

A Reappraisal of Metoclopramide

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SUMMARY

Metoclopramide is still the most widely prescribed anti-emetic in Australia, despite the lack of evidence supporting its use at the recommended doses. It has not been convincingly shown to decrease postoperative ileus after gut surgery, and it may cause dystonia in susceptible patients by virtue of its antidopaminergic properties. Has the time come to discard this drug from our formulary, or is it merely misunderstood?

If we consider the available data on metoclopramide and its effects on dopaminergic and serotonergic neurotransmission, then the latter is probably correct. Much of the early clinical data on the drug was attributed to incorrect mechanisms, yet has been retained in textbooks and prescribing recommendations, and we probably should reconsider our use of metoclopramide in light of this newer data.

The following discourse will review the known mechanisms of action of the drug, discount some early theories, highlight appropriate uses and suggest novel benefits, including myocardial protection.

BACKGROUND

Metoclopramide (MCP) was developed experimentally in the early 1960s as a dopamine antagonist drug, with clinical use first described by Justin-Besancon and associates in 1964. The drug is produced by the addition of a 5-chloro and 2-methoxy aryl group to the benzene ring in procainamide, which itself stems from the local anaesthetic, procaine.¹ More widespread use of metoclopramide commenced around 1968 in Europe, where it was used to treat nausea and vomiting in pregnancy. However, it was not studied in America until around 1975, when interest arose regarding its role as a dopaminergic antagonist in the gastrointestinal tract, and in the treatment of smooth muscle disorders.

By 1983, four distinct mechanisms had been postulated to explain the anti-emetic and prokinetic effects of metoclopramide:

1. Direct activation of intramural cholinergic neurons was surmised in the earliest studies, as the gut effects of 10 mg MCP persisted despite vagotomy, but could be abolished by 10 mcg/kg atropine. These effects also depended upon intrinsic stores of acetylcholine, unlike the case with conventional cholinergic compounds.¹
2. Central nervous system mediated antiemesis was attributed to central nervous system dopamine blockade, as therapeutic success did not always correlate with gastric emptying, and vomiting produced by apomorphine acting on the chemoreceptor trigger zone could be reversed with MCP, as well as the phenothiazines.¹

3. Promotion of gastrokinesis by dopaminergic blockade had been assumed after dopamine (DA) was presented in 1975 as being a significant inhibitory neurotransmitter in the autonomic nervous system, with specific receptors identified in the GIT, renal, and coronary circulations.² The oesophageal and gastric effects of MCP were able to be reversed to some extent by the administration of levodopa, a dopamine precursor, lending support to this mechanism as the cause of increased gastrokinesis.¹
4. Direct effects on smooth muscle were suggested by the persistence of MCP induced lower oesophageal sphincter contraction in the opossum, despite treatment with either tetrodotoxin (a sodium channel blocker) or atropine. Large doses of MCP were used in this study however, and a separate experiment using isolated gastric guinea pig smooth muscle did show MCP effect reversal with tetrodotoxin and hexamethonium, implicating postganglionic acetylcholine release as the final pathway.¹
None of these above mechanisms were shown to be correct.

CLINICAL APPLICATIONS

The pharmacological properties of MCP are now much better understood, and many effects aside from gastric prokinesis and anti-emesis have been identified. These are probably unrecognised by routine prescribers, and arise from a molecular configuration which allows for binding with many receptor subtypes. MCP has most affinity for the dopamine (DA)₂ and serotonin (5HT)₂ receptor subtypes, where it acts as an antagonist, but is also a DA₁, alpha-2 and 5HT₃ antagonist, and 5HT₁ and 5HT₄ partial agonist.³

The clinical utility of these effects in anaesthetic practise may be considered under the following headings:

