Effects of prophylactic anticholinergic medications to decrease extrapyramidal side effects in patients taking acute antiemetic drugs: a systematic review and meta-analysis

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ABSTRACT

Objectives To determine the effectiveness of prophylactic anticholinergic medications in reducing extrapyramidal symptoms in patients taking acute antiemetics with a dopamine D2 receptor antagonist effect.

Methods Systematic searches of all published studies through March 2017 were identified from PubMed, Cochrane library, Embase, Web of Science and Scopus. Only randomised controlled trials of patients receiving dopamine D2 antagonist antiemetic therapy for acute migraine in which an anticholinergic or placebo was compared were included. Pooled ORs were calculated for incidence of extrapyramidal symptoms and sedation.

Results Four placebo-controlled randomised controlled trials consisting of 737 patients met the inclusion criteria for our meta-analysis. The effect of diphenhydramine differed depending on the method of administration of the antiemetic. When the antiemetic was delivered as a 2 min antiemetic bolus, the odds of extrapyramidal symptoms were significantly reduced in the diphenhydramine group compared with placebo (OR 0.42; 95% CI 0.22 to 0.81; P=0.01). However, when the antiemetic was given as a 15 min infusion, there was no significant difference in extrapyramidal symptoms with or without diphenhydramine (OR 1.06; 95% CI 0.58 to 1.91; P=0.85). The lowest incidence of extrapyramidal symptoms was observed in patients receiving a 15 min antiemetic infusion without diphenhydramine prophylaxis (9.8%). In two trials including 351 patients that dichotomously reported sedation scales, diphenhydramine had significantly higher rates of sedation (31.6% vs 19.2%, OR 2.01, 95% CI 1.21 to 3.33; P=0.007).

Conclusion Prophylactic diphenhydramine reduces extrapyramidal symptoms in patients receiving bolus antiemetic therapy with a dopamine D2 antagonist effect, but not when it is given as an infusion. Because of significantly greater sedation with diphenhydramine, the most effective strategy is to administer the D2 antagonist antiemetic as a 15 min infusion without prophylaxis.

INTRODUCTION

Antiemetics with a dopamine D2 receptor antagonist effect are well-known effective treatments for nausea and acute migraine in emergency settings.1 2 Despite their effectiveness, this class of antiemetics induces distressing movement disorders broadly classified under extrapyramidal symptoms (EPS),3-4 with studies citing EPS incidence between 4% and 25% with metoclopramide5-6 and 25% and 67% with prochlorperazine. Although parkinsonism and tardive dyskinesia in more chronic presentations of EPS are well known,7-9 acute reactions of dystonia and akathisia are more frequently encountered in the emergency setting. The spectrum of acute symptoms may include torticolis, oculogyric crisis, cramps and bulbar type of speech and, if left untreated, may lead to dehydration, infection, pulmonary embolism, rhabdomyolysis and, in rarer instances, lethal respiratory stridor and obstruction.10-12

Standard treatment of EPS involves discontinuation of the inciting agent and administration of injectable anticholinergic or antihistaminic drugs, most commonly benztropine and diphenhydramine.13 Although common in medical practice, controversy has existed on the prophylactic use of anticholinergic agents to prevent EPS. A consensus statement by WHO recommended against the use of prophylactic anticholinergic agents, noting that they are overprescribed and lead to additional side effects, most notably sedation.14 However, nearly 62% of emergency providers indicated their concern for EPS was considerable enough to warrant administration of prophylactic diphenhydramine,15 particularly because adjuvant diphenhydramine does not alter the efficacy of antiemetics16 and may actually even potentiate the effect of aborting headaches and nausea via its antihistaminic properties.17

To better delineate the evidence behind this controversy, we set out to perform a meta-analysis of the literature that describes the use of prophylactic anticholinergic medications to decrease the incidence of EPS in patients receiving antiemetics for nausea, vomiting or migraines.

