Review Article

Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials

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Background: Diphenhydramine and its theoclate salt dimenhydrinate are traditional antiemetics still in use. However, so far the quantitative effect of dimenhydrinate in the prophylaxis of postoperative nausea and vomiting (PONV) has not been evaluated systematically.

Methods: Results from randomized controlled trials investigating the efficacy of dimenhydrinate vs. a control to prevent PONV were included in a meta-analysis. Studies were systematically searched through MEDLINE, EMBASE, the Cochrane-Library, manually screening of reference lists of matching review articles and current issues of locally available peer-reviewed anesthesia journals, up to June 2001. The numbers of patients with complete absence of PONV within 6 h and within 48 h after surgery were extracted as the main end point. Pooled relative benefits (RB) and numbers-needed-to-treat (NNT) with their corresponding 95% confidence intervals (CI) were calculated using a random effects model. This quantitative systematic review was performed following the recommendations of the QUORUM statement.

In all, 18 trials with 3045 patients were included in the analysis:

1658 patients received a placebo (control) and 1387 patients received dimenhydrinate.

Results: The RB to stay completely free of PONV was 1.2 (95% CI: 1.1–1.4) for the early period (NNT = 8; 95% CI: 5–25) and 1.5 (1.3–1.8) for the overall investigated period (NNT = 5; 95% CI: 3–9).

Conclusion: Dimenhydrinate is a traditional and inexpensive antiemetic with an efficacy that might be considered as clinically relevant. Although in use for a long time, the dose-response, precise estimation of side-effects, optimal time of administration and the benefit of repetitive doses still remain unclear.

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Key words: antiemetics; antihistamines; dimenhydrinate; diphenhydramine; meta-analysis; postoperative complications, postoperative nausea and vomiting (PONV); quantitative systematic review

Dimenhydrinate for prophylaxis of PONV

Menhydrinate’ compared to an inactive control. The Cochrane Library, MEDLINE and EMBASE were searched without language restriction. Free text search terms included ‘dimenhydrinate’ or ‘diphenhydramine’ or ‘dramamine’ and ‘nausea’ or ‘vomiting’ or ‘emesis’. The last electronic search update was performed in June 2001. The reference lists of retrieved reports, review articles and locally available anesthesia journals were checked to find additional reports.

Data extraction
Two of the authors (P.K and L.E) extracted the following data from each study independently from each other: absence of postoperative nausea (PN), postoperative vomiting (PV) and PONV and other relevant features. If the extracted data were conflicting they were checked and in the case of further disagreement, consensus was reached with a third author (A.M).

Study end points
The main end point was the number of patients that stayed completely free from PONV. This was defined as absence of any nausea, retching or vomiting. All other patients were defined as having PONV. Secondary end points were the absence of PN, PV and side-effects. Since some studies used different observation periods postoperatively, absence of symptoms was extracted for two separate intervals: the first 6h postoperatively (‘early’) and the first 48h postoperatively (‘overall’).

Critical appraisal
Quality of reporting in the trials was scored using the three-item, five-point Oxford scale (13). Thus, the minimum score of an included trial according to the above-mentioned inclusion criteria (randomized trials) was 1 and the maximum score could be 5.

Statistics
Data entry and statistical calculations were performed using the computer program RevMan 4.1 (14). A randomeffects model was applied to calculate the relative benefit (RB) with 95% confidence intervals (CI) (15). A RB > 1 means that an intervention is associated with an increased likelihood to stay completely free from PONV. The difference between two groups was judged statistically significant when the 95% CI of the RB did not include the value 1.00. As an estimate of the clinical relevance of any difference between active and control, we calculated the number-needed-to-treat (NNT) with 95% CI.

Results
Excluded and included trials
Forty-two potentially relevant reports were identified and initially screened (Fig.1). Of these, 38 were clinical trials in which data on PONV could be obtained. A total of 20 trials had to be excluded subsequently due to lack of or inappropriate randomization. Thus, 18 reports with 3045 patients remained for final analysis: 1658 patients in the control group and 1387 patients who received dimenhydrinate. The median Oxford-Score of the analyzed trials was 4 (range: 1 (only randomization reported) to 5 (full report of features described in the Oxford scale)). Two reports were scored ‘1’, three reports scored ‘2’, two reports scored ‘3’, six reports scored ‘4’ and five reports scored ‘5’. The median number of patients per trial receiving placebo and dimenhydrinate was 46 (range: 20–420) and 40 (range: 20–423), respectively.