Propofol pain prevention

Pain on injection of propofol is a common problem, affecting around 70% of patients who are not given any preventative.⁴ The mechanism which causes this pain remains unknown. However, the symptoms may be decreased by the addition of various drugs to either the propofol mixture itself or into the cannulated vein prior to injection. The drug traditionally used for this is lignocaine, although others have been trialled. An Australian study compared the addition of either 20 mg MCP or 10 mg lignocaine to the propofol mixture in 100 patients undergoing minor surgery. It found no difference in propofol pain scores between the groups, although it must be noted that the lignocaine dose was relatively low.⁵ A later systematic review covered data from 6264 patients and analysed treatment with the following agents: lignocaine, opioids, MCP and heating or cooling the mixture. Results for different treatment modalities were compared by assessment of number needed to treat (NNT), which refers to the number of patients exposed to the active intervention before one will gain benefit. The best result was obtained when lignocaine 60mg was given into a vein occluded by tourniquet prior to propofol injection; this gave a NNT of 1.6. This increased to 2.4 if lignocaine 20 mg was mixed with propofol, a more common regime, and was in fact bettered by 10 mg MCP using a tourniquet technique (NNT 2.2). MCP was less effective if given without a tourniquet, where the NNT increased to 2.7, but it is obvious that both mechanisms are effective. Temperature adjustment or opiate use was minimally helpful, excepting pethidine with a tourniquet technique, which had a

NNT of 1.9, possibly because of a direct local anaesthetic effect. Other agents were noted to have been trialled in this systematic review, including ondansetron, droperidol, ketamine, aspirin, ketorolac and others. However, no meaningful conclusions could be drawn from their respective studies.⁴

Gastric prokinetic effects

These effects appear to be mediated via gastrointestinal 5HT₄ receptors,^{6, 7, 8} akin to the method of action of the drug cisapride. They promote an increase in lower oesophageal sphincter pressure tone, along with accelerated gastric emptying through both more frequent and more intense antral and duodenal contractions.¹ Cisapride has been shown to be seven times more potent than MCP in promoting rat gastric emptying, despite the fact that both drugs are 5HT₄ agonists.⁹ One possible reason why MCP is less effective is that 5HT₁ activation with sumatriptan, a specific 5HT₁ agonist, mediates suppression of gastric emptying, and may be mimicked by the weaker 5HT₁ effects of MCP.¹⁰ The side effect which led to cisapride being withdrawn in some countries (QT prolongation and ventricular dysrhythmias) has been experimentally related to class III anti-arrhythmic effects of the cisapride molecule which also blocks voltage dependant potassium channels, and not the 5HT₄ receptor.¹¹

The oesophageal and gastrokinetic effects of MCP are blocked with concurrent use of atropine 10 mcg/kg owing to the involvement of intramural cholinergic modulation in the prokinetic pathway.⁶ The decrease in gastric emptying seen with opiates is a separate issue, and occurs due to increased resting tone within the gastrointestinal tract. It is likely that the increased lower oesophageal sphincter tone due to MCP will persist in this setting, although it does not appear to have been assessed specifically.

The time to onset of gastrointestinal effects, if measured using oesophageal sphincter tone as an end point, is 1-3 minutes after IV injection, 10-15 minutes after IM injection, and 30-60 minutes after oral ingestion. (Peak plasma levels measured after a 20 mg MCP dose were around 84 ng/ml po or 221 ng/ml iv.)¹²

MCP has been used effectively to treat delayed gastric emptying in patients with diabetic gastroparesis. One study using isotope labeled egg salad sandwiches showed an accelerated gastric clearance at sixty and ninety minutes following dosage with MCP, such that the residual volume dropped to around two thirds of that in the untreated group. However, the emptying rate remained less than that of normal subjects.¹

Post surgical ileus has been treated with MCP with varying results. Chronic gastric emptying abnormalities following vagotomy or gastric resection may improve significantly, although acute postoperative ileus has not shown accelerated resolution, despite some degree of symptomatic improvement.^{1, 13} However, it should be remembered that increased gut wall tension without distal outflow may be undesirable where anastomoses in the upper GIT have been newly created, as the risk of leakage or rupture is enhanced.

Anti-emesis

Despite routine use as a first line anti-emetic, there remains much controversy about this role. MCP demonstrates a proven anti-emetic effect in adults only at higher doses (1-4 mg/kg) as used during some chemotherapy regimes. This has been related to its low affinity 5HT₃ receptor antagonism, and it appears that the drugs antidopaminergic properties are irrelevant here, except in producing dose limiting side effects, including

behavioural depression.¹⁴ A Cochrane Review of the literature from 1966 to 1998, considering only randomized controlled trials, found data on eighteen different MCP regimes for postoperative nausea and vomiting (PONV) prophylaxis. These included an adult dosage range of either 5-30 mg or 0.25-0.5 mg/kg MCP, yet at all dosage levels the outcome was the same: there was no statistical difference between metoclopramide and placebo in the prevention of PONV. In children, however, MCP was found to be more effective than placebo at preventing vomiting (most studies did not assess nausea) with a number needed to treat (NNT) of 7.9 (95% confidence interval 4.6, 28). The authors conclusions included a recommendation for randomized dose finding studies, as there was a suggestion that higher MCP doses in adults could prevent vomiting, although this did not reach clinical significance in the studies considered. Interestingly, there were no significant differences between MCP and placebo in the incidence of all adverse reactions, despite a predicted 10% incidence overall with MCP.¹⁵

