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Benefits and Risks of Newer Treatments for Chemotherapy-Induced and Postoperative Nausea and Vomiting

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Abstract

Nausea and vomiting are common adverse effects of chemotherapy, radiation therapy, anaesthesia and surgery. The incidence of chemotherapy-induced nausea and vomiting (CINV) is estimated to vary from 30 to 90%, depending on the type of chemotherapeutic agent used. Radiation-induced emesis varies with anatomical site radiated but is estimated to have an overall incidence of approximately 40%. The incidence of postoperative nausea and vomiting (PONV) depends on the type of anaesthesia and surgery, but overall is estimated to be 20–30%. Evidence-based medicine and meta-analysis have been used to direct medical therapy to help determine equivalence, optimal dose, timing, safety and efficacy of antiemetic medications. Concepts such as the number needed to treat and number needed to harm are helpful to guide the clinician regarding the benefits and risks of a particular treatment.

The serotonin 5-HT_3 receptor antagonists ondansetron, granisetron, tropisetron and dolasetron have been important additions to the antiemetic armamentarium. The 5-HT_3 receptor antagonists are similar in chemical structure, efficacy and adverse effect profile. They appear to have no important differences among themselves in clinical outcomes for CINV and PONV. Headache, dizziness, constipation and diarrhoea are their most common adverse effects, and when they occur they are usually mild and easily managed. Haemodynamic changes and extrapyramidal adverse effects are uncommon. ECG changes such as prolonged corrected QT (QTc) interval are infrequent, dose-related and overall judged to be clinically insignificant. As most studies with the 5-HT_3 antagonists have been conducted on relatively healthy patients, caution should be exercised when these drugs are used in susceptible patients with co-morbidities. The clinician must weigh the benefit of administering an antiemetic for CINV or PONV against the risk of occurrence of an adverse event.

1. Evidence-Based Medicine

1.1 Principles

Evidence-based medicine is a new and important area of medicine that is helping to direct current medical therapy. Jamrozik[1] has reviewed the reasons why evidence-based medicine is important for epidemiology and medical therapy: (i) evidence from experiments is more persuasive than that from observational studies; (ii) in assessing quality of evidence, a hierarchy is used, ranging from the highest to the lowest level of evidence; and (iii) the greatest strength of evidence is given to randomised, controlled trials.

The highest level of evidence is the meta-analysis of numerous randomised controlled trials. The next levels of evidence are individual large randomised controlled trials of high quality, followed by case reports and finally by expert opinion, which is assigned the lowest level.[1,2] Statistical meta-analysis of previously performed randomised controlled trials has received increased attention as a research methodology in evidence-based medicine to determine the equivalence, optimal dose, safety and efficacy of drugs.

Jones et al.[3] have described methods to assess equivalence trials, stating that one of the aims of such trials is to determine the therapeutic equivalence of two different treatments, one of which is a new medication under study that is compared with an existing standard treatment (same class of medication or type of treatment). Jones et al.[3] state that basic principles regarding the design, conduct and completion of equivalence trials are not well understood by most investigators. They state that equivalence trials often have too few patients or a design bias, as these trials are planned

and analysed as if they were comparative studies. The lack of a statistically significant difference is often taken as proof of equivalence, leading to false conclusions. The size of the equivalence trial should be based on a null hypothesis of non-equivalence and an alternative hypothesis of equivalence, with conclusions drawn on an appropriate confidence interval for the sample size based on an adequate number of patients using a prespecified criteria of equivalence. The design of an equivalence trial should follow the previously conducted trial of the comparator medication, and the data obtained should provide some evidence of efficacy, which might be an efficacy rate compared with placebo or other clinically important changes as similarly reported in previously published trials.[3]

Laupacis et al.[4] described a methodology to determine clinically useful measures of the consequences of treatment. First, the method would compare the consequences of doing nothing with the potential benefits of doing something. Secondly, the method would summarise the harm that would occur with the treatment, as described by adverse effects and toxicity. Thirdly, the method would identify patients who are at high risk for an adverse effect that might occur in response to therapy. Fourthly, the method would compare the consequences of applying one approach to the diagnosis, prevention and treatment of one condition with the consequences of applying other approaches to other conditions, making it possible for an individual clinician to decide the best therapy.

Two clinical concepts that have proved to be useful when applying the results of randomised clinical trials to actual clinical situations are the concepts of the number needed to treat (NNT; the inverse of the absolute risk reduction) and the number needed to harm (NNH; the inverse of the absolute risk increase). Laupacis et al.[4] introduced NNT and NNH as methods that can be utilised to summarise the efficacy of a treatment in terms of the number of patients a clinician needs to treat to get an expected result and the number of adverse events that can be expected.

Cook and Sackett[5] state that the relative benefit of an active treatment group over a control group can be expressed as: (i) relative risk; (ii) relative risk reduction; and (iii) odds ratio. They define relative risk as the probability of an event in the active treatment group divided by the probability of an event in the control group, with values <1 indicating benefit from the treatment. However, for clinical decision-making, the NNT appears to be more meaningful, useful and understandable than the relative risk, since it takes into account the baseline risk of an event. NNT conveys both statistical and clinical significance to the clinician and helps clinical interpretation in terms of the number of patients who actually need to be treated to obtain a positive outcome rather than the relative values that often appear in publications of randomised, controlled trials. NNT values can be adjusted to allow for the baseline risk of an individual clinical patient compared with that of the typical study patient in a randomised clinical trial. Similarly, NNT can be used to extrapolate published findings to a clinical patient situation, summarising efficacy data from randomised controlled trials in a way that is easily understood and readily appreciated.[4,5]

Relative risk for an adverse event is similarly defined as the probability of an adverse event (harm) occurring in the treatment group divided by the probability of an adverse event occurring in the control group, with values >1 indicating harm from the treatment. Similar to NNT, the concept of NNH has been used to compare the adverse events of various medications. The NNH is the number of patients needed to be treated with the medication for one patient to show harm who would not have done so if the patient had not received the medication. Analogously, calculation of NNH takes into account the baseline risk of that event, which should be determined prior to starting treatment. The expected benefit of a treatment could decrease or increase, respectively, as the baseline risk of an adverse event increases or decreases.[4,6]

1.2 Application to Studies of Antiemetics

Tramèr[6,7] conducted a meta-analysis of data from multiple studies on more than 55 000 patients in 430 randomised controlled trials of antiemetics used for postoperative nausea and vomiting (PONV), using a four-step process: (i) systematic search for relevant reports; (ii) methodological scoring of retrieved reports using predefined validity criteria; (iii) extraction of data; and (iv) analysis of the combined data. He was then able to synthesise data at a high level of evidence on the true efficacy and adverse events of antiemetics for prevention and treatment of PONV.

Tramèr[6] utilised the NNT concept in his meta-analysis of studies of PONV. A measurement of antiemetic efficacy was defined as the improvement of the treatment compared with placebo. He used as an example that a 20% improvement in treatment efficacy above the placebo response indicated that 20% of patients who received the medication would benefit from the treatment. If a perfect response is defined as 100%, then a 20% response gives an NNT of 5 (100% divided by 20%) and five patients would need to receive the medication for it to have a positive effect in one patient. Specifically for antiemetic medication, an NNT of 5 indicates that five patients at risk for PONV would need to receive the medication in order for one patient not to vomit who would have vomited had he or she not received the medication (figure 1).

Determining the underlying baseline risk of PONV and CINV is important for treatment of the population being studied to help guide the choice of therapy. A placebo group is necessary in randomised controlled trials to determine the true underlying baseline risk of the patient population being studied. Justifying the use of the NNT concept in meta-analysis studies of antiemetics, Tramèr[6,7] stated that if the placebo control group has a high baseline incidence rate of PONV, this indicates that the investigated study group was also at high risk for PONV. Conversely, if the comparator placebo control group had a low incidence rate of

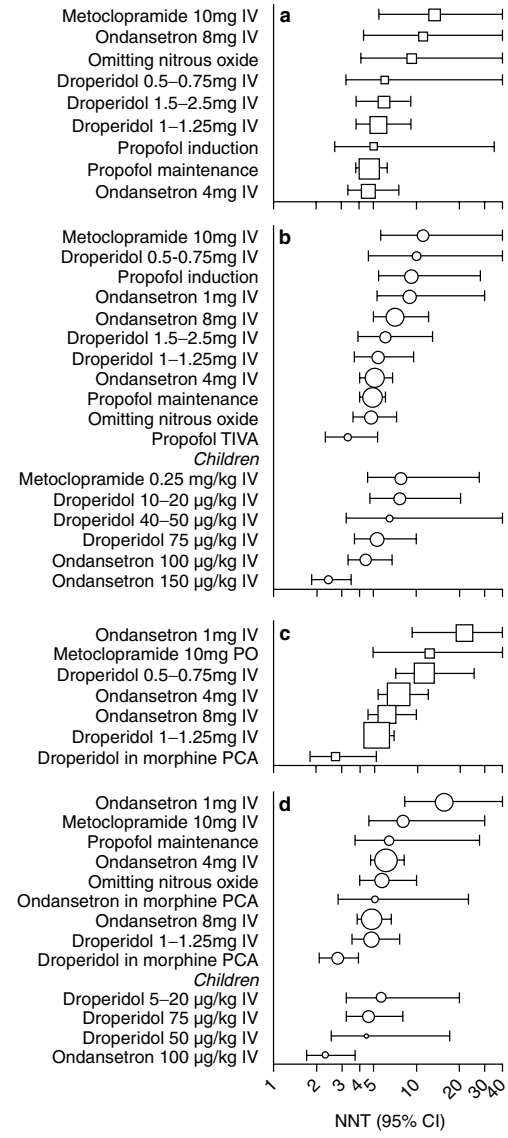

Fig. 1. Number needed to treat (NNT) of antiemetics used for postoperative nausea and vomiting (PONV). The endpoint is prevention of nausea (**a** and **c**) or vomiting (**b** and **d**) within 6 hours after surgery ('early' efficacy; **a** and **b**) or within 24 hours after surgery ('late' efficacy; **c** and **d**). Areas of symbols are proportional to the numbers of patients analysed, and horizontal bars are 95% CIs. If the upper boundary of the 95% CI lies within what might be considered to be the minimally clinical relevant effect (for example an NNT of 5 to prevent PONV), this indicates a definitely useful treatment (reproduced from Tramèr,[6,8] with permission from BMJ Books). **IV** = intravenous; **PCA** = patient-controlled anaesthesia; **PO** = oral; **TIVA** = total intravenous anaesthesia.

PONV, the study group also most likely represented a population at low baseline risk for PONV.

