J. Pharm. Pharmacol. 1996, 48: 774–781
Received September 9, 1995
Accepted March 22, 1996

Clinical Pharmacokinetics of Ondansetron. A Review

KAREN H. SIMPSON AND FIONA M. HICKS

Level 8, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF, UK

5-HT_3 receptors are ubiquitous in the enteric, sympathetic, parasympathetic and sensory nervous systems and in the central nervous system (CNS) (Kilpatrick et al 1990). In man 5-HT_3 receptors are mainly situated on enterochromaffin cells in the gastrointestinal mucosa, which are innervated by vagal afferents (Reynolds et al 1989), and the area postrema of the brain stem, which forms the chemoreceptor trigger zone. Ondansetron is a selective antagonist at 5-HT_3 receptors. It is 100 times more potent than metoclopramide at this site (Tyers 1992). It shows limited binding to other receptors and has a wide therapeutic window. Ondansetron is a useful antiemetic which probably has both central and peripheral actions in patients undergoing radiotherapy, cytotoxic chemotherapy or general anaesthesia (Naylor & Rudd 1992). This paper reviews the pharmacokinetics of ondansetron in health and disease to provide information for clinicians; it might alter prescribing and alert them to possible drug interactions.

Chemistry

Ondansetron was synthesized in 1983 as the hydrochloride dihydrate salt (Fig. 1). Its structure is similar to that of 5-HT; both have an indole nucleus. It has one asymmetric centre and is a 1 : 1 racemic mixture of the D and L enantiomers (Fig. 2; Mackinnon & Coll 1989). Both isomers are selective antagonists at 5-HT_3 receptors. Animal studies show some differences between the effects of the isomers in-vitro (Butler et al 1988); there is no information about man. Ondansetron is stable under normal conditions for 4 years. It has a pK_a of 7·4 and an aqueous pH of 4·6.

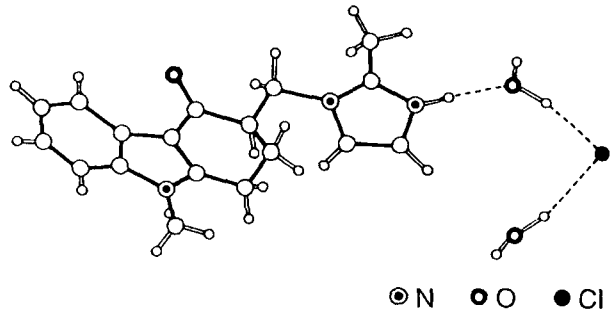

FIG. 2. X-ray structure of ondansetron.

Assay Methods

Ondansetron is measured in plasma by high-performance liquid chromatography (HPLC), after solid-phase extraction, with detection by ultraviolet absorption at 305 nm (Colthup & Palmer 1989). The range of the assay is 1·0–20 ng mL^{-1} plasma. The assay is sensitive, precise and accurate. Intra-assay and inter-assay coefficients of variation are less than 7·5%. The assay does not differentiate between the isomers. It is specific for ondansetron and its metabolites and is not affected by other drugs.

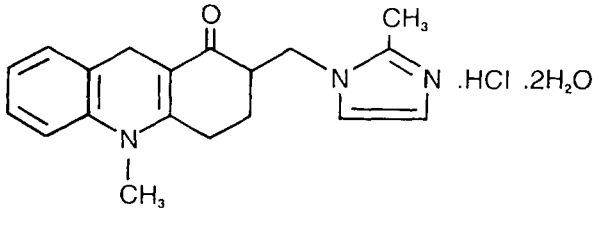

FIG. 1. Structure of ondansetron.

Correspondence: K. H. Simpson, Level 8, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF, UK.

Ondansetron Pharmacokinetics in Young Healthy Volunteers

The pharmacokinetics of ondansetron have been investigated in healthy volunteers and there is good agreement between most studies. Most subjects were young men and many studies involved small numbers (Blackwell & Harding 1989; Colthup & Palmer 1989; Saynor & Dixon 1989; Colthup et al 1991; Frazer & Palmer 1992; Hysu et al 1994b). There were no clinically significant differences in absorption, distribution or elimination of ondansetron with any of the regimens studied. There was no drug accumulation at steady state.

Routes of Administration

Pharmacokinetic data vary with the route of administration and are largely unchanged by repeated dosing (Table 1). No alterations in dosing are necessary when ondansetron is given over three to five days.

Intravenous route

Ondansetron has been given as an intravenous (i.v.) infusion of 8 mg over 5 min (Colthup & Palmer 1989), a single infusion of 8 mg over 15 min or an 8-mg infusion over 15 min fol-

Table 1. Pharmacokinetic data after different routes of ondansetron administration in healthy volunteers.

	Oral 8 mg single dose Mean (95% CI)	Oral steady state Mean (95% CI)	Intravenous 8 mg 5 min infusion Mean (s.d.)	Intramuscular 4 mg single dose Median (range)	Colonic 8 mg infusion Mean (s.d.)	Rectal 8 mg single dose Mean (s.d.)
T_{max} (h)	1·0* (0·8–2·0)	1·0* (0·8–1·5)	0·12 (0·05)	– (0·08–0·17)	1·1 (0·3)	1·3 (0·7)
C_{max} (ng mL^{-1})	31·2 (25·6–38·1)	38·9 (31·2–48·4)	80 (33·0)	24 (12–30)	28 (13·0)	26 (14·0)
t½ (h)	3·2 (2·4–5·8)	3·3 (3·3–8·1)	2·8 (0·6)	– –	6·9 (1·4)	6·8 (0·9)
CL (mL min^{-1})	–	–	702 (167)	–	–	–
AUC (ng h^{-1} mL^{-1})	–	130·3 (106·0–160·2)	–	– (103)	236 (64)	180

*Median (range)

lowed by 1 mg h^{-1} over 24 h (Blackwell & Harding 1989). The time to reach peak plasma drug concentration (T_{max}) of 7 min, t½ of 3–3·5 h and total-body clearance (CL) of 600 mL min^{-1} were similar after all three regimens. Intravenous ondansetron provided more rapid onset of action than the oral route.