Phaeochromocytoma detection

A single paper suggested that the injection of 10 mg MCP intravenously could be a useful provocative test to screen for suspected phaeochromocytoma. A review of three such cases showed a mean systolic blood pressure rise of 15 mmHg, and an increase in serum arginine vasopressin levels following injection. This response returned to normal after tumour excision.¹⁶ Most product information however, lists phaeochromocytoma as a contraindication, due to potential and unpredictable hormonal responses. Perhaps more than three cases need to be assessed before this procedure can be recommended. A more sensible use of this knowledge would be to consider the diagnosis of phaeochromocytoma in patients who develop hypertension instead of the expected drop in blood pressure following MCP injection, particularly when there is an associated history of paroxysmal hypertension.

Hormone release

Documented effects on other hormone levels include: a transient increase in serum aldosterone levels mediated by action on the 5HT₄ receptor,^{7, 17, 18} a transient increase in serum cortisol levels,^{17, 19} particularly with higher doses, and increased prolactin release.¹ A dose of 10 mg MCP tds has been advocated in obstetric practice to stimulate lactation by increasing prolactin levels, but the other hormonal effects described have not yet been shown to have any perioperative application.

Migraine treatment

Recent advances in migraine pathophysiology have implicated the release of a neuropeptide, calcitonin gene-related peptide (CGRP), by trigeminal nerve vascular afferents in the initiation and maintenance of migraine pain.²⁰ The resultant inflammation and accompanying meningeal blood vessel dilatation respond to treatment with drugs such as sumatriptan, a selective 5HT₁ agonist. This newer class of antimigraine drugs, known as triptans, act via 5HT_{1b/1d} receptors to cause both selective cranial blood vessel constriction and repression of CGRP secretion and transcription.^{20, 21}

This knowledge has provided a basis for further research in migraine treatment, yet it is worth noting that an older treatment modality using aspirin, when combined with MCP has been shown to be similarly effective. A double blinded placebo controlled

trial in 1995, randomised 421 pts who fulfilled International Headache Society criteria for migraine to receive either aspirin 900 mg with MCP 10 mg, or sumatriptan 100 mg at headache onset. Similar improvement was found between both groups ($P=0.5$) when compared with placebo ($P<0.006$), using an outcome of a decrease in headache intensity; from severe or moderate to mild or no pain.²² The mechanism for the first group was attributed to more rapid absorption of aspirin in nauseated migraine sufferers when given MCP, although the actions of MCP as a 5HT1 agonist are probably significant, given the specific 5HT1 actions on migraine pathology. 5HT2 mediated vasodilatation, which MCP also produces, is unlikely to interfere with this specific mechanism and is supported by the experimental finding that 5HT2 blockade by ketanserin does not interfere with sumatriptan induced contractions in isolated middle meningeal artery specimens.²³

Myocardial protection

Clinical data in humans has shown that normal epicardial coronary arteries dilate in response to serotonin, probably by activation of endothelial 5HT1 receptors, which initiate the release of endothelium derived relaxing factors. On the other hand, diseased atherosclerotic coronary arteries constrict due to activation of 5HT2 receptors on smooth muscle cells.²⁴ In both cases, MCP will favour vasodilatation.