Therapeutic recommendations concerning the efficacy and safety of antiemetic medications used for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) and PONV have resulted from analysis of multiple randomised controlled clinical trials. Reviews such as this have attempted to synthesise data and reach conclusions on the large amount of published information that is available. However, in spite of these analyses, there are many unanswered questions regarding the proper medication, optimal dose, timing, adverse effects (table I), risks, benefits and efficacy of antiemetic therapy. In particular, since the incidence of adverse events has been reported to be low with the serotonin 5-HT_3 antagonists, it is difficult, even after analysing multiple randomised controlled trials in CINV and PONV, to determine the true incidence of adverse events with these agents.[7]

Table I. Adverse effects of currently available antiemetics

Adverse effect	Drugs
Sedation	Phenothiazines
	Antihistamines
	Droperidol
Hypotension	Promethazine
	Prochlorperazine
	Droperidol
Extrapyramidal symptoms	Benztropine
	Metoclopramide
	Droperidol
Dry mouth	Atropine
	Scopolamine
	Antihistamines
Dysphoria	Scopolamine
	Droperidol
Headache/light-headedness	Ondansetron
	Granisetron
	Tropisetron
	Dolasetron
Constipation	Ondansetron
	Granisetron
	Tropisetron
	Dolasetron

2. Mechanism of Antiemetic Activity

The 5-HT_3 receptor antagonists have been shown to be effective therapy for CINV, radiation-induced emesis (RIE) and PONV.[9-13] Dopamine D_2 receptor antagonists initially had been found to be effective during CINV. A key finding that the 5-HT_3 receptor was an important contributing factor for nausea and vomiting resulted from the use of high-dose metoclopramide. Metoclopramide was found to have weak 5-HT_3 receptor blocking properties in addition to dopamine D_2 blocking activity, and was an effective therapy for CINV.[14] Other emetogenic antagonists that blocked histamine and/or cholinergic receptors were found to have minimal or no effect in CINV.[9,13]

The majority of total body serotonin is located peripherally in the gastrointestinal tract within the enterochromaffin cells of the duodenum.[12,13,15] The 5-HT_3 receptor antagonists as a class have been found to act centrally and peripherally. 5-HT_3 receptors are present peripherally on afferent vagal nerve pathways in abdominal visceral afferent neurons and centrally in high concentrations at the base of the fourth ventricle in the chemoreceptor trigger zone of the area postrema. The nausea and vomiting induced by chemotherapeutic agents result from a sequence of events that begins with cytotoxic drug-induced cellular damage to the gastrointestinal mucosa, especially the ileum, resulting in the release of serotonin from enterochromaffin cells of the duodenum.[9,10,13,16] Serotonin stimulates 5-HT_3 receptors on the afferent vagus nerve, which in turn stimulates the chemoreceptor trigger zone, area postrema and nucleus tractus solitarius in the CNS, initiating the vomiting reflex. Blocking the afferent vagal pathways with a 5-HT_3 receptor antagonist has been found to be an effective means of preventing vomiting during CINV.[13,15]

Risk factors for CINV are listed in table II. Hesketh et al.[16] have proposed an algorithm for classifying the acute emetogenic level of single, dual and triple chemotherapy combinations. The

Table II. Risk factors for chemotherapy-induced nausea and vomiting (from ASHP Commission on Therapeutics,[9] with permission)

Type of factor	Factor
Treatment-specific	Chemotherapy drug
	High doses of chemotherapy drugs
	High infusion rates of chemotherapy drugs
Patient-specific	Age <50 years
	Sex: women > men
	Alcohol use
	History of motion sickness or nausea during pregnancy
	Prior exposure to chemotherapeutic agents

acute emetogenic levels of single chemotherapeutic agents, and the percentage of patients who experience emesis are listed in table III.

The aetiology, risk, efficacy and adverse effects of antiemetics for CINV and RIE appear to be better understood than for PONV. Eberhart et al.[17] analysed three risk scores to predict PONV and concluded that the true underlying risk of PONV in individual patients can be unpredictable and difficult to determine. Over the last 40 years, the incidence of PONV has remained the same overall, occurring in approximately 20–30% of patients undergoing surgical procedures and anaesthesia.[18] Further analysis of nausea alone yields an estimate of 20% incidence during the first 2 hours postoperatively in the postanaesthesia care unit (PACU), and 50% in the following 2–24 hours. Vomiting alone is estimated to occur at approximately a 5% incidence during the first 2 postoperative hours in the PACU and 25% during the following 2–24 hours.[6]

Factors that are thought to increase the baseline risk for PONV in adults include patient, anaesthesia and surgery-related factors. Patient-related risk factors are: (i) gender – women have a 2- to 3-fold increased incidence of PONV compared with men because of their monthly variations of progesterone and estrogen hormone levels; (ii) age – children have twice the incidence of emesis compared with adults; (iii) prior history of motion sickness or PONV; and (iv) no history of tobacco smoking.[18-20]

Anaesthesia is an important risk factor, because anaesthetic techniques using opioids, inhalation agents and nitrous oxide-based balanced anaesthesia, or hypnosedatives such as etomidate or ketamine, can increase the risk for PONV.[18] Also, a drug-related risk factor is the postoperative use of opioids with stimulation of central emetogenic opioid neuroreceptors.

Type of surgery is a significant risk factor, with laparoscopy being one of the most common outpatient procedures that can cause PONV. Other emetogenic operations include: (i) strabismus repair; (ii) mastoid/inner ear; (iii) adenotonsillectomy; (iv) intra-abdominal; (v) breast; (vi) shoulder; (vii) testicular; and (viii) oral, plastic or ear, nose and throat (ENT) procedures that may involve the swallowing of blood, as blood is a very strong emetogenic stimulus. Duration of surgery increases baseline PONV risk by approximately 60% for each 30-minute increase in surgery time.[21] In the PACU, pain, movement, hypovolaemia and orthostatic hypotension can also increase the risk for PONV.[18] Risk factors in children are similar to those in adults, with the exception that only vomiting is treated in randomised controlled trials in children.[22] Risk factors for PONV are listed in table IV.

One of the first groups to develop a simplified PONV risk score was Koivuranta and co-workers.[19] Their data were combined with that of Apfel et al.[20] to develop a simplified PONV risk score. Four main factors were found to increase the risk of PONV, and when used together were useful clinically to determine the underlying risk of PONV. These factors were: (i) prior history of PONV or motion sickness; (ii) non-smoker; (iii) female gender; and (iv) patient receiving postoperative opioids. Patients with zero, one, two, three or four of these risk factors have PONV risks of approximately 10, 21, 39, 61 and 79%, respectively (table V).

The rate of unplanned overnight admissions due to symptoms of PONV, although infrequent, has

Table III. Emetogenic levels of single chemotherapeutic agents (from Hesketh et al.,[16] with permission)

Emetogenic level	Patients with emesis (%)[a]	Agent
5	>90	Carmustine >250 mg/m^2
		Cisplatin ≥50 mg/m^2
		Cyclophosphamide >1500 mg/m^2
		Dacarbazine
		Mechlorethamine
		Streptozocin
4	60–90	Carboplatin
		Carmustine ≤250 mg/m^2
		Cisplatin <50 mg/m^2
		Cyclophosphamide >750 to ≤1500 mg/m^2
		Cytarabine <1 g/m^2
		Doxorubicin <60 mg/m^2
		Methotrexate >1000 mg/m^2
		Procarbazine (oral)
3	30–60	Altretamine (oral)
		Cyclophosphamide ≤750 mg/m^2
		Cyclophosphamide (oral)
		Doxorubicin 20–60 mg/m^2
		Epirubicin ≤90 mg/m^2
		Idarubicin
		Ifosfamide
		Methotrexate 250–100 mg/m^2
		Mitoxantrone <15 mg/m^2
2	10–30	Docetaxel
		Etoposide
		Fluorouracil <1000 mg/m^2
		Gemcitabine
		Methotrexate >50 to <250 mg/m^2
		Mitomycin
		Paclitaxel
1	<10	Bleomycin
		Busulfan
		Chlorambucil (oral)
		Cladribine
		Fludarabine
		Hydroxycarbamide (hydroxyurea)
		Methotrexate ≤50 mg/m^2
		L-Phenylalanine mustard (oral)
		Thioguanine (oral)
		Vinblastine
		Vincristine
		Vinorelbine

a Without effective antiemetic prophylaxis.

often been used as one of the endpoints for the evaluation of PONV and need for therapy. Gold et al.[23] reported an unplanned admission rate of 0.18% due to intractable PONV. Fancourt-Smith et al.,[24] using large retrospective studies, reported that hospital admission rates due to PONV from 1977 to 1987 at the surgical day centre of Vancouver General Hospital were 2 per 90 234 (0.002%). Tramèr et al.[25] reviewed 33 randomised controlled trials and determined that the rate of unplanned admission in outpatient surgery patients was 0.6%. Henzi et al.[26] reviewed 17 randomised controlled trials and determined an unplanned hospital admission rate of 0.8%. Fortney et al.[27] found an unexpected hospital admission rate of 2%. Interestingly, in these randomised controlled trials, unexpected hospital admissions occurred in patients who had received prophylactic antiemetic medications such as ondansetron, droperidol or metoclopramide.

When a medication is administered, there is always the possibility of the occurrence of an adverse event causing harm to a patient that would not have occurred had the medication not been administered. Tramèr[6,7] stated that the relationship between poor efficacy and harm challenges the usefulness of all prophylactic antiemetic interventions.

The NNH is the number of patients needed to be treated with the medication for one patient to show harm (adverse reaction) who would not have done so if the patient had not received the medication. Figure 1 illustrates the NNT and figure 2 the NNH of various antiemetic medications.[6]

Tramèr[6] defined the optimal dose of an antiemetic medication as the dose that showed efficacy with an 'acceptable' degree of risk, stating that lack of valid data equals lack of evidence. This statement is important, because most of the older antiemetic medications have been poorly studied specifically for PONV in randomised controlled trials and, thus, have minimal documented efficacy when used solely for PONV. Superficially, there appears to be an increased risk of adverse events when using the older antiemetics alone and/or in

Table IV. Risk factors for postoperative nausea and vomiting (PONV)

Patient-related factors
Sex (males > females)
Prior history of PONV or motion sickness
No history of smoking
Anaesthesia-related factors
Nitrous oxide
Opioid analgesics
Inhalation anaesthetics
Surgery-related factors
Duration
Type
Breast
Intra-abdominal
Laparoscopy
Mastoid-inner ear
Oral, plastic or ENT procedures (involving swallowing of blood)
Shoulder
Strabismus repair
Testicular
Tonsillectomy
PACU-related factors
Pain
Patient movement
Hypovolaemia
Orthostatic hypotension

ENT = ear, nose and throat; **PACU** = postanaesthesia care unit.

combination with each other for CINV and PONV. The adverse effect profile of the older antiemetics was one of the reasons for the development of the 5-HT_3 receptor antagonists. However, further research is needed to identify: (i) the most efficacious regimens for antiemetic prophylaxis and treatment; (ii) the minimal effective dose; (iii) optimal drug combinations; (iv) optimal timing of administration; and (v) the patients who are most likely to benefit from antiemetic therapy and least likely to have an adverse event.

There has been a lack of uniformity when reporting adverse events of antiemetics in randomised controlled studies. The presence or absence of adverse effects always should be reported, and is especially important for rare but potentially major adverse events (such as electrocardiographic [ECG] changes). As the incidence of adverse effects cannot confidently be determined from one or two small clinical studies, meta-analysis of combined data from several studies can yield a larger patient database, allowing the determination of antiemetic efficacy as well as risk factors and the aetiology and incidence of adverse events.[6] Tramèr's[6] conclusions from a meta-analysis of antiemetic therapy were as follows: (i) prophylaxis of PONV with antiemetic monotherapy does not work well; (ii) there is a finite risk of adverse drug reactions with most antiemetic medications; (iii) overall, antiemetic treatment is more cost effective than prophylaxis.

3. Ondansetron

3.1 Pharmacology

The chemical structures of serotonin and the 5-HT_3 receptor antagonists are shown in figure 3. Ondansetron is a carbazole compound with a structure similar to that of serotonin. Ondansetron has been determined to be a highly selective competitive antagonist of serotonin neurotransmission at the 5-HT_3 receptor.[28] Although the exact location (central versus peripheral) of the antiemetic activity of ondansetron has not been definitely determined, ondansetron has been shown to block peripherally afferent stimuli from the gastrointestinal tract as well as have a central action in the chemoreceptor trigger zone, thereby preventing or reducing emesis.[9,29]

Table V. Simplified risk score for predicting postoperative nausea and vomiting (PONV) [from Apfel et al.,[20] with permission]

No. of risk factors present[a]	Incidence of PONV (%)[b]	PONV risk
0	10	Low
1	21	Mild
2	39	Moderate
3	61	High
4	79	Extremely high

a Risk factors are: (i) female gender; (ii) history of PONV and/or motion sickness; (iii) no history of smoking; and (iv) postoperative opioids.

b Incidence increases as the total number of risk factors present increases. Each additional risk factor increases the incidence of PONV by approximately 20%.