Whole population
Early events (0–6h postoperatively)
Data on the incidence of the investigated outcome during the early postoperative period was available for PONV in eight trials with 884 control patients and 813 actively treated patients (16–23) (Table1). PV could be extracted in 6 trials with 429 patients in the control group and 355 patients receiving dimenhydrinate (16, 17, 19, 21). Data on PN were reported in two trials with 53 and 54 patients in the active and placebo group, respectively (22, 23). Dimenhydrinate was associated with a higher incidence of patients without emetic symptoms in this
period. While this benefit failed to reach statistical significance for PN (only two trials were available for pooled analysis), it was significant for PV and the main outcome PONV (Table 1). For the combined data the RB for PONV was 1.21 (95% CI: 1.07–1.35). The NNT with an average control event rate (CER) of 54% was in the range of 8 (95% CI: 5–25).

Overall events (0–48 h postoperatively)

Data were more consistently reported and available for PONV in 16 trials with 1604 control patients and 1334 actively treated patients (16–21, 24–33) (Table 2). PV could be extracted in 14 trials with 1118 patients in the control group and 800 patients receiving dimenhydrinate (16, 17, 19, 20, 24, 26–33). Data on PN were reported in seven trials with 741 control and 445 actively treated patients for this period (16, 20, 24, 27–29, 33). Table 3 summarizes the pooled results.

Side-effects

Reporting of side-effects was inconsistent and sparse. In many of the studies it was stated that side-effects did not differ between the groups but no binary data were given. No major harm associated with the use of dimenhydrinate was reported. Due to the sparse reporting it was felt inappropriate to calculate a pooled effect since information would not exceed that obtained from the single studies.

### Table 1

Results of studies investigating the relative efficacy of dimenhydrinate vs. placebo for the early period (0–6 h). The given benefit represents the likelihood of being free from PONV (main outcome) for patients receiving dimenhydrinate. All studies are listed according to their relative benefit.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dimenhydrinate</th>
<th>Placebo</th>
<th>Relative weight of the study</th>
<th>Relative benefit (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(16)</td>
<td>33/85</td>
<td>70/165</td>
<td>9.4</td>
<td>0.92 (0.66–1.26)</td>
</tr>
<tr>
<td>(18)</td>
<td>248/423</td>
<td>230/420</td>
<td>24.9</td>
<td>1.07 (0.95–1.20)</td>
</tr>
<tr>
<td>(22)</td>
<td>22/28</td>
<td>21/29</td>
<td>10.5</td>
<td>1.09 (0.81–1.46)</td>
</tr>
<tr>
<td>(20)</td>
<td>31/35</td>
<td>24/35</td>
<td>12.9</td>
<td>1.29 (1–1.67)</td>
</tr>
<tr>
<td>(21)</td>
<td>122/153</td>
<td>87/148</td>
<td>24.0</td>
<td>1.36 (1.16–1.59)</td>
</tr>
<tr>
<td>(23)</td>
<td>19/25</td>
<td>14/25</td>
<td>6.4</td>
<td>1.36 (0.90–2.05)</td>
</tr>
<tr>
<td>(19)</td>
<td>12/24</td>
<td>8/22</td>
<td>2.7</td>
<td>1.38 (0.69–2.72)</td>
</tr>
<tr>
<td>(17)</td>
<td>36/40</td>
<td>25/40</td>
<td>12.4</td>
<td>1.44 (1.11–1.87)</td>
</tr>
<tr>
<td>Total</td>
<td>523/813 (64%)</td>
<td>479/884 (54%)</td>
<td>100.0</td>
<td>1.21 (1.07–1.35)</td>
</tr>
</tbody>
</table>