Oral route

Ondansetron tablets are bioequivalent to the oral solution. The tablet dissolves quickly and completely in-vivo (Pritchard 1992). The mechanism of intestinal absorption was studied in-vitro using a well differentiated human intestine cell line generated from colorectal carcinoma (Gan et al 1993), an excellent model for intestinal drug absorption. Ondansetron is lipophilic and diffuses passively via transcellular pathways. This suggests a similar rate of diffusion throughout the gastrointestinal tract. Oral ondansetron is well absorbed, with a bioavailability of approximately 60–70%. First-pass metabolism removes 30–40% of the drug (Colthup & Palmer 1989; Colthup et al 1991). The presence of food in the gastrointestinal tract causes a small, clinically insignificant, increase in bioavailability. The use of antacids does not alter bioavailability (Pritchard 1992).

After oral administration of ondansetron there is a 30-min lag-time before the drug can be measured in plasma (Colthup & Palmer 1989). This indicates that it is absorbed in the upper gastrointestinal tract. The time to reach peak plasma drug concentration (C_{max}) is 1–1·5 h and t½ is 3–3·5 h. Pharmacokinetic data were similar when a single oral dose of 8 mg ondansetron was compared with the steady state reached after 6 days administration of 8 mg three times per day.

Intramuscular route

Intramuscular (i.m.) administration of ondansetron has been described in two volunteer studies (Frazer & Palmer 1992; Palmer et al 1993). The drug was rapidly absorbed with a t½ of 5–10 min. The t½ and absorption were similar to those after intravenous injection. Both studies used a similar dose (4 mg, i.m., in 2 mL solution). The volume of injectate limits the dose that can be comfortably given intramuscularly. Pain at the injection sites after administration of ondansetron was either less than or similar to that for placebo. The nature of the placebo was not reported in one study (Palmer et al 1993). In clinical practice intravenous and intramuscular ondansetron can be used interchangeably, but the intravenous route enables the administration of a larger dose.

Colonic route

A study describing colonic administration of ondansetron, used a solution of 8 mg (Hsyu et al 1994b). Six young male volunteers were given the drug through a nasogastric tube passed to the caecum and proximal transverse colon. The t½ after colonic administration was comparable with that after oral dosing. C_{max} was reduced and the t½ prolonged to almost 7 h. Bioavailability (74%) was not significantly different from that after oral administration. Ondansetron is absorbed as well in the colon as it is in the upper gastrointestinal tract. It may be possible to develop a modified release preparation. Dose modification is unnecessary after bowel resection.

Rectal route

Rectal administration was investigated in the same study as colonic administration, using a retention enema in the same six volunteers (Hsyu et al 1994b). T_{max}, C_{max} and t½ were similar to those after colonic administration. Bioavailability (58%) was not significantly different from that after oral or colonic dosing. Development of a suppository formulation should be possible.

Sublingual and subcutaneous routes

The lipophilicity of ondansetron suggests that sublingual or subcutaneous administration would result in good absorption. Subcutaneous infusion of ondansetron may be of benefit in circumstances such as palliation of intractable emesis. There are no published data on these routes of administration.

Distribution

The apparent volume distribution at steady state (V_{SS}) in young, healthy volunteers is approximately 1·8 L kg^{-1}, which is greater than the 0·9 L kg^{-1} representing total body water (Pritchard et al 1992). This reflects the high lipid solubility of ondansetron, which has a log D (octanol/water) of 1·3 at pH 7·4. Ondansetron is 67% ionized at blood pH. Protein binding is about 70%, which does not greatly influence pharmacokinetics. Alpha 1 acid glycoprotein, which can change significantly in cancer, is not a major binding protein for ondansetron. The blood : plasma ratio of ondansetron is 0·83, implying that it distributes into red cells (Pritchard 1992). The brain : plasma ratio in animals is less than 0·5, suggesting slow penetration into the CNS. This is supported by low cerebrospinal fluid (CSF) concentrations, about 10% of plasma concentrations seen in man after oral dosing (Simpson et al 1992).

Metabolism and Elimination

Metabolism

The major route of clearance of ondansetron (95%) is by hepatic metabolism (Pritchard 1992). The enzyme systems involved are on cytochrome P450, particularly CYP2D6 and CYP3A (Fischer et al 1994). Ondansetron is metabolized by hydroxylation at the indole moiety to 7- and (mainly) 8-hydroxyondansetron, followed by glucuronide or sulphate conjugation (Saynor & Dixon 1989); 6- hydroxylation and demethylation are minor routes of metabolism. Forty percent of ondansetron is metabolized to the active compound 8-hydroxyondansetron, which is not detected in plasma as it is rapidly conjugated in the liver. It does not contribute to the activity of the parent drug.

Clearance

Plasma clearance is approximately 40% of hepatic blood flow. Changes in blood flow should not change hepatic clearance. Repeated dosing for 4 days does not alter clearance, indicating that the drug does not inhibit or augment its own metabolism (Lazarus et al 1990). Renal clearance of ondansetron is low; less than 5% of the drug is excreted unchanged in urine. Total plasma clearance is 600–700 mL min^{-1} and renal clearance is about 20 mL min^{-1} after an intravenous dose (Colthup & Palmer 1989). A review of clearance in a group of 86 healthy, young, male volunteers showed a four- to fivefold range in values (Pritchard 1992). The area under the plasma concentration-time curve (AUC) relates directly to clearance, and may vary widely between healthy volunteers given the same dosing schedules. There is no evidence for bimodal or trimodal distribution, and, therefore, no genetic polymorphism in ondansetron clearance. No discrete groups of patients have inherently lower clearance.

