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The 5-Hydroxytryptamine Receptor Antagonists as Antiemetics: Preclinical Evaluation and Mechanism of Action

P.L.R. Andrews and P. Bhandari

INTRODUCTION

IN THE past few years major advances have been made in the treatment of emetic side-effects induced by radio- and chemotherapy used in the treatment of cancer. This review will discuss the development, characterisation, mechanism and sites of action of the 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists currently in clinical development and use.

IDENTIFICATION OF 5-HT_3 RECEPTOR ANTAGONISTS

The origin of the 5-HT_3 receptor antagonists in present clinical use as antiemetics can be traced directly back to the substituted benzamide metoclopramide which was first introduced clinically in 1964 [1]. The family of substituted benzamides are all derived by substitution of the benzene ring of the parent compound procainamide; hence, the name metoclopramide is an acronym for 2-methoxy-5-chloro-procainamide. It is important to realise that the screen used for identification of the potential antiemetic properties of a compound was its ability to antagonise apomorphine-induced emesis, usually in the dog. Apomorphine, an agonist at the dopamine receptor, is a potent emetic agent in man and animals with a site of action on the area postrema located at the caudal extremity of the fourth ventricle in the brain stem. The area postrema (AP) was designated as the "chemoreceptor trigger zone" for vomiting [2]; and, since it was generally assumed that all types of emesis were mediated by the AP, the apomorphine-test was considered to be adequate for identification of antiemetic agents. However, this assumption was flawed as the AP is not required for all types of emesis (eg. motion [3], gastric irritation [4]) and, moreover, by using a dopamine agonist, this test preferentially selects compounds which are dopamine antagonists. It was through this test that the antiemetic properties of metoclopramide and the butyrophenone domperidone were first identified. Both agents are dopamine receptor antagonists. It is a salutary thought that the antiemetic properties of the 5-HT_3 receptor antagonists would not have been identified had they been screened using only apomorphine as they are ineffective against this stimulus [5].

In addition to its direct antiemetic effects, metoclopramide is also a gastric motility stimulant and this may contribute to its antiemetic action in an indirect way. Gastrointestinal motility may be disordered for extended periods prior to vomiting [6]; and, since activation of gut afferents can induce emesis [7], it was thought that abnormal gut motor patterns could lead to abnormal activation of afferents and hence emesis. On this basis it was suggested that agents which restore gut motility to normal may have some antiemetic or antinauseant properties. The extent to which this contributes to the antiemetic effects of metoclopramide or domperidone in chemotherapy-induced emesis in man is not known but this indirect effect is clearly important when these agents are used to treat nausea and vomiting arising from gastrointestinal disorders [8–10].

Studies by Fozard and co-workers [11] beginning in the late 1970s revealed that metoclopramide was an antagonist of some of the neuronally mediated effects of 5-HT [12]. These receptors best fitted the "M" sub-type previously described by Gaddum and Picarelli in 1957 [13] and which are now considered to be 5-HT_3 receptors. An example of a reflex involving these receptors is the von Bezold–Jarisch reflex in which rapid injection of 5-HT into the cardiac circulation activates unmyelinated vagal afferents which project to the medulla and evoke a discharge in vagal efferents to the heart leading to bradycardia (Fig. 1). This reflex can be antagonised by high doses of metoclopramide, with the presumed site of action being on the terminal portion of the vagal afferents in the heart.

Whilst studies with metoclopramide led directly to identification of 5-HT_3 receptors, metoclopramide itself is a relatively weak antagonist. Other substituted benzamides have been synthesised which are considerably more potent when assayed against the von Bezold–Jarisch reflex: ID_{50} values in μg/kg intravenous doses in the rat: metoclopramide 188, batanopride 70, renzapride 3.3, zacopride 0.12–0.5 [14]. In addition to its effects on 5-HT_3 receptors, as metoclopramide is also a dopamine receptor antagonist it produces dose limiting side-effects like dystonia and dyskinesia. This action has been synthesised out of the novel benzamides and hence compounds such as zacopride and renzapride are inactive against apomorphine-induced emesis.

