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**Title:** Using haloperidol as an anti-emetic in palliative care: informing practice through evidence from cancer treatment and post-operative contexts

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## **Abstract**

Background: Nausea and vomiting are common symptoms in palliative care. Haloperidol is often used as an antiemetic in this context though direct evidence supporting this practice is limited.

Objective: To evaluate the efficacy and clinical use of haloperidol as an antiemetic in non-palliative care contexts to inform practice.

Methods: Rapid review of i) published evidence to supplement existing systematic reviews, and ii) practical aspects affecting the use of haloperidol including formulations and doses that are commonly available internationally.

Results: In nausea and vomiting related to cancer treatment, haloperidol was superior to control in two small studies. In post-operative nausea and vomiting (PONV), two randomised controlled trials found treatment with haloperidol comparable to ondansetron. In palliative care, an observational study found a complete response rate of 24% with haloperidol (1 in 4 patients) which would be consistent with an NNT of 3 to 5 derived from PONV.

Conclusion: There remains insufficient direct evidence to definitively support the use of haloperidol for the management of nausea and vomiting in palliative care. However, generalising evidence from other clinical contexts may have some validity.

**Keywords:** haloperidol, nausea and vomiting, postoperative nausea and vomiting, palliative care

## **Introduction**

The butyrophenone haloperidol was first licensed as an antipsychotic in 1958<sup>1</sup>. Early studies also showed that haloperidol effectively protected against apomorphine-induced emesis<sup>2</sup>. Subsequently the anti-emetic properties of haloperidol have been demonstrated in a plethora of animal studies. These include efficacy of haloperidol against dopamine agonist-induced emesis in dogs<sup>3, 4</sup> and ferrets<sup>5</sup>. These effects have led to its use in the management of nausea and vomiting in palliative care; indeed, haloperidol is internationally considered to be one of the essential medications in palliative care<sup>6</sup>.

Haloperidol acts as an antagonist and has strong affinity for the dopamine D2 receptor, accounting for its antipsychotic activity. The emetogenic process involves the chemoreceptor trigger zone (CTZ) in the brain. This is the site of action of most anti-emetic drugs and the key neurotransmitters involved in the emetic process are dopamine, serotonin and substance P<sup>7</sup>. This region is particularly dopamine-rich; therefore the antagonism of dopamine D2 receptors by haloperidol in the CTZ is a generally accepted mechanism of reducing nausea and vomiting<sup>8</sup>.

Although haloperidol is often prescribed for the management of nausea and vomiting in palliative care, systematic reviews have shown the lack of definitive studies confirming its efficacy<sup>9, 10, 11</sup>. In the most recent systematic review (2009) Perkins and Dorman<sup>11</sup> found no RCTs and the identified 26 non-RCT studies were all excluded. Keeley, in 'Clinical Evidence'<sup>12</sup> cites the 2001 systematic review by Critchley<sup>9</sup> in his summary statement that: *“Although haloperidol is almost universally used for nausea, especially where the cause is chemical or metabolic, there is no RCT evidence that it is beneficial. However, there is consensus, based largely on case series, that haloperidol is an effective antiemetic for chemical and metabolic*

*causes of nausea and vomiting, such as opioid-induced nausea, renal failure, and hypercalcaemia*".

The aim of this rapid review was to bring together published evidence on the efficacy, safety and clinical use of haloperidol as an anti-emetic to inform its use in a palliative care context.

## **Methods**

### *Data search method*

Searches were undertaken of MEDLINE, PsycInfo, EMBASE, Web of Science and the Cochrane library covering the period from November 1<sup>st</sup> 2011 to March 1<sup>st</sup> 2012. The basic search strategy was ("haloperidol") AND ("nausea" OR "vomiting"), modified for each database. The reference lists of studies that were retrieved for the detailed evaluation were hand-searched for any additional relevant citations.

### *Setting and types of intervention*

We included studies where haloperidol was used to treat nausea or vomiting (alone or in addition to other agents) including any dose of haloperidol, via any route, over any duration of follow up. All types of studies or trials were included from the following settings – cancer, chemotherapy, radiation, postoperative nausea and vomiting (PONV).

