Dexamethasone for the Prevention of Postoperative Nausea and Vomiting: A Quantitative Systematic Review

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The role of dexamethasone in the prevention of postoperative nausea and vomiting (PONV) is unclear. We reviewed efficacy and safety data of dexamethasone for prevention of PONV. A systematic search (MEDLINE, EMBASE, Cochrane Library, hand searching, bibliographies, all languages, up to April 1999) was done for full reports of randomized comparisons of dexamethasone with other antiemetics or placebo in surgical patients. Relevant end points were prevention of early PONV (0 to 6 h postoperatively), late PONV (0 to 24 h), and adverse effects. Data from 1,946 patients from 17 trials were analyzed: 598 received dexamethasone; 582 received ondansetron, granisetron, droperidol, metoclopramide, or perphenazine; 423 received a placebo; and 343 received a combination of dexamethasone with ondansetron or granisetron. With placebo, the incidence of early and late PONV was 35% and 50%, respectively. Sixteen different regimens of dexamethasone were tested, most frequently, 8 or 10 mg IV in adults, and 1 or 1.5 mg/kg IV in children. With these doses, the number needed to treat to prevent early and late vomiting compared with placebo in adults and children was 7.1 (95% CI 4.5 to 18), and 3.8 (2.9 to 5), respectively. In adults, the number needed to treat to prevent late nausea was 4.3 (2.3 to 26). The combination of dexamethasone with ondansetron or granisetron further decreased the risk of PONV; the number needed to treat to prevent late nausea and vomiting with the combined regimen compared with the 5-HT_3 receptor antagonists alone was 7.7 (4.8 to 19) and 7.8 (4.1 to 66), respectively. There was a lack of data from comparisons with other antiemetics for sensible conclusions. There were no reports on dexamethasone-related adverse effects. **Implications:** When there is a high risk of postoperative nausea and vomiting, a single prophylactic dose of dexamethasone is antiemetic compared with placebo, without evidence of any clinically relevant toxicity in otherwise healthy patients. Late efficacy seems to be most pronounced. It is very likely that the best prophylaxis of postoperative nausea and vomiting currently available is achieved by combining dexamethasone with a 5-HT_3 receptor antagonist. Optimal doses of this combination need to be identified.

(Anesth Analg 2000;90:186–94)

Although dexamethasone has antiemetic properties in patients undergoing highly emetogenic chemotherapy (1), the mechanism of its antiemetic action is not well understood. A commonly held theory is that corticosteroids exert their antiemetic activity via prostaglandin antagonism (2). Others have suggested that the usefulness of dexamethasone in the control of chemotherapy-related emesis may be caused by the release of endorphins, resulting in mood elevation, a sense of well-being, and appetite stimulation (3).

More recently, dexamethasone has been added to a 5-HT_3 receptor antagonist for use in chemotherapy (4,5). There are several reasons why this combination should be especially effective in controlling emetic symptoms. First, corticosteroids may reduce levels of 5-hydroxytryptophan in neural tissue by depleting its precursor tryptophan (6). Second, the antiinflammatory properties of corticosteroids may prevent the release of serotonin in the gut (7). And third, dexamethasone may potentiate the main effect of other antiemetics by sensitizing the pharmacological receptor (8). Thus, the combination of dexamethasone with a 5-HT_3 receptor antagonist seems to be a logical choice for the control of chemotherapy-induced nausea and vomiting.

The role of dexamethasone in the surgical setting is less well understood. The first clinical trial that suggested that dexamethasone may prevent postoperative nausea and vomiting (PONV) was published in 1993 (9). Subsequent studies indicated that dexamethasone, alone or in combination with a 5-HT_3 receptor antagonist, may indeed be an interesting alternative

MRT funded by Prosper Grant No. 3233–051939.97 from the Swiss National Research Foundation.

Accepted for publication September 21, 1999.

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0003-2999/00

for the control of emetic symptoms in the postoperative period. The aim of this quantitative systematic review was to define the antiemetic efficacy and safety of dexamethasone in the prevention of PONV.