Excretion

Following intravenous administration of radiolabelled ondansetron, more than 60% of its metabolites are excreted in urine. The remainder are found in faeces (Saynor & Dixon 1989). As a lipophilic drug, which diffuses easily, ondansetron will probably pass across the placenta and into milk; there are, however, no published data on these phenomena. Ondansetron is not recommended during pregnancy and lactation.

Factors Affecting Ondansetron Pharmacokinetics

The elderly

The effect of increasing age on ondansetron pharmacokinetics has been studied in a small number of healthy young or elderly volunteers (Colthup et al 1991; Pritchard et al 1992). The results may not be directly comparable with the frail elderly, but no data on these have been published. The first study compared 16 men between the ages of 18 and 40 years, with 16 men over 65 years (Colthup et al 1991). C_{max} was higher in the older men after intravenous administration but similar in the two groups after oral dosing. T_{max} was not significantly different between the two groups. The AUC was greater after both intravenous and oral administration of ondansetron. Plasma clearance was slower in the elderly. V_{SS} was larger in the older population and in these subjects t½ was prolonged from 3 to 5 h after oral and intravenous administration in older subjects. The second study (Pritchard et al 1992) compared three groups of healthy volunteers. Eleven subjects were 21 to 38 years (young), twelve were 61 to 74 years (elderly) and eleven were 75 to 82 years (aged). This study confirmed that C_{max} and AUC increased with advancing age. T_{max} was similar in the three groups. In contrast with the first study, V_{SS} was not significantly different between the groups. The major age-related difference was in the t½ values after oral and intravenous dosing. This varied from 3·4 h in the young, to 4·5 h in the elderly and 5·4 h in the aged. The findings are compatible with an age-related decrease in hepatic metabolism. Elderly subjects may be prone to accumulation of ondansetron if prolonged dosing schedules with frequent dosing intervals are used. There is, however, considerable overlap in drug clearance between individuals. Adverse drug events were no more frequent in the elderly population. Dose modification is not recommended for the elderly because age accounts for a small part only of the variability in clearance.

Children

Ondansetron pharmacokinetics have been studied in healthy children undergoing general anaesthesia (Lerman et al 1993). Twenty-one children were grouped as 3–7 and 7–11 years. The younger group received 2 mg and the older group 4 mg of ondansetron by intravenous infusion. C_{max} in both groups was similar to that in adults. Plasma clearance was greater in the younger group, reflecting increased elimination. The volume of distribution (V_d) corrected for body weight was not affected by age. Fifteen children receiving ondansetron and cytotoxic chemotherapy have been studied (Bryson et al 1991). The groups were 4–12 and 13–18 years; they received 0·15 mg kg^{-1} ondansetron for three doses. The half-life was shorter in the younger children, reflecting a greater rate of elimination. The significance of these findings in terms of dose modification in younger children is not clear.

Gender

Most studies of ondansetron pharmacokinetics have been performed in male volunteers. There is some evidence that clearance is slower in females of similar age, even when body weight is taken into account (Pritchard 1992). Women also show a higher bioavailabilty after oral dosing, which is probably a result of reduced first-pass metabolism (Pritchard et al 1992). C_{max} and AUC after a single oral dose were greater in

females than in males. The weight-normalized V_d was smaller in females, which resulted in plasma t½ being similar in both sexes. Although these differences are significant in pharmacokinetic terms, adverse drug events are comparable between the sexes despite similar dosing. The number of women in this study was only 17 and male volunteers show a wide range of clearance values (Pritchard 1992). Routine alteration in dosing is not recommended for women.

Genetic factors

Genetic factors influencing the cytochrome P450 enzyme system can be investigated by using volunteers who are known poor or extensive metabolizers of debrisoquine. In a study with six subjects in each group, there were no significant differences between the C_{max}, AUC, CL, or t½ values for ondansetron in poor and extensive metabolizers (Ashforth et al 1994). Metabolic pathways other than cytochrome P450 are likely to be involved in ondansetron metabolism. No alteration in dose or frequency of administration is, therefore, necessary because of this genetic factor.

Race

There are no published data on the effect of race. A paper describing oral ondansetron therapy in patients on chemotherapy included 12 Caucasian and 8 black subjects (Hsyu et al 1994a). There were no significant differences in pharmacokinetics between the ethnic groups.

Circadian rhythms

In a study of 24 young, healthy volunteers, the diurnal variation in steady-state plasma concentrations of ondansetron was measured after oral dosing of 8 mg three times a day for nine doses (Pritchard & Powell 1991). Absorption was highest after the morning dose and declined by 15% by the night-time dose. C_{max} was significantly lower and T_{max} more prolonged as the day progressed. These changes may reflect diurnal variations in hepatic metabolism and gastric motility. They are not sufficient to recommend changes to dosing schedules.

Pregnancy

There are no published data relating to use of ondansetron in pregnancy and lactation.

Renal failure

Ondansetron administration was studied in renal failure in 23 patients with systemic lupus erythematosus (Amantea et al 1993). All received cyclophosphamide and either oral or intravenous ondansetron. Creatinine clearance and route of administration were not related to variations in ondansetron pharmacokinetics. Less than 5% of ondansetron is excreted in the urine, therefore adjustment of dosing is unnecessary for patients with renal problems.