### Table 2

Results of studies investigating the relative efficacy of dimenhydrinate vs. placebo for the overall period (0–48 h). The given benefit represents the likelihood of being free from PONV (main outcome) for patients receiving dimenhydrinate. All studies are listed according to their relative benefit.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dimenhydrinate</th>
<th>Placebo</th>
<th>Relative weight of the study</th>
<th>Relative benefit (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28)</td>
<td>18/28</td>
<td>17/28</td>
<td>6.6</td>
<td>1.06 (0.71–1.59)</td>
</tr>
<tr>
<td>(18)</td>
<td>228/423</td>
<td>210/420</td>
<td>10.0</td>
<td>1.08 (0.95–1.23)</td>
</tr>
<tr>
<td>(33)</td>
<td>38/58</td>
<td>35/60</td>
<td>8.2</td>
<td>1.12 (0.85–1.49)</td>
</tr>
<tr>
<td>(32)</td>
<td>17/48</td>
<td>16/51</td>
<td>4.9</td>
<td>1.13 (0.65–1.97)</td>
</tr>
<tr>
<td>(19)</td>
<td>5/24</td>
<td>4/22</td>
<td>1.7</td>
<td>1.15 (0.35–3.73)</td>
</tr>
<tr>
<td>(29)</td>
<td>30/40</td>
<td>25/40</td>
<td>8.0</td>
<td>1.20 (0.89–1.62)</td>
</tr>
<tr>
<td>(20)</td>
<td>27/35</td>
<td>22/35</td>
<td>7.8</td>
<td>1.23 (0.90–1.68)</td>
</tr>
<tr>
<td>(24)</td>
<td>68/133</td>
<td>135/353</td>
<td>9.1</td>
<td>1.34 (1.08–1.65)</td>
</tr>
<tr>
<td>(16)</td>
<td>21/85</td>
<td>29/165</td>
<td>5.5</td>
<td>1.41 (0.86–2.31)</td>
</tr>
<tr>
<td>(26)</td>
<td>22/40</td>
<td>19/60</td>
<td>5.9</td>
<td>1.74 (1.09–2.77)</td>
</tr>
<tr>
<td>(21)</td>
<td>106/153</td>
<td>59/148</td>
<td>9.0</td>
<td>1.74 (1.39–2.17)</td>
</tr>
<tr>
<td>(30)</td>
<td>18/30</td>
<td>11/36</td>
<td>4.8</td>
<td>1.96 (1.11–3.48)</td>
</tr>
<tr>
<td>(17)</td>
<td>28/40</td>
<td>14/40</td>
<td>5.8</td>
<td>2.00 (1.25–3.20)</td>
</tr>
<tr>
<td>(25)</td>
<td>26/67</td>
<td>10/66</td>
<td>4.2</td>
<td>2.56 (1.34–4.88)</td>
</tr>
<tr>
<td>(31)</td>
<td>17/20</td>
<td>6/20</td>
<td>3.8</td>
<td>2.83 (1.42–5.67)</td>
</tr>
<tr>
<td>(27)</td>
<td>81/110</td>
<td>10/60</td>
<td>4.7</td>
<td>4.42 (2.48–7.87)</td>
</tr>
<tr>
<td>Total</td>
<td>750/1334 (56%)</td>
<td>622/1604 (39%)</td>
<td>100.0</td>
<td>1.51 (1.27–1.78)</td>
</tr>
</tbody>
</table>


**Subgroups**

Pooled results used a variety of application modes (single vs. repetitive doses), routes of application (i.m. vs. i.v. vs. rectal) and patients (children vs. adults). Therefore, overall results were tested with respect to robustness by excluding certain subgroups and thus narrowing the interstudy variety. Since most data were available on ‘late PONV’, this was done solely for the main outcome (Table 4).

**Adults**

In adults we separately analyzed studies in which a single dose was applied and compared the results to those obtained by trials in which the first dose was administered in conjunction with anesthesia and dimenhydrinate was repetitively administered in the postoperative course via the rectal or i.v. route. Both regimens were superior to placebo. There was a trend of dimenhydrinate being more effective when at least one second dose was administered postoperatively (Table 4). However, it should not left unmentioned that five out of the six studies were published by a single center (author) in a rather homogeneous population.

<table>
<thead>
<tr>
<th>Population</th>
<th>Mode of application for dimenhydrinate</th>
<th>Trials</th>
<th>Relative benefit</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Single iv/im, 1–2mg/kg</td>
<td>(16, 18, 24)</td>
<td>1.20 (1.01–1.42)</td>
<td>14.29 (8.33–50.0)</td>
</tr>
<tr>
<td>Adults</td>
<td>Repetition 1 or 3×1.2 mg/kg rectal or iv after initial 1 mg/kg iv</td>
<td>(20, 25, 27–29, 33)</td>
<td>1.55 (1.05–2.29)</td>
<td>4.76 (2.50–50.00)</td>
</tr>
<tr>
<td>Children</td>
<td>Single i.v./i.m., 0.5–2.2mg/kg</td>
<td>(17, 19, 26)</td>
<td>1.80 (1.31–2.47)</td>
<td>4.76 (2.56–33.33)</td>
</tr>
<tr>
<td>Children</td>
<td>Single rectal, 2–3mg/kg</td>
<td>(31, 32)</td>
<td>1.71 (1.16–2.53)</td>
<td>3.57 (1.92–20.00)</td>
</tr>
</tbody>
</table>