Methods

Systematic Search and Inclusion Criteria

We did a systematic search for full reports of randomized, controlled trials that tested the effect of prophylactic dexamethasone compared with any comparator (active or placebo) on PONV after general anesthesia. Relevant trials had to report end points of interest in dichotomous form (i.e., presence or absence of the end point with both dexamethasone and control). We searched MEDLINE (from 1966), COCHRANE Library (issue 2, 1999), and EMBASE (from 1982) databases without restriction to the English language and used different search strategies with the free text terms "dexamethasone;" "nausea," "vomiting," or "emesis"; "randomized" or "randomised"; "surgery," "surgical," or "postoperative"; and combinations of these words. The last electronic search was performed in April 1999. Additional trials were identified from reference lists of retrieved reports and by manually searching locally available anesthesia journals. Abstracts, letters, review articles, and animal data were not considered.

Critical Appraisal

All authors independently read all reports that could possibly meet the inclusion criteria, and scored them for inclusion and methodological validity using the three-item, five-point Oxford scale (10). This score takes into account randomization, blinding, and description of withdrawals and dropouts. We met to reach a consensus by discussion. The minimal score of an included randomized controlled trial was one, the maximal score was five.

Data Extraction

We took information about patients, surgery, dose, and route of administration of dexamethasone and comparators, study end points, and adverse effects from each included report. We extracted the cumulative incidence of PONV within 6 h and 24 h after surgery. Incidences of PONV during the two time periods (i.e., 0–6 h and 0–24 h) were used as indicators of "early" and "late" antiemetic efficacy, respectively. These two periods were chosen to gather as much information as possible on the antiemetic efficacy of dexamethasone. The early observation period represents the maximal time an ambulatory patient would stay in the recovery room before leaving the hospital. The late observation period would report on the cumulative incidence of PONV in the postoperative period. Antiemetic efficacy on "delayed" PONV (for instance, 6 to 24 h) were not analyzed, because such data were inconsistently reported. When several incidences of events were reported at different times, we analyzed the cumulative values nearest to the 6th and 24th postoperative hours. Two different PONV events, nausea and vomiting (including retching), both early and late, were extracted in dichotomous form. These events were treated separately.

Quantitative Analysis

We defined antiemetic efficacy as prevention of a PONV event with dexamethasone or control (11,12). We made calculations for individual trials, and by combining dexamethasone and control arms of independent trials. We used both relative benefit and number needed to treat as estimates of antiemetic efficacy. As an estimate of the statistical significance of a difference between dexamethasone and control, we calculated relative "benefits" as relative risks with 95% confidence intervals (CI) (13). For combined data, a fixed effect model that considers within-study variation (14) was used when data from no more than two trials were combined or when there was no significant heterogeneity (i.e., $P > 0.1$). In all other situations, we used a random effects model (15). As an estimate of the clinical relevance of a treatment effect, we calculated numbers needed to treat (i.e., the reciprocal of the absolute risk reduction) (16) for both individual trials and combined data. For combined data we used the weighted means of the experimental and control event rates, respectively. A positive number needed to treat indicated how many patients had to be exposed to dexamethasone to prevent one particular PONV event in one of them, who would have had this event had they all received the control intervention. A negative number needed to treat suggested superiority of control. Thus, the number needed to treat has the advantage of applicability to critical practice, and shows the effect required to achieve a particular therapeutic target. A 95% CI around the number needed to treat point estimate was obtained by taking the reciprocals of the values defining the 95% CI for the absolute risk reduction (17). In text and tables, the actual upper and lower limits of the 95% CI around the number needed to treat, regardless of whether they were positive or negative, are reported (18).

When the 95% CI around the relative benefit did not include one, we assumed a statistically significant difference between dexamethasone and control. In this case, we would expect the 95% CI around the number needed to treat to range from a positive limit to a negative limit, indicating that the confidence interval

includes zero, and thus infinity. To estimate the additional risk of drug-related adverse effects, relative risk and number needed to harm as for number needed to treat (19) were calculated with 95% CI.

Results

Excluded and Included Trials

We considered 19 trials for analysis. Two were subsequently excluded; in one (20), PONV was not a study end point, and in another (21), the combination of dexamethasone 150 μg/kg with a small-dose of ondansetron (50 μg/kg) was compared with a larger dose of ondansetron (150 μg/kg).