MATERIALS AND METHODS

Search strategy

For our meta-analysis, we looked for studies that described interventions of prophylactic anticholinergic medications versus placebo to prevent EPS in patients receiving antiemetics with dopaminergic D2 receptor antagonism (ie, metoclopramide, prochlorperazine, chlorpromazine, droperidol). We searched all English academic articles identified...
from different electronic databases, including PubMed (1966–March 2017), Cochrane Central Register of Controlled Trials databases, Embase (1980–March 2017), Web of Science (1980–March 2017), Scopus (1996–March 2017) and from hand search of reference lists of identified publications. Broad MeSH terms and Boolean operators were selected for each database search, including terms and synonyms for extrapyramidal symptoms and anticholinergic medications (online supplementary appendix 1).

Our full study protocol can be found online (http://readinghospital.libguides.com/c.php?g=416927&p=2841192).

Study selection and quality assessment

We included all published randomised controlled trials (RCTs) and quasi-RCTs. Inclusion criteria included RCTs that evaluated patients receiving any intravenous antiemetic treatment (with dopamine D2 receptor antagonism) for a chief complaint of nausea, vomiting or headache; studies that intervened with a standard dose of anticholinergic medication (ie, diphenhydramine, benzotropine) for EPS prophylaxis; and studies that measured primary or secondary outcome of incidence of EPS. Exclusion criteria comprised the following: articles without abstracts or full publications, studies that do not address incidence of EPS or a component along the EPS spectrum, studies that do not explicitly describe one or more interventions, trials without randomisation of patients into two relevant groups and study designs that are not RCTs (ie, case-control studies, prospective cohort studies, cross-sectional studies, review articles, letters to the editor). Two authors (RSD and CM) independently conducted searches of the below listed databases using the following search strategies, and a third author (AD) adjudicated discrepancies.

Data extraction

The following data were extracted: (1) demographic data of participants; (2) indication for antiemetic therapy and type of antiemetic therapy prescribed (name, dose, length of treatment, mode of delivery); (3) type of prophylactic anticholinergic therapy in intervention group (name, dose, length of treatment, mode of delivery); (4) subtype of EPS being studied (dystonia, akathisia, parkinsonism, tardive dyskinesia), duration for monitoring EPS and type of EPS measuring scale used; (5) primary outcome of interest (incidence of EPS) in intervention versus placebo groups and other secondary outcomes of interest including treatment scores of nausea or headache, and incidence of side effects (sedation, blurred vision, constipation and dry mouth). In studies in which data were missing or unclear, we contacted the investigators for clarification. For each eligible study, two of the reviewers (RSD and CM) extracted all the relevant data independently. Kappa scores for inter-rater variability between the two reviewers for included and excluded studies was 0.849, correlating to very good agreement. Any disagreement was resolved by a third reviewer (AD) who was the adjudicator and made the final decision.

Assessment of risk of bias

The quality of studies was independently evaluated by two reviewers (RSD and CM) using the guidelines provided by the Cochrane Collaboration ACROBAT-NSBI.5 Disagreements were adjudicated by a third reviewer (AD). Risk of bias was assessed in reference to a hypothetical generic target blinded, randomised trial designed to randomly assign patients receiving antiemetic therapy with dopaminergic D2 receptor antagonism

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Figure 1  Flow chart of the study selection and inclusion process.

to intervention (anticholinergic prophylaxis) and control groups (placebo). The effect of interest of the target trial would be incidence of EPS following completion of the intervention.

In reference to this target trial, biases were assessed in the following domains including bias in selection of participants (including random sequence generation and allocation concealment), performance bias (including blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias due to missing data, reporting bias and other biases (including departures from intended interventions such as cross-contamination of groups). The risk of bias in each domain was assigned at low risk, high risk or unclear risk.