**Discussion**

The main finding of this meta-analysis is that dimenhydrinate increases the chance of staying free from PONV by 40% if the CER is high (about 60%). In terms of a NNT this means that – under these circumstances – about five patients need to receive prophylaxis with dimenhydrinate for one patient to stay free from PONV who otherwise would have suffered from these symptoms. Although these efficacy data do not appear impressive, they are in the range that have been reported for newer or more common
antiemetics such as serotonin receptor antagonists (34), droperidol (12, 35) and dexamethasone (36, 37).

Although meta-analyses are frequently used, there remain many issues related to the methodology that are currently being discussed intensively (38–41). Therefore, we will briefly focus this discussion on the major controversies that arise from this review.

First, in contrast to newer antiemetics that have been investigated more recently, when more rigid and controlled conditions are applied in the studies as prerequisites, dimenhydrinate has already been in use for many decades. This means that the systematic review covers studies that have been performed and published over a long period of time. Although we excluded reports that were obviously not randomized, it should be kept in mind that anesthetic techniques as well as pre- and postoperative management has been changed greatly, which might lead to the criticism that pooling the results is not appropriate. However, efficacy data were rather homogeneous and results did not vary when reports published before 1996 (16, 18, 24, 26, 27) were excluded (data not shown). Therefore, at least as far as the estimate of the ‘common effect’ is concerned, pooling all studies seems justified.

Second, we first calculated overall efficacy data including all trials that met the inclusion criteria and thus combined a large variety of application modes. This raises the issue as to what extent data-pooling across trials is justified and reasonable. A compromise must agreed upon, balancing the aim to increase power and to lower the uncertainty of the point estimate of the applied measure of effect (‘lumping’) against the reasonable demand only to combine comparable interventions to calculate combined efficacy data (‘splitting’). In the literature, both strategies have been applied in meta-analyses. While possible heterogeneity, caused for instance by the use of different techniques in acupuncture (invasive vs. non-invasive interventions), has been judged slight enough to justify pooling of the data (42), and possible heterogeneity induced by combining different serotonin antagonists has been judged clinically negligible (12), other authors have put more emphasis on well-defined— and therefore more comparable— subgroups and have only combined data of trials with a rather precisely matching design (35, 36). The latter approach, however, means that sometimes each subgroup comprises only a small number of studies, which may lead to broad confidence limits, although overall evidence is not as weak as it seems.

In this analysis we formed subgroups of adults and children. We also analyzed whether in adults a repetitive application increases antiemetic efficacy and whether, in children, efficacy data vary depending on the application—rectal vs. i.v./i.m. In these analyses, at least, we found no clinically relevant difference in efficacy between rectal and i.v./i.m. application of the investigated doses. In adults, repeating the application of dimenhydrinate was associated with an increased benefit compared to single application. However, these subgroup findings should be considered with caution as no direct comparisons are available. In addition, in the single application subgroup, all the studies are older than trials that investigated repetitive dosages of dimenhydrinate. In the latter group, five out of six studies were published by one author. The differences may therefore be explained by some underlying variables not controlled or whose relative influence was difficult to analyze retrospectively.

Third, side-effects were not consistently reported and seldom available as a binary outcome. At least as far as serious side-effects are concerned, dimenhydrinate does not appear to be different from placebo. Non-significant differences or comparable incidences of side-effects were usually only stated but no data were provided, making it impossible to calculate a common effect and to obtain an estimation of the risk–to–benefit ratio. Thus, a potential advantage of a meta-analysis— to obtain an estimate of the frequencies of side-effects not apparent in small studies—could not be applied.

In conclusion, dimenhydrinate, although a traditional antiemetic, is worthwhile considering when an inexpensive antiemetic is needed. Antiemetic efficacy exceeds a placebo effect and is in the range that may be considered clinically relevant. However, to obtain relevant absolute risk reduction it seems essential to limit its use to patients who are prone to suffer from PONV (43). Although in use for a long time, dose–response is unclear. Repeating the application of dimenhydrinate may be associated with increased benefit in adults. Serious side-effects seem to be rare.

References


35. Henzi I, Sonderegger J, Tramer MR. Efficacy, dose–response, and adverse effects of droperidol for prevention of post-


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