Liver disease

The effect of liver disease on the pharmacokinetics of ondansetron has been the subject of two major studies (Figg et al 1992; Blake et al 1993). Four patients in each of three groups with mild, moderate or severe liver disease were compared with normal patients (Figg et al 1992). Each subject received 8 mg of ondansetron orally or intravenously. The V_d was unchanged by the presence of liver disease. There was no effect on mental state. Clearance was significantly prolonged in patients with liver disease, ranging from 10 h for mild liver disease to 20 h in cases of severe disease. There was a corresponding increase in bioavailability and C_{max}. Similar results were obtained when 19 patients with liver disease were compared with six healthy controls (Blake et al 1993). Patients with severe liver disease had lower CL and increased AUC, with a t½ of 21 h. The pharmacokinetic data for mild and moderate liver disease fell between that for normal subjects and that for those with severe liver disease. V_d was greater in this study in all patients with liver disease, but the difference was small and did not relate to the severity of the liver disease. The interval between doses should be increased in patients with liver disease. A single daily dose is sufficient for patients with severe liver disease.

Gastrointestinal dysmotility

Ondansetron is well absorbed throughout the gastrointestinal tract (Hysu et al 1994b). No alteration in dosing is required in patients with gastrointestinal dysmotility.

Surgery

Ondansetron pharmacokinetics in patients having surgery may be affected by the concomitant use of anaesthetics and analgesics. In a study involving eight patients having hysterectomy or cholecystectomy, ondansetron pharmacokinetics were unchanged intraoperatively, but its elimination was prolonged after surgery (Baber et al 1992). The postoperative t½ was 5·6 h, comparable with that in healthy, elderly volunteers. This may be related to changes in postoperative metabolism, blood flow and V_d. Ondansetron was well tolerated in this small group. A change in dose is not routinely recommended for patients undergoing surgery.

Malignant disease

The effect of malignant disease on the pharmacokinetics of ondansetron has been studied in patients receiving chemotherapy. In a study of 12 such patients, the pharmacokinetics of ondansetron after intravenous administration were similar to those for normal volunteers (Lazarus et al 1990). The mean t½ was 3·9 h (range 2·5–6·6). These patients were of various ages and liver function was not recorded. In a study of 20 patients having total-body irradiation the mean t½ was 3·5 h after oral administration of ondansetron (Spitzer et al 1994). The CL was lower than that in healthy subjects. A study of 20 patients reported significant changes in the pharmacokinetics of oral ondansetron in cancer patients compared with healthy volunteers (Mackinnon & Coll 1989). There was increased bioavailability; 86% compared with 60–70% in health. Large variation was seen in cancer patients. The study showed similar pharmacokinetics between cancer patients and healthy volunteers after intravenous administration of ondansetron. Malignancy may, by itself, alter oral ondansetron pharmacokinetics, but has less effect after intravenous administration. A reduction in first-pass metabolism in cancer is likely. Plasma proteins may be altered in patients with cancer, but as ondansetron is not highly protein bound, this has little effect. As ondansetron is almost exclusively cleared by hepatic metabolism, changes in liver function from metastatic disease resulting in severe hepatic impairment must be considered when deciding on dosing schedules (Hsyu et al 1991).

Concomitant Drugs and Ondansetron Pharmacokinetics

Because the main use of ondansetron is as an antiemetic during cytotoxic chemotherapy and post-operatively, it is often given in combination with other drugs. Ondansetron does not affect gastric emptying or small bowel transit time and should not alter the absorption of other drugs from the gastrointestinal tract (Sommers et al 1994).

Cytotoxic chemotherapeutic agents

The effects of chemotherapy on the pharmacokinetics of ondansetron have been studied by several groups (Lazarus et al 1990; Hsyu et al 1991, 1994a; Parr et al 1992). Ondansetron was given intravenously to 12 patients receiving cisplatin, with either carmustine, etoposide, or a combination of all three drugs, over 5 days (Lazarus et al 1990). Pharmacokinetic data were collected on days 1 and 4. There was no difference between the pharmacokinetics on these two days, or between these patients and normal volunteers. Twenty patients were given oral ondansetron before chemotherapy and after 5-days treatment with cisplatin or 5-fluorouracil or both (Hsyu et al 1991). Patients acted as their own controls. The pharmacokinetics were unchanged by chemotherapy. Six patients receiving cisplatin were given intravenous ondansetron but inadequate samples were collected in the distribution phase (Parr et al 1992). Twenty-one patients who received oral ondansetron with cisplatin and 5-fluorouracil were studied (Hysu et al 1994a). Pharmacokinetics were unchanged during administration of chemotherapy. These studies show that cytotoxic chemotherapy does not modify the pharmacokinetics of oral or intravenous ondansetron.

Anaesthetic agents

In a study of eight patients, ondansetron pharmacokinetics were not affected by benzodiazepine premedication or anaesthetic agents (Baber et al 1992).

Opioid analgesics

The only study examining the use of ondansetron in patients taking morphine was conducted on postoperative patients (Baber et al 1992). Elimination of ondansetron was prolonged in this group, but this may be because of postoperative changes in physiology rather than use of the opioid.

Drugs causing enzyme inhibition or induction

Ondansetron is mainly metabolized by cytochrome P450 enzymes (CYP2D6 and CYP3A) (Saynor & Dixon 1989; Fischer et al 1994). Ondansetron does not affect its own metabolism. It is unlikely that ondansetron interacts with other drugs metabolized by CYP2D6, as the therapeutic plasma concentration of ondansetron is less than that required to inhibit CYP2D6. Drugs with a high affinity for CYP2D6, such as haloperidol, could inhibit the metabolism of ondansetron; other CP450 enzymes may, however, compensate for this effect. Hepatic enzyme inducers, such as carbamazepine, increase the clearance of ondansetron and may reduce its efficacy (Pritchard 1992). Although dose adjustment may be needed in some of these situations, it is difficult to extrapolate these findings to the clinical situation.

