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Mini Review

Metoclopramide: An Antiemetic in Chemotherapy Induced Nausea and Vomiting

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Abstract

Chemotherapy induced nausea and vomiting (CINV) are two of the most feared adverse events experienced by cancer patients undergoing chemotherapy. Metoclopramide was derived from procainamide in the 1950s and one of the first drugs investigated in the prophylaxis of nausea and vomiting induced by chemotherapy. The breakthrough came in 1981 with the recognition that high-dose metoclopramide was effective and tolerable in the prevention of cisplatin-induced nausea and vomiting. A combination of high- dose metoclopramide and a corticosteroid was the standard antiemetic recommendation until the serotonin $(5\text{-HT})_3$-receptor antagonists, ondansetron, granisetron, tropisetron and dolasetron became available in the beginning of the 1990s.

The development of these highly selective $(5\text{-HT})_3$-receptor antagonists with a superior effect and a preferable tolerability profile has limited the use of metoclopramide to be prescribed as a rescue antiemetic, when guideline recommended antiemetic therapy fails.

ABBREVIATIONS

CINV: Chemotherapy-Induced Nausea and Vomiting; MCP: Metoclopramide; NK_1-Receptor Antagonist: Neurokinin $(NK)_1$-Receptor Antagonist; 5-HT_3-Receptor Antagonist: 5-Hydroxytryptamine $(5\text{-HT})_3$-Receptor Antagonist

INTRODUCTION

Metoclopramide (MCP) is a dopamine receptor antagonist, and is the most intensively investigated drug of this class as regards prophylaxis of chemotherapy-induced nausea and vomiting (CINV).

MCP (2-methoxy-5-chloro-procainamide) was originated in the 1950s as a substituted benzamide derived from procainamide a drug with local anesthetic and antiarrhythmic properties [1]. In therapeutic doses, MCP is almost devoid of these effects, but instead enhances gastrointestinal motility and possesses antiemetic effect.

MCP was tested in the early 1960s by Justin-Besancon, Laville, and Thominet [2] and soon proved to be effective against nausea and vomiting induced by a number of non-malignant conditions such as dyspepsia, delayed gastric emptying and postoperative nausea and vomiting [1,3].

The emetic risk of chemotherapy is divided in high emetic risk (risk of vomiting 0-24 hours after chemotherapy > 90%), moderate emetic risk (30-90%), low emetic risk (10-30%) and minimal emetic risk (< 10%). This paper will review studies with MCP in the prophylaxis of nausea and vomiting in patients receiving high and moderate emetic risk chemotherapy, primarily cisplatin (high risk), anthracyclines (moderate risk), cyclophosphamide (moderate risk) and the combination of an anthracycline and cyclophosphamide (high risk). The most important randomized studies are summarized in Table 1.

The early trials (1960-1989)

Conventional, low doses of MCP: In randomized, double-blind trials, oral doses of MCP 20 mg x 2-3 were equal to placebo or to prochlorperazine, (but both were ineffective) and inferior to dexamethasone or domperidone against nausea and vomiting induced by both non-cisplatin-based and cisplatin-based chemotherapy [4-7]. It should be noticed, that in these early trials, only the first 24 hours after chemotherapy was evaluated, and it can therefore be concluded, that MCP in oral doses up to 20 mg is no better than placebo in the period 0-24 hours after chemotherapy. The interest in investigating MCP in conventional doses was therefore modest during the 1960s and 1970s.

Table 1: Important randomized studies 1960-2017 in the development of metoclopramide as an antiemetic in the prophylaxis of CINV.

