmed the greater exposure to donepezil during multiple dosing than after administration of a single dose in both hepatically impaired patients and healthy controls. At steady state, mean values for $AUC_{0-24\text{ h}}$, $C_{\max}$, C_{ss} and R_A were all significantly increased in the hepatically impaired patients compared with the healthy controls. These observations confirm that the greater exposure to donepezil observed in hepatically impaired patients following a single dose of donepezil also occurs, and is increased, at steady state. The mean increase in the $C_{\max}$ of hepatically impaired patients compared with the healthy cohort was 39% at steady state, which is comparable to the 37% increase in this parameter observed in the single-dose study [15].

The inhibition of AChE is believed to be responsible for the clinical efficacy of ChE inhibitors in the treatment of AD [19]. Indeed, a significant correlation between RBC AChE inhibition and improvements in cognitive function and global function has been reported for donepezil-treated patients with AD [4]. Although the PD profile of donepezil has been investigated following single [20] and multiple [18] oral doses in healthy subjects, it has not previously been explored in hepatically impaired patients [15]. The results of this study demonstrated that RBC AChE inhibition was increased in hepatically impaired patients compared with healthy controls, although these increases were not significant. However, it should be noted that this study was not statistically powered to detect a difference in PD parameters. In comparison, in AD patients, RBC AChE inhibition was measured at $63.9 \pm 0.9\%$ in patients treated with 5 mg day⁻¹, and $74.7 \pm 1.2\%$ for those administered 10 mg day⁻¹, following 12 weeks of treatment [4]. The increased donepezil exposure observed in hepatically impaired patients in this study would contribute considerably to reducing the difference in observed RBC AChE inhibition between the 5 mg day⁻¹ and 10 mg day⁻¹ donepezil doses.

Donepezil was well tolerated by both hepatically impaired patients and healthy controls. This statement is based on the finding that there were no discontinuations due to AEs and no patient experienced a serious AE. Furthermore, despite the increased exposure to donepezil in hepatically impaired patients, there were no clinically or statistically significant increases in the

incidence of AEs or vital signs compared with healthy controls. Many of the AEs reported were likely related to the cholinomimetic action of donepezil (e.g. diarrhoea and nausea) and have previously been described following treatment with donepezil HCl in clinical trials [3–7] and in the previous single-dose hepatic impairment study [15].

The significance of the higher incidence of abnormal glucose levels in hepatically impaired patients than in healthy controls is unclear. Abnormal glucose levels are consistent with the disturbances of carbohydrate metabolism observed in patients with liver disease [21]. However, it would be reasonable to closely monitor glucose levels in patients with hepatic impairment who are receiving donepezil and who are known to have glucose intolerance or diabetes.

This study has demonstrated that, under steady-state, multiple-dosing conditions, exposure to a once-daily oral 5 mg dose of donepezil HCl is significantly greater in hepatically impaired subjects than in healthy subjects. However, while this increase in exposure to donepezil HCl in hepatically impaired patients is accompanied by an increase in the inhibition of AChE activity, donepezil was safe and well tolerated in this cohort. These results suggest that patients with Alzheimer's disease and mild to moderate hepatic impairment can be safely treated with donepezil HCl 5 mg day⁻¹, and that this dose is associated with increased AChE inhibition in this population. There are no data for patients with severe hepatic impairment.

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References

- 1 Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* 1976; 2: 1403.
- 2 Dooley M, Lamb MM. Donepezil. A review of its use in Alzheimer's disease. *Drugs Aging* 2000; 16: 199–226.
- 3 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; 50: 136–45.
- 4 Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease. A 15-week, double-blind, placebo-controlled study. *Arch Intern Med* 1998; 158: 1021–31.
- 5 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT. The effects of donepezil in Alzheimer's disease – results from a multinational trial. *Dement Geriatr Cogn Disord* 1999; 10: 237–44.
- 6 Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P; Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; 57: 489–95.
- 7 Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD; "312" Study Group. A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; 57: 481–8.
- 8 Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E; Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; 57: 613–20.
- 9 Ohnishi A, Mihara M, Kamakura H, Tomono Y, Hasegawa J, Yamazaki K, Morishita N, Tanaka T. Comparison of the pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy young and elderly subjects. *J Clin Pharmacol* 1993; 33: 1086–91.
- 10 Mihara M, Ohnishi A, Tomono Y, Hasegawa J, Shimamura Y, Yamazaki K, Morishita N. Pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy male volunteers. *Int J Clin Pharmacol Toxicol* 1993; 31: 223–9.
- 11 Tiseo PJ, Perdomo CA, Friedhoff LT. Metabolism and elimination of ¹⁴C-donepezil in healthy volunteers: a single-dose study. *Br J Clin Pharmacol* 1998; 46(Suppl. 1): 19–24.
- 12 ARICEPT® (donepezil hydrochloride tablets). US package insert, December 2000. Teaneck, NJ: Eisai Inc.
- 13 Woodhouse K, Wynne HA. Age-related changes in hepatic function. Implications for drug therapy. *Drugs Aging* 1992; 2: 243–55.
- 14 Regev A, Schiff ER. Liver disease in the elderly. *Gastroenterol Clin North Am* 2001; 30: 547–63, x–xi.
- 15 Tiseo PJ, Vargas R, Perdomo CA, Friedhoff LT. An evaluation of the pharmacokinetics of donepezil HCl in patients with impaired hepatic function. *Br J Clin Pharmacol* 1998; 46(Suppl. 1): 51–5.
- 16 Pugh RNH, Murray-Lyon IM, Dawson J, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646–9.
- 17 Height and Weight Standards. New York: Metropolitan Life Insurance Company, 1983.
- 18 Rogers SL, Cooper NM, Sukovaty R, Pederson JE, Lee JN, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following multiple oral doses. *Br J Clin Pharmacol* 1998; 46(Suppl. 1): 7–12.
- 19 VanDenBerg CM, Kazmi Y, Jann MW. Cholinesterase inhibitors for the treatment of Alzheimer's disease in the elderly. *Drugs Aging* 2000; 16: 123–38.
- 20 Rogers SL, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following single oral doses. *Br J Clin Pharmacol* 1998; 46(Suppl. 1): 1–6.
- 21 Petrides AS, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. *Hepatology* 1994; 19: 616–27.