Alcohol

Ondansetron may reduce some of the pleasurable effects of alcohol (Johnson et al 1993). The interaction between alcohol and ondansetron has been investigated using eight healthy, male volunteers. Oral ondansetron did not affect absorption of the alcohol.

Smoking

As smoking induces hepatic enzymes, it may increase the clearance of ondansetron. This has not been studied. No dose adjustment is recommended for smokers.

Ondansetron and Pharmacokinetics of Concomitant Drugs

Cytotoxic chemotherapeutic agents

The effect of ondansetron on the pharmacokinetics of cytotoxic agents has not been studied extensively. In one animal study no significant change was documented in the pharmacokinetics of cisplatin with and without ondansetron (Brouwer et al 1992)

Benzodiazepines

Chronic co-administration of ondansetron in mice potentiated the development of physical dependence on diazepam (Mizoguchi et al 1993). This effect may be because of the action of ondansetron on CNS 5-HT pathways, but ondansetron alone did not cause benzodiazepine-like physical dependence. Because in this study the pharmacokinetics of diazepam were not affected by co-administration of ondansetron, the potentiation of physical dependence was not likely to be a pharmacokinetic interaction between the two drugs. Although 5-HT_3 receptors may be involved in the development of diazepam physical dependence, these findings are yet to be examined in man.

Drugs used in general anaesthesia

Pharmacokinetic interaction between ondansetron and anaesthetic drugs has not been studied, but dynamic effects have been observed. The pharmacodynamics of barbiturates, morphine, alfentanil, atracurium, atropine and neostigmine did not change when these drugs were given with ondansetron (Baber et al 1992)

Pyridostigmine

Ondansetron may affect the pharmacokinetics of pyridostigmine in the guinea-pig model to increase the activity of the compound (Capacio et al 1993).

Pharmacokinetics and Pharmacodynamics of Ondansetron

Knowledge of the relationship between pharmacokinetics and pharmacodynamics will enable the optimum dose to be given to each patient group, thus reducing adverse effects. If ondansetron at 5-HT_3 receptors in the CNS and gastrointestinal tract is in rapid equilibrium with ondansetron in plasma, the plasma concentration-time curve should relate to antiemetic efficacy. It is, however, difficult to find a simple relationship between efficacy and plasma ondansetron concentrations because emesis is several steps removed from interactions at the 5-HT_3 receptor.

Cytotoxic drugs and emesis

Several studies have attempted to relate efficacy to ondansetron dose and pharmacokinetics in patients receiving cytotoxic chemotherapy. In a dose-ranging study, ondansetron efficacy decreased at 0·01 mg kg^{-1} (Grunberg et al 1990). There was association between ondansetron dose and antiemetic effect in patients receiving high-dose cisplatin. A study of 28 cancer patients showed wide interpatient variation (Grunberg et al 1989). Correlation between efficacy and AUC was suggested, with a trend towards better emetic protection with greater AUCs. A similar trend was seen in other patients receiving cisplatin (Lazarus et al 1990). In a study of 55 cancer patients receiving cisplatin, AUC was estimated using a calculation based on the plasma concentration 4 h after a dose of ondansetron (Pritchard & Wells 1992). The risk of emesis was greatest for patients with a small AUC and a high dose of cisplatin. There was no relationship between dose and adverse events. High-dose cisplatin therapy should be accompanied by a higher than standard dose of ondansetron.

Radiotherapy and emesis

The efficacy of oral ondansetron in controlling emesis during total-body irradiation has been assessed in a placebo-controlled study of two groups of ten young adults (Spitzer et al 1994). All patients taking placebo, compared with four taking ondansetron, required rescue anti-emetics. No relationship was seen between C_{max} or AUC and the number of emetic episodes. In total-body irradiation, ondansetron efficacy may be related to the amount of drug at the CNS and gastrointestinal receptors rather than plasma concentrations.

Postoperative emesis

There is no published work relating the pharmacokinetics of ondansetron with its efficacy against postoperative nausea and vomiting. Several studies have shown a dose-response relationship (Claybon 1994; Pearlman 1994; Rust & Cohen 1994). It is not known whether plasma concentrations of ondansetron relate to efficacy against postoperative nausea and vomiting.

The elderly and emesis

One study has compared the antiemetic efficacy of ondansetron in elderly patients (over 65 years), and younger patients (less than 60 years) receiving cisplatin (Kennard et al 1991). Control of emesis was superior in the elderly, and, except for headache, there were no differences between the frequencies of adverse events. This suggests that reduced clearance leads to greater antiemetic efficacy in the elderly. In similar groups of patients receiving non-cisplatin therapy or radiotherapy there was, however, no difference between the occurrence of emesis or of adverse events in the two age groups.

Children and emesis

In 15 children receiving different cytotoxic regimens the efficacy of ondansetron in preventing emetic episodes was related to the AUC, irrespective of the type of chemotherapy used (Bryson et al 1991). Children with an AUC greater than 300 ng h^{-1} mL^{-1} had no emesis. Post-marketing surveillance of ondansetron in 210 children examined the efficacy of the drug (McQueen & Milton 1994). The survey showed that 55% of children had no emetic episodes; 31% showed a major response and 14% a minor response or treatment failure. No relationship was found between ondansetron dose and emesis, but 26% of children were under 4 years of age. There are no pharmacokinetic data on children of this age and doses were based on those used for older children. Relatively larger doses may be required for very young children because of their increased clearance.