Reference	Number of patients	Chemo-therapy	Investigational Arm	Comparator	Primary parameter	Results*
Moertel et al. 1969 [4],	144	Non-CIS	MCP 20 mg x 3 po	PLA MPZ 5 mg x 3 po	Incidence of nausea and vomiting days 1-4	MCP = MPZ = PLA
Frytak et al. 1981 [6],	100	CIS	MCP 20 mg x 3 po	PCP	Vomiting	MCP > PCP, both ineffective
Gralla et al. 1981[8],	41	CIS	MCP 2 mg/kg x 5 iv	PLA PCP 10 mg x 5 im	Number of EE 0-24 hours	MCP > PLA MCP > PCP
Grunberg et al. 1984 [19],	28	CIS	MCP 2 mg/kg x 5 iv	HAL 3 mg/kg x 5 iv	Number of EE 0-24 hours	MCP > HAL
Kris et al. 1985 [9],	60(24 received 3 mg/kg x 2	CIS	MCP 2 mg/kg x 5 iv	MCP 3 mg/kg x 2 iv	Number of EE 0-24 hours	3 mg/kg x 2 iv = 2 mg/kg x 5 iv
Warrington et al. 1986 [11],	33	CIS	MCP 7 mg/kg divided in 5 bolus infusions + DEX 20 mg iv	MCP 3 mg/kg followed by 4 mg/kg (8 hour continuous infusion) + DEX 20 mg iv	Nausea and vomiting 0-24 hours	Nausea, vomiting and patient preference in favor of the continuous regimen
Kris et al. 1987 [22],	120	CIS	MCP 3mg/kg x 2 iv + DEX 20 mg iv + DPH 50 mg iv	MCP 3mg/kg x 2 iv + DEX 20 mg iv + L 1.5 mg/m2 iv	Number of EE 0-24 hours Safety	No difference in EE, but less restlessness with L
Roila et al. 1989 [10],	367	CIS	MCP 1 mg/kg x 4 iv + MP 250mg x 2 iv	MCP 3 mg/kg x 2 iv + DEX 20 mg iv + DPH 50 iv	Complete protection from vomiting/nausea 0-24 hours, Safety	MCP 3 mg/kg superior as concerns EE, nausea and safety (<extrapyramidal AE)
Marty et al. 1990 [33],	97	CIS	OND 8 mg iv + OND 1 mg/h iv for 24 hours	MCP 3 mg/kg iv + MCP 0.5 mg/kg/h for 8 hours	Number of patients with 0-2 EE 0-24h	OND > MCP
De Mulder et al. 1990 [34],	125	CIS	OND 8 mg iv + OND 1 mg/h iv for 24 hours + OND 8 mg x 3 po days 2-6	MCP 3 mg/kg iv + MCP 0.5 mg/kg/h for 8 hours+ MCP 20 mg x 3 po days 2-6	Number of patients with 0-2 EE 0-24 h Number of patients with 0-2 EE days 2-6	0-24 h: OND > MCP Day 2-6: Vomiting: OND = MCP Nausea:Ond
Bonneterre et al. 1990 [39],	75	FAC or FEC	OND 4 mg iv + OND 4 mg po day 1 + OND 8 mg x 3 po for 3-5 days	MCP 60 mg iv + MCP 20 mg po day 1 + MCP 20 mg x 3 po for 3-5 days	Number with 0-2 EE (day 1) Number with 0-2 EE (days 2-3)	EE: OND > MCP (days 1-3) Nausea: OND > MCP (day 1) Nausea: OND = MCP (days 2-3)
Kaasa et al. 1990 [40],	93	AC or EC	OND 8 mg iv day 1 + OND 8 mg x 3 po for 3-5 days	MCP 60 mg iv + MCP 20 mg po x 3 for 3-5 days	EE (day 1) but not specified if the primary parameter was number with 0 EE or with 0-2 EE. EE (days 2-3) same comment	0 EE: OND > MCP (day 1) 0 EE: OND = MCP (days 2-3) Nausea: OND > MCP (day 1) Nausea: OND = MCP (days 2-3)
Marschner et al. 1991[41],	122	EC or FEC	OND 8 mg po + OND 8 mg x 3 po for 3-5 days	MCP 60 mg iv + MCP 20 mg po x 3 for 3-5 days	Number of patients with 0-2 EE 0-24 h.	OND = MCP
Warr et al. 1993 [35],	151	CIS	GRA 80 µg/kg iv	MCP 2 mg/kg x 5 iv+ DEX 10 mg iv + DPH10 mg iv	Mean nausea score (day 1) Number of patients with 0 EE (day 1)	GRA = DEX + MCP + DPH
Chevallier et al.1993 [36],	281	CIS	GRA 40 µg/kg iv +up to 2 more doses of GRA if breakthrough emesis within the first 24h	MCP 3 mg/kg iv + MCP 0.5 mg/kg/h for 8 hours + DEX 12 mg iv	Number of patients with no vomiting and no or only mild nausea 0-24 h	GRA = DEX + MCP
Roila et al. 2015 [52],	303 of 480 planned	CIS	PAL 0.25 mg iv + DEX 12 mg iv + APR 125 mg x 1 po day 1+ DEX 8 mg x 1podays 2-4 + MCP 20 mg x 4 po days 2-4	PAL 0.25 mg iv + DEX 12 mg iv + APR 125 mg x 1 po day 1+DEX 8 mg x 1 po days 2-4+ APR80 mg x 1 podays 2-3	Complete response (no EE and no rescue antiemetics) days 2-5	MCP + DEX = APR + DEX

