■ CLINICAL INVESTIGATIONS

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Efficacy, Dose–Response, and Safety of Ondansetron in Prevention of Postoperative Nausea and Vomiting

A Quantitative Systematic Review of Randomized Placebo-controlled Trials

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Objective: **The authors reviewed efficacy and safety data for ondansetron for preventing postoperative nausea and vomiting (PONV).**

Methods: **Systematically searched, randomized, controlled trials (obtained through MEDLINE, EMBASE, Biological Abstracts, manufacturer's database, manual searching of journals, and article reference lists) were analyzed. Relevant end points were prevention of early PONV (within 6 h after surgery) and late PONV (within 48 h) and adverse effects. Relative benefit and number-needed-to-treat were calculated. The number-needed-to-treat indicated how many patients had to be exposed to ondansetron to prevent PONV in one of them who would have vomited or been nauseated had he or she received placebo.**

Results: **Fifty-three trials were found that had data from 7,177 patients receiving 24 different ondansetron regimens and from 5,712 controls receiving placebo or no treatment. Average early and late PONV incidences without ondansetron were 40% and 60%, respectively. There was a dose response for oral and intravenous ondansetron. Best number-needed-to-treat to prevent PONV with the best documented regimens was between 5 and 6. This was achieved with an intravenous dose of 8 mg and an oral dose of 16 mg. Antivomiting efficacy was consistently better than antinausea efficacy. Efficacy in children was poorly documented. Ondansetron significantly increased the risk for elevated liver enzymes (number-needed-to-harm was 31) and headache (number-needed-to-harm was 36).**

Conclusions: **If the risk of PONV is very high, for every 100 patients receiving an adequate dose of ondansetron 20 patients will not vomit who would have vomited had they received placebo. The antinausea effect is less pronounced. Of these 100, three will have elevated liver enzymes and three will have a headache who would not have had these adverse effects without the drug. (Key words: Antiemetics: ondansetron. Postoperative complications: nausea, vomiting. Statistics and epidemiology: systematic review; metaanalysis; number-needed-to-treat.)**

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SINCE the first clinical trials of the antiemetic efficacy of ondansetron to prevent postoperative nausea and vomiting (PONV) were published in 1991, the manufacturer has run an extensive clinical research program to establish the optimal dose and route of administration.[1,2] The manufacturer concluded that in adults, 4 mg ondansetron was the best intravenous dose for preventing PONV, whereas 16 mg ondansetron was the most effective prophylactic oral dose.[2] Other researchers suggested that three 8-mg oral doses administered over 16 h was the optimal regimen.[3]

This quantitative review of systematically searched, randomized, controlled trials had several goals: first, to define ondansetron's antiemetic efficacy compared with placebo or no treatment to prevent PONV; second, to test dose-response evidence; third, to identify the

optimal dose for oral and intravenous routes; fourth, to compare antinausea with antivomiting efficacies; and fifth, to investigate ondansetron's potential for toxic effects in the surgical setting.

Methods

Systematic Search

We did a systematic search for full reports of randomized, controlled trials that tested the effect of prophylactic ondansetron compared with placebo or no treatment on PONV (general anesthesia), and reported the outcome in dichotomous form (*i.e.*, presence or absence of PONV). We searched the MEDLINE (providers: Knowledge Finder 4.0, Silver Platter 3.25), Biological Abstracts, and EMBASE databases, without restriction to the English language, and we used different search strategies with free text combinations (date of the last electronic search: 19 September 1996). Additional reports were identified from reference lists of retrieved reports and review articles of PONV and ondansetron, and from manual search of locally available anesthesia journals. We compared our database with the database of published trials provided by the manufacturer. We did not search for unpublished trials or consider abstracts. We contacted authors of reports to clarify duplicate reports. We did not analyze efficacy data of ondansetron as a treatment of established PONV[4] or reports without a placebo or no treatment arm.

Validity Score

Each of us read independently each report that could possibly meet the inclusion criteria, and we scored them for inclusion and methodologic validity using a three-item, five-point scale.[5] Afterward we met to reach a consensus. To reports that were described as "randomized," we assigned one point and a further point if the method of randomization was described and adequate (such as a table of random numbers). We had a *pre hoc* agreement that trials that did not conceal treatment allocation (allocation according to patients' date of birth, for instance) would be excluded from further analysis because of the documented risk of overestimation of treatment effect in such trials.[6,7] We gave one point when the trial was described as "double blind." When the method of double blinding was described and adequate (identical ampules, for instance), we gave an additional point. Finally, we gave one point to reports that described the number and reasons for withdrawals. Thus the minimum score of an included randomized, controlled trial was one, and the maximum score was 5.

Data Extraction

We took information about patients, surgery, dose, and route of administration of ondansetron, study end points, sponsorship, and adverse effects from each included report. Sponsorship was assumed when it was acknowledged as such on the report or the journal issue, or when one of the coauthors was an employee of the manufacturer.

We extracted cumulative incidence of early (within 6 h after surgery) and late (within 48 h) PONV. When several incidences of events were reported at different times, we analyzed the cumulative values nearest to the sixth and the forty-eighth postoperative hours. Events "during recovery" or "postoperatively" were considered early data. Estimates of efficacy during the two time periods (0–6 h and 0–48 h) were used as indicators of early and late efficacy, respectively. Three different PONV events, both early and late, were extracted in dichotomous form: nausea, vomiting (including retching), and any emetic event (nausea, vomiting, or nausea and vomiting). These events were treated separately. When ondansetron was given repeatedly (three times 8 mg given intravenously for 24 h, for instance), we considered the first dose (in this case, 8 mg) for estimation of early efficacy and to test the evidence of a dose-response or early outcomes. We used the cumulative 24-h dose (in this case, 24 mg) to estimate late efficacy and to establish the dose-response relation for late outcomes. We did not assign weights for grades of nausea, number of or time to first vomiting episodes, number of patients needing antiemetic rescue medication, delay until discharge, *post hoc* analyses, stratified data analyses (by sex, for instance), or scores of patient satisfaction.