Seventeen trials with data from 1,946 patients (1,961 patients had initially been randomized) were analyzed (9,22–37). Of those, 598 received dexamethasone, 582 received ondansetron, granisetron, droperidol, metoclopramide, or perphenazine, 423 received a placebo, and 343 received a combination of dexamethasone with a 5-HT_3 receptor antagonist (ondansetron or granisetron). The average number of patients per trial was 108 (range, 49 to 270), and per group was 55 (range, 22 to 135). The median validity score was 3 (range, 2 to 5). Ten trials were in adults, and seven were in children. Sixteen different dexamethasone regimens were tested, oral and IV, fixed doses (full milligrams), and variable doses (micrograms per kilogram body weight). In all trials, dexamethasone was given as a single prophylactic dose, either orally as a premedication or IV at induction. The most frequently used regimens of dexamethasone were 8 or 10 mg IV in adults, and 1 or 1.5 mg/kg IV in children. In most pediatric trials, the incidence of vomiting was the only end point.

Dexamethasone Versus Placebo

Dexamethasone was compared with placebo in four trials in adults and in three trials in children (Table 1, A and B, and Figure 1). In adults, dexamethasone 8 and 10 mg, orally or IV, was tested, in children, dexamethasone 0.5 mg/kg, 1 mg/kg, and 1.5 mg/kg IV. All results were statistically significant in favor of dexamethasone, except early nausea with dexamethasone 8 mg IV in a small trial with 25 treated adults (Table 1A) and late vomiting with dexamethasone 0.5 mg/kg IV in a trial with a very low control event rate (the incidence of vomiting with placebo was only 9%) in children (Table 1B). When data were combined to increase power, the number-needed-to treat to prevent early and late vomiting with any dose of dexamethasone compared with placebo in adults and children was 7.1 (95% CI 4.5 to 18) and 3.8 (95% CI 2.9 to 5). Two adult trials analyzed dexamethasone's antinausea effect (Table 1B); the number needed to treat was 4.3 (95% CI 2.3 to 26).

Dexamethasone Versus Other Antiemetics

In adults, dexamethasone 8 mg was compared with ondansetron 4 mg, granisetron 3 mg, or droperidol 0.02 mg/kg, in one trial each (Table 1, C and D, and Figure 1). In children, dexamethasone 150 μg/kg was compared with perphenazine 70 μg/kg in one trial (Table 1C). Two results were statistically significant, both in favor of the comparator antiemetic. The combined data from the comparisons of dexamethasone with ondansetron and granisetron, respectively, suggested superiority of the 5-HT_3 receptor antagonists for the prevention of early vomiting (Table 1C); the number needed to treat was −5.9 (95% CI −3.5 to −20). In one large trial in children (Table 1C), perphenazine 70 μg/kg was significantly more effective in preventing early vomiting than dexamethasone 150 μg/kg; the number needed to treat was −4.4 (95%CI −3.0 to −8.5).

Concomitant Use of Dexamethasone with Other Antiemetics

Dexamethasone alone was compared with the combination of dexamethasone with a 5-HT_3 receptor antagonist (ondansetron or granisetron) in eight trials (Table 2, A and B, and Figure 2), with the combination of dexamethasone with droperidol in one trial (Table 2e), and with the combination of dexamethasone with metoclopramide in one trial (Table 2f). Only the concomitant use of dexamethasone with a 5-HT_3 receptor antagonist showed a statistically significant improvement. The combined data from adults and children suggested a long-term benefit with dexamethasone 8 mg plus ondansetron 4 mg, or granisetron 40 μg/kg, or granisetron 3 mg, respectively, compared with the respective 5-HT_3 receptor alone; the number needed to treat to prevent late nausea (adult data only) and vomiting (data from adults and children) was 7.8 (95% CI 4.1 to 66), and 7.7 (95% CI 4.8 to 19) (Table 2B).

Dexamethasone Added to a 5-HT_3 Receptor Antagonist Versus Placebo

Dexamethasone 8 mg added to granisetron 20 or 40 μg/kg was compared with placebo in two trials only, both in adults (Table 2, C and D, and Figure 2). Event rates with the combination therapy were very low, between 2% and 5% for both early and late outcomes. The number needed to treat point estimate to prevent early nausea and vomiting with the combination therapy compared with placebo was approximately 4 and to prevent late nausea and vomiting was 3.7 and 5.5.