### *Data collection and analysis*

We judged the potential relevance of studies based on their titles and abstracts, and obtained studies which we anticipated might meet the inclusion criteria. We read these to assess suitability for inclusion.

#### *Use of haloperidol in clinical practice*

Haloperidol preparations available in the UK were identified from the British National Formulary and their Summaries of Product Characteristics (SPC) were obtained from the Electronic Medicines Compendium (eMC) and reviewed for licensed indications.

## **Results**

#### *Chemotherapy and Radiotherapy*

Büttner et al.<sup>13</sup> found that no conclusions could be drawn from their meta-analysis of the efficacy of haloperidol in treating nausea and vomiting induced by chemotherapy or radiation treatment. In a small chemotherapy trial it was found that haloperidol was superior to benzquinamide in the prevention of acute vomiting, with patients preferring haloperidol for emesis induced by nitrogen mustard (67% vs. 16%; 17% had no preference) or cis-platinum (78% vs. 22%)<sup>14</sup>. In a radiation therapy trial, haloperidol was superior to placebo in the prevention of delayed vomiting with 96% of patients taking haloperidol reporting reduced vomiting, compared to 20% of patients receiving placebo<sup>15</sup>. There have not been any clinical studies since the meta-analysis of Büttner et al.<sup>13</sup> to suggest the efficacy of haloperidol for the management of nausea and vomiting induced by chemotherapy or radiation treatment.

#### *Post-operative nausea and vomiting*

The anti-emetic efficacy of haloperidol (1 or 2 mg) was shown to be strong and comparable to other anti-emetics that are used for the prevention and treatment of post-operative nausea and vomiting [PONV]<sup>13, 16</sup>. The Büttner meta-analysis found efficacy at doses between 0.5 and 4 mg haloperidol, but not for 0.25 mg; the relative benefit to PONV with haloperidol compared with placebo was 1.26 to 1.51 (number needed to treat [NNT], 3.2 to 5.1). Two randomised, double-blinded studies have since compared haloperidol (i.v. administration) to ondansetron (4 mg) for PONV prophylaxis in a mixed surgical population. In Lee et al.<sup>17</sup>, patients on 2 mg haloperidol or 4 mg ondansetron reported a low incidence of PONV (<30%, the expected incidence of PONV in this study was 60%) within 24 hours post-operatively with no significant difference between the two drugs. In the second RCT, Rosow et al.<sup>18</sup>, showed that haloperidol 1 mg had similar efficacy to ondansetron 4mg for prevention of PONV, with 78.2% and 76.8% of patients having complete response, defined by no nausea or vomiting. A randomised double-blinded study in women found treatment with 1 mg haloperidol reduced the incidence of PONV 0-4 hours after surgery from 49% of patients in the saline group to 24%, an effect comparable with 0.625 mg droperidol (23%); furthermore, 4-24 hours post-operatively haloperidol treatment reduced the incidence of PONV from 30% of patients in the saline group to 11%, this significant reduction in PONV was not observed in the droperidol group (14%)<sup>19</sup>.

Low doses of haloperidol have also been shown to be efficacious in combination with other anti-emetics to prevent PONV. A randomised blinded trial found that the cumulative incidence of vomiting in a group combining 1.5 mg haloperidol and 8 mg dexamethasone was significantly lower at 24 hours (RR 0.54, 95% CI: 0.31-0.86) post-operatively than with dexamethasone alone<sup>20</sup>. However, the incidence of nausea was not different between the two study arms. A randomised double-blind study combining 2 mg haloperidol and 4 mg ondansetron