Long-term therapy

The pharmacokinetics of ondansetron are unchanged with repeated dosing (Lazarus et al 1990). The antiemetic efficacy of ondansetron was studied in cancer patients receiving the drug over ten treatment cycles; there was no reduction in antiemesis with prolonged therapy (Adler et al 1991).

Psychiatric illness

Ondansetron is effective in animal models of schizophrenia (Costall et al 1987). Uncontrolled clinical trials have suggested that it may have a role in man. This is supported by a single case report of a patient with refractory disease (White et al 1991). 5-HT_3 antagonists have an anxiolytic profile different from those of benzodiazepines and they may reverse rebound anxiety on benzodiazepine withdrawal in animals (Jones et al 1988; Costall et al 1990). Co-administration of benzodiazepines and ondansetron may enhance physical dependence on benzodiazepines in mice (Mizoguchi et al 1993).

Adverse Events after Administration of Ondansetron

In 223 adult volunteers who received single or multiple ondansetron doses by various routes, less than one adverse event was recorded for every nine doses (Blackwell & Harding 1989). This was less than after placebo, metoclopramide or hyoscine. All side-effects were mild. Ondansetron has no adverse effects on the cardiovascular, respiratory or haemostatic functions (Baber et al 1992). Reviews of 181 and 210 children receiving ondansetron reported adverse events in 18% and 13% (Stevens 1991; McQueen & Milton 1994). Adverse events were no more common in children under four years of age.

Headache

Headache is the most frequent problem in adults and children, with 17% of adults affected after a single dose compared with 5% after placebo (Blackwell & Harding 1989). The incidence of headache after repeated dosing (31%) did not differ from placebo (28%). There was no correlation between dose and headache.

Constipation

Ondansetron slows transit through the colon, but does not affect gastric emptying or small bowel transit in healthy volunteers (Talley et al 1990). The effect is most marked in the left colon and is not age- or gender-related. Those most affected had rapid baseline transit times. Constipation was seen in 0·5% of adult volunteers after a single dose and in 7·1% after repeated dosing (Blackwell & Harding 1989).

Extrapyramidal side-effects

As ondansetron is a specific antagonist of 5-HT_3 receptors, extrapyramidal side-effects would not be expected. Large clinical trials with ondansetron in volunteers and patients did

not report any extrapyramidal reactions (Grunberg et al 1989). There are now three case reports of extrapyramidal effects associated with the use of ondansetron which may be dose-related. Dobrow et al (1991) reported on a patient who had also received droperidol, so that the drug reaction could not unequivocally be attributed to the ondansetron (Kanarek et al 1992). A report by Garcia-del-Muro et al (1993) was of a 65 year old woman who received 0·15 mg kg^{-1} intravenous ondansetron with 8 mg of oral ondansetron 8-hourly for 4 days during the first two cycles of cytotoxic chemotherapy without a reaction. During the third chemotherapy cycle, she received intravenous ondansetron throughout, and on the third day of treatment she experienced a short-lived extrapyramidal reaction immediately following a slow injection of ondansetron. Further doses of ondansetron were given diluted over a 15-min infusion without adverse effects. Halperin & Murphy (1992) report a clear association between intravenous ondansetron administration (0·15 mg kg^{-1}) and an extrapyramidal reaction in a 58-year-old man. As re-challenge with a 25% dose reduction produced the same effect, dose-related effect is suggested; no extrapyramidal reaction occurred with 50% of the original dose, however.

Acute anxiety

There is a case report of a patient who suffered anxiety after administration of ondansetron which seemed clearly related to the drug (Mitchell et al 1994). Mild anxiety was reported by 3 of 43 adult patients receiving cisplatin chemotherapy and given ondansetron in a dose equal to or greater than 0·18 mg kg^{-1} (Grunberg et al 1989). None of the patients had a history of psychiatric problems or was receiving chronic medication or psychotherapy. As 38 of the patients were having chemotherapy for the first time, however, this finding is difficult to interpret. Further studies more specifically aimed at detecting anxiety are required.

Elevated liver transaminases

Ondansetron may cause an elevation in plasma hepatic transaminases (increase from a normal pretreatment value to an abnormal level or doubling of a previously abnormal value). In 43 adult cancer patients, 19% developed elevated transaminases that were not related to ondansetron dose (Grunberg et al 1989). Some children showed increased transaminases (Stevens 1991). Transaminases returned to normal after treatment and were not associated with any clinical problems. It is difficult to separate the effects of cancer and concomitant treatments from those of ondansetron. No elevation of transaminases has been observed in studies on healthy volunteers.

Conclusion

Knowledge of the pharmacokinetics of ondansetron in health and disease may enable the clinician to maximize efficacy and reduce toxicity. Caution should, however, be exercised in directly relating pharmacokinetic observations and clinical practice.

References

Adler, M., Marschner, N., Janicke, F. (1991) Antiemetic efficacy of ondansetron in long term therapy. Eur. J. Cancer 27 (Suppl. 1): S27

Amantea, M. A., Yarboro, C., Forrest, A., Pucino, F., Klippel, J. H. (1993) Population pharmacokinetics of intravenous and oral ondansetron in patients with systemic lupus erythematosus (SLE). J. Clin. Pharmacol. 33: 1004

Ashforth, E. I. L., Palmer, J. L., Bye, A., Bedding, A. (1994) The pharmacokinetics of ondansetron after intravenous injection in healthy volunteers phenotyped as poor or extensive metabolizers of debrisoquine. Br. J. Clin. Pharmacol. 37: 389–391

Baber, N., Palmer, J. L., Frazer, N. M., Pritchard, J. F. (1992) Clinical pharmacology of ondansetron in postoperative nausea and vomiting. Eur. J. Anaesthesiol. 9 (Suppl. 6): 11–18