Table 1. Dexamethasone Versus Placebo or Versus Other Antiemetics: Efficacy Data in Adults and Children

Comparisons and end points (prevention of)	Trials (No.)	Event rates		Number with end point/total number		Relative benefit (95% CI)	*P*	Number needed to treat (95% CI)	References
		Dexa	Placebo	Dexa	Placebo				
1A. Dexa versus placebo, early outcomes									
Dexa 8 mg IV or 10 mg po versus placebo									
Early nausea (adults)	1	20%	40%	20/25	15/25	1.33 (0.92 to 1.94)		5.0 (2.2 to −21)	(28)
Early vomiting (adults)	2	8%	36%	45/49	32/50	1.43 (1.14 to 1.80)		3.6 (2.3 to 8.0)	(9,28)
Dexa 1 to 1.5 mg/kg IV versus placebo									
Early vomiting (children)	3	25%	35%	125/167	113/174	1.17 (1.02 to 1.34)	<0.01	10 (5.1 to 426)	(22,33,35)
All regimens combined (early vomiting data only)	5	21%	35%	170/216	145/170	1.21 (1.08 to 1.36)	<0.01	7.1 (4.5 to 18)	(9,28,32,33,35)
1B. Dexa versus placebo, late outcomes									
Dexa 8 mg IV versus placebo									
Late nausea (adults)	2	34%	57%	31/47	20/47	1.55 (1.06 to 2.26)		4.3 (2.3 to 26)	(25,28)
Late vomiting (adults)	3	25%	48%	58/77	40/77	1.27 (1.00 to 1.61)	<0.01	4.3 (2.6 to 12)	(25,28,29)
Dexa 0.5 mg IV versus placebo									
Late vomiting (children)	1	6%	9%	33/35	31/34	1.03 (0.91 to 1.18)		32 (6.5 to −11)	(30)
Dexa 1 to 1.5 mg/kg IV versus placebo									
Late vomiting (children)	3	27%	59%	111/152	68/167	1.80 (1.47 to 2.21)	0.60	3.1 (2.3 to 4.5)	(33,35,37)
All regimens combined (late vomiting data only)	7	24%	50%	202/264	139/278	1.50 (1.07 to 2.09)	<0.01	3.8 (2.9 to 5.0)	(25,28,29, 30,33,35, 37)
1C. Dexa versus active, early outcomes		Dexa	Active	Dexa	Active				
Dexa 8 mg versus ondansetron 4 mg IV									
Dexa 8 mg versus granisetron 3 mg IV									
Early nausea (adults)	2	23%	11%	50/65	58/65	0.86 (0.74 to 1.01)		−8.1 (−4 to 245)	(27,28)
Early vomiting (adults)	2	23%	6%	50/65	61/65	0.82 (0.71 to 0.95)		−5.9 (−3.5 to −20)	(27,28)
Dexa 10 mg[a] versus droperidol 0.02 mg/kg IV									
Early nausea (adults)	1	10%	13%	43/48	41/47	1.03 (0.89 to 1.19)		43 (6.6 to −9.5)	(34)
Early vomiting (adults)	1	4%	2%	46/48	46/47	0.98 (0.91 to 1.05)		−49 (−11 to 20)	(34)
Dexa 150 μg/kg versus perphenazine 70 μg/kg IV									
Early vomiting (children)	1	36%	13%	73/114	97/112	0.74 (0.63 to 0.86)		−4.4 (−3.0 to −8.5)	(36)
1D. Dexa versus active, late outcomes									
Dexa 8 mg vs ondansetron 4 mg IV									
Late nausea (adults)	1	40%	48%	15/25	13/25	1.15 (0.70 to 1.89)		13 (2.8 to −5.1)	(28)
Late vomiting (adults)	1	32%	24%	17/25	19/25	0.89 (0.63 to 1.27)		−13 (−3.0 to 6.0)	(28)

Active = ondansetron or granisetron or droperidol or perphenazine, Dexa = dexamethasone, early = 0 to 6 h, late = 0 to 24 h.
[a] 0.17 mg/kg = 10 mg (assuming an average body weight of 60 kg).