The benzamide series is not the only source of clinically useful 5-HT_3 receptor antagonists. Fozard *et al.* [15] showed that (−)cocaine and structurally related compounds also antagonised the von Bezold–Jarisch reflex. These studies suggested that compounds structurally related to cocaine could have 5-HT_3 antagonist properties and led to the testing of substituted benzoic acid esters of tropine. From these studies the first selective non-benzamide 5-HT_3 receptor antagonist MDL 72222 was identified [16]. Subsequent studies have led to the identification of a number of very potent and selective 5-HT_3 receptor antagonists, e.g. GR 38032 (ondansetron), BRL 43694 (granisetron).

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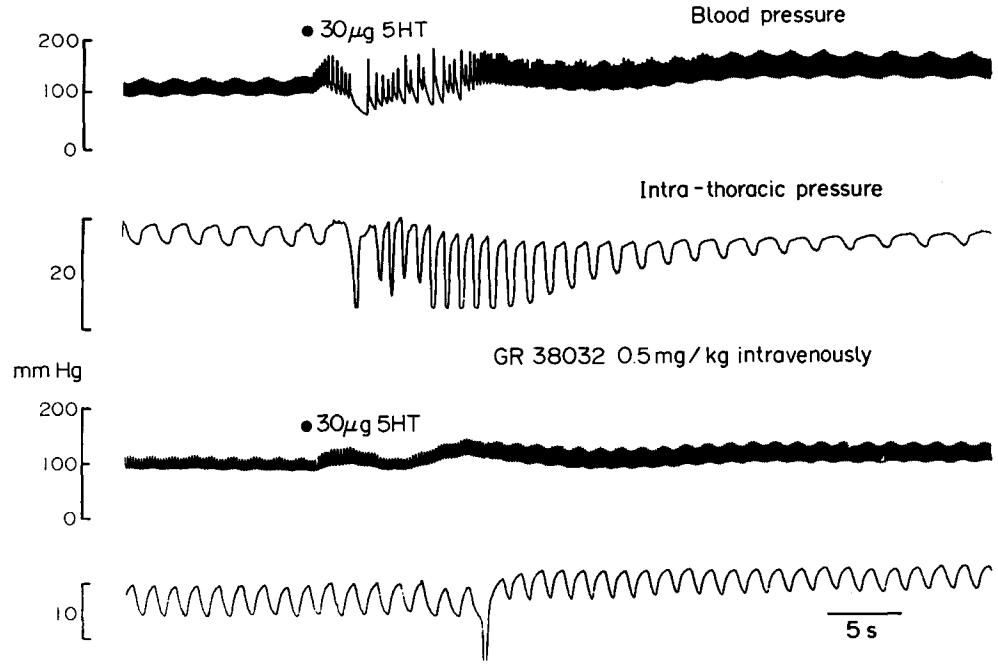

Fig. 1. The effect of GR 38032 (0.5 mg/kg intravenous dose) on the cardiovascular (BP) and respiratory (intra-thoracic pressure) responses to a rapid intravenous injection (jugular) injection of 5-HT (30 μg) in the ferret.