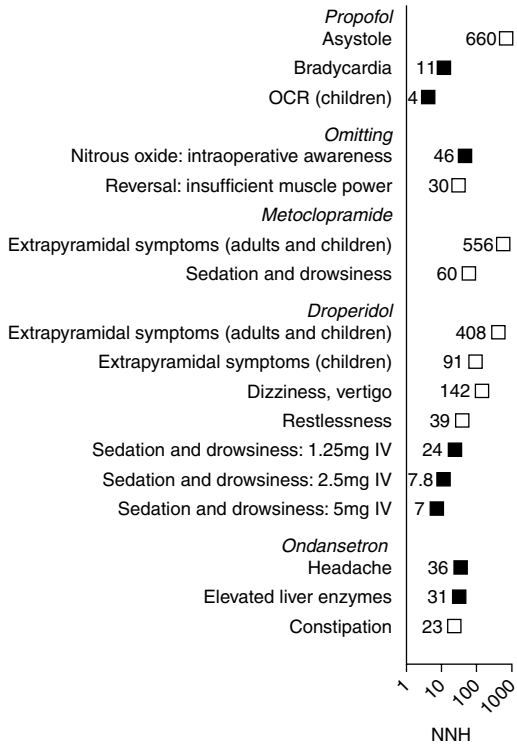

Fig. 2. Number needed to harm (NNH) of antiemetics used for postoperative nausea and vomiting (PONV). Symbol areas are fixed, and no confidence intervals are shown since some values are based on limited numbers of patients who showed the adverse drug reaction. Filled symbols represent adverse events that occurred statistically significantly more often ($p < 0.05$) with the intervention; open symbols indicate absence of statistical significance (reproduced from Tramèr,[6,8] with permission from BMJ Books). **IV** = intravenous; **OCR** = oculocardiac reflex.

3.2 Pharmacokinetics

Ondansetron can be administered either orally or by intravenous injection, with peak plasma concentrations achieved within 60–90 minutes after oral administration and 20–30 minutes after intravenous injection (table VI).[30] Ondansetron has been administered by intramuscular injection and found to have similar tolerability and pharmacokinetics as via the intravenous route.[31] Jarosinski and Hirschfeld[32] reported that ondansetron caused a white precipitate in alkaline solutions. The pH values of the ondansetron and bicarbonate solutions were 4.0 and 8.6, respectively, before and 7.8 after combination of the solutions.

Grunberg et al.[33] determined that there was a positive correlation between antiemetic efficacy and ondansetron plasma concentrations with increasing doses of intravenous ondansetron from 0.01 to 0.48 mg/kg administered every 4 hours for three doses to patients receiving cisplatin for the first time.

In healthy volunteers, ondansetron was determined to be 57% protein bound and have a bioavailability of approximately 60% after oral administration.[30] Ondansetron has a plasma elimination half-life of 3.5–4.5 hours, undergoing metabolism in the liver by hydroxylation and glucuronide conjugation with no active metabolites (table VII).[28] Dixon et al.[34] reported that ondansetron undergoes metabolism by multiple forms of the cytochrome P450 (CYP) enzyme (CYP1A1, CYP1A2, CYP2D6 and CYP3A4), with no single CYP enzyme type predominating in the overall metabolism. Ondansetron is excreted 60% in the urine and 25% in the faeces. Clearance of ondansetron decreases approximately 31% in the elderly.[30]

Kaiser and colleagues[35] proposed a hypothesis for variation of response to the 5-HT_3 receptor antagonists during CINV and PONV, arising from the fact that there is variation in drug biotransformation by genetically polymorphic enzymes such as hepatic CYP2D6, and determined that antiemetic treatment with ondansetron could be improved by adjustment for CYP2D6 genotype. Approximately 50 subjects would have to be genotyped to protect one patient from severe emesis.

Because ondansetron is eliminated mainly by liver metabolism, liver disease or failure can affect its clearance and elimination. Figg et al.[36] studied the pharmacokinetics of ondansetron 8mg administered orally and intravenously in patients with different degrees of hepatic insufficiency. Clearance decreased in patients with liver failure, mean absolute bioavailability increased with increased hepatic insufficiency due to a reduced first-pass

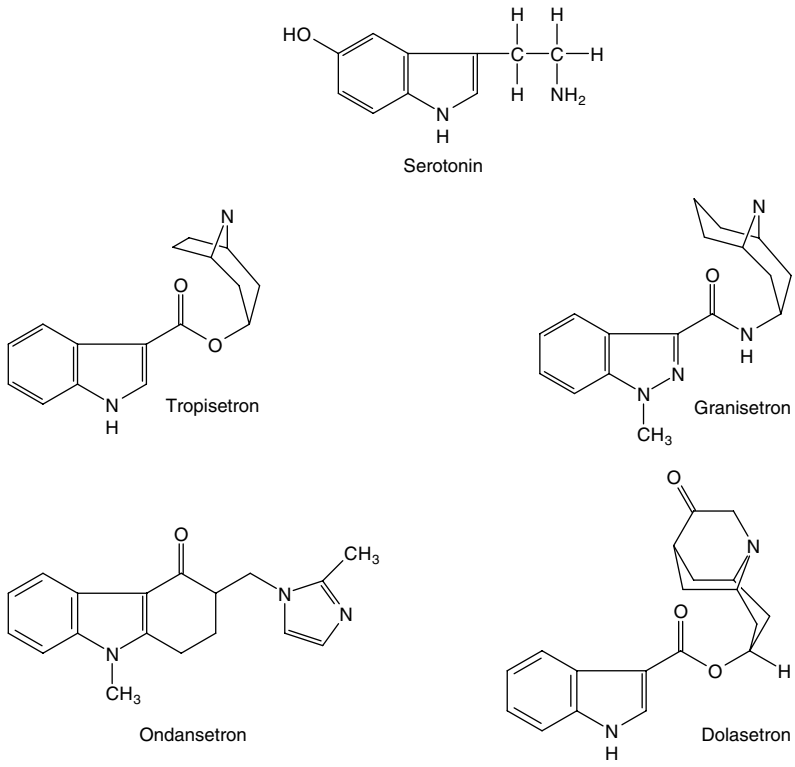

Fig. 3. Chemical structures of serotonin and the 5-HT_3 receptor antagonists.

effect, and less ondansetron was bound to plasma proteins. The recommendation of Figg et al.[36] was to limit the total daily dose of ondansetron to 8mg in adults (or 0.15 mg/kg in children) in patients with liver disease (table VII). The recommended dosage of ondansetron for CINV and PONV is listed in table VIII.

3.3 Adverse Reactions

Serotonin in normal healthy volunteers causes transient bradycardia and hypotension, the Belzold-Jarisch reflex. In animal studies, the 5-HT_3 receptor antagonists have been chemically identified by their ability to block this reflex. 5-HT_1 receptors may be responsible for bradycardia of central origin, while peripherally induced bradycardia by serotonin is thought to be primarily due to activation of vagal afferents through the 5-HT_3 receptors of the heart and great vessels.[38]

Talley et al.[39,40] and Gore et al.[41] determined in healthy volunteers that the 5-HT_3 receptor antagonists are involved in the regulation of colonic transit times, reporting that ondansetron slowed gastric and colonic transit.

Laboratory studies[42] determined that transiently elevated plasma concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have occurred in patients who received ondansetron. However, these increases were reported to result in no clinically significant liver changes or other sequelae. In an analysis of more than 1400 patients with a range of medical conditions and 650 volunteers, ondansetron has been shown to have a wide therapeutic index and

Table VI. Pharmacokinetics of the serotonin 5-HT_3 receptor antagonists

Drug	t_{max} (min)		$t_{½β}$ (h)		Liver metabolism	Metabolite excretion (%)	
	PO	IV	PO	IV		urine	faeces
Ondansetron	60–90	20–30	3.1–6.2	3.5–5.5	CYP2D6, 2E1, 1A1, 1A2, 3A4	60	25
Granisetron	60–90	30	3.1–6.23	6.3	CYP3A subfamily (CYP3A3/4, CYP3A5, CYP3A7)	49	36
Tropisetron	70–80	30	8.6[a]	7.3[a]	CYP2D6	80	15
			41.9[b]	30.3[b]			
Dolasetron[c]	60	30–35	7.2–8.1	6.9–7.3	Carbonyl reductase (plasma), CYP2D6, CYP3A	67	33

a Good metabolisers.

b Poor metabolisers.

c Values are for hydrodolasetron.

CYP = cytochrome P450; **IV** = intravenous; **PO** = oral; t_{max} = time to reach peak plasma concentration; $t_{½β}$ = terminal elimination half-life.

no reported adverse effects such as hypotension,[43] drug interactions with commonly prescribed drugs,[44] dystonic reactions[44] or ventilatory depression.[45] Ondansetron has not been reported to increase awakening time or cause sedation[46] or impair psychomotor ability[47] following general anaesthesia. These findings are similar to those found with the other 5-HT_3 receptor antagonists.

Clinical experience in both CINV[28,30,48] and PONV[28,49,50] has shown ondansetron to be effective and well tolerated with a wide therapeutic index. The main adverse effects are constipation, headache and increases in liver function tests.[50,51] The most common adverse effects reported in various studies of CINV were headache (5–27%), constipation (1–9%), diarrhoea (1–16%), fever (1–8%) and malaise/fatigue (1–13%).[10,28,30,42] The most common adverse effects reported in various studies of PONV were mild headache (about 11%) and constipation (about 4%).[49,52-56] These adverse effects were frequently found to have an incidence similar to placebo. The headache appears to respond well to analgesics, such as paracetamol (acetaminophen). Increases of liver function tests initially had been thought to be due to the underlying cancer disease and/or metastases or coadministration of chemotherapy.[51] However, Tramèr et al.[44] in their meta-analysis on ondansetron determined that a rise in liver enzymes occurred in 3 of 100 patients who would not have had this symptom if they had not been treated with ondansetron. This suggests an aetiology that occurs irrespective of whether or not ondansetron is administered for CINV or PONV. This suggests that the rise in liver enzymes in 3 of 100 patients is due to ondansetron and not due to whether the patients have received chemotherapy or have cancer.

Similar conclusions about efficacy and adverse event profile have been determined in children in trials in CINV[9,30] and PONV.[9,57-59]

Table VII. Half-lives of intravenous 5-HT_3 receptor antagonists

5-HT_3 antagonist	Cancer patients	Severe liver impairment		Severe renal impairment	
	$t_{½β}$ (h)	$t_{½β}$ (h)	dose adjustment	$t_{½β}$ (h)	dose adjustment
Ondansetron	4.0–4.5	20	Yes	3.5–5.5	No
Granisetron	10.6	6.0	No	6.0	No
Dolasetron[a]	7.5	11.7	No	10.9	No

a Values are for hydrodolasetron.

$t_{½β}$ = terminal elimination half-life.