found that the combined treatment group had a significantly higher ( $p < 0.05$ ) complete response rate at 24 hours after surgery (79%) compared to haloperidol alone (61%) and ondansetron alone (62%); patient satisfaction scores were also significantly ( $p < 0.05$ ) higher in the combined group ( $8.3 \pm 1.8$ ) than in the haloperidol alone group ( $7.0 \pm 2.4$ ) and ondansetron alone group ( $7.2 \pm 2.5$ ; Feng et al., 2009)<sup>21</sup>. In another randomised double-blind study a combination of 1 mg haloperidol in addition to 4 mg ondansetron in a mixed surgical population produced more complete responders than ondansetron alone (76.2% vs 59.2%)<sup>22</sup>. In addition, Chu et al<sup>23</sup> found in a randomised double-blind study in women, that the incidences of PONV in the 2 mg haloperidol (37%), 1.25 mg droperidol (36%) and 5 mg dexamethasone (38%) groups were all significantly lower than the incidence of PONV in the saline group (65%). Moreover, the combination of 2 mg haloperidol and 5 mg dexamethasone had the lowest incidence of PONV (19%) and was significantly lower than the other single treatment groups<sup>23</sup>.

#### *Cancer-related nausea and vomiting*

A recent open-label uncontrolled trial did suggest efficacy of haloperidol as an anti-emetic in the management of nausea and vomiting not related to anti-cancer treatment in patients with cancer<sup>24</sup>. The endpoint was adjusted to assess the patient response at day 2 of a 5-day study due to low recruitment rate and high attrition. At day 2, 8 out of 33 patients (24%; 95% confidence interval [CI]: 10%-39%) had complete control of nausea and vomiting and 12 had partial control (36%; 95% CI: 20%-53%), giving an overall response rate of 61% (95% CI: 44%-77%)<sup>24</sup>. The authors report that the results were similar to those seen for methotrimeprazine in a previous study using the same methodology<sup>25</sup>. In this study, at day 2, 33/53 (62%) patients showed some

improvement in nausea and vomiting, and at day 5, improvement was seen in 20/34 (58%) patients.

### **Practical use of haloperidol in palliative care**

Based on their meta-analysis, Büttner and colleagues conclude that the antiemetic efficacy of haloperidol in the reviewed studies was reached at doses of 1-4 mg once or twice daily when administered orally or by i.m. injection<sup>13</sup>. Easily and accurately administered small doses of haloperidol are particularly important in palliative care because of some patients' difficulties in swallowing. Haloperidol is available as tablets (0.5, 1.5, 5, 10, 20 mg, as oral solution (Haldol 2 mg/mL; Dolpin 5mg/5mL & 10mg/5mL) and for i.m. injection (5 mg/mL). The licensed indications of haloperidol products vary, and some but not all of the oral solutions list 'nausea and vomiting' in their Summary of Product Characteristics (eMC).

Oral solutions of haloperidol are potentially more usable than solid dosage forms in palliative care but the volumes involved are very small, need to be measured with an oral syringe and solutions of different strengths may lead to confusion and dosing errors. 'Melt in mouth' (orodispersible) formulations may be of value but there are no published data on whether and how such formulations might be used in clinical practice<sup>26</sup>. Transdermal patches have also been suggested to both provide a continuous low dose which might diminish side effects<sup>27</sup>.

### **Conclusions**

There is limited evidence within cancer chemotherapy and post-operative contexts to support haloperidol as an antiemetic, with a number needed to treat (NNT) of 3 to 5. However, haloperidol at doses of 1-4 mg daily appears to be equivalent to ondansetron in PONV, and

combinations of haloperidol with either ondansetron or dexamethasone appear to be superior to either alone in this context.

There remains insufficient evidence from randomised controlled trials to definitively support the use of haloperidol for the management of nausea and vomiting in palliative care. However, generalising evidence from other contexts (e.g. PONV) may have some validity. Observational studies in palliative care that found a complete response rate of 24% (1 in 4 patients)<sup>24</sup> would be consistent with an NNT of 3 to 5 derived from PONV (i.e. between 1 in 3 and 1 in 5 patients achieve a complete response)<sup>13</sup>. This supports the use of haloperidol as an effective antiemetic for chemical and metabolic causes of nausea and vomiting, including opioid-induced nausea, renal failure, and hypercalcaemia. The current range of available formulations of haloperidol is not well suited to patients' needs in the palliative care context. Novel dosage forms could overcome these challenges in the future.

### **Declaration of Interest**

The authors report no conflicts of interest.

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