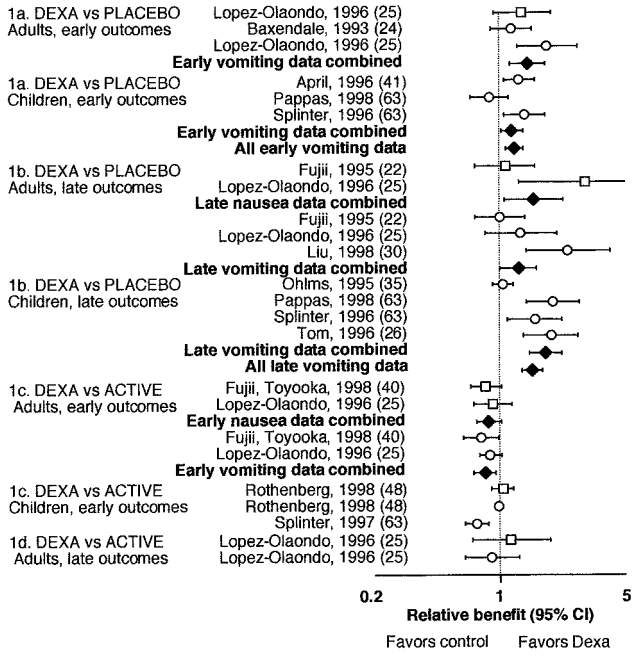

Figure 1. Forrest plot of relative benefits (95% confidence interval) of dexamethasone (Dexa) compared with control in individual trials and combined data (see Table 1). Nausea = white squares, vomiting (including retching) = white circles, combined data = black diamonds. In parentheses are numbers of patients who received Dexa.

Incidence of PONV with Placebo, Dexamethasone, 5-HT$_3$ Receptor Antagonists, and Combination Therapy

To get qualitatively more insight into the potential usefulness of the combination of dexamethasone with a 5-HT$_3$ receptor antagonist, we plotted graphically the incidence of nausea and vomiting with placebo, with dexamethasone, with any 5-HT$_3$ receptor antagonist, and with the combination of dexamethasone with a 5-HT$_3$ receptor antagonist from any trial that included one of these treatment arms (Figures 3 and 4). This was done with data from both direct comparisons (23–28,31,32,34,36) and independent trials (9,22,23,28–30,33,35,37); there was no attempt to analyze these data quantitatively.

With placebo, the average incidence of early nausea and vomiting was 33% (95% CI 22% to 44%), and 34% (95% CI 28% to 40%), respectively (Figure 3). With the combination therapy, the average incidence of early nausea was 3.9% (95% CI 1% to 7%) and of early vomiting was 1.4% (95% CI 0.2% to 3%). Average incidences of both dexamethasone and 5-HT$_3$ receptor antagonist alone were between those of placebo and combination therapy.

For late outcomes, there was a similar distribution of PONV incidences with the different therapies (Figure 4). With placebo, the average incidence of late nausea was 45% (95% CI 36% to 54%) and of late vomiting was 48% (95% CI 42% to 54%). With the combination therapy, these incidences were 25% (95% CI 18% to 32%), and 17% (95% CI 13% to 21%).

Adverse Effects

Adverse effects were most frequently reported for the association of dexamethasone with a 5-HT$_3$ receptor antagonist. Adverse effects were headache (23–28), dizziness (23–27), drowsiness and sedation (23–27), constipation (24–27), and muscle pain (24–27). There was no statistically significant difference between dexamethasone, 5-HT$_3$ receptor antagonists, and placebo for these adverse effects. In one trial, pneumonia was reported in 1 of 41 children, and secondary hemorrhage in 1 of 41 children treated with dexamethasone (22).

In one trial in children undergoing adenotonsillectomy (22) and in one trial in adults undergoing molar extraction (9), surgical edema and inflammation was an end point. In both trials, edema and inflammation in the postoperative period was significantly less severe with dexamethasone compared with placebo, and delay until first oral intake was significantly shortened (9,22). Adults undergoing extraction of third molars reported significantly less intense pain with dexamethasone compared with placebo (9). Two patients (0.8% of all day case patients) needed unplanned hospital admission because of intractable PONV; both had received a placebo (35).

Discussion

Although much attention has been paid to the prevention of PONV during the last decades, the optimal antiemetic regimen for both adults and children in the surgical setting has still not been established. The optimal antiemetic regimen would decrease the incidence of nausea and vomiting without increasing the risk of unacceptable adverse effects.

There is evidence from systematic review that interventions now used to prevent PONV either do not work very well (38–40) or are not antiemetic (41). Furthermore, all these interventions increase the risk of adverse reactions. Thus, the value of prophylaxis of PONV may be questioned. There are three main results from this systematic review on the antiemetic efficacy and safety of prophylactic dexamethasone in the surgical setting.