Table VIII. Recommended dosages of the 5-HT_3 receptor antagonists for chemotherapy-induced nausea and vomiting (CINV) [from ASHP Commission on Therapeutics,[9] with permission] and postoperative nausea and vomiting (PONV) [from Kovac,[37] with permission]

Drug	Route	Dosage
CINV		
Ondansetron	PO	Adult: (tablet or suspension) 24mg 30 min prior to chemotherapy
	IV	Adult: 8mg 30 min prior to chemotherapy
	PO	Child 4–11y: 4mg 30 min prior and 4 and 8h after chemotherapy; may also be given as a single 12mg dose 30 min prior to chemotherapy
		Child >11y: 8mg 30 min prior and 4 and 8h after chemotherapy; may also be given as a single 24mg dose 30 min prior to chemotherapy
	IV	Child >3y: 0.15 mg/kg 30 min prior to and 4 and 8h after chemotherapy
Granisetron	PO	Adult: 2mg 30 min prior to chemotherapy
	IV	Adult: 10 μg/kg 30 min prior to chemotherapy
		Child ≥3y: 20–40 μg/kg 30 min prior to chemotherapy
Tropisetron	PO	5mg 30 min prior to chemotherapy
	IV	5mg 30 min prior to chemotherapy
Dolasetron	PO	Adult: 100mg 30 min prior to chemotherapy
	IV	Adult: 1.8 mg/kg 30 min prior to chemotherapy
	PO	Child: 1.8 mg/kg 30 min prior to chemotherapy
PONV		
Ondansetron	PO	Adult: 8–16mg 1–2h prior to anaesthesia
	IV	Adult: 4mg (prevention) at start of anaesthesia
		Adult: 4mg (treatment)
		Child: 0.1 mg/kg (maximum 4mg) [prevention and treatment]
Granisetron	IV	Adult: 1mg (prevention) at start or end of anaesthesia
	IV	Adult: 1mg (treatment)
Tropisetron	IV	Adult: 2mg (prevention) at start of anaesthesia
		Adult: 2mg (treatment)
Dolasetron	PO	Adult: 100mg (prevention) 1–2h prior to anaesthesia
	IV	Adult: 12.5mg (prevention) 15–30 min prior to end of anaesthesia
	IV	Adult: 12.5mg (treatment)
	PO	Child: 1.2 mg/kg (maximum 100mg) [prevention] 1–2h prior to anaesthesia
	IV	Child: 0.35 mg/kg (maximum 12.5mg) [prevention and treatment]

IV = intravenous; **PO** = oral.

4. Granisetron

4.1 Pharmacology

Granisetron (figure 3) is a potent azabicyclic compound that binds strongly and selectively to the 5-HT_3 receptor with 4000 to 40 000 times greater affinity for the 5-HT_3 receptor than for other receptors, including 5-HT_1, 5-HT_2, dopamine D_2, histamine H_1, benzodiazepine and opioid receptors.[60-62] Similar to ondansetron, the mechanism of action of granisetron to prevent RIE[61] and CINV[62-65] is peripheral antagonism of the effects of serotonin at 5-HT_3 receptors on abdominal vagal afferents supplying the upper small intestine, and centrally at the area postrema and chemoreceptor trigger zone in the CNS.

4.2 Pharmacokinetics

After rapid intravenous administration of 20 and 40 μg/kg to healthy volunteers, peak granisetron plasma concentrations were determined to be 13.7 and 42.8 μg/L, respectively, occurring 30 minutes after intravenous administration.[60] The mean plasma elimination half-life in healthy vol-

unteers was determined to be 3.1–5.9 hours. The plasma elimination half-life in cancer patients was found to be 10–12 hours, because the total body clearance of granisetron was lower in cancer patients (table VII).[66] These results were believed to reflect differences in drug elimination due to underlying disease processes, the patient's stage of cancer or other factors.

Elimination of granisetron is primarily by nonrenal mechanisms, with only 8–15% of the parent compound recovered in the urine.[60,62] Granisetron is metabolised primarily by hepatic CYP3A enzymes, and is not reported to induce or inhibit CYP enzymes. However, inducers or inhibitors of CYP enzymes may alter the clearance and half-life of granisetron. Bloomer et al.[67] determined *in vitro* via enzyme kinetics that there are at least two enzymes that contribute to the 7-hydroxylation of granisetron. They reported that CYP3A3/4 was involved in granisetron 9′-demethylation and a different enzyme was involved in the 7-hydroxylation (table VI).

4.3 Therapeutic Use

Compared with placebo, clinical trials in cancer patients have demonstrated that granisetron significantly reduced the incidence of CINV for 24 hours after administration of high-dose cisplatin.[60,68] In large comparative trials, patients who received granisetron prior to cisplatin or other chemotherapy experienced inhibition of vomiting, with little or no nausea for 24 hours after chemotherapy administration.[62,63,68] The efficacy of granisetron for CINV has been found to be similar to that obtained with high-dose metoclopramide plus dexamethasone,[64] and superior to a combination of chlorpromazine plus dexamethasone.[65]

Dose-response studies[60,68] showed no significant difference in the antiemetic response of cancer patients receiving chemotherapy to single intravenous doses of granisetron at either 40 or 160 μg/kg. Emesis was completely inhibited with no or only mild nausea in 57–81% of patients in these studies. Granisetron was found to be significantly superior to placebo in preventing the emesis evoked by cisplatin, and was very effective as an interventional medication, quickly abolishing emesis in most patients unresponsive to placebo.[68] The recommended dose of granisetron for CINV is 2mg orally and 10 μg/kg intravenously before chemotherapy in adult patients. For children ≥3 years, granisetron 20–40 μg/kg is given intravenously 30 minutes prior to chemotherapy (table VIII).[66]

Granisetron has been shown to be effective for the prevention[69-73] and treatment[74] of PONV in adults and children and, while used worldwide, has recently received approval for this indication from the USFDA. Wilson et al.[69] determined from a dose-ranging study of intravenous granisetron 0.1, 1 and 3mg in adult patients that 1mg was the optimum effective single dose when administered immediately before the start of anaesthesia. Fujii et al.[70] determined that intravenous granisetron 40 μg/kg was the optimal prophylactic dose for adults, and Cieslak et al.[73] determined that the same dose was optimal for prophylaxis in children. Mikawa et al.[75] conducted a prophylactic dose-ranging study in gynaecological surgery patients of 2, 5, 10 and 20 μg/kg intravenously versus placebo to determine the optimal dose of granisetron. They concluded that 5 μg/kg (0.35mg in a 70kg patient) of granisetron was the optimal dose. Taylor et al.[74] evaluated the effect of intravenous granisetron 0.1, 1 and 3mg compared with placebo for treatment of PONV following surgery with general anaesthesia. All intravenous granisetron doses were significantly more effective than placebo in preventing emesis, with freedom from emesis in 38, 46 and 49% of patients receiving granisetron 0.1, 1 and 3mg, respectively, compared with 20% of patients receiving placebo. Granisetron 0.1mg was determined to be the lowest effective optimal dose for this treatment study, which is lower than the FDA-approved dose of 1mg. The recommended dosages of granisetron for CINV and PONV are listed in table VIII.

4.4 Adverse Reactions

Similar to the other 5-HT_3 receptor antagonists, granisetron has no reported drug interactions with anaesthetic medications, benzodiazepines, opioids or cancer chemotherapies. Granisetron has been administered with no adverse effects to patients also receiving antipsychotics and anti-ulcer medications commonly prescribed for antiemetic treatment.[60,62]

Granisetron has been well tolerated by various patient populations in many clinical trials. In paediatric patients, granisetron has been administered without problems to children 2–16 years of age.[73] Patients 65 years of age and older have received granisetron with an efficacy and safety profile similar to that in patients in younger age groups.[60,70,72-74]

The principal adverse events reported in clinical trials with granisetron have been headache, somnolence, diarrhoea, constipation and asthenia, and appear to be related to the dose administered.[60,62-64,76] Similar to ondansetron, the most frequently reported adverse event has been headache, which occurred in 10–15% of chemotherapy patients and <2% of PONV patients.[69-74]

During cisplatin chemotherapy, following the administration of granisetron there have been reports of elevations in AST and ALT at more than twice the upper limit of normal in 2.8 and 3.3% of patients, respectively. However, the elevations of liver enzymes were believed to be not significantly different from those seen with other comparative antiemetic medications.[64,68]

Transient changes in blood pressure have been observed with granisetron, which resolved without treatment and were considered to be clinically insignificant. Hypertension has been reported in 2% of patients who received granisetron. Hypotension, arrhythmias and ECG abnormalities (such as bradycardia, atrial fibrillation, transient tachycardia, varying degrees of atrioventricular block and ventricular ectopy) have been observed rarely.[60,68] Granisetron showed no pro-arrhythmic effects during or after exercise in healthy subjects. However, Watanabe et al.[76] showed that possible cardiac adverse effects could occur when granisetron was used in patients with bone or soft-tissue sarcomas and who received cytotoxic chemotherapy.

Agitation, anxiety, CNS stimulation and insomnia have been reported in <2% of patients. The extrapyramidal syndrome rarely occurs with granisetron, and only in the presence of other concurrently used drugs such as metoclopramide. Hypersensitivity or anaphylactic reactions have been reported rarely. There have been no reported drug interactions with haloperidol, droperidol or the benzodiazepines.[60,62,68,77]

Adverse events with granisetron occurred more frequently during the use of higher doses that were administered to patients undergoing chemotherapy (≥3mg total dose) as compared with the lower doses administered for PONV (≤3mg total dose). In the PONV studies, adverse events have been low, occurring in less than 2% of study subjects, and there was no major difference between the comparator drugs or placebo.[60,69-74]

A variety of studies with granisetron in PONV have been conducted in Japan by Fujii et al.[70-72] In these studies, the most frequently reported adverse events were headache, dizziness and drowsiness or sedation. No extrapyramidal symptoms were observed. Postoperatively, the incidence of adverse events was not found to be different among dose groups and when compared with placebo.

5. Tropisetron

5.1 Pharmacology

Tropisetron (figure 3) is an indole compound that is a potent and highly selective antagonist of 5-HT_3 receptors. Tropisetron has chemical structure, efficacy and adverse effect profile similar to those of other 5-HT_3 receptor antagonists. Tropisetron also has been found to have a strong antagonist effect at the 5-HT_3 receptor and a weak antagonist effect at the 5-HT_4 receptor. However, tropisetron has no affinity for the 5-HT_1, 5-HT_2,

dopamine D_2, benzodiazepine or adrenergic receptors.[78-80]

Similar to other 5-HT_3 receptors, tropisetron has been found to prevent CINV,[78-82] RIE[83] and PONV[84,85] by antagonising the effects of serotonin at both peripheral vagal sites and in the CNS. In these clinical trials, tropisetron appeared to be well tolerated with a low adverse effect profile. Regarding therapeutic efficacy in cancer patients, Seinen et al.[81] found no significant difference in the antiemetic response to single intravenous doses of tropisetron 5, 10 or 20mg given 15 minutes prior to cisplatin chemotherapy. Tropisetron has been found to be more effective than placebo for prevention[84] and treatment[85] of PONV in patients following surgery. The recommended tropisetron dosage for CINV and PONV is listed in table VIII.

5.2 Pharmacokinetics

After a single oral dose of tropisetron 20 or 100mg to healthy volunteers, mean peak plasma concentrations of 24.7 and 173 μg/L, respectively, occurred at 1.3 and 1.1 hours post-dose, respectively.[78,79] Tropisetron undergoes dose-dependent first-pass hepatic metabolism, and the absolute bioavailability of the 20 and 100mg doses was 52 and 66%, respectively. Tropisetron was determined to have high tissue affinity, with a volume of distribution of 554L following intravenous administration.