THE LINK BETWEEN 5-HT$_3$ RECEPTORS AND EMESIS

The identification of a role for 5-HT$_3$ receptors in emesis derives mainly from the synthesis of a number of clinical and pharmacological observations by Gralla [17] and Sanger [18, 19]. The main links are, first, high-dose metoclopramide is more effective clinically against most emetogenic cytotoxic chemotherapies than conventional doses [17]. These doses are very much in excess of those required for gut motility effects and in fact there is evidence from animal studies that high doses of benzamides may actually be less effective. In addition, they are also considerably greater than those required to block apomorphine-induced emesis. From these observations it can be tentatively concluded that the antiemetic action of metoclopramide (in the cytotoxic drug context only) is not due to gut motility stimulation or dopamine antagonism. This hypothesis was tested in animal studies which revealed that benzamides devoid of dopamine antagonism (e.g. renzapride [20]) were considerably more potent than metoclopramide and, in addition, the gut stimulant properties of the benzamides did not predict antiemetic efficacy. The non-benzamide 5-HT$_3$ receptor antagonists (e.g. granisetron) are very potent antiemetics but in general do not stimulate gastric motility. Thus, the antiemetic effects of high-dose metoclopramide were not explained by its conventional actions. Second, the recognition that metoclopramide at high doses was a 5-HT$_3$ receptor antagonist (against the von Bezold–Jarisch reflex) provided a possible mechanism to account for Gralla's clinical observations. The key experiment linking 5-HT$_3$ receptors and antiemesis was the study by Miner and Sanger in 1986 demonstrating block of cisplatinum-induced emesis in the ferret by the selective 5-HT$_3$ receptor antagonist MDL 72222 [19]. This observation has now been repeated many times both in animal and human studies using the ever growing range of 5-HT$_3$ receptor antagonists (Table 1).

Table 1. List of 5-HT$_3$ receptor antagonists

AS 5370	ICS 205-930 (tropisetron)
BRL 24924 (Renzapride)	LY 278584
BRL 43694 (Granisetron)	LY 191617
Dazopride	MDL 72222
GR 38032F (Ondansetron)	MDL73147EF
GR 65630	Quipazine
GR 67330	Zacopride

It is important to realise that whilst we refer to these compounds generally as 5-HT$_3$ receptor antagonists there are marked individual differences between them in their structure (e.g. zacopride is a benzamide whereas granisetron is an indazole), potency (ID_{50} on von Bezold–Jarisch reflex in μg/kg intravenously: ondansetron 3.6, granisetron 0.7 [14]) and pharmacological spectrum of action (e.g. at high concentrations ICS-205-930 is a 5-HT$_4$ receptor *antagonist* whereas zacopride is a 5-HT$_4$ receptor *agonist* [21]). There are also probably differences in the duration of action but these have not been thoroughly studied although they may be clinically relevant in determining the antiemetic dosing regime in relation to cytotoxic drug administration.

PRECLINICAL EVALUATION

This section discusses the range of antiemetic effects of the 5-HT$_3$ receptor antagonists and for the sake of brevity this will be a generalisation. The majority of animal studies have been carried out in the ferret and dog. It is vital to understand that these agents are not universal antiemetics. With few exceptions they are only effective against vomiting evoked by radiation and cytotoxic drugs (Table 2). Because their antiemetic effect is by selective blockade of 5-HT$_3$ receptors they will only be effective in conditions where 5-HT$_3$ receptors are activated in some way by the emetic stimulus. At present this seems only to occur in response to radiation and cytotoxic

Table 2. Effect of 5-HT$_3$ antagonists on emetic stimuli

Blocked/reduced	*Unaffected*
Actinomycin D	Apomorphine
Doxorubicin*	Erythromycin
Carboplatin*	Histamine
Cisplatinum*	Hydergine
Cycloheximide	Loperamide
Cyclophosphamide	Morphine
Dacarbazine	Motion*
Emetine	p-CPA
Epirubicin*	Pilocarpine
Melphalan*	
Mustine	
Mechlorethamine	
Peptide YY	
Radiation*	

*Indicates data available from clinical trials; for details see [5].

drugs but it is likely that other indications will be forthcoming.

Dose–response studies in animals have revealed that these agents are extremely potent. For example, our studies with the effects of granisetron (BRL 43694) on radiation-induced (200 rads, whole body X-ray) emesis give an ID_{50} value of 11.22 μg/kg with all animals in a group of 6 being protected at a dose of 50 μg/kg (Fig. 2).

Animal studies have revealed that different doses of the same antagonist may be required to block the effect of the various emetic stimuli and this suggests that in the clinic the dose may need to be adjusted according to the therapeutic regime used (Fig. 3). One remarkable property of these antagonists identified in animal studies and subsequently shown in the clinic is their ability to stop vomiting once it has started and hence they may be used as an intervention therapy too [22].