**Data analysis: statistical methods**

The meta-analysis was conducted by the Review Manager software V5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We assessed statistical heterogeneity between study estimates through a standard χ² test with a significance set at a P value of 0.1. The quantity of heterogeneity was measured through the I² statistic. An I² value of 50% or above indicated substantial heterogeneity. Data were meta-analysed using a random effects Mantel-Haenszel model, except for all analyses that only included two studies each. OR and 95% CIs were calculated for dichotomous outcomes, including EPS and sedation events. Our subgroup analyses were determined a priori. Specifically, we planned to analyse EPS outcomes in patients receiving a 2 min antiemetic bolus versus a 15 min antiemetic infusion, as some studies have shown a lower EPS incidence with infusion dosing. In addition, it was predetermined to include a subgroup analysis based on diphenhydramine dose strength as it was conceivable to have a better therapeutic effect from higher doses. Publication bias was not assessed since too few studies were found to interpret a funnel plot. A P value of < 0.05 was used as the level of significance.

**RESULTS**

**Search results**

We identified a total of 2537 citations as potentially relevant. By screening the title, reviewing the abstract and reading the manuscript, four placebo-controlled RCTs were identified that eventually fulfilled the eligibility criteria for quantitative

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**Table 1 Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Mean age (SD)</th>
<th>Gender (F/M)</th>
<th>Antiemetic name, dose, route, duration</th>
<th>Diphenhydramine dose, route, duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erdur et al</strong>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>75</td>
<td>37.1 (14.3)</td>
<td>56/19</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>20 mg intravenously over 15 min infusion</td>
</tr>
<tr>
<td>Placebo</td>
<td>75</td>
<td>34.8 (12.4)</td>
<td>50/25</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>2 min</td>
</tr>
<tr>
<td><strong>Vinson and Drotts</strong>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>50</td>
<td>31 (12)</td>
<td>35/15</td>
<td>Prochlorperazine 10 mg intravenously over</td>
<td>50 mg intravenously over 2 min</td>
</tr>
<tr>
<td>Placebo</td>
<td>50</td>
<td>28 (9)</td>
<td>32/18</td>
<td>Prochlorperazine 10 mg intravenously over</td>
<td>2 min</td>
</tr>
<tr>
<td><strong>Friedman et al</strong>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention subtype A</td>
<td>71</td>
<td>39 (13)</td>
<td>51/20</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>25 mg intravenously over 15 min infusion</td>
</tr>
<tr>
<td>Intervention subtype B</td>
<td>72</td>
<td>39 (12)</td>
<td>52/20</td>
<td>Metoclopramide 20 mg intravenously over</td>
<td>25 mg intravenously over 15 min infusion</td>
</tr>
<tr>
<td>Placebo A</td>
<td>72</td>
<td>40 (13)</td>
<td>55/17</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>15 min</td>
</tr>
<tr>
<td>Placebo B</td>
<td>71</td>
<td>42 (14)</td>
<td>52/19</td>
<td>Metoclopramide 20 mg intravenously over</td>
<td>15 min</td>
</tr>
<tr>
<td><strong>Friedman et al</strong>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>104</td>
<td>34 (11)</td>
<td>88/16</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>50 mg intravenously over 15 min infusion</td>
</tr>
<tr>
<td>Placebo</td>
<td>104</td>
<td>36 (10)</td>
<td>92/12</td>
<td>Metoclopramide 10 mg intravenously over</td>
<td>15 min</td>
</tr>
</tbody>
</table>

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analysis. The four RCTs included a total of 737 patients eligible for data extraction and meta-analysis. Figure 1 displays the flow chart of included and excluded studies.

Quality assessment
Table 1 summarises data from the included RCTs: of the 737 total patients (181 men and 563 women), the individual sample sizes from each trial ranged from 100 to 286 patients. A total of 367 patients were administered anticholinergic prophylaxis medication (diphenhydramine) for EPS prevention, and the remaining 370 patients received placebo.

