Br. J. clin. Pharmac. (1993), **35**, 441–443

The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment

J. C. BLAKE[1], J. L. PALMER[2], N. A. MINTON[2] & A. K. BURROUGHS[1]
[1]University Department of Medicine, Royal Free Hospital and School of Medicine, London NW3 2QG and [2]Clinical Pharmacology Division, Glaxo Group Research Ltd, Greenford, Middlesex UB6 0HE

The pharmacokinetics of the 5-HT_3 receptor antagonist ondansetron were investigated following a single 8 mg intravenous dose given over 5 min in 19 patients with varying degrees of hepatic impairment and in six young healthy subjects. In comparison with the healthy controls, the patients with severe hepatic impairment had a lower mean plasma clearance (96 ml min^{-1} *vs* 478 ml min^{-1}) and increased AUC (1383 ng ml^{-1} h *vs* 279 ng ml^{-1} h) and $t_{1/2}$ (21 h *vs* 3.6 h). These differences were all statistically significant ($P < 0.001$). The corresponding values for patients with mild or moderate hepatic impairment fell between these extremes. V_{ss} was greater in all patient groups than the control group, but the magnitude of the change was smaller than for the other parameters and did not reflect the increasing severity of hepatic impairment. There were no significant changes in C_{max}. There were no drug-related adverse events in the patients studied. It is recommended that the dosing frequency of ondansetron be limited to once daily in patients with severe hepatic impairment.

Keywords ondansetron pharmacokinetics hepatic impairment

Introduction

Ondansetron is a potent and selective antagonist at 5-HT_3 receptors (Tyers *et al.*, 1989) and, as the hydrochloride dihydrate, is licensed in a number of countries as an anti-emetic for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. The pharmacokinetics of ondansetron in healthy volunteers, including the elderly, have been described previously (Colthup *et al.*, 1991; Pritchard *et al.*, 1992). The primary route of ondansetron clearance is by hepatic phase I metabolism, and less than 5% of an i.v. dose is excreted unchanged in the urine (Saynor & Dixon, 1989).

As ondansetron is cleared primarily by phase I metabolism, it was anticipated that its clearance would be impaired in patients with hepatic impairment. This study was designed to investigate the kinetics of ondansetron following a single 8 mg dose, given as an i.v. infusion, in such patients and in a control group of healthy subjects.

Methods

Six healthy subjects (four males and two females, 19 to 23 years of age) and nineteen patients with hepatic impairment (six with mild, six with moderate and seven with severe impairment; eleven males and eight females, 20 to 69 years of age) were entered into the study. Written informed consent was obtained from all subjects and Ethics Committee approval was granted by the Royal Free Hospital Ethical Practices Sub-Committee. Patients had documented, chronic, stable hepatic disease, confirmed by biopsy or by clinical, biochemical and radiological features. The severity of the liver disease was assessed according to Pugh's modification of Child's classification (Howden *et al.*, 1989).

A single dose of ondansetron 8 mg (as the hydrochloride dihydrate) was given as an i.v. infusion over 5 min. Blood samples for plasma ondansetron assay were taken before dosing and at 5, 15 and 30 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after the start of the infusion. Additional samples were taken at 28, 32 and 48 h from the patients. Plasma ondansetron concentrations were measured using a reverse phase h.p.l.c. procedure with a limit of quantification from a 1 ml plasma sample of 1 ng ml^{-1} (Colthup *et al.*, 1991). The coefficient of variation for the assay at the limit of quantification was 6.2%.

The maximum measured plasma drug concentration (C_{max}) was obtained directly from the concentration-

Correspondence: Dr J. C. Blake, University Department of Medicine, Royal Free Hospital and School of Medicine, London NW3 2QG

time data. The terminal elimination rate constant (λ_z) was determined by linear least-squares regression using the logarithmically transformed points in the terminal phase, and the terminal half-life was calculated from ln $2/\lambda_z$. The AUC from zero final to the last measurable concentration was calculated by a combination of linear and logarithmic trapezoidal methods. The linear method was used when plasma drug concentrations were rising and the logarithmic method when concentrations were declining. The area was extrapolated to infinite time using C_z/λ_z were C_z is the last quantifiable plasma drug concentration. The total plasma clearance (CL) was calculated from Dose/AUC$_\infty$. The volume of distribution at steady state (V_{ss}) was calculated from:

$$V_{ss} = (\text{Dose.AUMC/AUC}^2) - (t.\text{Dose})/(2.\text{AUC})$$

where t is the time over which the i.v. dose was infused and AUMC is the first moment about $t = 0$ of the AUC, interpolated as described above and extrapolated to infinite time.

Statistical comparisons for all parameters were made using a one-way analysis of variance. All statistical tests were carried out at the 5% level of significance and comparisons were made with respect to the control group.

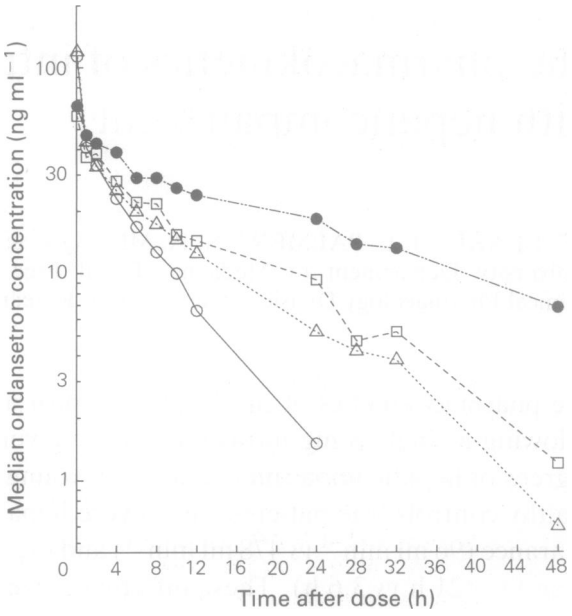

Figure 1 Median plasma ondansetron concentrations following a single 8 mg intravenous infusion of ondansetron given over 5 min in healthy subjects (○, $n = 6$) and patients with mild (□, $n = 6$), moderate (△, $n = 6$) and severe (●, $n = 7$) hepatic impairment.