SITE AND MECHANISM OF ACTION

To identify the most likely site of action of 5-HT$_3$ receptor antagonists it is necessary to consider briefly the pathways by which cytotoxic drugs and radiation may act to induce emesis. The studies of Wang and Borison over the past 50 years have implicated the AP based largely on lesion studies. However, a review of the literature reveals that the effects of AP ablation are variable and the degree of effect of the lesion depends on the species and the cytotoxic drug used [23]. Recent studies

Fig. 2. Dose–response curve of BRL 43694 against 200 rads X-ray whole body radiation in ferrets ($n = 4$–6 at each dose).

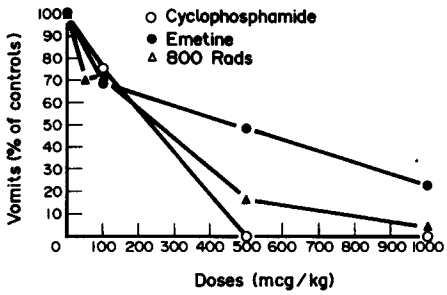

Fig. 3. Dose–response curve of GR 38032F in the ferret against different emetic agents showing that different doses of 5-HT$_3$ antagonists are required for different indications ($n = 4$–6 at each dose).

in the ferret have demonstrated that abdominal vagotomy can markedly reduce or abolish the emetic response to a variety of cytotoxic drugs (e.g. cisplatinum, emetine, cyclophosphamide) and whole body radiation. This lesion does not interfere with the ability of the animal to vomit as they will still respond to apomorphine [24], loperamide (Bingham, personal communication) and motion [25]. The apparent discrepancy between the AP ablation and vagotomy studies can be reconciled if the emetic stimuli is thought to act by activating abdominal vagal afferents which are known to project to the subnucleus gelatinosus of the nucleus tractus solitarius immediately subjacent to the area postrema (Fig. 4). These vagal afferents appear to be capable of activating the area postrema [5, 26]. Thus area postrema ablation may damage these vagal afferents at a central site or by destroying the AP remove a relay in the pathway by which vagal afferents activate the "vomiting centre". With these considerations in mind we can now discuss the site of action of the 5-HT$_3$ receptor antagonists.

The lack of effect of these antagonists against all forms of emesis argues against a site in the vomiting centre. Their inability to affect emesis induced by dopamine and opiate receptor agonists, which act via the AP, argues against a generalised effect here but does not exclude specific effects. In the ferret Andrews *et al.* [5] have provided preliminary evidence for a vagal afferent site of action by demonstrating that 5-HT$_3$ receptor antagonists are only effective as antiemetics against emetic agents whose action is also influenced by abdominal vagotomy. Binding studies have demonstrated the presence of 5-HT$_3$ receptors in the nucleus tractus solitarius (the medullary region where vagal afferents terminate), the area postrema and on vagal afferent terminals in the medulla but the functional significance, if any, of these central sites has been little studied. In man, the binding of 5-HT$_3$ ligands is very low in the area postrema in comparison to the nucleus tractus solitarii (NTS) [27]. Based on a variety of evidence Andrews *et al.* [23] proposed that (in the ferret) cytotoxic drugs and radiation induced emesis by stimulating the release of 5-HT from intestinal enterochromaffin cells which then induced activation (and sensitisation) of the abdominal vagal afferents known to terminate in close proximity to these cells. Electrophysiological studies have shown that 5-HT can activate abdominal vagal afferents and this response can be blocked by antiemetic doses of the 5-HT$_3$ receptor antagonist ondansetron [28]. From these studies it is proposed that in the ferret the major site of antiemetic activity of 5-HT$_3$ receptor antagonists is on vagal afferent terminals in the upper small intestine although central vagal sites may also be involved