First, dexamethasone showed antiemetic efficacy compared with placebo. Efficacy in children and adults were similar. We therefore combined data to further increase power. Late efficacy of dexamethasone was most pronounced. Approximately four patients, adults or children, need to be treated with one prophylactic dose of dexamethasone for one not to vomit within 24 hours, who would have done so had they all received a placebo (Table 1B). For antinausea

Table 2. Concomitant Use of Dexamethasone with Other Antiemetics Versus Active or Placebo-Control: Efficacy Data in Adults and Children

End point (prevention of)	Trials (No.)	Event rates		Number with end point/total number		Relative benefit (95% CI)	*P*	Number needed to treat (95%)	References
2A. Dexa plus anti-5-HT$_3$ versus anti-5-HT$_3$, early outcomes									
Dexa 8 mg plus ondansetron 4 mg versus ondansetron 4 mg IV (adults)									
Dexa 8 mg plus granisetron 40 μg/kg versus granisetron 40 μg/kg IV (adults)									
Dexa 8 mg plus granisetron 3 mg versus granisetron 3 mg IV (adults)		Dexa + anti-5HT$_3$	anti-5-HT$_3$	Dexa + anti-5-HT$_3$	anti-5-HT$_3$				
Early nausea	3	4%	11%	106/110	98/110	1.08 (1.00 to 1.17)	0.99	14 (7.1 to 210)	(26–28)
Early vomiting	3	2%	7%	108/110	102/110	1.06 (1.00 to 1.13)	0.32	18 (9.2 to −32,054)	(26–28)
2B. Dexa plus anti-5-HT$_3$ versus anti-5-HT$_3$, late outcomes									
Dexa 8 mg plus ondansetron 4 mg versus ondansetron 4 mg IV (adults)									
Dexa 8 mg plus granisetron 20 μg/kg versus granisetron 20 μg/kg IV (adults)									
Dexa 8 mg plus granisetron 40 μg/kg versus granisetron 40 μg/kg IV (adults)									
Late nausea	4	28%	41%	95/132	78/132	1.16 (1.04 to 1.29)	0.02	7.8 (4.1 to 66)	(23,25,28,32)
Late vomiting	5	23%	35%	172/223	144/221	1.13 (1.05 to 1.21)	0.01	8.4 (4.9 to 28)	(23,25,28,31,32)
Dexa 4 mg plus granisetron 40 μg/kg versus granisetron 40 μg/kg IV (children)									
Late vomiting (children)	1	7%	27%	28/30	22/30	1.27 (1.01 to 1.61)		5.0 (2.6 to 55)	(24)
All regimens combined (late vomiting data only)	6	21%	34%	200/253	166/251	1.14 (1.06 to 1.22)	<0.01	7.7 (4.8 to 19)	(23–25,28,31,32)
2C. Dexa plus anti-5-HT$_3$ versus placebo, early outcomes									
Dexa 8 mg plus granisetron 40 μg/kg versus placebo IV (adults)		Dexa + anti-5-HT$_3$	Placebo	Dexa+ anti-5-HT$_3$	Placebo				
Early nausea	1	4%	29%	43/45	32/45	1.34 (1.10 to 1.64)		4.1 (2.6 to 10)	(26)
Early vomiting	1	2%	27%	44/45	33/45	1.33 (1.11 to 1.60)		4.0 (2.6 to 9.2)	(26)
2D. Dexa plus anti-5-HT$_3$ versus placebo, late outcomes									
Dexa 8 mg plus granisetron 20 μg/kg versus placebo IV (adults)									
Late nausea	1	5%	32%	21/22	15/22	1.40 (1.04 to 1.89)		3.7 (2.1 to 17)	(23)
Late vomiting	1	5%	23%	21/22	17/22	1.24 (0.97 to 1.58)		5.5 (2.6 to −73)	(23)
2E. Dexa plus active versus active, late outcomes									
Dexa 8 mg plus droperidol 1.25 mg versus droperidol 1.25 mg IV (adults)		Dexa + drop	Drop	Dexa+ drop	Drop				
Late nausea	1	24%	29%	34/45	32/45	1.06 (0.83 to 1.36)		23 (4.4 to −7.2)	(25)
Late vomiting	1	13%	18%	39/45	37/45	1.05 (0.88 to 1.26)		23 (5.2 to −9.5)	(25)
Dexa 8 mg plus metoclopramide 10 mg versus metoclopramide 10 mg IV (adults)		Dexa + meto	Meto	Dexa+ meto	Meto				
Late nausea	1	24%	31%	34/45	31/45	1.10 (0.85 to 1.42)		15 (4.0 to −8.5)	(25)
Late vomiting	1	18%	20%	37/45	36/45	1.03 (0.84 to 1.25)		45 (5.4 to −7.2)	(25)

dexa = dexamethasone, anti-5-HT$_3$ = ondansetron or granisetron, drop = droperidol, meto = metoclopramide, early = 0 to 6 h, late = 0 to 24 h.