Qualitative Analysis

We used the scatter of event rates (incidence of PONV) with ondansetron against event rates with control as a graphical means to explore consistency of ondansetron's efficacy and homogeneity of the data.[8] On such plots, a scatter lying predominantly between the line of equality and the axis of the control intervention (placebo) would suggest consistent efficacy with ondansetron and relative homogeneity.

Quantitative Analyses

We defined antiemetic efficacy as prevention of a PONV event with ondansetron or control. We made calculations by combining ondansetron arms for each dose separately and combining corresponding control arms. Data from placebo patients from dose ranging studies could be included in several analyses. However, we did not count patient data more than once for one ondansetron dose. We combined data only if the same PONV outcome was reported within the same observation period and with the same dose and route of administration of ondansetron.

We calculated relative benefit as relative risk and used 95% confidence intervals (CI).[9] We did formal heterogeneity testing only when we combined data from more than two trials. Homogeneity was assumed when $P > 0.1$. We used a fixed-effect model[10] when we combined data from no more than two trials or when there was no significant heterogeneity. In all other situations we used a random-effects model.[11] With the fixed-effect model, we assume that all trials estimated the same true fixed effect of treatment. With the random-effects model, we recognize that trials may be heterogeneous in the sense of having different true effects.

A statistically significant benefit of ondansetron over control was assumed when the lower limit of the 95% CI of the relative benefit was >1.

We calculated number-needed-to-treat and 95% CI for combined data.[12,13] A positive number-needed-to-treat indicated how many patients had to be exposed to ondansetron to prevent one particular PONV event in one of them, who would have had this event had he or she received a placebo or no treatment. Thus the number-needed-to-treat is a useful estimate of clinical relevance of treatment effect. Infinity indicated that the confidence interval included no benefit of ondansetron over control.

We analyzed evidence of a dose response in three steps. First we plotted a graph of log dose against efficacy (log number-needed-to-treat) and analyzed it qualitatively. Second, we tested evidence for a statistically significant difference between numbers-needed-to-treat of at least two different doses. We assumed such a difference when the 95% CIs of the two numbers-needed-to-treat did not overlap.[4,14] This is a conservative criterion because it involves the comparison of an improbable extreme for one estimate with an equally improbable extreme for the other. We regarded a statistically significant difference between at least two different doses as strong evidence for a dose-response. Third, we evaluated clinical relevance of a difference between numbers-needed-to-treat. Based on the preset definition of clinical relevance of antiemetic efficacy (number-needed-to-treat <5),[15] we considered an increase in efficacy of at least 20% as clinically relevant. Thus a decrease in the number-needed-to-treat from five to four (*i.e.*, treating four patients instead of five for one to benefit) would be regarded as a clinically relevant improvement, and, as a consequence, justify an increase in the dose. The optimal dose was defined as the dose that had, first, a number-needed-to-treat to prevent PONV of no more than five, and second, for which further increase in the dose would not lead to a further clinically relevant improvement.

Sensitivity Analysis

We calculated relative benefit and number-needed-to-treat for best documented doses (*i.e.*, 1, 4, and 8 mg) within two predefined ranges of control event rates: early outcomes within 20–60% of control event rate, and late outcomes within 40–80% of control event rate.[14] Given this, we excluded from analysis all outcomes from trials with a PONV incidence in placebo patients outside these ranges. Thus we could estimate ondansetron's relative efficacy compared with other antiemetic interventions without the need for direct comparisons.[14]

Adverse Effects

To estimate the frequency of drug-related adverse effects, the number-needed-to-harm was calculated in the same manner as the number-needed-to-treat. In trials with several ondansetron arms (*i.e.*, dose-ranging studies), we extracted a "worst-outcome" estimate for each adverse effect to calculate an overall estimate of harm. Given this, we extracted the worst outcome for a given adverse effect from such trials, independent of the ondansetron dose, and we used it to calculate a combined estimate of harm with data from other trials.

Calculations were performed using EXCEL (version 5.0; Microsoft, Redmond, WA) on a Power Macintosh 7100/66 (Apple Computers, Cupertino, CA).

Results

Included and Excluded Trials

We considered 85 trials for analysis but subsequently excluded 28 reports. Of these 28, 10 were not randomized, 12 contained duplicated data (*i.e.*, patient data that

were already published in another report), the number of patients per group was not mentioned in 2, the observation period was not specified in 1, general anesthesia was not used in 1, no cumulative PONV incidences were reported in 1, and dexamethasone treatment was not properly controlled in 1 trial. We could not (nor could the manufacturer) obtain copies of four reports cited in EMBASE (but not in MEDLINE or Biological Abstracts).

We analyzed data from 53 randomized, controlled trials that were published in 52 reports.[16-52(III),53-59 (I+II),60-67] Data extracted from these reports and references for the reports that we did not analyze are available on the World Wide Web at http://www.jr2.ox.ac.uk/Bandolier/painres/ondP/ondP.html.