Tropisetron is metabolised by CYP2D6. Because of the polymorphism of this enzyme, some patients are thought to metabolise tropisetron more rapidly (ultrametabolisers) than other patients.[35] Kaiser et al.[35] hypothesised that antiemetic treatment with tropisetron could be improved by adjustment for the CYP2D6 genotype. The mean elimination half-life following intravenous and oral administration was found to be 7.3 and 8.6 hours, respectively, in healthy volunteers classified as extensive good metabolisers, and 30.3 and 41.9 hours, respectively, in healthy volunteers classified as poor metabolisers. Approximately 80% of the administered dose is renally excreted, mainly as metabolites. Metabolic clearance is decreased in patients with impaired hepatic or renal function; however, because of the short-term nature of the treatment regimen, dose adjustment in poor metabolisers or patients with impaired hepatic or renal function is not required.[82,83,86,87]

5.3 Adverse Reactions

In a variety of chemotherapy studies, no serious adverse events related to tropisetron were reported.[80,86] The most frequent adverse effect of tropisetron was mild to moderate headache, occurring in 5–7% of CINV patients[80,82,88] and ≤2% of PONV patients.[84,85] Other adverse effects have included constipation and fatigue.[87] Extrapyramidal effects have been reported rarely, in only approximately 0.7% of patients treated with tropisetron. The cause and relationship of extrapyramidal symptoms, as well as muscle cramps or ataxia, has not been determined.[80,82,84-86]

Laboratory abnormalities with tropisetron have been reported and include increases in liver enzymes (AST, ALT, alkaline phosphatase and γ-glutamyl transpeptidase). Analysis of renal function tests has revealed no differences in serum creatinine values with tropisetron. Because tropisetron is excreted by the kidney, this was speculated as a possible site of interaction with cisplatin. However, there have been no reported cases of developing partial or total renal failure in patients who receive both cisplatin and tropisetron.[78,79,82]

One patient was reported to have an allergic reaction after intravenous infusion with tropisetron, with itching and reddening of the skin, which resolved within 30 minutes after the patient was treated with an antihistamine and corticosteroid. A causal relationship to tropisetron was considered likely but not proven.[89] Transient changes in blood pressure have been reported after tropisetron administration, including both hypertension and hypotension, which resolved without treatment.[86] ECG effects with tropisetron administration have not been observed at recommended dosages.[80]

6. Dolasetron

6.1 Pharmacology

Dolasetron (figure 3) is a pseudopelletirine derivative that has structural similarities to serotonin, and is highly selective for the 5-HT_3 receptor.[90] Dolasetron is rapidly metabolised by the enzyme carbonyl reductase to the more potent and longer acting derivative hydrodolasetron which has the addition of a hydrogen atom to the upper side chain. This metabolic conversion is rapid, complete, predictable, stable and not subject to drug interactions. Hydrodolasetron has approximately 50 times more chemical activity than the parent compound, dolasetron, and is considered to be responsible for the majority (approximately 80%) of clinical antiemetic activity.[90-92]

6.2 Pharmacokinetics

Hydrodolasetron appears rapidly in plasma and reaches its peak plasma concentration in approximately 60 minutes following oral administration and 30–35 minutes after intravenous administration. Concurrent food intake has no effect on the bioavailability of dolasetron.[92]

Reith et al.[93] studied the metabolism of dolasetron in healthy male volunteers who were given a single 300mg oral dose of [^{14}C]dolasetron mesylate. The major route of dolasetron metabolism was via carbonyl reductase, causing a conversion to hydrodolasetron. An average of 59% of the total amount of dolasetron was recovered in the urine and 25% in the faeces. The glucuronide of hydrodolasetron was the most abundant conjugate found in the urine. Less than 1% of radioactivity in the urine was identified as the anoxide of hydrodolasetron. Dow and Berg[94] determined that the (+)-(*R*)-enantiomer of hydrodolasetron was predominantly formed by the enzyme carbonyl reductase and that this enantiomer is the more active stereoisomer.

Boxenbaum et al.[95] determined that following intravenous administration of dolasetron 0.5–5 mg/kg to healthy male subjects, dolasetron disappeared extremely rapidly from the plasma and its concentrations were generally measurable for only 2–4 hours. Less than 1% of the initial dolasetron dose was excreted intact in the urine. The major reduced metabolite form, hydrodolasetron, peaked rapidly in approximately 0.6 hours, with a median elimination half-life of 7.5 hours (table VI). The reduction of dolasetron to hydrodolasetron is mediated by the plasma enzyme carbonyl reductase, but liver CYP2D6 and CYP3A enzymes were determined to be primarily responsible for the subsequent hydroxylation of hydrodolasetron to the 5′ and 6′-hydroxy metabolites, which were glucuronidated. Hydrodolasetron was determined to be excreted unchanged in the urine (53% of the administered intravenous dose, and 61% of the administered oral dose). Other urinary metabolites included the hydroxylated glucuronide and anoxide. Hydrodolasetron was found to be eliminated by multiple routes, including renal excretion and liver metabolism.[95]

Two-thirds of the administered dolasetron dose is recovered in the urine, and one-third in the faeces. The mean half-life is 7.3 and 8.1 hours following intravenous and oral administration, respectively. Plasma protein binding of hydrodolasetron is 69–77%. The apparent clearance of hydrodolasetron was determined to be decreased by approximately 42% by severe liver impairment, and by 44% with severe renal impairment.[95-99]

Boxenbaum et al.[95,96] determined that when dolasetron was administered orally to healthy male subjects at doses ranging from 50 to 400mg, the plasma concentrations of dolasetron were low, preventing pharmacokinetic analysis of dolasetron. However, the reduced metabolite hydrodolasetron peaked within 1 hour, with a median elimination half-life of 7.8 hours. The median values of proportion of dose excreted in urine and renal clearance were 22.2% and 2.56 ml/min/kg, respectively. The renal clearance of dolasetron increased with increased dose administered, but this was believed to be of little therapeutic consequence. These results compared similarly with those of other researchers.[97,98]

Dimmitt et al.[98] studied the pharmacokinetics of oral and intravenous dolasetron administered to control patients with normal renal function and patients with renal impairment. These researchers found no pharmacokinetic changes related to the degree of renal dysfunction, although the urinary excretion of hydrodolasetron and its metabolites decreased with decreasing renal function. These researchers found that dolasetron was well tolerated by patients with renal failure, and concluded that no dosage adjustments were necessary. Similarly, no dosage adjustments are believed to be necessary for patients with hepatic impairment or for elderly patients.[99]

Pharmacokinetic data for the 5-HT_3 receptor antagonists are listed in tables VI and VII.

6.3 Adverse Reactions

Dixon et al.[100] evaluated the safety, tolerability and pharmacokinetics of single escalating doses of oral dolasetron mesylate in 120 healthy male volunteers who received either placebo or dolasetron at doses of 50, 100, 150, 200, 250, 300 or 400mg. Compared with placebo, the subjects receiving dolasetron reported a greater frequency of headache, light-headedness, dizziness, increased appetite and nausea. There were no clinically significant changes in laboratory values. Adverse events were judged to be transient, mild or moderate in severity, and similar to those observed after single intravenous doses of dolasetron. Although ECG changes occurred, judged by lengthening of the QRS complex and dose-dependent increases in the PR and corrected QT (QTc) intervals observed 1–2 hours after dolasetron administration, these ECG effects were believed to be asymptomatic and mainly associated with higher dolasetron doses ≥300mg. These authors concluded that, overall, dolasetron was well tolerated when administered as single oral doses up to 400mg in healthy volunteers.

Hunt et al.[101] reported the safety and tolerability of administering single doses of intravenous dolasetron to 80 healthy male volunteers who received either placebo or escalating doses of dolasetron 0.6 to 5 mg/kg. The study subjects were monitored for adverse events, vital signs, laboratory alterations and changes in ECG intervals or EEG patterns. Overall, the percentage of patients reporting adverse events was similar in those receiving dolasetron (44/64; 68.8%) or placebo (10/16; 62.5%). Most adverse events were rated as mild in severity. The subjects who received dolasetron reported a higher incidence of CNS (headache, dizziness, light-headedness), gastrointestinal (nausea, increased appetite, taste alteration) and visual adverse events. Transient, asymptomatic and clinically insignificant ECG changes (small mean increases in PR interval and QRS complex duration versus baseline) were noted in several study subjects 1–2 hours after infusion at doses ≤3 mg/kg. Transient mild blood pressure changes were observed in five study subjects, including one subject who received placebo. Overall, these researchers[101] believed that dolasetron was well tolerated in single intravenous doses up to 5 mg/kg.

Hunt et al.[102] evaluated the safety, tolerability and pharmacokinetics of increasing dose levels of oral dolasetron in 40 healthy volunteers. There were eight subjects at each dose level, randomised to receive dolasetron 25, 50, 100, 150 or 200mg as a single oral dose on days 1 and 9, and twice per day on days 2–8, or placebo for 9 days. These authors concluded that oral dolasetron was well tolerated when administered in doses up to 200 mg/day for 9 days in healthy volunteers. The most frequently reported adverse effects were headache, constipation, flatulence and light-headedness. However, these adverse effects were rated as mild, and no adverse effect was severe. No dose-response relationship was apparent for any adverse event. There were no clinically significant changes in laboratory values or vital signs. Asymptomatic ECG changes were consistent with the electrophysiological properties of the drug. The authors concluded that the pharmacokinetics of the reduced metabolite hydrodolasetron were dose-independent, and that multiple-dose exposure to

the metabolite can be predicted from its single-dose values.

Lerman et al.[103] studied the pharmacokinetics, safety and tolerability of the active metabolite hydrodolasetron administered to 40 anaesthetised children ranging in age from 2 to 12 years. Patients received oral or intravenous dolasetron 1.2 mg/kg. Oral dolasetron was administered to 12 children 1–2 hours prior to anaesthesia. Intravenous dolasetron was administered to 18 children at the time of induction of anaesthesia. Asymptomatic ECG changes of prolonged QRS were seen in five and six children in the oral and intravenous groups, respectively. The QTc interval exceeded the upper limit of normal for age by <10% in all children except for one in the oral group, which was recorded immediately after surgery. Transient ECG changes (QRS and QTc intervals) were seen in one of the children who received the oral dolasetron 6 mg/kg dose. These investigators did not consider the ECG changes to be clinically significant, and they did not require treatment. All ECG changes resolved by the end of the 24-hour monitoring period. No significant changes in laboratory values were seen, except that one child in the oral group had elevation of delta-bilirubin concentration that was five times greater than normal, and this child had a presumptive diagnosis of Gilbert's disease. Blood pressure decreased in several children, and these changes were attributable to the effects of general anaesthesia. The pharmacokinetics of dolasetron were similar after both oral and intravenous administration. The oral bioavailability was estimated to be 59%. The investigators believed dolasetron and its metabolite hydrodolasetron were well tolerated in children, with no serious adverse events reported.[103]

6.4 Therapeutic Use

6.4.1 Chemotherapy

Dolasetron has been administered by intravenous and oral routes as a single dose for CINV.[104,105]

Hesketh et al.[104] conducted an open-label non-randomised study to evaluate the efficacy and safety of intravenous dolasetron in the prevention of emesis in patients receiving doxorubicin in the range of 25–75 mg/m^2 and/or cyclophosphamide in the range of 400–1200 mg/m^2. Overall, these authors found that 61% of patients had no emesis. Adverse events were generally considered to be mild and included headache, chills, light-headedness, fever, diarrhoea, dizziness and asymptomatic prolongation of ECG intervals. These authors considered intravenous dolasetron to be well tolerated and effective in the prevention of emesis produced by doxorubicin and/or cyclophosphamide.

The overall adverse event rates for patients receiving the 5-HT$_3$ receptor antagonists were assessed in a direct comparator study and were found to be comparable, with 60% of dolasetron patients and 56% of patients receiving the comparator 5-HT$_3$ receptor antagonists reporting some form of adverse events.[99] In CINV, the most frequently reported adverse events were headache, diarrhoea, fever and pain, and none of these adverse events appeared to be dose-related. Headache was the most frequently reported adverse event across all groups of patients, occurring in 23, 19 and 23% of patients receiving dolasetron, ondansetron and granisetron, respectively. Headache and dizziness are considered to be class-related effects of the 5-HT$_3$ receptor antagonists. Diarrhoea was reported in 13, 8 and 6% of dolasetron, ondansetron and granisetron recipients, respectively, but many chemotherapeutic agents, especially high-dose cisplatin and fluorouracil, may induce diarrhoea. The overall incidence of liver function abnormalities was 4, 2 and 4% of patients who received dolasetron, ondansetron and granisetron, respectively, and did not appear to be related to dose.[99] In all the studies evaluated, these increases in liver function tests were believed to be infrequent, clinically asymptomatic and reversible on discontinuation of the study drug. However, it is also possible that in cancer patients the combination of underlying disease, chemotherapy and concomitant medications all could have contributed to an elevation of liver function tests.