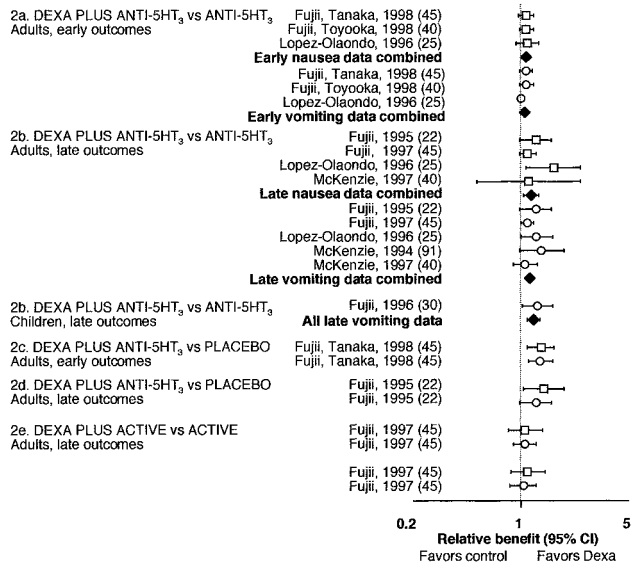

Figure 2. Forrest plot of relative benefits (95% confidence interval) of dexamethasone (Dexa) compared with control in individual trials and combined data (see Table 2). Nausea = white squares, vomiting (including retching) = white circles, combined data = black diamonds. In parentheses are numbers of patients who received Dexa.

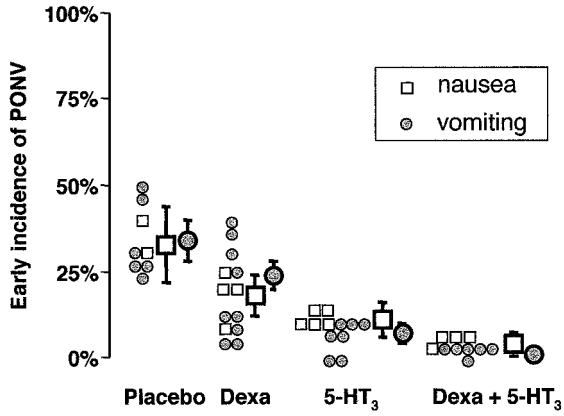

Figure 3. Incidence of early nausea and vomiting (up to 6 h) with placebo, dexamethasone (Dexa), 5-HT_3-receptor antagonists (ondansetron or granisetron), and the combination of Dexa with a 5-HT_3-receptor antagonist. Each symbol represents one outcome of one trial. Several symbols may be from one trial (23,24,26–28). Large symbols are average values with 95% confidence intervals.

efficacy, the message was less clear; there were two trials with only a limited number of adult patients reporting nausea data (23,28). The number needed to treat point estimate, however, suggested that dexamethasone's late effect on nausea was similar to its late effect on vomiting. Reasons for the increased late efficacy are unclear. Dexamethasone has a biological half-life of 36 to 72 hours (42). Thus, the late antiemetic efficacy may be a result of favorable pharmacokinetics. In chemotherapy, there is some evidence that delayed emesis (i.e., beyond 24 hours) is better controlled with dexamethasone compared with classic antiemetics (43,44). A dose-response relationship for

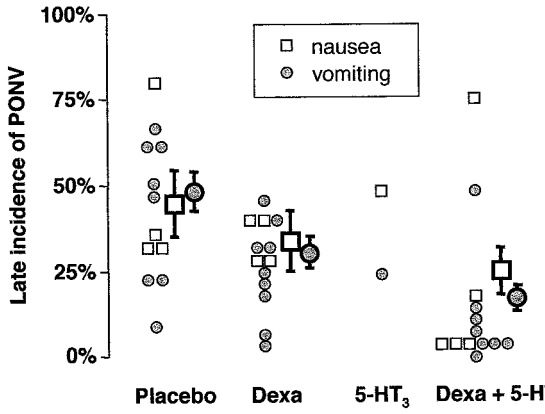

Figure 4. Incidence of late nausea and vomiting (up to 24 h) with placebo, dexamethasone (Dexa), 5-HT_3-receptor antagonists (ondansetron or granisetron), and the combination of Dexa with a 5-HT_3-receptor antagonist. Each symbol represents one outcome of one trial. Several symbols may be from one trial (23,24,26–28). Large symbols and vertical bars are average values with 95% confidence intervals.

dexamethasone could not be established. This may mainly be because of the narrow ranges of doses used both in adults and in children. Thus, we do not know if smaller doses would still be effective, or if it was worthwhile to test larger doses. This should define the research agenda.