Results

Median plasma ondansetron concentrations are shown in Figure 1 and the pharmacokinetic parameters are listed in Table 1. The plasma clearance of ondansetron declined from a mean of 478 ml min^{-1} in the control group to 96 ml min^{-1} in those with severe hepatic impairment ($P < 0.001$). AUC increased from a mean of 279 ng ml^{-1} h in the control group to a mean of 1383 ng ml^{-1} h in the severely impaired group ($P < 0.001$). The terminal plasma half-life increased from a mean of 3.6 h in the control group to 21 h in the severely impaired group ($P < 0.001$). The corresponding values for the patients with mild and moderate impairment fell

Table 1 Pharmacokinetic parameters. Data are presented as geometric means and 95% confidence intervals with the exception of $t_{1/2}$ (harmonic mean and 95% CI). C_{max} = maximum measured plasma concentration, AUC = area under the plasma concentration-time curve extrapolated to infinite time, CL = total plasma clearance, V_{ss} = apparent volume of distribution at steady state, $t_{1/2,z}$ = terminal plasma half-life

	Control group	*Hepatically impaired patients*		
		Mild	*Moderate*	*Severe*
C_{max} (ng ml^{-1})	97.2 (58.7–161.0)	68.6 (41.5–113.7)	105.5 (63.7–174.6)	93.7 (58.8–149.5)
P value	–	0.322	0.814	0.912
AUC (ng ml^{-1} h)	279 (200–388)	633 (455–880)	446 (311–641)	1383 (995–1924)
P value	–	0.002	0.058	<0.001
CL (ml min^{-1})	478 (344–665)	211 (151–293)	299 (208–429)	96 (69–134)
P value	–	0.002	0.058	<0.001
V_{ss} (l)	153 (127–184)	224 (186–269)	230 (187–281)	179 (149–216)
P value	–	0.007	0.006	0.216
$t_{1/2,z}$ (h)	3.6 (3.0–4.6)	9.1 (6.0–19.6)	9.2 (5.8–22.0)	20.6 (9.4–*)
P value	–	<0.001	<0.001	<0.001

All *P* values are quoted for the comparison with the control group.
* The 95% CI for the terminal elimination rate constant included a negative value. As this equates to a net input of drug, it has been disregarded.

between these extremes. There was a slight increase in volume of distribution at steady state in all patients in comparison with the control group. However, it did not increase with increasing hepatic impairment. There were no significant changes in C_{max}. Ondansetron was well tolerated in both the control group and patients with hepatic impairment. There were no drug-related adverse events.

Discussion

As expected for a drug which is cleared predominantly by hepatic phase I metabolism, the results show marked differences in disposition between patients exhibiting different degrees of hepatic impairment. However, the patients classified as having mild or moderate hepatic impairment could not be distinguished from one another on the basis of their pharmacokinetic parameters alone. It is probable that this is a limitation of the classification system used.

The changes in plasma clearance are unlikely to have been the result of changes in plasma protein concentration associated with liver disease as ondansetron is not extensively protein bound (70–76%). The changes in clearance seen in the patients are probably related to both a decrease in intrinsic hepatic metabolic function and changes in hepatic blood flow (including shunting) (Howden *et al.*, 1989). The majority of the increases $t_{1/2}$ in the patients can be attributed to the reduction in plasma clearance, although the slight increase in V_{ss} will have also contributed to this change.

The patient group in this study were older than the healthy control group and increasing age has previously been shown to be associated with a decline in ondansetron clearance (from 0.349 l h^{-1} kg^{-1} in a group aged 21–38 years to 0.279 l h^{-1} kg^{-1} in a group aged 60–74 years) (Pritchard *et al.*, 1992). Volume of distribution was shown to be unaffected by age. However, the magnitude of the changes seen here exceed the relatively small effect of age alone.

The results indicate that compared with patients with normal hepatic function, a reduction in dosing frequency is advisable in patients with severe hepatic impairment. Based on these data, once daily dosing would appear appropriate.

References

Colthup, P. V., Felgate, C. C., Palmer, J. L. & Scully, N. L. (1991). The determination of ondansetron in plasma and its pharmacokinetics in the young and elderly. *J. pharm. Sci.*, **80**, 868–871.

Howden, C. W., Birnie, G. G. & Brodie, M. J. (1989). Drug metabolism in liver disease. *Pharm. Ther.*, **40**, 439–474.

Pritchard, J. F., Bryson, J. C., Kernodle, A. E., Benedetti, T. L. & Powell, J. R. (1992). Age and gender effects on ondandsetron pharmacokinetics: evaluation of aged healthy volunteers. *Clin. Pharmac. Ther.*, **51**, 51–55.

Saynor, D. A. & Dixon, C. M. (1989). The metabolism on ondansetron. *Eur. J. Cancer clin. Oncol.*, **25** (Suppl. 1), S75–S77.

Tyers, M. B., Bunce, K. T. & Humphrey, P. P. A. (1989). Pharmacological and anti-emetic properties of ondansetron. *Eur. J. Cancer clin. Oncol.*, **25** (Suppl. 1), S15–S20.

(Received 30 July 1991, accepted 6 November 1992)