Because trials were inconsistent in reporting intention-to-treat data, we used efficacy data. We analyzed data from 13,580 patients, of whom 7,321 received ondansetron. The median number of patients per trial was 131 (range, 30-1,345). The median validity score was 3 (range, 1-5). We tested 24 different ondansetron regimens: oral and intravenous routes; fixed doses (full milligrams), and variable doses (micrograms per kilogram, milligrams per square meter); single, double, and triple administrations per 24 h. A "no treatment" control was used in two trials,[19,47] but all others used placebo. Data from no treatment controls were regarded as placebo.

Thirty-eight trials were in adults, 23 of them in women only. Eleven trials were done in children. Four trials were in children and adults, and we could not separate data for the two age groups. Sixteen trials (30% of all analyzed trials) were sponsored by the manufacturer of ondansetron.

Qualitative Analysis

The event rate scatter suggested consistent efficacy with ondansetron (fig. 1). The average incidences of early nausea and vomiting with placebo were 41% and 33%, respectively. The average incidences of late nausea and vomiting with placebo were 68% and 53%, respectively.

Fixed Doses: Early Events (within 6 h)

All outcomes indicated statistically significant improvement with intravenous ondansetron compared with placebo, except for preventing early nausea with 8 mg in 88 treated patients (table 1A). Only the 4-mg dose achieved consistent and clinically relevant efficacy compared with placebo; the number-needed-to-treat to prevent early PONV with intravenous ondansetron 4 mg compared with placebo were between five and six. No dose response could be established (fig. 2A).

Early outcomes with oral doses were poorly documented (table 1B). One trial, with 42 patients given 16 mg ondansetron orally, yielded better estimates of early efficacy than any of the intravenous doses (number-needed-to-treat, about three) but with wide confidence intervals, and with a nausea-plus-retching outcome. No dose-response could be established (data not shown).

Fixed Doses: Late Events (within 48 h)

All outcomes indicated significant improvement with ondansetron compared with placebo, except for prevention of late nausea with 1 mg given intravenously in more than 360 treated patients (table 1C) and for prevention of any late event with 3 mg given orally (3 × 1 mg) in more than 240 treated patients (table 1D). With all regimens, prevention of vomiting showed consistently lower number-needed-to-treat (*i.e.*, better efficacy) than prevention of nausea.

Combined analysis of data from 4 mg ondansetron given intravenously suggested that the antinausea effect with this dose was better (number-needed-to-treat, 4.6) than with any other dose. Two trials reported numbers-needed-to-treat of 1.4 and 1.7, respectively, to prevent late nausea with 4 mg ondansetron compared with placebo.[55,60] This was more than twice as good as any of the other 16 trials that reported this outcome. One of these trials was small and reported a control event rate (*i.e.*, an incidence of nausea in placebo patients) of 96%.[50] When this trial was excluded from combined analysis, the number-needed-to-treat increased slightly to 4.8. The second outlier was a large multicenter trial with more than 920 patients.[66] When we excluded this trial from the combined analysis, the number-needed-to-treat to prevent nausea with 4 mg ondansetron was 16 (table 1C).

Dose Response

A dose response was suggested graphically for late outcomes with 1-16 mg intravenous ondansetron (fig. 2B). Confidence intervals of numbers-needed-to-treat to prevent late nausea did not overlap between 4 and 8 mg doses (table 1C). Confidence intervals of number-needed-to-treat to prevent late vomiting did not overlap between the 1-mg and both 4- and 8-mg doses (table 1C). Increasing the dose from 4 mg to 8 mg led to a decrease of more than 20% in the number-needed-to-treat (*i.e.*, an improvement) for prevention of both nausea and vomiting. When the dose was further increased

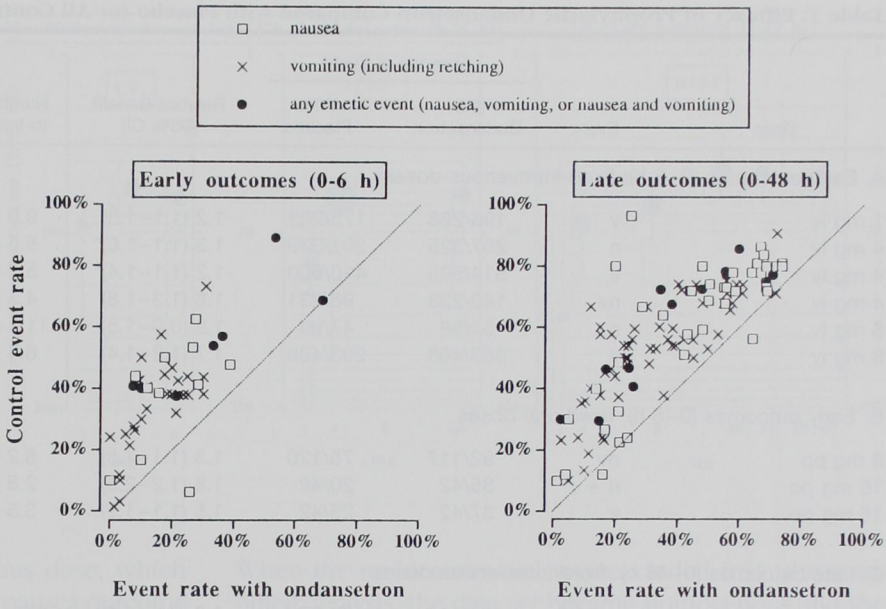

Fig. 1. Event-rate scatter. Early and late emetic event rates with ondansetron (any dose and route) compared with control (placebo or no treatment). Symbols are comparisons between ondansetron and control arms. One trial may report one to three different emetic events (see key), both early and late. A scatter lying predominantly between the line of equality (*dotted*) and the y-axis indicates consistent efficacy of ondansetron compared with control and relative homogeneity of the data set. The area of the symbols does not account for trial size.

to 16 mg, no clinically relevant improvement was achieved. Therefore, we considered 8 mg ondansetron as the optimal fixed intravenous dose tested in these trials. With 8 mg, the number-needed-to-treat to prevent nausea or vomiting up to 48 h compared with placebo was 6.4 and 5, respectively.