*> means a statistical significant difference; = means no statistical significant difference, but numerical differences may appear.
0-24 hours means from start of cisplatin infusion until 24 hours after. EE, emetic episodes; AE, adverse events; PCP, prochlorperazine; MCP, metoclopramide; DOM, domperidone; MPZ, metopimazine; DEX, dexamethasone; MP, methylprednisolone; DPH, diphenhydramine; L, lorazepam; HAL, haloperidol; OND, ondansetron; GRA, granisetron; PAL, palonosetron; PLA, placebo; APR, aprepitant; CIS, cisplatin; F, 5-fluorouracil; A, doxorubicin; E, epirubicin; C, cyclophosphamide.

High-dose MCP: Gralla and coworkers were some of the first to investigate the effect of high-dose MCP in prevention of cisplatin-induced nausea and vomiting [8]. Their study, published in 1981, actually consisted of two double-blinded randomized trials, the first comparing high-dose MCP to placebo (n = 21) and the second a comparison with prochlorperazine (n = 20). The dose of MCP was 2 mg/kg intravenously administered 5 times, starting 30 minutes before chemotherapy and ending 8.5 hours following cisplatin-based (120 mg/m^2) chemotherapy, yielding a total dose of MCP10 mg/kg. The primary parameter was the number of emetic episodes within the first 24 hours following cisplatin. Patients receiving MCP had significantly fewer episodes of emesis than patients receiving placebo (median number of emetic episodes 1.0 versus 10.5, p = 0.001) or prochlorperazine (median 1.5 versus 12.0, p = 0.005). MCP also significantly reduced the volume of emesis and shortened the duration of nausea. Adverse events included mild sedation in 76 % of patients receiving MCP versus 50%/40% of patients receiving placebo/prochlorperazine, and one patient in the MCP group experienced an extrapyramidal reaction. This study is the most important one investigating the effect of MCP in CINV, because it was now possible for the first time to prevent nausea and vomiting in cisplatin-treated patients.

Subsequent studies tried to fine-tune the high-dose MCP regimen, by comparing 4-5 bolus doses of MCP 1-2 mg/kg with two bolus doses of 3 mg/kg [9,10] or with a bolus dose followed by continuous infusion of MCP [11]. Some of these studies also investigated if the antiemetic effect of MCP was correlated to the plasma concentration of MCP [11-16], but inconsistent results were obtained and no clear-cut plasma level was defined.

High-dose MCP was also investigated in non-cisplatin chemotherapy [17], but never obtained the same success as in cisplatin-based chemotherapy. Other dopamine receptor antagonists such as prochlorperazine [18] and haloperidol [19] were investigated in high doses and compared with high-dose MCP, but no advantages with any of these agents were observed.

High-dose MCP combined with a corticosteroid: Even though high-dose MCP was considered the golden standard of antiemetic treatment for patients receiving cisplatin-based chemotherapy, the treatment only prevented nausea and vomiting in about 30-40% of the patients [20]. In 1984-1987 a number of studies demonstrated that the addition of either methylprednisolone [21,22] or dexamethasone [23,24] improved the effect of MCP and in the same time reduced MCP induced adverse events, in particular diarrhea.