Second, there was evidence of an increased antiemetic effect when dexamethasone was added to a 5-HT_3 receptor antagonist. With 5-HT_3 receptor antagonists alone, the risk of PONV was decreased compared with placebo (Figures 3 and 4). This is in agreement with the quantitative analysis of systematically searched placebo-controlled ondansetron trials in the surgical setting (40). When dexamethasone was given concomitantly with a 5-HT_3 receptor antagonist, the absolute risk of PONV was even lower (Figures 3 and 4). We do not know if the combination of dexamethasone with a 5-HT_3 receptor antagonist leads to improved control of PONV symptoms via an additive or a synergistic effect. Only one trial attempted to address this issue (21). These authors found a better antiemetic efficacy with the combination of dexamethasone with a small dose of ondansetron compared with a three times higher dose of ondansetron alone. However, there is evidence that the small dose of ondansetron used in this trial (50 μg/kg) is as effective as the larger dose (150 μg/kg) (40,45). Thus, the trial of Splinter and Rhine (21) may support the hypothesis of an additive (but not a synergistic) antiemetic effect when dexamethasone and ondansetron are combined.

Third, adverse effects were rarely reported, and they were mainly related to 5-HT_3 receptor antagonists (i.e., headache, constipation). The problem is that only a limited number of patients was tested in these trials (598 received dexamethasone alone and 343 received dexamethasone combined with another antiemetic), and patients were preselected. For instance,

patients with a history of gastrointestinal disease, diabetes, corticosteroid therapy, immunosuppression, recent tuberculosis, Cushing's syndrome, cataract, or hypertension were not included in these trials. Also, in none of the trials was functional capacity and potential inhibition of the hypothalamic-pituitary-adrenal axis tested. This should define the research agenda for adverse effects of dexamethasone in the surgical setting. In patients without risk factors who received dexamethasone 20 mg per day for five days for the control of chemotherapy-induced emesis, there was no evidence of immunosuppression or dysfunction of the hypothalamic-pituitary-adrenal axis (46). However, we still do not know if a single bolus dose of dexamethasone 8 or 10 mg (the most frequently used doses in these trials) is safe in patients at risk of corticosteroid-related adverse effects, nor do we know if a single dose of dexamethasone would suppress adrenal function in otherwise healthy patients during surgical stress, if suppression of adrenal function should happen in these patients, or if this was clinically relevant (for instance, if it increased the risk of wound dehiscence or infection).

A final issue relates to the definition of the most appropriate end points in PONV trials. In the surgical setting, a truly effective antiemetic regimen would be expected to increase a patient's comfort, to shorten a stay in the recovery room (and thus enable early discharge after day case surgery), and to prevent unplanned hospital admission caused by intractable PONV. It has been claimed that nausea and vomiting are surrogate end points in this context (47). However, unless antiemetic regimens for the prevention of PONV are truly effective, we cannot expect them to have an impact on patient satisfaction or duration of hospital stay. The combination of dexamethasone with a 5-HT_3 receptor antagonist is likely to be the most effective prophylactic antiemetic intervention currently available for the control of PONV. It seems to be worthwhile to test the impact of this combination therapy on so-called true end points in valid trials.

In conclusion, in the surgical setting, a single prophylactic dose of dexamethasone is antiemetic compared with placebo without evidence of any clinically relevant toxicity in otherwise healthy patients. Late (i.e., up to 24 hours) efficacy seems to be most pronounced. It is likely that the best prophylaxis of PONV currently available is achieved by combining dexamethasone with a 5-HT_3 receptor antagonist. Optimal doses of this combination need to be identified.

We thank Daniel Haake from the Documentation Service of the Swiss Academy of Medical Sciences (DOKDI) for his help in searching electronic databases.

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