In the use of oral dolasetron for CINV, the most frequently reported adverse events have been

headache, diarrhoea and fatigue.[90,105] The overall adverse event rate in cancer patients receiving oral dolasetron was slightly lower (50%) than that reported in cancer patients receiving intravenous dolasetron (60%), intravenous ondansetron (64%) or intravenous granisetron (45%). Headache was reported in 20% and fatigue in 4% of patients who received oral dolasetron. It was noted by the authors of these studies that fatigue was also a common symptom in cancer patients, and therefore was not believed to be due to dolasetron. Diarrhoea was reported less frequently (5%) with intravenous dolasetron than in cancer patients receiving oral dolasetron (13%), ondansetron (8%) or granisetron (6%).[99]

Audhuy et al.[106] conducted a randomised trial to compare the clinical efficacy and safety of single intravenous doses of dolasetron and granisetron in the prevention of acute emesis and nausea due to high-dose cisplatin therapy. Single intravenous doses of dolasetron 1.8 or 2.4 mg/kg or granisetron 3mg were administered. These authors found that the treatment groups were comparable in their response to CINV. The overall incidence of adverse events was comparable among the groups, with headache and diarrhoea rated as the most common. No significant differences were observed in the extent of nausea with either dolasetron dose compared with granisetron. All antiemetic treatments were well tolerated. Asymptomatic ECG changes were recorded with both dolasetron and granisetron. These authors concluded that a single intravenous dose of dolasetron mesylate 1.8 or 2.4 mg/kg had comparable safety and efficacy to a single intravenous dose of granisetron 3mg in patients receiving cisplatin chemotherapy.[106]

6.4.2 Postoperative Nausea and Vomiting

Dolasetron has been administered by intravenous and oral routes as a single dose for PONV.[107]

Prevention with Oral Dolasetron

The overall adverse event rate of dolasetron at the oral doses used for PONV did not exhibit a dose-response relationship. Interestingly, the lowest adverse event rate of 34% was seen with the 200mg dose, while the highest (42%) was seen with the 25mg dose. The most frequently occurring adverse events for all doses of dolasetron were headache and hypotension. However, hypotension occurred with similar frequency in the dolasetron and placebo groups, and was believed to be due to anaesthesia and/or the surgical procedure. Overall, the incidence of headache was similar for the dolasetron and placebo patients at 7 and 5%, respectively. Dizziness had an overall occurrence rate of 3%.[108]

Prevention with Intravenous Dolasetron

The overall adverse event rate in patients who received intravenous dolasetron did not exhibit a dose-response relationship, and the incidence of adverse events was similar among all dolasetron dose groups. Similar to oral administration, the most frequently occurring adverse events for all dolasetron doses were headache and dizziness; however, neither adverse event was believed to dose related. Headache occurred slightly more often in patients treated with intravenous dolasetron than in placebo patients. Among the different dose groups, dolasetron 12.5, 25, 50 and 100mg, the incidence of headache was 9, 7, 9 and 10%, respectively, compared with 7% in placebo patients. Dizziness that was believed to be related to dolasetron had an overall occurrence rate of 5%. None of the less frequently reported adverse events were believed to be dose related, and they occurred at a similar frequency in placebo patients.[109,110]

Treatment with Intravenous Dolasetron

The percentage of patients reporting one or more adverse events was similar among all intravenous dolasetron doses (12.5, 25, 50 and 100mg). The incidence of adverse events in the placebo patients was similar to that of the dolasetron-treated patients. The most frequently reported adverse events for all doses of dolasetron were headache and dizziness. However, none of these adverse events was believed to be dose related.[111]

6.5 Intravenous Dolasetron Dose-Response Studies

6.5.1 Prevention of Chemotherapy-Induced Nausea and Vomiting

Whitmore et al.[112] conducted a pooled analysis of 14 clinical trials on the use of a single fixed intravenous dose of dolasetron for the prevention of cisplatin-induced nausea and vomiting. The pooled results showed that the 100mg intravenous dolasetron dose produced the highest rate (53%) of complete response (no emetic episodes and no rescue medication) in the 24-hour period following initiation of chemotherapy. Chevallier et al.[113] reported a multicentre comparison of intravenous dolasetron and metoclopramide for the prevention of nausea and vomiting in cancer patients receiving high-dose cisplatin. As single intravenous dose of dolasetron 1.8 mg/kg was determined to be more effective than metoclopramide 7 mg/kg.

6.5.2 Prevention of Postoperative Nausea and Vomiting

Graczyk et al.[114] evaluated the effect of intravenous dolasetron 12.5, 25 or 50mg for the prevention of PONV in 635 female outpatients undergoing laparoscopic gynaecological surgery. Complete response rates were significantly ($p < 0.0003$) higher with each dolasetron 12.5, 25 or 50mg dose (50, 52 and 56%, respectively) compared with placebo (31%). The dolasetron patient group had lower mean nausea scores and higher satisfaction scores than the placebo group.

Diemunsch et al.[115] evaluated intravenous dolasetron doses of 12.5, 25, 50 and 100mg compared with placebo for the prevention of PONV in 281 female inpatients undergoing gynaecological surgery. The complete response rates for the dolasetron doses were 45, 67, 59 and 59%, respectively. All doses except the 12.5mg dose produced complete response rates that were significantly ($p < 0.012$) greater than with placebo (43%). Patients who received dolasetron were significantly ($p < 0.048$) more likely to report no nausea than those who received placebo. From the above studies, dolasetron 12.5mg was determined to be the optimal intravenous prevention dose for PONV when administered 15–30 minutes before the end of surgery.

6.5.3 Treatment of Postoperative Nausea and Vomiting

In an intravenous PONV treatment study comparing dolasetron versus placebo, Kovac et al.[111] compared four doses of dolasetron to placebo in 620 outpatients (514 females, 106 males) who required intravenous treatment for PONV following general anaesthesia. Patients were administered the study drug if they had an emetic episode, nausea for 15 minutes, or at patient, medical or nursing staff request. The complete response rates for all dolasetron doses (12.5, 25, 50 and 100mg) were significantly ($p < 0.05$) superior (35, 28, 29 and 29%, respectively) compared with placebo (11%). Diemunsch et al.[116] also reported the results of a multicentre, placebo-controlled study of intravenous dolasetron for the PACU treatment of PONV in 337 adult patients (319 females, 18 males) following surgery under general anaesthesia. Significantly ($p < 0.05$) higher complete response rates were observed with dolasetron at doses of 12.5 25, 50 and 100mg (24.2, 27.7, 37.3 and 25.0%, respectively) compared with placebo (11.3%). Analysing nausea visual analogue scores 8 hours after study drug administration, a significantly ($p < 0.05$) greater percentage of patients who received dolasetron (12.5, 25 and 100mg) reported no nausea than those who received placebo. In the above studies, dolasetron 12.5mg was determined to be the optimal intravenous dose for PONV treatment.

6.6 Overview

Dolasetron has been administered to a large number of patients with chemotherapy-induced and postoperative nausea and vomiting. Oral and intravenous dose-response studies have determined the efficacy of dolasetron in CINV and PONV.[112-116]

The recommended dosage of dolasetron for CINV and PONV is listed in table VIII.

Of the most frequent adverse events in patients who received dolasetron and the comparator 5-HT_3 receptor antagonists, headache was the adverse event most clearly related to the study medication and appears to be a class-related effect. Dizziness or light-headedness may also be a class-related effect, but occurred at a lower frequency than headache. Diarrhoea was attributed to cancer chemotherapy and occurred infrequently in patients with PONV. Vital sign changes following dolasetron were believed to be minimal and not dose-related, with changes similar to those with the other 5-HT_3 receptor antagonists.[90]

Regarding laboratory variables, a possible contributing effect of dolasetron was found on increases in ALT, AST and total bilirubin. The frequency of liver enzyme elevations was similar in patients receiving ondansetron, dolasetron or granisetron, suggesting a class-related effect reflecting the ability of these antiemetics to increase serum transaminases.[90,91]

7. Cardiac Effects of the 5-HT_3 Receptor Antagonists

The clinical safety of medications used for antiemetic therapy is important to determine in healthy volunteers as well as in patients with pre-existing disease. Whether any pro-arrhythmic effects are caused solely by the 5-HT_3 receptor antagonists is not easy to determine in patients with cancer and receiving chemotherapy, as there are many confounding issues. These include the chemotherapeutic agent the patient is taking (which itself may be cardiotoxic), potential drug interactions, concomitant medications, the patient population and the CYP2D6 genotype of the individual (ultrarapid or slow metabolisers). Ultrarapid metabolisers may have a poor antiemetic outcome and poor metabolisers may have increased adverse effects, because deficiency of the CYP2D6 enzyme can result in increased drug accumulation. There are more data available regarding the ECG effects of dolasetron than for the other 5-HT_3 receptor antagonists. However, more single-agent and comparative data are becoming available for the other 5-HT_3 receptor antagonists, and these data tend to suggest that the ECG effects may be class-related.

Various researchers[76,106,117-122] have reported cardiotoxicity with the 5-HT_3 antagonists as, depending on dose, each of the 5-HT_3 receptor antagonists has been reported to cause changes in vital signs and ECG parameters. Hesketh et al.[118] reported that ondansetron caused a prolongation of the PR, QRS, QT, QTc and JT intervals. However, the ECG changes were determined to be clinically asymptomatic, transient and of minor magnitude. Audhuy et al.[106] reported that dolasetron increased QTc and PR intervals. Jantunen et al.[119] reported that granisetron caused no significant changes in the QRS duration, cardiac rhythm or QTc interval, but that an increase in the PR interval occurred. Wantanabe et al.[76] reported that granisetron caused sinus bradycardia, changes in P wave, junctional widening and elongation of PQ intervals. Lofters et al.[120] reported that dolasetron and ondansetron caused prolongation of QTc and QRS intervals. Ballard et al.[121] reported that ondansetron was associated with chest pain. Baltzer et al.[122] reported that dolasetron and ondansetron increased the PR, QRS and QT intervals, and that ondansetron decreased heart rate.

Overviews of the clinical experience with dolasetron[90,92] indicate that the drug has been reported to cause PR, QTc and JT prolongations and QRS widening. These ECG changes were self-limiting, did not require treatment, resolved within 24 hours and were related in magnitude and frequency to the plasma concentrations of hydrodolasetron. For patients with PONV receiving the recommended 12.5mg intravenous dose, the ECG changes were similar to those observed with the placebo group. In the treatment of PONV, asymptomatic ECG changes such as bradycardia, tachycardia and T-wave changes were observed at incidence rates less than or equal to those in the placebo group.[90,92]

Benedict et al.[123] reported in healthy volunteers the ECG effects of intravenous dolasetron mesylate compared with intravenous ondansetron.

This was a single-blind, randomised, five-way, crossover, safety and tolerability study conducted to determine whether intravenous dolasetron, ondansetron or placebo induced any changes in ECG intervals in healthy volunteers. Thirty healthy male volunteers received intravenous dolasetron (1.2, 1.8 and 2.4 mg/kg), ondansetron 32mg and placebo on five separate days, with ECGs recorded at various intervals during the 24 hours following study drug administration. These researchers found a statistically significant increase in QTc intervals with dolasetron and ondansetron. Ondansetron also produced a slight but statistically significant increase in the JT interval and a decrease in heart rate. These ECG changes were usually observed between 0 and 4 hours after administration, and all parameters returned to baseline within 8 hours post-dose. Although Benedict et al.[123] showed that both dolasetron and ondansetron prolonged the QTc interval, they determined that dolasetron predominantly altered the ECG parameters indicative of ventricular depolarisation with its effect on the QRS duration, whereas ondansetron predominantly affected ventricular repolarisation as measured by prolongation of the JT interval.