Also for oral doses a dose response to prevent late outcomes was suggested graphically (fig. 2C). Confidence intervals of numbers-needed-to-treat did not overlap between 3 mg (3 × 1 mg) and 24 mg (3 × 8 mg) when prevention of nausea was the end point, nor did they overlap between 3 and 16 mg, 24 mg (3 × 8 mg), 32 mg (2 × 16 mg), and 48 mg (3 × 16 mg) when prevention of vomiting was the outcome (table 1D). An increase in the oral dose from 3 to 4 mg led to an improvement of more than 20% in efficacy, as did an increase from 4 to 8 mg, and so did an increase from 8 to 16 mg (by 39% to prevent nausea and by 37% for prevention of vomiting). A further dose increase was of no benefit. Therefore, 16 mg ondansetron was regarded as the optimal fixed oral dose tested in these trials. The numbers-needed-to-treat to prevent nausea and vomiting with 16 mg oral ondansetron up to the 48th h compared with placebo were 5.9 and 4.4, respectively.

Variable Doses: Early (within 6 h) and Late (within 48 h) Outcomes

Ten different regimens with variable ondansetron doses (micrograms per kilogram body weight or milligram per square meter body surface) were investigated in 11 trials. Most included children, and in most only data on preventing vomiting were available.

The best documented regimen was 100 μg/kg intravenous ondansetron, with data from 204 treated children in four trials reporting early vomiting as an outcome (table 2A). The number-needed-to-treat to prevent vomiting up to the sixth hour with this dose was five (range, 3.7–7.6). This number-needed-to-treat was close to the 4-mg intravenous dose in adults (number-needed-to-treat to prevent early vomiting, 5.5). To prevent late vomiting with the same regimen, the combined number-needed-to-treat with data from three trials (86 treated patients) was 2.7 (range, 2.0–4.2; table 2B). All other regimens were documented in only one or two trials and with a limited number of patients (table 2A, B). We could not establish a dose response (fig. 3).

Sensitivity Analysis

Some trials reported early or late incidences of nausea and/or vomiting with placebo below the 20% or the 40% boundary of the comparator control event-rate ranges, respectively.[17,19,25,28,33–35,37,40,47,52(III),54,56,65] Some trials reported early or late incidences of nausea or vomiting with placebo above the 60% or the 80% boundary, respectively.[42,46,49,50,58,59(II),63]

All numbers-needed-to-treat were similar regardless of whether they were calculated across all trials (tables 1 and 2) or within the comparator ranges (table 3). All results were homogenous (*i.e.*, $P > 0.1$), except combined

Table 1. Efficacy of Prophylactic Ondansetron Compared with Placebo for All Control Event Rates: Fixed Doses