Human and animal laboratory studies go as far as to suggest a role for MCP in prevention of acute coronary artery thrombosis. Atherosclerotic plaque rupture is the usual initiating event in coronary thrombosis,²⁵ and may be precipitated by mechanical stress from blood pressure changes during intubation in susceptible individuals. This leads to clotting activation and platelet aggregation by the extrinsic pathway. The platelet response, which includes serotonin release, promotes arteriospasm and further platelet aggregation, but has been shown to be attenuated by both 5HT2 blockade and thromboxane A2 inhibition.²⁶ These effects are synergistic and the response has been shown to be useful in human radial and internal mammary artery specimens,²⁶ as well as in animal models of coronary artery occlusion.^{27, 28}

The human studies have been directed specifically at preventing vasospasm related to platelet activity in the setting of coronary artery grafting, whereas animal studies have assessed experimental lesions and provocation of coronary thrombosis. A canine model of coronary artery thrombosis assessed cyclic flow variation (CFV) to demonstrate sequential thrombosis and embolisation in a critically stenosed circumflex coronary artery, with a controlled arterial lesion at the site of stenosis. The findings in this case were that the combination of aspirin 0.1 mg/kg and MCP 0.3 mg/kg lead to a drop in CFV from 6.7 ± 0.5 to 0.8 ± 0.4 cycles per hour ($P<0.01$), indicating a significant antithrombotic effect. Neither agent alone produced significant results, indicating synergism between the two.²⁸ A separate experiment involving a rat model of critical arterial stenosis, given hypotonic saline with serotonin to initiate thrombosis, showed significant antithrombotic effect from MCP, as well as synergism with aspirin.²⁷

The human experimental data showed significant antispasmodic effect on both types of arterial specimen from 5HT2 blockade, particularly after removal of endothelium.²⁶ These results suggest that the metoclopramide alone, or in combination with aspirin, may decrease the risk of perioperative myocardial infarction caused by coronary plaque rupture. A definitive study in humans remains to be carried out. The potential risks of impaired coagulation during surgery when metoclopramide has been given do

not appear to have been investigated, but there are no reported problems of this nature in the literature.

Pain relief

A recent study investigated the possibility that MCP enhances analgesic efficacy. Fifty-six patients were randomised to receive either metoclopramide or placebo prior to undergoing laparoscopic tubal ligation, then assessed postoperatively using a numeric pain rating scale. Opioid requirements were also documented. The pain scores were similar in both groups at all three time intervals examined, but the morphine requirements were significantly higher in the placebo group ($P=0.031$). The data allowed a conclusion that the addition of metoclopramide was opiate sparing, but did not assess for direct analgesic efficacy.²⁹ The mechanism of opiate sparing was not determined although 5HT1 and 5HT4 receptor activation may be important if we consider that the analgesic drug tramadol acts partially by enhancing serotonin release,³⁰ but can be rendered less efficacious by concurrent strong 5HT3 blockade with ondansetron.^{31,32}

ADVERSE REACTIONS

Aside from these useful applications, MCP may also cause a number of unwanted side effects. Those which are not widely known will be considered, as well as the symptoms commonly known as dystonias, movement disorders or extrapyramidal reactions, which are infrequent but striking responses to the drug.

Plasma cholinesterase inhibition

MCP may prolong the effects of suxamethonium¹² and does prolong mivacurium induced neuromuscular block, by decreasing plasma cholinesterase activity. A recent study randomized 45 patients to receive either placebo, MCP 10 mg or MCP 20 mg prior to induction of a relaxant anaesthetic including mivacurium. Neuromuscular block was monitored with a force transducer using train of four stimulation and found the time to spontaneous recovery of 90% twitch height was increased from 32 ± 9 min to 44 ± 15 min following 10 mg MCP, or 57 ± 10 min after 20 mg MCP. A slight but significant decrease in plasma cholinesterase activity was found in the 20 mg group.³³ This may be significant if reversal agents are to be avoided on the assumption of spontaneous reversal with mivacurium within the above time frames. The finding warrants confirmation of reversal with a nerve stimulator where MCP has been given.

Raised intracranial pressure (ICP)

Although the mechanism was not determined, a case report on one head injured patient with diffuse axonal injury, showed a reproducible increase in ICP from a 15-20 mmHg baseline up to 39 mmHg, following 10 mg IV MCP. The patient was given the same dose during transcranial doppler studies the next day; this gave rise to a similar increase in ICP and an associated blood velocity increase from 122 cm/s to 150 cm/s in the middle cerebral artery.³⁴ A possible explanation is that rapid injection of MCP does cause transient systemic hypotension due to vasodilatation,³⁵ the intracranial component of which would compress the intracranial contents further, causing the observed rise in ICP.

