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JOURNAL OF PALLIATIVE MEDICINE
Volume 15, Number 10, 2012

DOI: 10.1089/jpm.2012.0111

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

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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.[1] 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).[2]

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 "unreidentifiable" 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,[3] it is timely

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Accepted May 30, 2012.

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.[1] 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.[4] 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.[5] Specifically, question 4 (drug readministration), question 6 (same side effect when placebo administrated), 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 1. Key Facts: Metoclopramide

Mechanism of action	Central	*Patient effects*	*Anti-nausea*
		Physiological effects	Acts on the chemoreceptor trigger zone and the vomiting centre
		Molecular effects	Dopamine 2 antagonist at clinical doses
	Peripheral	*Patient effects*	*Less early satiety*
		Physiological effects	Increased gastric and small bowel peristalsis, pyloric sphincter relaxation
		Molecular effects	Dopamine 2 antagonist at clinical doses
Pharmacokinetics		Bioavailability	70% oral
		Clearance	80% metabolized, 20% renal, Metabolized by: cytochromes P450 (CYP) 2D6 (major) and 3A (minor)
		Volume of distribution	3.5l/kg, crosses blood–brain barrier
		Half life	5–6 hours
		Dose modifications	**Reduce dose in severe renal impairment** (one-quarter normal dose) **and severe liver failure** (half normal dose)
*Frequently reported **adverse effects***		Short-term use, or at any time	Restlessness, fatigue, extra-pyramidal side effects
		Long-term use	**Irreversible tardive dyskinesia**
			Consequences
Important examples of drug interactions in hospice/palliative care		Additive effect with other dopamine antagonists (haloperidol)	Increased likelihood of extrapyramidal effects
		Inhibition of metabolism by CYP2D6 inhibitors (fluoxetine)	
		Blocking of prokinetic effects (anticholinergics such as hyoscine butylbromide)	Reduced anti-nausea effect
Contraindications		Reason: dopamine blockade	**Parkinson's disease** **Phaeochromocytoma** **Prolactinoma**
Monitoring		Clinical	Symptom burden
		Biochemical	n/a

Note: Bolded sections are serious or irreversible events.

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

		N *(%)*	*Median*	*Range*
Age		53	70	20–97
Gender (male)		20 (39)		
Australian- modified Karnofsky Performance Status score		53 (96)	50	20–90
Charlson Co-morbidity Index score		53 (100)	6	0–12
Body mass index		46 (83)	19	15–46
C reactive protein		19 (35)	33	6–300
Calculated creatinine clearance		24 (44)	62	17–150
			National Cancer Institute Common Toxicity Criteria grading for most severe symptom	
Indication for metoclopramide[a]	Nausea	40 (76)	2	1–3
	Vomiting	21 (40)	2	1–4
	Hiccups[b]	4 (8)		
	Reflux[b]	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		

[a]There may be more than one indication for the medication.
[b]On one occasion for each was this the most severe symptom.

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 3. Net Clinical Effects (Individual Patients)

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

[a]Reported at 2 days.
[b]Reported at 7 days.
[c]National Cancer Institute's Common Toxicity Criteria.
[d]More than one response is allowed.
PRN, *pro re nata.*

Table 4. Harms at Any Time in the 2 Weeks after Initiating Metoclopramide in Hospice/Palliative Care

			Response n = *40 people*				
	N *(%) harms*[a]	*Severity*[b] *median (range)*	*Cessation* n = *11*	*Other medication introduced* n = *7*	*Dose reduction* n = *0*	*No change in medication* n = *12*	*Other* n = *2*
Rigidity	0						
Akathisia	4 (10)	2.5 (1–4)	3	3		2	
Gait change	0						
Tremor	2 (5)	1 (1)	1	1		1	
Headache	4 (10)	2 (1–4)	2	1		2	
Dizziness	1 (3)	2 (2)	1	1			
Abdominal pain	4 (10)	2 (1–2)				4	
Vomiting	2 (5)	2 (1–2)				2	
Other	7 (18)	3 (1–3)	3	1		1	2

[a]Participants can have more than one harm but can also have more than one response.
[b]National Cancer Institute's Common Toxicity Criteria (NCI CTC).
Other: Drowsiness (2), diarrhea, bowel perforation (2), sweats, blood in feces.

NCI CTC grade III or greater. Despite this, 3 of the 5 experienced clinical reduction in nausea (one patient with akathisia, one with abdominal pain, and one with drowsiness); 2 of the 5 did not experience clinical benefit (both had headaches).

Discussion

This study details the actual performance of metoclopramide 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 experienced harms. Given the wide use of metoclopramide in hospice/palliative care, this study suggests that careful attention to eliciting symptoms including akathisia (restlessness 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 antagonists (e.g., haloperidol, promethazine) that can also induce these 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 chemotherapy 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 controlled data to support their use.[8] There was no evidence metoclopramide has an effect on opioid-induced emesis.[8] Glare and colleagues note that randomized controlled trials (RCTs) had much lower response rates to single arm, open label studies, and the findings of the current pharmacovigilance 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 pharmacovigilance 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 recognition 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 aggregate 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 including direct care and consultative inpatient services, 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.

Acknowledgments

Thanks go to Sunshine Coast Specialist Palliative Care Service, Queensland, Dr. Louise Welch; Braeside Hospital, New South Wales, A/Prof. Meera Agar; Calvary Mater Newcastle, New South Wales, A/Prof. Katherine Clark; Calvary Health Care, New South Wales, Dr. Christine Sanderson; Greenwich Hospital, New South Wales, Dr. Melanie Lovell; Peter MacCallum Cancer Centre, Victoria, Dr. Odette Spruyt; St. Vincent's Health, Victoria, Dr. Jennifer Philip; Barwon Health, Victoria, A/Prof. Peter Martin; Sir Charles Gairdner Hospital, Western Australia, Dr. David Dunwoodie; Christchurch Hospital Palliative Care Service, New Zealand, Dr. Wendy Pattemore; Mercy Hospice, New Zealand, Dr. Bruce Foggo; North Shore Hospice, New Zealand, Dr. Moira Camilleri, their research teams, all the clinicians who have contributed to this program, and other members of the study subcommittee for metoclopramide, Prof. Rod Macleod and Dr. Kate Grundy.

The Australian Palliative Care Clinical Studies Collaborative is supported by funding from the Palliative Care Branch of the Australian Government's Department of Health and Ageing.

Author Disclosure Statement

No competing financial interests exist.

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