Dose	Event	Absence of Event: With Ondansetron	Absence of Event: With Placebo	Relative Benefit (95% CI)	Number-needed-to-treat (95% CI)	References
A. Early outcomes (0–6 h): fixed intravenous doses						
1 mg iv	v	196/268	175/282	1.2 (1.1–1.3)	9.0 (5.3–30)	39, 41
4 mg iv	n	257/325	201/329	1.3 (1.1–1.6)*	5.6 (4.0–9.0)	20, 40, 44, 47, 53, 54, 61, 63
4 mg iv	v	514/595	410/600	1.2 (1.1–1.4)*	5.5 (4.4–7.5)	20, 39–41, 44, 47, 50, 53, 61, 63
4 mg iv	nv	149/233	96/231	1.6 (1.3–1.8)	4.5 (3.2–7.4)	18, 23, 26, 29, 61
8 mg iv	n	54/88	47/90	1.2 (0.9–1.5)	11 (4.2–∞)	62
8 mg iv	v	353/465	293/486	1.7 (1.2–1.4)	6.4 (4.7–10)	39, 41, 42, 49, 62
B. Early outcomes (0–6 h): fixed oral doses						
8 mg po	nv	92/117	75/120	1.3 (1.1–1.5)	6.2 (3.6–21)	27
16 mg po	n + r	35/42	20/42	1.8 (1.2–2.5)	2.8 (1.8–5.9)	43
16 mg po	v	37/42	25/42	1.5 (1.1–1.9)	3.5 (2.2–9.3)	43
C. Late outcomes (0–48 h): fixed intravenous doses						
1 mg iv	n	101/364	86/374	1.2 (0.9–1.6)	21 (9.1–∞)	36, 41
1 mg iv	v	219/495	195/517	1.2 (1.0–1.4)	15 (8.0–210)	36, 39, 41
4 mg iv	n	724/1,412	494/1,412	1.6 (1.1–1.4)*	16 (10–47)	18, 20, 28, 30, 33, 35, 37, 40, 41, 44, 47, 52 III, 53, 54, 58, 61 (50, 66 excluded)
		1,119/1,908	588/1,585	1.5 (1.1–1.9)*	4.6 (4.0–5.5)	4 mg iv late nausea outcome, ref 50 and 66 included
4 mg iv	v	1,483/2,058	980/1,740	1.4 (1.3–1.5)*	6.4 (5.3–7.9)	20, 28–30, 33, 35, 37, 39–41, 44, 47, 50, 52 III, 53, 54, 58, 61, 66
4 mg iv	nv	198/327	124/323	1.6 (1.2–2.0)*	4.4 (3.4–6.8)	18, 23, 29, 30, 33, 48, 61
8 mg iv	n	256/521	179/536	1.4 (1.0–1.8)*	6.4 (4.6–10)	19, 34 ,36, 37, 41, 62
8 mg iv	v	409/722	271/740	1.4 (1.2–1.7)*	5.0 (4.0–6.7)	24, 34, 36, 37, 39, 41, 49, 62
8 mg iv	nv	39/40	28/40	1.4 (1.1–1.7)	3.6 (2.4–8.0)	19
16 mg or 2 × 8 mg iv	n	91/311	58/316	1.6 (1.2–2.1)	9.2 (5.7–23)	36, 46
16 mg or 2 × 8 mg iv	v	138/311	89/316	1.6 (1.3–2.0)	6.2 (4.2–11)	36, 46
D. Late outcomes (0–48 h): fixed oral doses						
3 mg (3 × 1 mg) po	n	75/241	67/249	1.2 (0.9–1.5)	24 (8.2–∞)	38
3 mg (3 × 1 mg) po	v	121/241	117/249	1.1 (0.9–1.3)	31 (8.3–∞)	38
3 mg (3 × 1 mg) po	nv	70/241	57/249	1.3 (0.9–1.7)	16 (7.2–∞)	38
4 mg po	n	154/538	107/531	1.4 (1.2–1.8)	12 (7.4–30)	59 I + II
4 mg po	v	220/538	158/531	1.4 (1.2–1.6)	9.0 (5.9–18)	59 I + II
4 mg po	nv	37/49	25/47	1.4 (1.0–1.9)	4.5 (2.4–27)	45
8 mg po	n	185/567	125/561	1.5 (1.2–1.8)	9.7 (6.4–19)	16, 59 I + II
8 mg po	v	256/568	173/561	1.5 (1.3–1.7)	7.0 (5.0–12)	16, 59 I + II
16 mg po	n	204/550	107/531	1.8 (1.5–2.3)	5.9 (4.5–8.6)	59 I + II
16 mg po	v	290/550	158/531	1.8 (1.5–2.1)	4.4 (3.5–5.8)	59 I + II
24 mg (3 × 8 mg) po	n	166/362	98/369	1.7 (1.4–2.1)	5.2 (3.8–8.0)	27, 38
24 mg (3 × 8 mg) po	v	241/362	165/369	1.5 (1.3–1.7)	4.6 (3.5–6.7)	27, 38
24 mg (3 × 8 mg) po	nv	160/362	83/369	2.0 (1.6–2.5)	4.6 (3.5–6.6)	27, 38
32 mg (2 × 16 mg) po	n + r	30/42	14/42	2.1 (1.3–3.4)	2.6 (1.7–5.4)	43
32 mg (2 × 16 mg) po	v	31/42	17/42	1.8 (1.2–2.7)	3.0 (1.9–7.5)	43
48 mg (3 × 16 mg) po	n	111/247	67/249	1.7 (1.3–2.1)	5.6 (3.8–10)	70
48 mg (3 × 16 mg) po	v	170/247	117/249	1.5 (1.3–1.7)	4.6 (3.3–7.5)	70
48 mg (3 × 16 mg) po	nv	109/247	57/249	1.9 (1.5–2.5)	4.7 (3.4–7.6)	70

∞ = infinity (absence of a statistically significant difference); CI = confidence interval; n = nausea; v = vomiting (retching included); nv = nausea, vomiting, or nausea and vomiting; n + r = nausea plus retching.

* Random effects model ($P < 0.1$).

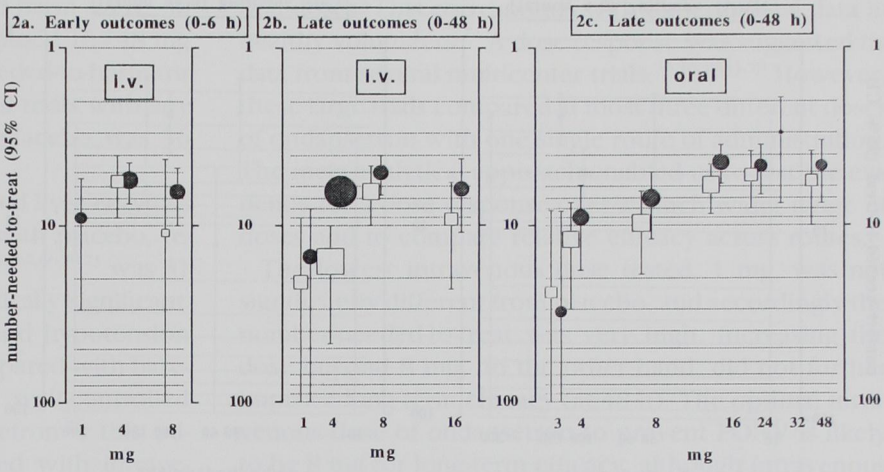

Fig. 2. Dose response with fixed doses. White squares = nausea; dark circles = vomiting. The number-needed-to-treat indicates how many patients have to be treated with the respective dose of ondansetron to prevent nausea or vomiting in one of them who would have been nauseated or vomited had they received a placebo. In multiple-dose trials, only the first dose accounted for early outcomes (A). The area of symbols is proportional to the total number of patients who received the respective dose. Exact values are shown in table 1. No nausea data were available for early outcomes with 1 mg ondansetron given intravenously and for late outcomes with 32 mg given orally.

analysis of data from the 4-mg intravenous dose, which showed significant heterogeneity for the nausea outcome (table 3B). This was again due to the multicenter trial, which reported a number-needed-to-treat of 1.7 to prevent nausea with 4 mg ondansetron compared with placebo.[66] When the multicenter trial was excluded from the combined analysis, the data set became homogenous and the number-needed-to-treat to prevent nausea with 4 mg ondansetron came close to the number-needed-to-treat to prevent vomiting.