Using an *in vitro* electrophysiological model, Kuryshev et al.[124] studied the effect of granisetron, dolasetron, hydrodolasetron and ondansetron on human sodium and potassium channel inhibition. Medications that block the sodium channel may cause widening of the QRS interval and increase the risk for ventricular arrhythmias. Medications that block potassium channels may produce a prolonged QT interval. They concluded that all the 5-HT_3 antagonists tested blocked human cardiac sodium channels, probably by interacting with the inactivated state. They hypothesised that this may lead to clinically relevant sodium channel blockade, especially when high heart rates or depolarised/ischaemic tissue is present. The ability of these agents to block sodium or potassium channels is a dose-related phenomenon and appears related to their ability to block 5-HT_3 receptors. This study appears to confirm the fact that ECG changes are a dose-dependent, class-related effect of 5-HT_3 receptor antagonists. Whether or not this is clinically relevant depends on the dose administered, patient population, concurrent medications, history, medical condition, type of chemotherapy or radiation therapy and CYP2D6 enzyme metabolism.

8. Specific Patient Populations at Increased Risk for Adverse Events

In the US, it is estimated that 61% of all malignancies occur in patients 65 years of age and older. Persons in this age group have a cancer risk that is estimated to be 11 times greater than that in patients less than 65 years old.[125] A review of cancer patients aged greater than 55 years determined that two common major comorbidities in elderly patients were hypertension and cardiovascular disease.[126] Thus, it is important to be aware of the cardiotoxicity of various chemotherapeutic agents, as this can determine the maximum dosage that elderly patients can be expected to tolerate.[127]

Opioids and antidepressant medications, which may be used more frequently in elderly patients with cancer, are metabolised via the CYP2D6 enzyme system, raising the possibility of drug interactions with the 5-HT_3 antagonists. Furthermore, many chemotherapeutic agents are metabolised by the CYP isoenzymes (CYP1A3, CYP2D6 and CYP3A4).[128,129]

Specific patient populations in which the use of antiemetics can be considered to involve a higher risk for adverse events, or in which the ratio of risk to benefit is increased, are: (i) the elderly; (ii) patients with hepatic impairment; (iii) patients with renal impairment; and (iv) patients receiving low to intermediate emetogenic chemotherapy. However, considering age alone, no dosage adjustments for any of the 5-HT_3 antagonists are believed to be necessary in elderly patients.

8.1 Long QT Syndrome

Various medications can affect the QT interval (table IX), and current information is available on

Table IX. Medications that may prolong the corrected QT (QTc) interval and/or induce torsade de pointes (see Woosley[130] for online updates)

Amitriptyline	Gatifloxacin	Pimozide
Amiodarone	Halofantrine	Probucol
Arsenic	Haloperidol	Procainamide
Bepridil	Ibutilide	Quetiapine
Chlorpromazine	Imipramine	Risperidone
Clomipramine	Isradipine	Salmeterol
Cisapride	Levofloxacin	Sertraline
Desipramine	Levacetylmethadol	Sotalol
Disopyramide	Mesoridazine	Sparfloxacin
Dolasetron	Moexipril	Tamoxifen
Dofetilide	Moxifloxacin	Thioridazine
Droperidol	Naratriptan	Tizanidine
Erythromycin	Nicardipine	Venlafaxine
Felbamate	Octreotide	Ziprasidone
Fluoxetine	Paroxetine	Zolmitriptan
Foscarnet	Pentamidine	

the internet[130] on drugs that prolong QTc and/or induce torsade de pointes. Along with the medications that can prolong the QT interval, it is important to be aware of medical conditions that can have the same effect (table X) and a syndrome called the long QT syndrome (LQTS). This is a rare, usually inherited and occasionally fatal syndrome affecting the electrical system of the heart. Three hypotheses that have been proposed for the mechanism of LQTS are: (i) imbalance of the sympathetic nervous system; (ii) intracardiac abnormality secondary to an imbalance of potassium currents; and (iii) shortened QT interval during an increase in heart rate. Often these patients do not have any ECG problems until they become physically or emotionally stressed, at which time they may experience syncope, ventricular tachycardia, cardiac arrest and/or sudden cardiac death. A QT interval longer than 440 msec is normally considered to be prolonged. In LQTS, the extent of QT interval prolongation is variable and may not be correlated with a syncopal episode. The ECG is not always diagnostic since the QT interval may be prolonged for other reasons, including pre-excitation syndrome, CNS disease or use of tricyclic antidepressants or antiarrhythmic medications.[131]

A prolonged QTc interval can be a sign of abnormal ventricular depolarisation, which can predispose a patient to ventricular tachycardia of the torsade de pointes variety. This may occur as the result of a congenital disorder or exposure to toxins, drugs or electrical imbalances. An autosomal genetic pattern for LQTS has been found in the Romano-Ward syndrome (autosomal dominant), and the Jervell-Lange-Nielson syndrome (autosomal recessive). Using gene mapping, a single gene mutation at a locus on the short arm of chromosome 11 has been discovered predisposing patients to ventricular arrhythmias and sudden death. DNA markers may help identify patients and families with LQTS.[132,133]

Family history may reveal a prior history of LQTS. This is important to determine, as patients with a family history of fainting spells or sudden unexpected death at an early age may have congenital or hereditary LQTS. The syncopal episodes are believed to be due to torsade de pointes, which can degenerate into ventricular fibrillation. The syncopal episodes triggering LQTS often coincide with sudden increases in sympathetic nervous system activity due to violent emotion, physical activity or sudden awakening.[131-133]

LQTS has been found to be familial in 85% of cases with: (i) long QT intervals; (ii) tachycardia; and (iii) history of cardiac abnormalities. There is

Table X. Medical conditions that may prolong the corrected QT (QTc) interval

Congestive heart failure
Bradycardia
Hypertension
Heart block
Cardiac hypertrophy
Hypomagnesaemia
Medications (see table IX)
Diuretics
Antihypertensives
Antidepressants
Antiarrhythmics

an increased risk in females with the onset of menses compared with males. A single ECG may not be diagnostic of LQTS because QT intervals may vary from person to person and from day to day. The diagnosis of LQTS may be missed even if an ECG is obtained.[117]

For treatment of LQTS, β-blockers have proven effective in preventing syncope in 75–80% of patients. However, 20–25% of patients with LQTS may continue to have syncopal episodes and remain at high risk for sudden death. Treatment has involved limiting physical activity and having emergency medications and equipment available. In addition to β-blockers, an implantable artificial pacemaker or defibrillator has been used to prevent syncope. In patients unresponsive to therapy, a high thoracic left sympathectomy has proven to be a successful treatment. A prospective study of left cardiac sympathetic denervation showed an increase from 1 to 55% in the proportion of patients who were symptom-free.[134]

9. Cardiotoxicity of Chemotherapeutic Agents

Careful evaluation to identify a medical diagnosis of hypertension or cardiac disease is necessary in patients who receive cardiotoxic chemotherapy[126] Several chemotherapeutic agents (anthracyclines, paclitaxel, flurouracil, trastuzumab and arsenic) are considered to be cardiotoxic.[117,135]

The anthracyclines can cause cardiomyopathy, pericarditis, myocardia, arrhythmias and ECG changes. Several mechanisms are proposed to explain anthracycline cardiotoxicity. Anthracycline-mediated depletion of adenosine triphosphate and phosphocreatine may result in depression of myocardial contractility. Doxorubicinol, a metabolite of doxorubicin, can alter calcium transport and interfere with normal cardiac conduction and contractility. Anthracyclines also generate hydroxyl free radicals that can damage mitochondrial membranes.[135]

Paclitaxel can cause sinus bradycardia. Flurouracil can cause coronary spasm with prolonged infusion. Trastuzumab can cause cardiomyopathy. Arsenic can prolong the QT interval and cause heart block.[135]

There are limited data on the use of 5-HT_3 antagonists administered with cardiotoxic chemotherapy. Keefe[117] reviewed the cardiotoxic potential of the 5-HT_3 receptor antagonists and stated that there are significant ECG changes with some 5-HT_3 antagonists, indicating a potential for significant cardiac effects in patients predisposed to cardiac complications. She concluded that the best option may be to choose the antiemetic with the fewest apparent cardiac effects.

Knowing the cardiotoxic effects of the chemotherapeutic agents, research data are lacking on the significance of administering a 5-HT_3 antagonist in combination with cardiotoxic chemotherapy to a high-risk patient with cardiac or other medical comorbidities. The guidelines[9] and published data for the 5-HT_3 receptor antagonists indicate that the ECG adverse effects are a class-related effect and overall are clinically insignificant. However, the safety of 5-HT_3 receptor antagonists in the particular situation of combination with chemotherapeutic agents or in high-risk patients with comorbidities is not as clear. Most randomised controlled clinical trials in CINV and PONV were conducted on relatively healthy patients (for example, American Society of Anesthesiologists physical class 1–3 patients for PONV). The real question that needs to be answered is whether or not these ECG effects are clinically significant in the higher-risk patient population with comorbidities such as hypertension and cardiovascular disease. Susceptible patients should be monitored by ECG and examined for possible adverse effects or drug interactions. It is not known what 5-HT_3 receptor antagonist, if any, to choose for these patients and which 5-HT_3 receptor antagonist may have the least harmful effects on the ECG.[9,122]

Potential drug interactions between the 5-HT_3 antagonists and other medications also must be considered. Pharmacokinetic and pharmacodynamic interactions with other medications have been reported. Dolasetron has been reported to de-

crease the clearance of atenolol by 27%, whereas rifampicin (rifampin) decreased the clearance of hydrodolasetron by 28%. Conversely, cimetidine has been reported to increase the clearance of hydrodolasetron by 25%.[92] There have been reports of drug reactions between ondansetron and cyclophosphamide, temazepam, alfentanil, fluorouracil and cisplatin.[30]

10. Droperidol

Droperidol has been shown to be an effective antiemetic drug.[136] In comparative studies, droperidol has been shown to have efficacy equal to that of the 5-HT_3 receptor antagonists.[27,137] Adverse effects previously reported with droperidol (table I) include sedation and extrapyramidal reactions.[138] Lischke et al.[139]reported that droperidol causes a dose-dependent prolongation of the QT interval. However, in December 2001 the FDA issued a new 'black box' warning of cardiac effects to be included in the package insert of droperidol.[140]

In a discussion of the background to that warning, McCormick[141] reported that in January 2001 the FDA examined its database for evidence of cardiovascular events with droperidol reported in the US and globally. In June 2001, the FDA concluded that the available information confirmed a greater cardiovascular risk than previously reported. Their review revealed approximately 100 unique reports of cardiovascular events, of which there were approximately 20 unique reports of torsade de pointes and/or QT/QTc prolongation. Of the 28 of 38 cases receiving droperidol in which dose was reported, 12 cardiovascular adverse events occurred at doses at or below 2.5mg. These included torsade de pointes (three cases), cardiac arrest (three cases) and death (four cases). At doses below 2mg there were five reports, including one death, one cardiac arrest and one torsade de pointes. The maximum QT interval reported in this group was 600 msec in a patient receiving a single dose of droperidol 0.625mg. This patient experienced nonfatal torsade de pointes. The finding of dose-dependent prolongation of the QTc, coupled with actual reports documenting torsade de pointes at and below the labelled dose, was considered a serious risk with no margin of safety.[141]

Previously, droperidol had a warning regarding potential for sudden cardiac death when administered at high doses (>25mg) to psychiatric patients. The revised warning cautioned that even low doses such as 0.625mg for PONV should be used only when other first-line antiemetic medications are not effective.[140] This revised warning conflicts with the conclusions of Fortney et al.[27] and Tang et al.,[137] whose studies demonstrated that droperidol 0.625 compared favourably with ondansetron 4mg for PONV in adult patients with regard to adverse effects and efficacy. Henzi et al.[138] and Tramèr et al.[44] reported that the NNTs for ondansetron and droperidol in the prevention of PONV were similar at 5–6. Similarly, Eberhart et al.[136] conducted a meta-analysis of 72 studies covering 5370 patients. They concluded that the NNT for preventing one patient from having PONV was 5.8 and 6.4 for early and late PONV, respectively. Data regarding the NNH of cardiac effects with droperidol are not available because of the low number of adverse events reported.

