Pharmacovigilance in Hospice/Palliative Care: Rapid Report of Net Clinical Effect of Metoclopramide

David C. Currow, M.P.H., FRACP, Jane Vella-Brincat, BPharm, Belinda Fazekas, R.N., B.Sc., Katherine Clark, MMed, FRACP, Matthew Doogue, MBChB, FRACP, and Debra Rowett, BPharm

Abstract

Background: Understanding the performance of prescribed medications in day-to-day practice is important to minimize harm, maximize clinical benefits, and, eventually, better target the people who are most likely to benefit, especially in hospice/palliative care where there may be limited time to optimize prescribing. Metoclopramide, a benzamide prokinetic antiemetic, is widely used for a number of indications including nausea, vomiting, hiccups, and reflux. It has recently had a new “black box” warning issued by the Food and Drug Administration in relation to tardive dyskinesia to limit use to 12 weeks.

Methods: A consecutive cohort of patients from 12 participating centers in two countries who were having metoclopramide initiated had data collected at three time points—baseline, 2 days (clinical benefit), and day 7 (clinical harm). Additionally, harms could be recorded at any time.

Results: Of the 53 people included in the cohort, 23 (43%) reported benefit at 48 hours, but only 18 (34%) of these people were still using it one week after commencing it. For the other 5, the medication was ceased due to harms. The most frequent harms were akathisia (n = 4), headache (n = 4), and abdominal pain (n = 4). Nine people (17%) had no clinical benefit and experienced harms.

Conclusion: Overall, one in three people gained net clinical benefit at one week. Limiting effects include side-effects that need to be sought actively in clinical care.

Introduction

The evidence base for prescribing in hospice/palliative care can be improved. In response to this need, a multinational initiative has commenced to improve the data for net clinical effect, and hence the evidence base on which to predicate prescribing in hospice/palliative care. This work is an extension of the phase III and IV studies that have been carried out by the Australian Palliative Care Clinical Studies Collaborative (PaCCSC). Rapid prospective reporting at agreed time points for assessment with standardized measures of clinical harms and benefits for frequently prescribed symptom control medications in hospice/palliative care can provide important information. This information is unique to hospice/palliative care and cannot be extrapolated from other patient populations. Immediate and short-term net clinical effects can be systematically studied this way during day-to-day practice.

Using secure web-based technology, de-identified and “undeidentifiable” data, and a small number of set fields focused on single medications, a new pragmatic tool for pharmacovigilance has been created. This approach ensures that a considerable amount of data can be rapidly brought together by aggregating data from a large number of centers simultaneously with minimal work for each individual clinician.

The first medicine studied by the collaborative is metoclopramide, a benzamide prokinetic antiemetic, widely used in hospice/palliative care practice for a number of indications including nausea, vomiting, hiccups, gastroesophageal reflux disease, and gastroparesis (including that caused by opioids). Although widely prescribed and affordable, the benefits and harms of metoclopramide have not been well quantified in hospice/palliative care patients. Given the new Food and Drug Administration “black box” warning issued in 2009 limiting recommended use to 12 weeks because of metoclopramide’s propensity to cause irreversible tardive dyskinesia, it is timely...
to assess the net clinical effect of this medication in hospice/palliative care practice. Key facts about metoclopramide are shown in Table 1.

The aim of this study was to describe the clinical effect of metoclopramide when prescribed routinely in a consecutive, prospective cohort of hospice/palliative care patients.

Methods

The study methods have been described in detail previously. In summary, participating sites entered data pro forma on consecutive patients started on this medication as part of routine clinical care. Nonidentifying demographic and clinical data were entered onto the 128-bit secure web portal. Prespecified clinical benefit and harm fields were defined by an expert committee based on the available literature. The National Cancer Institute’s Common Toxicity Criteria for Adverse Events (NCI CTC) Likert scales for grading harms were used. Clinical data were recorded at three set time points: baseline; after 48 hours (clinical benefit), and day 7 (short-term harm). Additionally, harms could be recorded at any time. Harms were attributed to metoclopramide if the criteria for NCI CTC were >0 at day 7. The domains within the Naranjo Score that are applicable in this clinical setting were used to help attribute the relationship between the medication and any reported harms. Specifically, question 4 (drug readministration), question 6 (same side effect when placebo administered), and question 8 (did harmful effects change with dose?) were not included as they are not appropriate for hospice/palliative care practice.

Descriptive data are presented.

Ethical waivers (by the relevant research ethics committees that consider this an audit) or approval for low risk research (where this program of work is considered research) were granted for all participating sites.