Table 2. Efficacy of Prophylactic Ondansetron Compared with Placebo for All Control Event Rates: Variable Doses (Only Vomiting Outcomes Shown)

Dose	Absence of Event: With Ondansetron	Absence of Event: With Placebo	Relative Benefit (95% CI)	Number-needed-to-treat (95% CI)	References
A. Early outcomes (0–6 h): variable intravenous and oral doses					
10 μg/kg iv	25/32	19/33	1.4 (0.9–1.9)	4.9 (2.3–∞)	67
50 μg/kg iv	29/32	19/33	1.6 (1.2–2.2)	3.0 (1.9–7.5)	67
60 μg/kg iv	69/70	68/70	1.0 (0.9–1.0)	∞	65
100 μg/kg iv	192/204	155/209	1.3 (1.2–1.4)	5.0 (3.7–7.6)	21, 25, 64, 67
150 μg/kg iv	78/91	41/91	1.9 (1.5–2.4)	2.5 (1.9–3.6)	31, 55
300 μg/kg iv	21/28	18/32	1.3 (0.9–1.9)	5.3 (2.4–∞)	32
5 mg/m2 iv	32/35	26/35	1.2 (1.0–1.5)	5.8 (2.9–∞)	17, 22
100 μg/kg po	98/109	87/124	1.3 (1.1–1.5)	5.1 (3.4–10)	60
B. Late outcomes (0–48 h): variable intravenous and oral doses					
10 μg/kg iv	15/32	14/33	1.1 (0.6–1.9)	22 (3.5–∞)	67
50 μg/kg iv	26/32	14/33	1.9 (1.2–3.0)	2.6 (1.7–5.8)	67
60 μg/kg iv	62/70	56/69	1.1 (0.9–1.3)	13 (5.2–∞)	65
100 μg/kg iv	75/86	44/87	1.7 (1.4–2.2)	2.7 (2.0–4.2)	25, 51, 67
150 μg/kg iv	21/30	10/30	2.1 (1.2–3.7)	2.7 (1.7–7.6)	55
300 μg/kg iv	12/28	11/32	1.3 (0.7–2.4)	12 (3.0–∞)	32
75 μg/kg po	29/45	28/45	1.0 (0.8–1.4)	45 (4.5–∞)	56
100 μg/kg po	66/109	57/124	1.3 (1.0–1.7)	6.9 (3.7–53)	60
150 μg/kg po	39/46	28/45	1.4 (1.1–1.8)	4.4 (2.5–20)	56

∞ = infinity (absence of a statistically significant difference); CI = confidence interval.

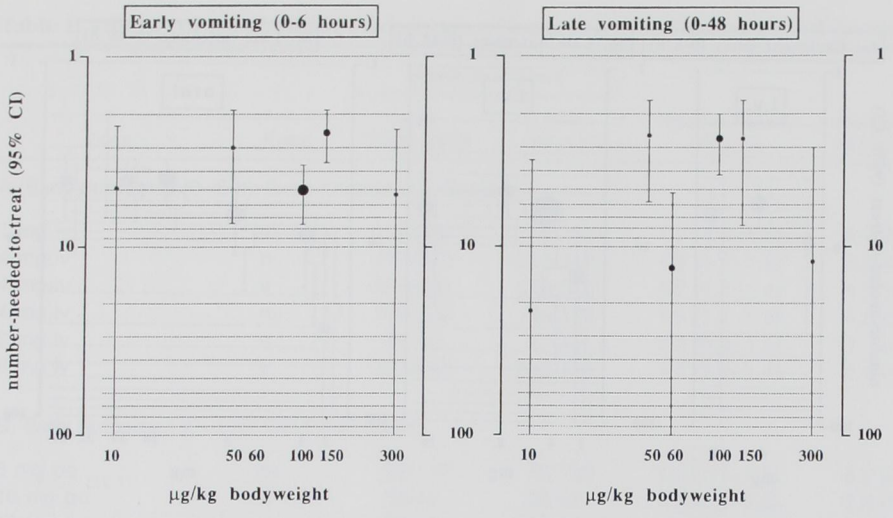

Fig. 3. Dose–response with variable doses (only µg/kg doses and only vomiting outcomes are shown). The number-needed-to-treat indicates how many patients have to be treated with the respective dose of ondansetron to prevent vomiting in one of them who would have vomited had they received a placebo. The 60-µg/kg dose was not significantly different from placebo for preventing early vomiting (number-needed-to-treat, ∞). The area of the symbols is proportional to the total number of patients who received the respective dose. Exact values are shown in table 2.

All late outcomes of trials investigating oral doses were within the preset comparator ranges. Thus the optimal oral dose was 16 mg in both analyses (*i.e.*, with all control event rates and within the comparator range). When our rules of statistical significance and clinical relevance were applied to the dose response of intravenous ondansetron, 8 mg was the optimal dose in both analyses.