Blackwell, C. P., Harding, S. M. (1989) The clinical pharmacology of ondansetron. Eur. J. Clin. Oncol. 25 (Suppl. 1): S21–S24

Blake, J. C., Palmer, J. L., Minton, N. A., Burroughs, A. K. (1993) The pharmacokinetics of ondansetron in patients with hepatic impairment. Br. J. Clin. Pharmacol. 35: 441–443

Brouwer, R., Jarrett, J. L., Nystrom, D. K., Anderson, D. L., Brown, K., Farrish, H. H. (1992) Efficacy of ondansetron in male mongrel dogs and effects of the pharmacokinetics of cisplatin. Pharm. Res. 9 (Suppl.): 267

Bryson, J. C., Pritchard, J. F., Shurin, S., Kernodle, A. E., Blumer, J. L. (1991) Efficacy, pharmacokinetics and safety of ondansetron in paediatric chemotherapy patients. Am. Soc. Clin. Pharmacol. Ther. 49: 161

Butler, A., Hill, J. M., Ireland, S. J., Jordan, C. C., Tyers, M. B. (1988) Pharmacological properties of GR38032F, a novel antagonist at 5-HT_3 receptors. Br. J. Pharmacol. 94: 397–412

Capacio, B. R., Byers, C. E., Matthews, R. L. (1993) Effect of pyridostigmine on pharmacokinetics of the 5-HT_3 receptor antagonist ondansetron. FASEB J. 7: A699

Claybon, L. (1994) Single dose intravenous ondansetron for the 24 hour treatment of postoperative nausea and vomiting. Anaesthesia 49 (Suppl.): 24–29

Colthup, P. V., Palmer, J. I. (1989) The determination in plasma and pharmacokinetics of ondansetron. Eur. J. Clin. Oncol. 25 (Suppl. 1): S71–S74

Colthup, P. V., Felgate, C. C., Palmer, J. L., Scully, N. L. (1991) Determination of ondansetron in plasma and its pharmacokinetics in the young and elderly. J. Pharm. Sci. 80: 868–871

Costall, B., Domeney, A. M., Naylor, R. J. (1987) Effects of the 5-HT_3 receptor antagonist GR 38032F on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. Br. J. Pharmacol. 92: 881–894

Costall, B., Naylor, R. J., Tyers, M. (1990) The psychopharmacology of 5-HT receptors. Pharmacol. Ther. 47: 181–190

Dobrow, R. B., Coppock, M. A., Hosenpud, J. R. (1991) Extrapyramidal reaction caused by ondansetron. J. Clin. Oncol. 9: 1921

Figg, W. D., Dukes, G. E., Pritchard, J. F., Hak, L. J., Songer, S. S., Lesesne, H. R., Kao, C. F., Hermann, D. J., Powell, J. R. (1992) Ondansetron pharmacokinetics in chronic liver disease. Clin. Pharmacol. Ther. 51: 171

Fischer, V., Vickers, A. E. M., Heitz, F., Mahadevan, S., Baldeck, J. P., Minery, P., Tynes, R. (1994) The polymorphic cytochrome P-4502D6 is involved in the metabolism of both 5-hydroxytryptamine antagonists, tropisetron and ondansetron. Drug Metab. Dispos. 22: 269

Frazer, N. M., Palmer, J. L. (1992) Tolerability and pharmacokinetics of intramuscular ondansetron 4 mg. Anesthesiology 77 (Suppl. 3A): A439

Gan, L. S., Hsyu, P. H., Pritchard, J. F., Thakka, D. (1993) Mechanism of intestinal absorption of ranitidine and ondansetron: transport across caco-2 cell monolayers. Pharm. Res. 10: 1722–1725

Garcia-del-Muro, X., Cardenal, F., Ferrer, P. (1993) Extrapyramidal reaction associated with ondansetron. Eur. J. Cancer 29A: 288

Grunberg, S. M., Stevenson, L. L., Russell, C. A., McDermed, J. E. (1989) Dose ranging phase 1 study of the serotonin antagonist GR38032F for prevention of cisplatin induced nausea and vomiting. J. Clin. Oncol. 7: 1137–1141

Grunberg, S. M., Groshen, S., Robinson, D. C., Stevenson, L. L., Sanderson, P. E. (1990) Correlation of antiemetic efficacy and plasma levels of ondansetron. Eur. J. Cancer 26: 879–882

Halperin, J. R., Murphy, B. (1992) Extrapyramidal reaction to ondansetron. Cancer 69: 1275

Hsyu, P. H., Haig, P., Bozigian, J., Pritchard, J. F., Kernodle, A., Panella, J., Hansen, L. A., Griffin, R. H. (1991) Effect of che-

motherapy on the pharmacokinetics of oral ondansetron. Pharm. Res. 8 (Suppl.): 257

Hsyu, P. H., Pritchard, J. F., Bozigian, H. P., Gooding, A. E., Griffin, R. H., Mitchell, R., Bjurstrom, T., Panella, T. L., Huang, T., Hansen, L. A. (1994a) Oral ondansetron pharmacokinetics: the effect of chemotherapy. J. Clin. Pharmacol. 34: 767–773

Hsyu, P. H., Pritchard, J. F., Bozigian, H. P., Lloyd, T. C., Griffin, R. H., Shamburek, R., Krishna, G., Barr, W. H. (1994b) Comparison of the pharmacokinetics of ondansetron solution (8 mg) when administered intravenously, orally, to the colon and to the rectum. Pharm. Res. 11: 156–159

Johnson, B. A., Rue, J., Cowen, P. J. (1993) Ondansetron and alcohol pharmacokinetics. Psychopharmacology 112: 145