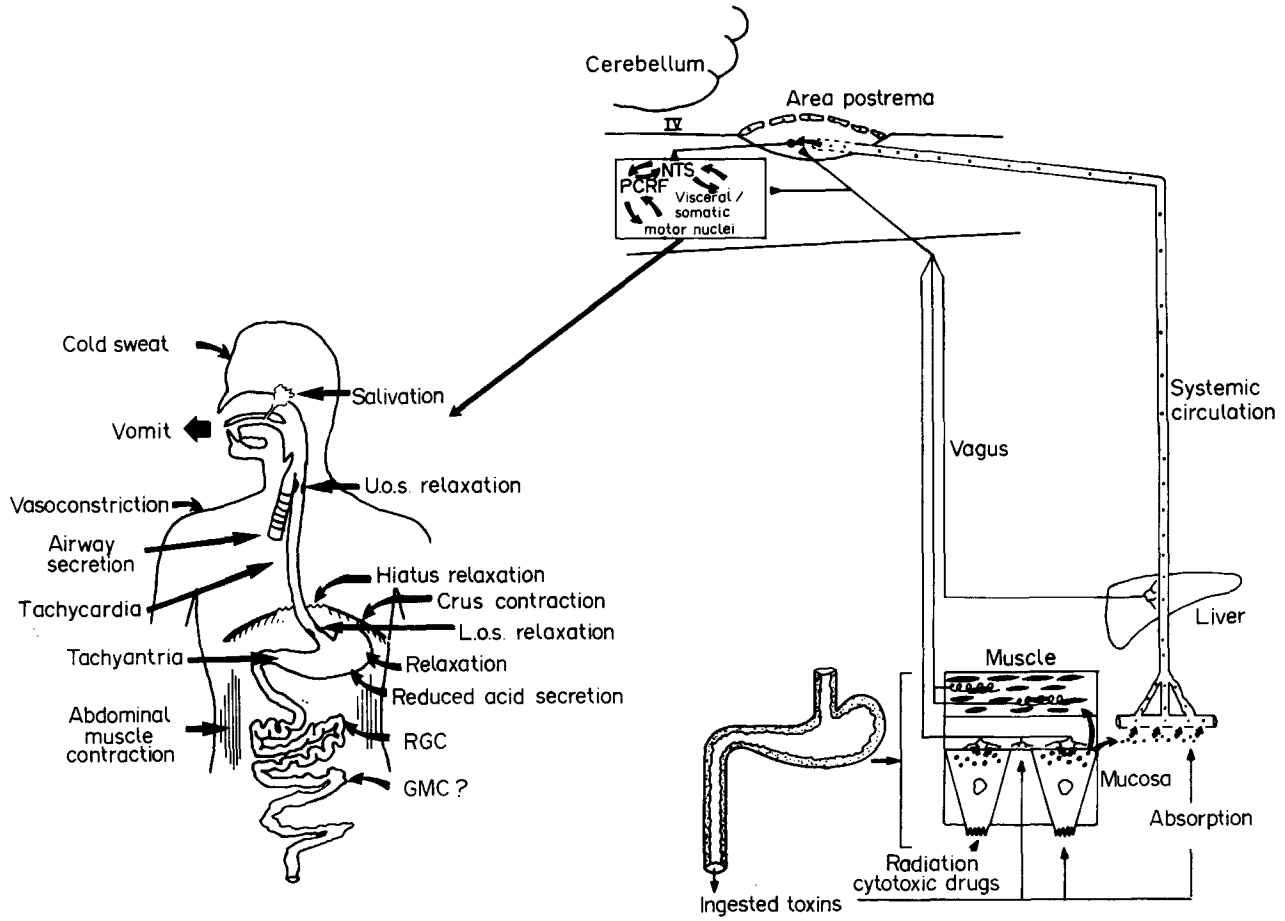

Fig. 4. A summary of the afferent and efferent components of the emetic reflex. On the left are shown some of the visceral and somatic motor changes occurring either prior to or during emesis. RGC = Retrograde giant contraction, GMC = giant migrating contraction. The association of this with emesis induced by all stimuli is uncertain. The right of the picture shows the major abdominal visceral drives to emesis from chemoreceptors in the gastrointestinal mucosa or the liver. It is envisaged that the mucosal chemoreceptors are represented by mucosal cells that when activated by a stimulus release a neuroactive agent (e.g. SP, 5-HT) to discharge vagal afferents terminating in close proximity. These (or other) neuroactive agents could also enter the circulation and activate neurones elsewhere. Mechanoreceptors in the muscle are discharged by overdistension or possibly by mucosally released neuroactive agents acting directly or indirectly by inducing muscle contraction. The top of the diagram illustrates the area postrema and some of the central circuitry involved in emesis (NTS = nucleus tractus solitarius, PCRF = parvicellular reticular formation). Redrawn from Andrews, *et al.* [23].

[29]. The location of 5-HT_3 receptors on the vagal afferents and related structures is shown in Fig. 5. An additional peripheral site of action which should not be overlooked could be the modulation of the release of 5-HT from the enterochromaffin cells [30]. The 5-HT_3 receptor antagonists in clinical trials penetrate the CNS to varying degrees and binding sites have been identified in several cortical areas [31]. Whilst these sites do not appear to be the main site of antiemetic action they may have some beneficial action particularly in man in view of their reported involvement in anxiety [32].