The FDA[140] recommended that all surgical patients should undergo 12-lead ECG monitoring prior to the administration of droperidol to determine if a prolonged QTc interval was present and to continue ECG monitoring for 3 hours after droperidol administration. Because of these recommendations, the use of droperidol has decreased worldwide and its use as an antiemetic in the future is controversial. Further research must be completed to resolve the role of droperidol as an antiemetic.[142] McCormick[141] states that the FDA has committed itself to conducting a definitive pharmacokinetic/pharmacodynamic study to evaluate the effect of droperidol dose on the QTc interval, evaluating doses of 0.625, 2.5 and 5mg against placebo in a crossover design in healthy volunteers receiving no concomitant medications.

Chang and Rappaport[143] state that "although the study was prematurely terminated because of

significant neuropsychiatric adverse effects, including dysphoria and anxiety, there were several findings of note". They report that "impressive QTc prolongations (approximately 80ms from baseline) were found in individuals following the 2.5mg and the 5mg doses, even though only seven and three subjects, respectively, received these doses. Compared with placebo, the 0.625mg dose did not appear to have a significant effect on QTc; however, this cannot be considered a definitive finding as only five individuals were studied at this dose." They advise that "additional investigation will be required to further define the relationship between QTc prolongation, potential for dysrythmia and various doses of droperidol. The FDA is now exploring options to obtain data that satisfy regulatory standards for the demonstration of safety and efficacy at doses lower than 2.5 mg". Chang and Rappaport urge practitioners to participate in the postmarketing safety assessment process by reporting all potential drug-related adverse events. The web site www.fda.gov/medwatch contains information on reporting adverse events.[143]

Concurrently, examination of alternative medications and their adverse effects is being conducted. Alternatives to droperidol for PONV may include dexamethasone, dimenhydrinate, scopolamine, prochlorperazine, promethazine and the $5HT_3$ antagonists, depending on the individual practitioner.

11. Dexamethasone

Antiemetic therapies for CINV and PONV may include the use of dexamethasone. Dexamethasone was first shown to be effective as an antiemetic medication for cancer chemotherapy, and its use for PONV is a more recent development. Corticosteroids such as beclomethasone and dexamethasone were found to be significantly more effective for preventing CINV than metoclopramide, prochlorperazine or droperidol.[142]

Proposed mechanisms of the antiemetic action of dexamethasone include: (i) prostaglandin antagonism; (ii) tryptophan depletion, with a corresponding decrease in CNS serotonin levels; (iii) endorphin release; (iv) change in permeability of cerebrospinal fluid to serum proteins; (v) anti-inflammatory membrane stabilising effects; and (vi) the neuropsychological activity of corticosteroids. However, there is no experimental proof for any of these proposed mechanisms.[142]

A common adverse event with dexamethasone following administration for PONV is skin flushing and perineal itching. This is believed to be due to the phosphate present in the injection solution. Long-term treatment with high dosages of corticosteroids has been implicated but not definitely proven in postoperative infection and delayed wound healing. However, there are no case reports suggesting that the single-dose administration of a corticosteroid interferes with wound healing or produces other major adverse effects.[142]

The plasma elimination half-life of dexamethasone is approximately 4–4.5 hours, and in cancer chemotherapy an intravenous dose of dexamethasone 8mg has been found to be as effective as 32mg in preventing nausea and vomiting. The lowest effective dose for PONV appears to be 4mg intravenously.[144,145]

Dexamethasone has been used frequently in ENT surgery for its anti-inflammatory effects on the airway. A study in tonsillectomy patients by Aouad et al.[146] reported the results of a comparison between dexamethasone 0.5 mg/kg and placebo. Dexamethasone was administered at the start of surgery, and the proportion of patients vomiting in the PACU (early) and after returning to their room (late) was studied. Fewer patients in both places had vomiting compared with placebo. Patients also had a shorter time to first oral intake, and the duration of intravenous hydration was shorter.

Timing of dexamethasone administration is important with regard to the onset of antiemetic effectiveness. Wang et al.[147] studied early versus late onset, comparing dexamethasone with placebo administered pre-induction versus at the end of surgery. When administered pre-induction, dexamethasone was more effective in the PACU at 0–2

hours after the end of surgery and on the floor from 2–24 hours. When given at the end of surgery, it was effective on the floor at 2–24 hours but not in the PACU at 0–2 hours.

12. Combination Antiemetic Therapy

The use of antiemetic combination therapy is increasingly popular, as none of the available antiemetics administered alone has 100% effectiveness in all patients. Combination antiemetic therapy is often effective, as it is logical to administer antiemetic medications working at different receptor sites. Combinations of antiemetics appear to act synergistically.

Combination antiemetic therapy was not frequently used with the older antiemetics, such as the butyrophenones, antihistamines or phenothiazines, because of the disadvantage of possible additive CNS adverse effects such as extrapyramidal symptoms, dry mouth or hypotension.[18] As the 5-HT_3 receptor antagonists are relatively free of adverse effects, recent studies have evaluated the use of the 5-HT_3 antagonists with other antiemetics.[9,18]

Various studies have investigated the use of combination antiemetics, especially adding dexamethasone to the 5-HT_3 receptor antagonists for CINV and PONV. McKenzie et al.[148-150] Fujii et al.[72,151-157] and Lopez-Olaondo et al.[158] have determined that adding dexamethasone to ondansetron or granisetron improves antiemetic efficacy in PONV on average by 14–32%.[159] McKenzie et al.[160] determined that a droperidol/ondansetron combination controlled PONV following tubal banding. Similarly, Fujii et al.[161-163] showed that combination antiemetic therapy adding dexamethasone to metoclopramide, dexamethasone to droperidol or dexamethasone to granisetron caused an improvement in antiemetic efficacy of 11–16%. Koivuranta et al.[164] showed that there was similar effectiveness in PONV when droperidol 0.75 or 1.25mg was added to ondansetron 8mg, but that less sedation occurred with the droperidol 0.75mg dose. Pueyo et al.[165] showed better PONV effectiveness with ondansetron plus droperidol than with either drug alone. Steinbrook et al.[166] determined that the combination of droperidol 0.625mg plus metoclopramide 10mg had more effectiveness in PONV than ondansetron 4mg alone.Sanchez-Ledesma et al.[167] conducted a combination comparison study in 90 women having major gynaecological surgery. The combination of intravenous ondansetron 4mg plus droperidol 1.25mg had equal efficacy to ondansetron 4mg and dexamethasone 8mg and both combinations had better efficacy than the combination of dexamethasone 8mg plus droperidol 1.25mg.

Eberhart et al.[168] performed a meta-analysis of 26 randomised controlled studies in 2561 patients and concluded that dexamethasone increased the antiemetic efficacy of the other partner antiemetic drug. Dexamethasone was found to be more effective than placebo and more effective than the other antiemetics alone. A summary of studies of combination antiemetics for PONV is shown in table XI.

13. Conclusion

Overall, the adverse effect profile of the 5-HT_3 receptor antagonists can be considered to be excellent, and as a class these agents are believed to be well tolerated. The adverse effect profiles of the individual 5-HT_3 receptor antagonists are not markedly different from one another, despite some pharmacological and pharmacokinetic differences. Adverse events, when they occur, are usually mild to moderate, self-limiting, transient and rarely require discontinuation of the drug. Headache is one of the more commonly observed 5-HT_3 antagonist adverse effects of these agents when used for the prevention of CINV and PONV. Extrapyramidal adverse effects are rare, and haemodynamic changes are uncommon. ECG changes such as prolonged QTc interval have been observed, but overall have been judged to be asymptomatic and clinically insignificant. Dose-dependent elevations in hepatic transaminases have also been observed with the 5-HT_3 receptor antagonists.

Ondansetron, tropisetron and dolasetron are all metabolised in the liver via CYP2D6. Dolasetron is initially converted by the enzyme carbonyl reductase to hydrodolasetron and subsequently undergoes liver metabolism. Granisetron is metabolised primarily by hepatic CYP3A enzymes. Some patients may metabolise these drugs more rapidly than other patients (fast versus slow metabolisers). Fast or slow metabolism, or drug interactions, can alter plasma drug concentrations and thereby efficacy and safety.

As most controlled studies with the 5-HT_3 antagonists have been conducted on relatively healthy patients, caution should be exercised when

Table XI. Studies of antiemetic combinations for postoperative nausea and vomiting [from Kovac,[37] with permission]

Study	Type of surgery (no. and sex of patients)	Regimen (dose in mg)	Complete response (%)[a]	Comments
McKenzie et al.[149]	Major gynaecological (180 F)	Ondansetron 4 + dexamethasone 8	52[b]	Ondansetron + dexamethasone > ondansetron (doses given during operation)
		Ondansetron 4	38	
McKenzie et al.[150]	Major gynaecological (80 F)	Ondansetron 4 + dexamethasone 20 + propofol	52.5[b]	Ondansetron + dexamethasone > ondansetron
		Ondansetron 4	37.5	
McKenzie et al.[160]	Minor outpatient gynaecological (80 F)	Droperidol 1.25	78.3	Ondansetron + droperidol > droperidol
		Droperidol 1.25 + ondansetron 4	91.6[b]	
Fujii et al.[151]	Major gynaecological (150 F)	Granisetron 2.5	84	Granisetron + droperidol > granisetron = droperidol
		Droperidol 1.25	54	
		Granisetron 2.5 + droperidol 1.25	96[b]	
Fujii et al.[153]	Major gynaecological (150 F)	Granisetron 20 μg/kg + dexamethasone 8	95[b]	Granisetron + dexamethasone > granisetron = dexamethasone = placebo
		Granisetron 20 μg/kg	77	
		Dexamethasone 8	77	
		Placebo	77	
Fujii et al.[152]	Major gynaecological (270 F)	Granisetron 40 μg/kg	80[b]	Granisetron + dexamethasone = granisetron > droperidol + dexamethasone = metoclopramide + dexamethasone = metoclopramide = droperidol
		Droperidol 1.25	49	
		Metoclopramide 10	51	
		Granisetron 40 μg/kg + dexamethasone 8	96[b]	
		Droperidol 1.25 + dexamethasone 8	60	
		Metoclopramide 10 + dexamethasone 8	62	
Lopez-Olaondo et al.[158]	Major gynaecological (100 F)	Ondansetron 4	52	Ondansetron + dexamethasone > ondansetron = dexamethasone > placebo
		Dexamethasone 8	60	
		Ondansetron 4 + dexamethasone 8	84[b]	
		Placebo	20	
Koivuranta et al.[164]	Laparoscopic (94 F)	Ondansetron 8 + droperidol 0.75	84	Ondansetron + droperidol 0.75 = ondansetron + droperidol 1.25 (less sedation with droperidol 0.75)
		Ondansetron 8 + droperidol 1.25	86	
Pueyo et al.[165]	Abdominal (100 F)	Placebo	28	Ondansetron + droperidol > ondansetron = droperidol > placebo (second dose of droperidol 1.25 at 12h after first dose)
		Droperidol 2.5 + 1.25	60	
		Ondansetron 4	56	
		Ondansetron 4 + droperidol 2.5 + 1.25	92[b]	
Steinbrook et al.[166]	Laparoscopic cholecystectomy (28 M/172 F)	Ondansetron 4	56	Droperidol + metoclopramide > ondansetron
		Droperidol 0.625 + metoclopramide 10	76[b]	
Sanchez-Ledesma at al.[167]	Major gynaecological (90 F)	Ondansetron 4 + droperidol 1.25	80	Ondansetron + droperidol = ondansetron + dexamethasone > dexamethasone + droperidol
		Dexamethasone 8 + droperidol 1.25	40	
		Ondansetron 4 + dexamethasone 8	70	

a No nausea, emesis or need for rescue medications.

b Indicates $p < 0.05$ versus placebo (or other) group.

F = female; **M** = male; = indicates the regimens were equivalent; **>** indicates significantly ($p < 0.05$) more effective.

these drugs are used in high-risk patients with comorbidities, particularly in the setting of potentially cardiotoxic chemotherapy.

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