Jones, B. J., Costall, B., Domeney, A. M. (1988) The potential anxiolytic activity of GR38032F, a 5-HT_3 receptor antagonist. Br. J. Pharmacol. 93: 985–993

Kanarek, B. B., Curnow, R., Palmer, J., Cook, S. F. (1992) Ondansetron: confusing documentation surrounding an extrapyramidal reaction. J. Clin. Oncol. 10: 506–507

Kennard, D., Butcher, M., Palmer, J., Beranek, P., Brown, G. W. (1991) The antiemetic efficacy, pharmacokinetics and safety of ondansetron in the elderly receiving cancer chemotherapy or radiotherapy. Eur. J. Cancer 27 (Suppl. 1): S27

Kilpatrick, G. J., Bunce, K. T., Tyers, M. B. (1990) 5-HT_3 receptors. Med. Res. Rev. 10: 441–475

Lazarus, H. M., Bryson, J. C., Lemon, E., Pritchard, J. F., Blumer, J. (1990) Antiemetic efficacy and pharmacokinetic analyses of the serotonin antagonist ondansetron (GR 38032F) during multiple day chemotherapy with cisplatin prior to autologous bone marrow transplantation. J. Natl. Cancer Inst. 82: 1776–1178

Lerman, J., Sphar-Schopfer, I. A., Sikich, N. (1993) Pharmacokinetics of intravenous ondansetron in healthy children. Can. J. Anaesthesiol. 40: A24

Mackinnon, J. W. M., Coll, D. T. (1989) The chemistry of ondansetron. Eur. J. Cancer Clin. Oncol. 25 (Suppl. 1): S61–S70

McQueen, K. D., Milton, J. D. (1994) Multicentre post marketing surveillance of ondansetron therapy in paediatric patients. Ann. Pharmacother. 23: 85–92

Mitchell, K. E., Popkin, M. K., Trick, W., Vercelotti, G. (1994) Psychiatric complications associated with ondansetron. Psychosomatics 35: 161–163

Mizoguchi, H., Suzuki, T., Mizawa, M. (1993) Effects of serotonergic anxiolytics on physical dependence on diazepam in mice. Neurosci. Lett. 160: 41–44

Naylor, R. J., Rudd, J. A. (1992) Pharmacology of ondansetron. Eur. J. Anaesthesiol. 9 (Suppl. 6): 3–15

Palmer, J. L., Frazer, N. M., Keene, O. N., Baber, N. S. (1993) Tolerability and pharmacokinetics of intramuscular ondansetron 4 mg. Am. Soc. Clin. Pharmacol. Ther. 53: 209–215

Parr, M. D., McIntyre, W. J., Henderson, L. M., MacDonald, J. S., Chandler, M. H. H. (1992) Pharmacokinetics of ondansetron in patients receiving cisplatin therapy. Clin. Pharm. 11: 1026–1029

Pearlman, M. H. (1994) Single dose IV ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 49 (Suppl.): 11–20

Pritchard, J. F. (1992) Ondansetron metabolism and pharmacokinetics. Semin. Oncol. 19 (Suppl. 10): 9–15

Pritchard, J. F., Powell, J. R. (1991) Circadian variations in the pharmacokinetics of ondansetron. Clin. Pharmacol. Ther. 49: 129

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

Pritchard, J. F., Wells, C. D. (1992) Relationship between ondansetron systemic exposure and antiemetic efficacy and safety in patients receiving cisplatin. Pharmacology 45: 188–194

Reynolds, D. J. M., Leslie, R. A., Grahame-Smith, D. G. M., Harvey, J. M. (1989) Localization of 5-HT_3 receptor binding sites in human dorsal vagal complex. Eur. J. Pharmacol. 174: 127–130

Rust, M., Cohen, L. A. (1994) Single dose ondansetron in the prevention of postoperative nausea and emesis. Anaesthesia 49 (Suppl.): 16–20

Saynor, D. A., Dixon, C. M. (1989) The metabolism of ondansetron. Eur. J. Clin. Oncol. 25 (Suppl. 1): S75–S77

Simpson, K. H., Murphy, P., Colthup, P. V., Whelan, P. (1992) Concentration of ondansetron in cerebrospinal fluid following oral dosing in volunteers. Psychopharmacology 109: 497–498

Sommers, D. K., van Wyk, M., Snyman, J. R., Moncrieff, J. (1994) Influence of granisetron, ondansetron and metoclopramide on gastric emptying, oro-caecal transit time and theophylline absorption from a sustained release formulation. Med. Sci. Res. 22: 329–331

Spitzer, T. R., Bryson, J. C., Cirenzo, E., Foebler, R., Wallerstadt, M., Stout, M., Kunka, R. L., Plagge, P. B., Dubois, A. (1994) Randomized double blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total-body irradiation. J. Clin. Oncol. 12: 2432–2438

Stevens, R. F. (1991) The role of ondansetron in paediatric patients: a review of three studies. Eur. J. Cancer 27 (Suppl. 1): S20–S22

Talley, N. J., Philips, S. F., Haddad, A., Miller, L. J., Twomey, C., Zinsmeister, A. R., MacCarty, R. C., Giociola, A. (1990) GR38032F (ondansetron), a selective 5-HT receptor antagonist, slows colonic transit in healthy man. Dig. Dis. Sci. 35: 477–480

Tyers, M. (1992) Pharmacology and preclinical antiemetic properties of ondansetron. Semin. Oncol. 19 (Suppl. 10): 1–8

White, A., Corn, T. H., Feetham, C., Faulconbridge, C. (1991) Ondansetron in the treatment of schizophrenia. Lancet 337: 1173