The mechanism by which 5-HT_3 receptor antagonists block serotonin activation of vagal afferents has not yet been investigated but studies of the molecular biology of 5-HT receptors indicate that they can be divided into two superfamilies depending upon their molecular mechanism of action [33]: 5-HT_1 and 5-HT_2 receptors being coupled to G-protein and 5-HT_3 receptors being directly coupled to ion channels. Thus, the antiemetic effect of the 5-HT_3 receptor antagonist may ultimately be by blocking 5-HT-induced depolarisation of the

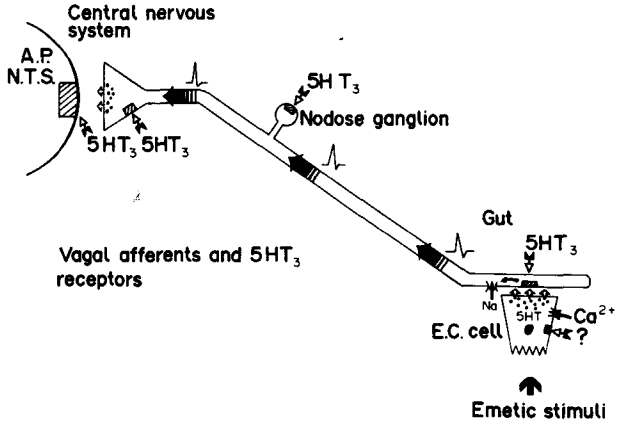

Fig. 5. Possible sites of location of 5-HT_3 receptors on vagal afferents. 5-HT_3 antagonists could, theoretically, act on any of these sites. EC = Enterochromaffin cell; AP = area postrema; NTS = nucleus tractus solitarii.

generator region of the vagal afferent thus preventing the induction of the action potentials which provide the emetic signal to the vomiting centre.

THE FUTURE

This short review has attempted to give a broad overview of current pre-clinical research into the involvement of 5-HT_3 receptors in cytotoxic and radiation-induced emesis. There are obviously a number of substantial gaps in our knowledge, in particular, the lack of direct evidence for the release of 5-HT from the gut wall or even the central nervous system at the correct time after cytotoxic drug administration to account for the various emetic patterns. Until this is done the evidence for the critical involvement of 5-HT relies upon the selective pharmacological actions of the antagonists. In the ferret the bulk of evidence supports a vagal afferent site of antiemetic action, probably in the gut wall. However, it is possible that both central and peripheral sites are implicated with different compounds acting predominantly at one site or other depending upon the degree of central nervous system penetration. Further studies to identify the site of action in animals are required.