Figure 2 and online supplementary appendix 2 summarise the criteria for methodological quality of all included studies. All four placebo-controlled RCTs generally had a low risk of bias. With the exception of Erdur et al., all included studies addressed allocation concealment via central randomisation by pharmacy centres. In addition, studies addressed blinding of outcome assessment through the use of research associates or blinded physicians. Although a low risk of attrition bias was ascribed to all included trials, Friedman et al. (2009) and Friedman et al. (2016) reported that 3 out of 289 participants (1%) and 7 out of 201 participants (3.5%) were lost to follow-up, respectively. Literature has shown that a drop-out rate of less than 5% is minor, and the calculated ratios of dropped participants to total events (3/34 and 7/15, respectively) were not significant to influence intervention effect. High risk for bias was noted for the 'Other bias' category in the Friedman et al. (2016) study as the trial was halted slightly past the halfway point due to enforcement of a stopping rule. This stopping rule was established prior to initiation of the trial and stated that the study was to be stopped if the absolute risk reduction of headache was less than 7.5% in the cohort receiving diphenhydramine and metoclopramide.

Different dosages and duration of drug delivery of anticholinergic and antiemetic medications were observed (table 1). For antiemetic therapy, three studies used metoclopramide and one study administered prochlorperazine. The dosage of metoclopramide ranged from 10 to 20 mg delivered intravenously either as a 2 min bolus or a 15 min infusion. The dosage of prochlorperazine was 10 mg delivered intravenously as a 2 min bolus. The type of anticholinergic medication used in all included studies was diphenhydramine. The dosage of diphenhydramine ranged from 20 to 50 mg delivered intravenously over 15 min.

Table 2 Extrapyramidal symptom (EPS) events in included studies and subgroup analyses

<table>
<thead>
<tr>
<th>Included studies and subgroups (N)</th>
<th>Overall no of EPS events/N (%)</th>
<th>No of EPS events/n (%) in diphenhydramine group</th>
<th>No of EPS events/n (%) in placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All four included studies (737)</td>
<td>100/737 (13.6%)</td>
<td>42/367 (5.7%)</td>
<td>58/370 (15.7%)</td>
</tr>
<tr>
<td>2 min antiemetic bolus subgroup (250)</td>
<td>51/250 (20.4%)</td>
<td>17/125 (6.9%)</td>
<td>34/125 (27.2%)</td>
</tr>
<tr>
<td>15 min antiemetic infusion subgroup (487)</td>
<td>49/487 (10.1%)</td>
<td>25/242 (5.2%)</td>
<td>24/245 (9.8%)</td>
</tr>
</tbody>
</table>

Table 2 Extrapiramidal symptom (EPS) events in included studies and subgroup analyses

antiemetic infusion and the cohort receiving a 2 min antie

Subgroup analysis was performed on patients receiving diphenhydramine in high and low dosages (>25 mg or ≤25 mg, respectively). There was no significant difference in EPS between high-dose diphenhydramine and the placebo group (diphenhydramine group 10.1%; placebo 16.4%; OR 0.58; 95% CI 0.14 to 2.32; P=0.44) or the low-dose diphenhydramine and the placebo group (diphenhydramine group 12.4%; placebo 15.1%; OR 0.79; 95% CI 0.46 to 1.38; P=0.41). However, since there was significant heterogeneity present in this subgroup analysis (I²=73%), we did not incorporate these findings in our conclusion.

Incidence of sedation
Data on sedation symptoms were available in three included trials with a total of 451 patients. However, because the Vinson and Drotts group reported sedation scores as a continuous variable using a scale without a cut point, their data could not be dichotomously analysed and pooled with the other studies. In the two remaining studies, 55 of 174 patients (31.6%) experienced sedation in the diphenhydramine group, while 34 of 177 patients (19.2%) experienced sedation in the placebo group. The pooled results (figure 5) indicated that there was a statistically significant increase in the incidence of sedation in the diphenhydramine group versus placebo group (OR 2.01, 95% CI 1.21 to 3.33; P=0.007). There was significant heterogeneity in the finding (τ²=0.16, χ²=2.01, df=1, I²=54%, P=0.14) among the included studies.