High-dose MCP combined with a corticosteroid and diphenhydramine or lorazepam: Acute dystonic reactions induced by high-dose MCP are a significant problem, particularly in younger patients [25,26]. It was soon verified that the addition of diphenhydramine or lorazepam resulted in a significant reduced incidence of extrapyramidal adverse effects. A modified high-dose MCP regimen (3 mg/kg x 2 i.v. or 4 mg/kg x 1 i.v.) combined with dexamethasone and lorazepam or diphenhydramine (to decrease the incidence of extrapyramidal adverse effects) was the standard regimen in cisplatin–based chemotherapy [10,27] until the serotonin receptor antagonists became available in the early 1990s.

The later trials (1990-1999)

High-dose MCP versus a serotonin-receptor antagonist: Studies published 1978-1986 demonstrated that the effect of high-dose MCP is not due to antagonism at dopamine receptors, but is caused by antagonism at 5-HT$_3$ receptors [28-31]. This recognition led to the development of a new class of antiemetic agents - the serotonin receptor antagonists of which the first clinical study was published in 1987 [32].

In 1990 two randomized double-blind studies in patients receiving cisplatin-based chemotherapy used a cross over design and compared the antiemetic effect of the serotonin receptor antagonist, ondansetron, with high dose MCP [33,34]. In the first [33] study (n = 97), ondansetron was more effective than MCP in the prevention of acute (0-24 hours) nausea and vomiting and more patients preferred the ondansetron regimen (55% versus 26%, p = 0.006). The second [34] study (n = 125) also found that ondansetron was superior to MCP in the first 24 hours after cisplatin and more patients preferred ondansetron (54% versus 30%, p = 0.012), but MCP was actually more effective in the prevention of delayed nausea (days 2-6, p = 0.016). Also other 5-HT$_3$-receptor antagonists, such as granisetron [35, 36], tropisetron [37] and dolasetron [38] were compared to either MCP alone [38] or a combination of MCP and dexamethasone [35-37] in patients treated with cisplatin. The conclusion from these studies is that the 5-HT$_3$-receptor antagonist was superior to single agent MCP [38] and non-inferior to the combination of MCP and dexamethasone [35-37].

Three randomized, double-blind studies published 1990-1991 compared MCP and ondansetron in patients receiving anthracycline-cyclophosphamide (AC)-based chemotherapy [39-41]. The AC combination was in 1990 classified as moderately emetogenic, but is today recognized as highly emetogenic [42]. In two studies including a total of 178 evaluable patients [39,41], all were women with breast cancer, and in the third study [39] the majority (n = 51) were women with breast cancer as well, but also patients with non-Hodgkin's lymphoma (n = 31) and other tumor types (n = 11) were included. In two trials, ondansetron was significantly superior to MCP as concerns acute (0-24 hours) vomiting and nausea [39,40] and ondansetron was in one of these studies [39] also significantly superior in the prevention of vomiting (but not nausea) days 2-3. In the third trial [41] no statistical significant differences were seen.

These studies led to a shift in standard antiemetic therapy for both cisplatin-based and AC-based chemotherapy. A 5-HT$_3$-receptor antagonist was now recommended instead of MCP and subsequent studies demonstrated the advantage of combining a 5-HT$_3$-receptor antagonist with dexamethasone [43] and this combination was the golden standard until the first NK$_1$-receptor antagonist, aprepitant, became available in 2003.

MCP in the prevention of delayed nausea and vomiting: Until the mid-1980s, the vast majority of antiemetic studies evaluated patients during the first 24 hours after chemotherapy, only. Kris et al., extended the observation time to include the period from 24-120 hours after cisplatin-based chemotherapy and antiemetic prophylaxis with high-dose MCP (3 mg/kg x 2 i.v.) plus dexamethasone 20 mg i.v. combined with either

diphenhydramine or lorazepam to avoid extrapyramidal adverse reactions from MCP [44]. Patients received a prescription for oral prochlorperazine to be taken in case of delayed symptoms, but no routine antiemetics were prescribed. Although 63% of the patients did not vomit in the first 24 hours, both vomiting and nausea were frequently reported 24-120 hours after cisplatin, and particular day 3 (48-72 hours) were troublesome with 78% and 61% suffering from delayed nausea and vomiting, respectively [44]. In a subsequent trial, the same group randomized patients treated with high-dose cisplatin to delayed antiemetic prophylaxis with placebo, dexamethasone alone or dexamethasone plus MCP and found that the combination was superior to placebo and to dexamethasone alone [45]. Subsequent studies have confirmed the effect of this combination in the prophylaxis of delayed nausea and vomiting [46,47].