Results

Data including demographic and baseline clinical data (Table 2) were available on 53 people from 12 hospice/palliative care sites in two countries who commenced treatment with metoclopramide between October 2011 and January 2012. The majority of patients had cancer and metoclopramide was prescribed for prevention of nausea or

<table>
<thead>
<tr>
<th>Table 1. KEY FACTS: METOCLOPRAMIDE</th>
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<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
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<td>Peripheral</td>
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<td><strong>Dose modifications</strong></td>
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<td><strong>Frequently reported adverse effects</strong></td>
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<td><strong>Important examples of drug interactions in hospice/palliative care</strong></td>
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<td><strong>Contraindications</strong></td>
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<td><strong>Monitoring</strong></td>
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Note: Bolded sections are serious or irreversible events.
vomiting in the majority of patients. Patients were administered on average 32.9 mg of metoclopramide /24 hours (standard deviation 7.5; median 30 mg; range 10–60) in injectable or oral formulations.

By 48 hours, overall benefit was reported in 23 of 53 (43%) patients (Table 3). One in 4 patients (15/53) had one point or greater reduction in their relevant NCI CTC symptom score and no side effects at one week. Another 15% (8/53) had symptomatic benefit, but 5 of these patients had either ceased their medication (2) or had changed to another antiemetic (3) due to harmful effects. In total, at one week 18 of 53 (34%) were still taking metoclopramide with a net clinical benefit.

A total of 17 patients experienced 24 harms (Table 4). The most frequently encountered harms were akathisia (4 patients), headache (4 patients), and abdominal pain (4 patients). Eleven patients had metoclopramide ceased with recorded harms in this subgroup including akathisia (4), headache (4), abdominal pain (4), tremor (1), dizziness (1), and “other” (7) including sweats, drowsiness, fecal blood, and two patients with bowel perforations. Five patients experienced toxicity at

### Table 2. Baseline Clinical and Demographic Data: Rapid Reporting Metoclopramide Pharmacovigilance Study in Hospice/Palliative Care

<table>
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<tr>
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<th>N (%)</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age</td>
<td>53</td>
<td>70</td>
<td>20–97</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>20 (39)</td>
<td></td>
<td></td>
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<tr>
<td>Australian-modified Karnofsky Performance Status score</td>
<td>53 (100)</td>
<td>6</td>
<td>0–12</td>
</tr>
<tr>
<td>Charlon Co-morbidity Index score</td>
<td>46 (83)</td>
<td>19</td>
<td>15–46</td>
</tr>
<tr>
<td>Body mass index</td>
<td>19 (35)</td>
<td>33</td>
<td>6–300</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>24 (44)</td>
<td>62</td>
<td>17–150</td>
</tr>
<tr>
<td>Calculated creatinine clearance</td>
<td></td>
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</table>

**Indication for metoclopramide**

- Nausea: 40 (76) 2 1–3
- Vomiting: 21 (40) 2 1–4
- Hiccups: 4 (8)
- Reflux: 6 (12)

**Primary life-limiting illness**

- Cancer: 50 (94)
- End-stage renal disease: 0
- End-stage cardiac disease: 1 (2)
- End-stage respiratory disease: 0
- End-stage hepatic disease: 2 (4)
- AIDS: 0
- Neurodegenerative disease: 0
- Other: 0

*There may be more than one indication for the medication.

*On one occasion for each was this the most severe symptom.

### Table 3. Net Clinical Effects (Individual Patients)

<table>
<thead>
<tr>
<th>Benefit/s a (1 point NCI c reduction)</th>
<th>Harm(s) b</th>
<th>N (% of 53)</th>
<th>Action following harm(s)</th>
<th>N (% of 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (23)</td>
<td>No</td>
<td>15 (28)</td>
<td>Ceased (2); other med (1)</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>8 (15)</td>
<td>Cessation d</td>
<td>5 (9)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Change to other medication d</td>
<td>4 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose reduction d</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change in medication d</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other d</td>
<td>1 (2)</td>
</tr>
<tr>
<td>No (30)</td>
<td>No</td>
<td>21 (40)</td>
<td>Extra PRN dose (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>9 (17)</td>
<td>Cessation d</td>
<td>6 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change to other medication d</td>
<td>3 (6)</td>
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<td></td>
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<td>Dose reduction d</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No change in medication d</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other d</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Reported at 2 days.

*Reported at 7 days.

*National Cancer Institute’s Common Toxicity Criteria.

*More than one response is allowed.