DISCUSSION
We found a difference in the effect of prophylactic diphenhydramine dependent on the method of administration of the antiemetic. The odds of EPS was significantly lower in the diphenhydramine group if antiemetic was administered as a 2 min bolus but not when the antiemetic was administered as a 15 min infusion. A potential explanation for this finding is reflected in prior studies that showed higher peak concentrations of antiemetic in the plasma from bolus dosing may lead to increased occupancy of central dopamine D2 receptors, increasing the likelihood of
EPS^22^23^, thus, it is feasible that these at-risk patients would then stand to benefit the most from an intervention of prophylactic anticholinergic. Conversely, in the cohort receiving a slower infusion of antiemetic, protection against EPS may be afforded by permitting less occupancy of dopamine receptors, which has been confirmed by a prior meta-analysis showing that a slower infusion of metoclopramide is an effective intervention by itself at reducing EPS compared with bolus dosing.20

Finally, an association of increased sedation in the diphenhydramine group was statistically significant (P = 0.007). Notably, an additional study25 was not included in the analysis due to distinct use of a continuous variable for measuring sedation scores (instead of a dichotomous variable). However, this omitted study also found increased sedation scores in the diphenhydramine group, introducing the possibility that our meta-analysis may have achieved additional power if this study was included with dichotomous variables. If avoidance of sedation is desirable, the most effective strategy to prevent EPS is to solely administer the D2 antagonist antiemetic as a 15 min infusion without diphenhydramine instead of a 2 min bolus (incidence of EPS 9.8% vs 27.2%, respectively, two-tailed χ² test P < 0.0001; refer to table 2).

This meta-analysis included high-quality RCTs published in peer-reviewed journals, robust methodology with an a priori analysis plan and comprehensive quality assessment of included RCTs.

However, this meta-analysis also had several limitations. Only four RCTs satisfied eligibility criteria and sample sizes were small. One study was halted near the halfway point due to enforcement of a stopping rule, introducing the possibility that results may not reflect the actual outcome if the study was completed.24 In addition, a no-intention-to-treat analysis was performed for drop-outs. Significant heterogeneity was also present, which is particularly evident in the subgroup analysis of EPS outcomes in patients receiving high-dose diphenhydramine prophylaxis with an I² value of 73%. Possible reasons for this include differing indications for administration of anticholinergic, as well as variable antiemetic and anticholinergic drug class, dosage and rate of administration. Moreover, although we searched for trials that studied the whole EPS spectrum, only akathisia was measured in included studies, and a uniform definition was not used among trials. Therefore, although the overall methodological quality of the included RCTs was high, these aforementioned shortcomings should be taken into consideration when interpreting findings from our meta-analysis.

CONCLUSION

Based on the current literature, anticholinergic prophylaxis is unlikely to reduce extrapyramidal symptoms when the D2 antagonist antiemetic is administered as a 15 min infusion. However, if a 2 min antiemetic bolus is administered, prophylactic diphenhydramine may lead to a decrease in EPS. Prophylactic diphenhydramine increases sedation. As only four studies were included in our analysis, additional future well-powered studies are warranted.

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Contributors RS performed the conception and background of research, designed and performed the analysis and interpretation of data, drafted the manuscript and created all figures. CM performed the design, analysis and interpretation of data, revised the manuscript critically for intellectual content and gave final approval of the manuscript. EO performed the analysis and interpretation of data, revised the manuscript critically for intellectual content, validated the bias methods performed and gave final approval of the manuscript. SD performed background search and drafted the introduction section, performed the analysis and interpretation of data, revised the manuscript critically for intellectual content and gave final approval of the manuscript. AS performed background searches, partially drafted the introduction section, helped with bias assessment and revised the manuscript critically for intellectual content. JM performed background searches, helped with bias assessment and revised the manuscript critically for intellectual content. AS helped with formulating search strategies, performed background searches and revised the manuscript critically for intellectual content. AD performed the conception, design and interpretation of data, performed the study selection and bias assessment, revised the manuscript critically for intellectual content and gave final approval of the manuscript.

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