Adverse Effects

Postoperative headache was reported in 20 trials with a total of 4,755 patients.[24,27,36,39–41,44,46,47,49,52–54,59(I + II),62,65,66,68,69] With 1 mg ondansetron, the incidence of headache was not significantly different from placebo (number-needed-to-harm, 54). With higher doses of ondansetron, headache occurred significantly more often

Table 3. Sensitivity Analysis*: Efficacy of Prophylactic Ondansetron Compared with Placebo within Preset Ranges of Control Event Rates (Comparator Range) (Selected Fixed Intravenous Doses)

Dose	Event	Absence of Event: With Ondansetron	Absence of Event: With Placebo	Relative Benefit (95% CI)	Number-needed-to-treat (95% CI)	References
A. Early outcomes (0–6 h): sensitivity analysis within 20 to 60% control event rates						
1 mg iv	v	196/268	175/282	1.2 (1.1–1.3)	9.0 (5.3–30)	39, 41
4 mg iv	n	207/264	146/267	1.4 (1.3–1.6)	4.2 (3.2–6.3)	20, 44, 53, 54, 61, 63
4 mg iv	v	455/534	352/538	1.3 (1.2–1.4)	5.1 (4.0–6.8)	20, 39, 41, 44, 50, 53, 61, 63
8 mg iv	n	54/88	47/90	1.2 (0.9–1.5)	11 (4.2–∞)	62
8 mg iv	v	335/439	286/460	1.2 (1.1–1.3)	7.1 (5.0–12)	39, 41, 49, 62
B. Late outcomes (0–48 h): sensitivity analysis within 40 to 80% control event rates						
1 mg iv	n	101/364	86/374	1.2 (0.9–1.6)	21 (9.1–∞)	36, 41
1 mg iv	v	219/495	195/517	1.2 (1.0–1.4)	15 (8.0–210)	36, 39, 41
4 mg iv	n	372/692	288/718	1.3 (1.2–1.5)	7.3 (5.3–12)	18, 20, 30, 40, 41, 44, 52 III, 53, 54, 51, ref 66 excluded
		743/1,156	381/1,182	1.6 (1.1–2.3)	3.1 (2.8–3.6)	4 mg iv late nausea outcome when ref 66 is included
4 mg iv	v	708/1,164	362/821	1.6 (1.4–1.7)	6.0 (4.7–8.1)	20, 28–30, 33, 39, 40, 41, 44, 50, 53, 58, 61
8 mg iv	n	183/446	114/461	1.7 (1.4–2.0)	6.1 (4.5–9.7)	36, 41, 62
8 mg iv	v	355/604	235/618	1.5 (1.4–1.7)	4.8 (3.8–6.6)	24, 36, 39, 41, 62

n = nausea; v = vomiting (retching included); ∞ = infinity (absence of a statistically significant difference).

* Ranges of control event rates were predefined.[14]

than with placebo; numbers-needed-to-harm were 30 for 4 mg, 42 for 8 mg, and 38 for combined 16–48 mg data. The "worst outcome" number-needed-to-harm for headache with combined data across all trials with any dose of ondansetron compared with placebo was 36 (95% CI, 22–89).

The number-needed-to-harm for elevated liver enzymes with 4–48 mg ondansetron compared with placebo, reported in five trials with 1,831 patients,[43,62,66,70,71] was 31 (range, 18–128), a result that was statistically significant.

In one report on 116 adults, profound hypotension (>50% decrease in blood pressure compared with baseline) developed in four patients with well-controlled hypertension medicated with ondansetron[26]; this adverse effect was significantly associated with intravenous 4-mg ondansetron compared with placebo; the number-needed-to-harm was 12 (range, 6.3–72).

Constipation in adults was evaluated in two trials[27,36] and abdominal cramps in children in a further trial.[72] The number-needed-to-harm for these adverse effects (total number of patients, 769) with 1 mg intravenous ondansetron or 150 μg/kg, or 4 mg orally compared with placebo was 23. This estimate was not significantly different from placebo (relative risk, 1.43 [range, 0.98–2.09]).

Other adverse effects, possibly related to ondansetron, were diplopia,[73] visual disturbances,[49] flush,[68,69] rash,[73] pruritus,[46,69] bradycardia,[36] and nodal rhythm.[51]

Discussion

Efficacy

Of 100 patients having surgery who receive an adequate prophylactic dose of ondansetron, 20 (number-needed-to-treat, 5) will not vomit in the postoperative period who would have done so had they received a placebo. This estimate of antiemetic efficacy may be perceived as clinically relevant. However, the effect on nausea was less pronounced with most effective doses, and we must stress that this efficacy only relates to very high control-event rates; the incidence of PONV in placebo patients in these trials was on average 40% for early outcomes and 60% for late outcomes. These results, therefore, are only applicable to a high-risk setting.

Dose Response

A dose-response relation could be established quantitatively for late outcomes with fixed intravenous and oral doses. This corresponds with experimental data in healthy volunteers.[74] A dose response was suggested by data from several multicenter trials.[36,38,39,41,59] However, these large trials compared at most three different doses of ondansetron with one single route of administration. The meta-analytical approach enabled us to test the evidence for a dose response over a much wider range of doses and to compare relative efficacy across routes.

The lowest intravenous dose tested, 1 mg, was not significantly different from placebo, and accordingly the number-needed-to-treat was very high. Increasing the dose beyond 8 mg, on the other hand, did not further improve long-term efficacy (at 48 h). The optimal intravenous dose of ondansetron to prevent PONV is likely to be 8 mg for long-term efficacy, although intravenous doses between 4 and 8 mg were not tested in these trials.

When the oral dose was increased from 8 to 16 mg, the number-needed-to-treat to prevent nausea and vomiting improved by nearly 40%. A three- to fourfold increase in the dose (*i.e.*, up to 48 mg per 24 h) did not improve efficacy further. These results suggest that the optimal oral dose of ondansetron to prevent PONV is 16 mg, although again, doses between 8 and 16 mg were not tested in these trials.