PRN, pro re nata.
trolled data to support their use. 8 There was no evidence other widely used medications having no randomized con-
level of evidence available for any antiemetic with many
mide as first-line therapy for nausea, and this was the best
there was “moderate evidence” for the use of metoclopra-
limiting illnesses where symptoms were not related to che-
reviews that reflect the population with advanced life-
later than one week of treatment with metoclopramide.
Conversely, harms such as akathisia may have an onset much
increased number of patients who derive benefit subsequently.
if there is no clinical benefit further. This may in part be due to an inability to measure
census point later than 2 days may increase positive responses
is low given the prevalent use of metoclopramide, although a
other causes. Rates are likely to be higher when
metoclopramide is prescribed with other dopamine antago-
ness and motor agitation) and tremor are warranted, both of
which may be missed clinically if not specifically sought, or
attributed to other causes. Rates are likely to be higher when
metoclopramide is prescribed with other dopamine antago-
ists (e.g., haloperidol, promethazine) that can also induce
side effects in hospice/palliative care.6,7

Discussion

This study details the actual performance of metoclopra-
mide in daily hospice/palliative care practice across a range
of clinical settings by codifying clinical benefits and harms.
Although no new harms were identified, 32% of people ex-
perienced harms. Given the wide use of metoclopramide in
hospice/palliative care, this study suggests that careful
attention to eliciting symptoms including akathisia (restless-
ness and motor agitation) and tremor are warranted, both of
which may be missed clinically if not specifically sought, or
attributed to other causes. Rates are likely to be higher when
metoclopramide is prescribed with other dopamine antago-
ists (e.g., haloperidol, promethazine) that can also induce
side effects in hospice/palliative care practice.6,7

The overall positive response with acceptable harms of 34%
is low given the prevalent use of metoclopramide, although a
census point later than 2 days may increase positive responses
further. This may in part be due to an inability to measure the
benefit of prophylactic use. If there is no clinical benefit
at 48 hours, it is not clear that there will predictably be an
increased number of patients who derive benefit subsequently.
Conversely, harms such as akathisia may have an onset much
later than one week of treatment with metoclopramide.

The current data reflect the two most recent systematic
reviews that reflect the population with advanced life-
limiting illnesses where symptoms were not related to che-
otherapy or radiotherapy.8,9 Davis’ review concluded that there
was “moderate evidence” for the use of metoclopramide as first-line therapy for nausea, and this was the best
level of evidence available for any antiemetic with many
other widely used medications having no randomized con-
trolled data to support their use.8 There was no evidence metoclopramide has an effect on opioid-induced emesis.9
Glare and colleagues note that randomized controlled trials
(RCTs) had much higher response rates to single arm, open
label studies, and the findings of the current pharmacov-
igilance study demonstrate outcomes comparable with the
RCTs for nausea (response rates 23% to 36%) and emesis
(18% to 52%).9 It is expected that a prospective pharmacov-
igilance study would have net benefits at lower rates than
a selected population in a randomized controlled trial or a
retrospective case series.

Limitations

This study only addresses immediate and short-term
harms. Longer-term harms or rare but catastrophic harms will
need to be studied with either longer periods of surveillance or
by other mechanisms such as integrating prescribing datasets linked to comprehensive electronic medical records
or ad hoc clinician reporting. The latter is limited by recogni-
tion of only the most florid examples. The effects of pro re nata
(PRN) prescribing is not covered nor is there a way to simply
measure drug interactions.

The modified Naranjo score including only five of the
questions of relevance to practice was collected as an aggre-
gate number. This made its interpretation difficult, and the
individual scoring for each question is what is being collected
in subsequent studies.

It is a relatively small sample size in this, the first of these
studies.

Ensuring consistent interpretation for the measurement of
outcomes between sites is crucial to the quality of the data. For
subsequent studies, educational material will be developed
for each outcome in both clinical benefit and clinical harm.

Generalizability

The sample was drawn from a wide range of practices in-
cluding direct care and consultative inpatient services, com-
community care, and from outpatient clinics. The age distribution and
diagnoses represented reflect many hospice/palliative care practices around the world.

Implications for clinical practice

These data reiterate the need to understand the clinical
endpoints sought when initiating a new medication,10 and
the relatively low likelihood of this single pharmacological
intervention totally controlling nausea without any side
effects.
Future directions

Two people having bowel perforations seems high in this patient population. Rare but catastrophic events will need a separate reporting mechanism that is under consideration, which would include formal assessment of causality.

A different medication and one of its indications will be studied approximately every 3 months. We hope that more centers will join this initiative given the very limited impost on clinicians (10 minutes per participant in total), with the ability to accrue and collate relatively large amounts of data rapidly. (Contact david.currow@flinders.edu.au if your unit is interested in joining).

In the next medication, harm will be measured at baseline in addition to the data point specifically for harms to improve the ability to attribute the harms reported during the observation period to the index medication. Reasons for data not being available will also be systematically captured.

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Author Disclosure Statement

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References


Address correspondence to:
David C. Currow, M.P.H., FRACP
Discipline, Palliative and Supportive Services
Health Sciences Building
Repatriation General Hospital
Daw Park Road
Daw Park, South Australia
Australia 5041
E-mail: david.currow@flinders.edu.au