The newest trials and the evidence-based guidelines (2000-2017)

The first clinical trial with an NK_1-receptor antagonist was published in 1997 [48]. Today three agents of this drug class have been marketed, namely aprepitant, rolapitant and netupitant (given as NEPA in combination with the 5-HT_3-receptor antagonist, palonosetron). The recent interest in investigating MCP has been modest, because the 5-HT_3-receptor antagonists are superior with a more preferable adverse event profile. Therefore evidence-based guidelines of today do not recommend MCP (or other dopamine receptor antagonists) for routine use. MCP is therefore primarily recommended as a rescue antiemetic, when routine antiemetic therapy fails [42,43].

There are a few exceptions from the above statement. MCP is recommended (equally with dexamethasone or a 5-HT_3-receptor antagonist) in the prophylaxis of acute nausea and vomiting induced by chemotherapy with a low emetogenic potential [49]. Also MCP is recommended in the treatment of nausea and vomiting not induced by chemotherapy in patients with advanced cancer [50] and as prophylaxis or rescue in patients receiving radiotherapy of a low or minimal emetogenic potential [51], but none of these indications are within the scope of this review.

A recent study re-addressed the potential use of MCP as part of an antiemetic combination in the prophylaxis of delayed nausea and vomiting following cisplatin-based (≥ 50 mg/m^2) chemotherapy. In a randomized, double-blind study in which all patients (n = 303) received the same antiemetic prophylaxis for acute nausea and vomiting, patients were randomized to either dexamethasone plus aprepitant or to dexamethasone plus metoclopramide for delayed emesis protection [52]. Both combinations were equally effective in the prevention of delayed nausea and vomiting, and current guidelines therefore recommend the use of dexamethasone combined with either MCP or aprepitant in patients receiving non-AC highly emetogenic chemotherapy and aprepitant, a 5-HT_3-receptor antagonist and dexamethasone for acute CINV prophylaxis [42]. If another NK_1-receptor antagonist (rolapitant or netupitant) is used for prophylaxis day 1, dexamethasone alone is recommended [42].

Safety of metoclopramide: Common side-effects (≥ 1 % of patients) include somnolence, diarrhea, hypotension, akathisia, dry mouth, depression, fatigue and extrapyramidal symptoms [25,26] which can all be dose limiting. As previously mentioned, the addition of diphenhydramine or lorazepam to high-dose metoclopramide decreases the risk of extrapyramidal symptoms [10,26,27]. Metoclopramide must be used with caution in younger female patients in whom the risk of neurological side-effects is particularly high [53].

Both The European Medicines Agency (EMA) and The Food and Drug Administration (FDA) have advised against long-term use and use of high doses [54,55]. This means that metoclopramide is not to be used for more than five days and in a maximum dose of 10 mg x 3 daily. This is of course a barrier to the use as an antiemetic in CINV.

CONCLUSION

Although not originally developed as an antiemetic (contrary to the selective 5-HT_3- and NK_1- receptor antagonist antiemetics), MCP became the first milestone in the prophylaxis of CINV. This was primarily due to the effect of high-dose MCP, which was the first effective regimen in the prevention of cisplatin induced emesis [8], a group of patients previously facing an almost 100% risk of vomiting.

In countries with access to 5-HT_3-receptor antagonists and NK_1-receptor antagonists, MCP is rarely used as a routine antiemetic prophylaxis, but is still important as a rescue antiemetic. The modest pricing of metoclopramide compared to the more modern antiemetics still makes MCP an important resource in low-income countries.

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