Reversal of “renal dose” dopamine

It has been questioned whether the use of MCP is appropriate in patients who are being treated with a so called renal dose of dopamine (around 3 mcg/kg/min), as the consequent dopamine blockade may reverse the desired effect of renal vascular dilatation. Such reversal has been shown to occur in animal studies, with a 44% drop in dopamine induced vasodilatation after MCP 1 mg/kg, despite the drug having a relatively low affinity for the DA1 receptor responsible.³⁶ A study of stable patients in intensive care however, measured renal blood flow and creatinine clearance during dopamine infusion at the rate above, and showed no detrimental effect from 10 mg MCP.³⁷ The relevance of this remains questionable, as no convincing data has shown dopamine to be effective for renal function preservation.³⁸

Serotonin syndrome with selective serotonin reuptake inhibitors

Two patients were reported to have developed a serotonin syndrome after being given MCP whilst on the SSRI drugs, sertraline or venlafaxine. The symptoms were reproducible with re-administration in both cases and included agitation, dysarthria, movement disorder and diaphoresis. The symptoms met criteria for serotonin syndrome, and were thought to be due to a pharmacodynamic interaction, although a single drug effect from MCP could not be ruled out.³⁹ Concomitant use with SSRIs is not a listed contraindication to MCP use, but it would be prudent to avoid such use if alternatives exist.

Acute movement disorders

These are sometimes known as extrapyramidal symptoms; however, this terminology encompasses a range of descending spinal pathways and implies an anatomical basis for the problem. These disorders may occur with most antidopaminergic drugs, and are divided into three potential syndromes:¹

1. A range of dystonias affecting primarily the facial muscles and producing trismus, torticollis, facial spasms, opisthotonos, or oculogyric crises;
2. A parkinsonian like syndrome with agitation and impaired mobility; or,
3. Akathisia, a compulsion toward constant motor activity.

(Tardive dyskinesia is associated only with chronic administration and will not be considered specifically).

The largest prospective study to date assessing first prescriptions of all forms of metoclopramide found a total incidence of movement disorders of 0.5% in 2557 patients.⁴⁰ However, perioperative data from a meta-analysis of randomised controlled trials found no acute movement disorder in 220 children given parenteral MCP doses from 0.15 to 0.5 mg/kg, and one isolated episode in an adult given 20 mg intravenously, from a total of 1177 subjects given either MCP or placebo.¹⁵

It is interesting to note that, despite the above results, both the MIMS¹² and *Australian Medicines Handbook*⁴¹ do not recommend MCP use in children due to an increased risk of movement disorders. Some support for this notion is given by general practice data showing that high risk patients for these side effects include young children and females aged 12-19 years.⁴² There have also been reports suggesting an increased risk in patients with the acquired immune deficiency syndrome, where it may be associated with a disease related decrease in central nervous system dopamine activity.⁴⁰

Acute movement disorders may be unpleasant for the patient, but are not generally

dangerous. Fatal outcome has been reported due to pharyngeal muscle involvement, although it is extremely rare. It is recommended that these reactions be treated with parenteral benzotropine 1-2 mg.⁴¹

Of related interest, a pH neutral form of MCP (ph 6.9-7 instead of 2.5-3.5) has been developed, and initial testing shows decreased DA₂ affinity and increased 5HT₃ affinity, suggesting the possibility of significantly improving the safety and efficacy of the drug.¹⁵

CONCLUSION

It has now become obvious that a drug originally presented as a dopamine antagonist, in fact has no useful effects attributable to this mechanism, except perhaps prolactin release. It is probably better considered as a serotonin receptor modulating drug which has dose limiting anti-dopaminergic effects.

If one considers that the recommended uses of MCP are limited to treatment of nausea and vomiting, gastric stasis (post-surgical and diabetic) and difficult small intestinal intubation, with accepted indications of gastro-oesophageal reflux disease and gastrointestinal radiology, and that recommended adult doses are 10 mg 6-8 hourly for nausea and vomiting,⁴¹ then it is surprising that it continues to be prescribed postoperatively at all. The likelihood of a useful response with these indications is small. The use of MCP in anaesthesia may be better confined to preoperative and intraoperative use, where it has a number of known and potential benefits including minimisation of propofol injection pain, increased lower oesophageal sphincter tone, enhanced analgesia, myocardial protection, and enhanced gastric emptying.

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