Whilst the 5-HT_3 receptor antagonists are very effective in treating emesis in the first 24 h following chemotherapy, so far they appear to be less effective in treating the delayed emesis which may occur particularly with cisplatinum. The treatment of delayed emesis may require the development of agents which protect the gut against the cellular damage produced by cytotoxic drugs and radiation. In this context it is relevant that studies by Bhandari *et al.* demonstrated antagonism of the emetic effects of cisplatinum by diethyldithiocarbamate, an agent known to protect the kidney and bone marrow against the effects of cisplatinum [34]. In addition, prolonged disruption of gastrointestinal motility may occur as a result of the mucosal damage (cf. viral gastroenteritis) and, therefore, gut motility stimulants may be of some benefit. Finally, direct effects of the cytotoxic drugs on the central nervous system should not be excluded.

Animal studies have considerably advanced our knowledge of the physiology and pharmacology of emesis induced by anti-cancer therapies and led to the development of drugs for clinical use. The mechanisms identified from these studies now await clinical studies to test how closely our animal studies provide a model for man.

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Ondansetron

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Ondansetron is the first selective antagonist of the 5-hydroxytryptamine receptors (type 3) marketed for the prevention of emesis induced by antineoplastic agents. Ondansetron has been shown to be more active and less toxic than high-dose metoclopramide in patients submitted to cisplatin chemotherapy. Furthermore, when dexamethasone was added to ondansetron, its antiemetic efficacy increased significantly. In the prevention of emesis induced by a high single dose of cisplatin or by repeated low doses, ondansetron combined with dexamethasone has been shown to be the more efficacious and less toxic antiemetic treatment. However, in the prevention of delayed emesis from cisplatin, its role is still to be defined. In patients submitted to moderately emetogenic chemotherapeutic agents, ondansetron has shown an efficacy superior or equal to standard doses of metoclopramide, but is less toxic. Moreover, when compared with dexamethasone, its antiemetic efficacy and tolerability is similar; in this group of patients ondansetron should be used only when steroids fail. Ondansetron toxicity is generally mild; in particular, it does not induce extrapyramidal reactions. The most frequent side-effects are headache and constipation.
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INTRODUCTION

ONDANSETRON IS a potent, highly selective antagonist of the 5-hydroxytryptamine (5-HT) receptors (type 3) which has been found markedly efficacious in preventing vomiting induced by cisplatin, cyclophosphamide and radiation in ferrets [1]. The site of antiemetic action of ondansetron is still not precisely known. Cytotoxic drugs and radiation can induce damage in the enterochromaffin cells in the gastrointestinal tract and consequently the release of serotonin that can stimulate vagal and splanchnic nerve receptors that in turn elicit the activation of the vomiting centre. Ondansetron can act by blocking the afferent stimulus from the gut or directly at the chemoreceptor trigger zone. In fact, it has been shown that regions in or adjacent to the area postreme are particularly rich in 5-HT$_3$ receptors and that low doses of ondansetron injected directly into this region in ferrets inhibited emesis induced by cisplatin [2]

Ondansetron plasma half-life is approximately 3–3.5 h, while in the elderly it is prolonged to 5 h due to a reduction of plasma clearance. Ondansetron is extensively metabolised (less than 5–10% is recovered unchanged in the urine) and excreted both in the urine and faeces [3].

The drug is moderately bound to plasma protein (70–75%). Interpatient variability of plasma concentrations is considerable and there is no apparent correlation between plasma levels of ondansetron and antiemetic efficacy, although plasma levels may not necessarily reflect drug interaction at the target receptors [3].

Ondansetron is supplied both in parenteral and oral formulation. When administered orally its bioavailability is about 60%.

Even when administered at high doses for 2 years ondansetron has shown no mutagenic or oncogenic potential [4].

STUDIES IN CISPLATIN-TREATED PATIENTS

Cisplatin induces nausea and vomiting in almost all patients during the first 24 h after its administration (acute emesis).

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