The efficacy relation between oral and intravenous routes corresponds with experimental data. In healthy volunteers, oral bioavailability of ondansetron averaged 50–65% after an 8-mg dose.[75]

The finding of a dose-response relation with ondansetron to prevent PONV contrasts with the analysis of ondansetron's efficacy data to treat established PONV. No dose response between 1 mg and 8 mg could be established; the number-needed-to-treat to prevent further PONV in a nauseated or vomiting patient with the lowest dose tested, 1 mg, compared with placebo was between four and five, and higher doses were no more effective.[4] Thus 1 mg is as efficacious to treat established PONV as an eightfold higher dose (*i.e.*, 8 mg) is to prevent PONV. This challenges the utility of prophylactic ondansetron when risk-benefit and cost-benefit arguments are considered.

Variable Doses

Data on variable doses, mainly used in children, were too sparse for sensible conclusions to be drawn. The best documented regimen, 100 μg/kg given intravenously, had the same degree of efficacy in preventing early vomiting as 4 mg did when given intravenously. A dose response could not be established, although the

data suggested that it may not be worthwhile to increase the dose above 50 μg/kg, as other investigators have suggested.[67] Unfortunately, doses between 10 μg/kg and 50 μg/kg were not tested in these trials.

Sensitivity Analysis

Most of these systematically searched ondansetron trials were conducted in clinical settings with a high risk of PONV, such as gynecologic surgery. The average control event rate (*i.e.*, the incidence of PONV with placebo) was much higher than found previously.[15,76]

This created two problems. First, the clinical relevance of antiemetic efficacy based on these ondansetron data can be challenged because these trials do not represent daily clinical experience. Second, in trials with such high control event rates there is much more scope to show statistical significance with a prophylactic antiemetic intervention than in trials with lower control event rates. Thus any comparison of ondansetron's efficacy with meta-analytic estimates of efficacy of other interventions would be seriously confounded if these other antiemetics had been tested in settings with lower risk.

A further problem arose because in some trials event rates were either very low or extremely high. Event rates that are far from the average are disproportionally influential in determining the overall estimate of efficacy. This was the rationale for excluding such trials from the sensitivity analysis.[77]

We applied our previously described model of control event rate restriction to estimate ondansetron's relative antiemetic efficacy without the need for direct head-to-head comparisons.[14] Thus lower and upper boundaries of the comparator range were defined *pre hoc*. The model accounts for differences in control event rates and trial validity and is based on the assumption that there is a close relation between control event rate and true underlying risk. The truncation process[78] creates artificial data homogeneity, and indeed all combined data sets within the comparator ranges were highly homogenous, except for one occasion when heterogeneity could be easily explained by an exaggerated estimate from one trial.

Examining only a relevant range of data introduces a bias that may slightly confound the apparent accuracy of the overall estimate.[78] However, it has been shown that this bias is not large.[78] It may also be assumed that the same degree of bias applies to all truncated estimates of efficacy. Their relative efficacy will not, therefore, be affected. Ondansetron's antiemetic efficacy was not greatly affected by the truncation process, as indicated by the stable numbers-needed-to-treat. Optimal doses for oral and intravenous routes were 16 mg and 8 mg, respectively, with both analyses.

The degree of prophylactic antinausea and antivomiting efficacy puts the most effective doses of ondansetron into the same category as using a propofol maintenance anesthetic, and the antivomiting efficacy is comparable with the effect of omitting nitrous oxide from a general anesthetic.[14]

Drug-related Adverse Effects

There is good evidence that of 100 patients receiving prophylactic ondansetron, 3 will have transiently elevated liver enzymes, and 3 will have a headache who would not have had these adverse effects without the drug. Risk of a headache with the lowest dose tested (*i.e.*, 1 mg given intravenously) was lower than with the higher doses used. This may indicate that ondansetron-induced headache is dose dependent. For the other adverse effects, no such dose dependence could be established. The clinical relevance of the increased risk of elevated liver enzymes with ondansetron compared with placebo is unknown. Hypotension in hypertensive patients was another significant finding, although it was reported in only one trial. The incidence of constipation was not significantly different between patients receiving ondansetron and controls. Other potentially major adverse effects were bradycardia and nodal rhythm, but neither of these was definitely related to ondansetron.

Publication Bias and Duplicate Data

Our search strategy did not include unpublished data, leaving us open to the criticism of potential publication bias, because negative trials are said to be less likely to be published. The usual assumption is that publication bias leads to overestimation of treatment effect.[79] This meta-analysis, based on valid published data, shows that prophylactic ondansetron treatment does not prevent PONV very well. Any publication bias would be expected to show that ondansetron prophylaxis works even less well.

We discovered several reports that contained patient data that had already been published before. Covert duplicate publications are a threat to meta-analyses. The danger is that data from the same patient are analyzed more than once. This may lead to a biased estimate of treatment efficacy, exaggerated accuracy, and a false impression of drug safety. For instance, had we inadvertently included all published data on 4 mg ondansetron

given intravenously in this meta-analysis (*i.e.*, both original and duplicated data), ondansetron's antiemetic efficacy would have been overestimated by 23%.[80] This may partly explain why 4 mg is widely believed to be the most effective intravenous ondansetron dose to prevent PONV.

Conclusions

If the risk of PONV is very high, 20% of patients receiving an optimal prophylactic dose of ondansetron (8 mg given intravenously or 16 mg given orally) will not vomit who would have vomited had they received placebo. The effect on nausea is less pronounced. Three percent of treated patients will have elevated liver enzymes, and three will have a headache who would not have had these adverse effects without the drug.

Systematic reviews allow the comparison of different prophylactic strategies for PONV, comparison of treatment and prophylaxis, and estimation of risk-benefit ratios. They are likely to inform our future management.

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