Antiemetic Effect and Pharmacokinetics of High Dose Metoclopramide in Cancer Patients Treated with Cisplatin-Containing Chemotherapy Regimens

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Summary. Fifteen cancer patients receiving cisplatin-containing chemotherapy participated in two antiemetic studies. In Study 1 they received standard antiemetics in low doses on demand, and in Study 2 the same patients participated in an open randomized cross-over study between metoclopramide 1 and 2 mg/kg i.v. x 5.

Serum metoclopramide was determined by HPLC. Self-reporting of nausea using a visual analogue scale (VAS) was compared with observer rated scores. Tolerability and volume vomited were assessed by nurse observers.

The biological half-life of metoclopramide was 9.9 h, the volume of distribution was 9.9 l/kg and the clearance was 0.68 l/h/kg. The pharmacokinetics of high dose metoclopramide was linear in the range 0.15–2 mg/kg x 5, with very little accumulation.

Compared to standard antiemetics, both high dose regimens of metoclopramide had a significant effect on nausea, but no effect on the volume vomited. Self reports of nausea were significantly correlated with observer rated values. Tolerance of high dose metoclopramide was good except in 3 patients who left the study because of restlessness and trismus.

It is concluded that high dose metoclopramide probably can be administered for several consecutive days without appreciable accumulation of the drug. Self-reporting of nausea by patients on VAS is a simple and feasible method of evaluation. The finding that metoclopramide affects nausea but not vomiting supports the hypothesis that nausea and vomiting should be evaluated separately in assessing antiemetic efficacy.

Key words: metoclopramide; high dose, antiemetic efficacy, cancer patients, pharmacokinetics, cisplatin

Nausea and vomiting are considered to be the most severe and debilitating side effects of cancer chemotherapy. Combinations containing cisplatin in particular are highly emetogenic. Most cytostatic agents are thought to induce nausea and vomiting via the chemoreceptor trigger zone (CTZ) in the area postrema in the floor of the fourth ventricle [1]. The emetic effect of cisplatin has been variably attributed to stimulation at peripheral sites [2] and at the CTZ [3].

Metoclopramide, which is structurally related to procainamide, has been shown to block dopamine receptors in the CTZ and to exert a peripheral effect on the gastro-intestinal tract, leading to accelerated gastric emptying and intestinal transit [4]. It might therefore be the ideal antiemetic to treat the nausea and vomiting caused by cisplatin and other cytostatic agents. However, if given in low doses metoclopramide has only a limited antiemetic effect. In 1980 a Phase 1 trial of intravenous metoclopramide in cisplatin-induced nausea and vomiting showed good tolerance and useful antiemetic efficacy up to doses of 3.0 mg/kg 5 times over 11.5 h [5], and in a randomized study high dose metoclopramide showed antiemetic efficacy greatly superior to that of prochlorperazine and placebo [6]. Since then several trials with high dose metoclopramide have shown significant antiemetic control in cisplatin-treated patients, with 21% to 86% of the patients showing an antiemetic response [7–11]. The variability in response rate seems to be due to differences in the characteristics of the patients and in the methods used to evaluate the antiemetic effect.

Evaluation of nausea and vomiting caused by chemotherapy presents significant problems [12]. Nausea is a subjective symptom suitable for self reporting by patients, whereas vomiting can be measured objectively as volume per unit of time, or the number of emetic episodes, which is the most com-
monly employed measure. Nausea and vomiting probably do not represent the same phenomenon, so both should be assessed when evaluating the response to antiemetic therapy.

Few detailed studies of the kinetics of high dose metoclopramide have been published [13-16]. It was decided, therefore, to investigate the pharmacokinetics of high dose metoclopramide. The study had two main purposes: 1) to investigate whether administration of high dose metoclopramide resulted in accumulation of the drug, and 2) to evaluate nausea and vomiting separately, both by self reports and by external observation.

Materials and Methods

Design of Investigation

The present study was divided into two parts involving the same patients.

Study 1. During one course of chemotherapy patients received metoclopramide 10-20 mg, chlorpromazine 100 mg and diazepam 5-10 mg orally, rectally or intravenously on demand. Nausea, vomiting, and the tolerance of the antiemetic treatment were recorded regularly.

Study 2. During the next two consecutive courses of chemotherapy an open randomized cross-over study with metoclopramide 1 and 2 mg/kg intravenously 5 times over a 9-h period was performed. Metoclopramide was only given for 1 day. Metoclopramide (Primperan) ampoules 2 ml, 5 mg/ml were supplied by H. Lundbeck A/S, Copenhagen, Denmark.

Exclusion Criteria

1. Patients with other known causes of nausea and vomiting, e.g. bowel obstruction or hypercalcaemia.
2. Phaeocromocytoma.
3. Parkinsonism.
4. Known psychiatric disease.
5. Daily intake of neuroleptics or antidepressants.

All patients participating in Study 2 had experienced severe nausea and vomiting during Study 1. During Study 2 the only antiemetic allowed was metoclopramide in the stipulated dose. Diazepam 5-10 mg orally was allowed on the evening before chemotherapy.

All patients gave their informed consent to participation in the study, which was designed and conducted in accordance with the Helsinki Declaration II. The study was approved by the local Human Investigations Committee.

Patients

The same patients took part in both studies, except for a 41 year old woman who refused to participate in Study one.

The characteristics of the patients are shown in Table 1. Fifteen patients were studied, 14 women and one man. The median age was 58 years (range 37-64 years), and median weight 67 kg (range 47-99 kg). Thirteen patients had ovarian cancer Stage III-IV, one patient had uterine cancer Stage III N1, and one patient had seminomatous testicular cancer Stage II. Eight patients with ovarian cancer were treated with cyclophosphamide 500 mg/m² and cisplatin 60 mg/m² (CP) every 4 weeks. Five patients received the same cytostatics in identical doses and with the addition of adriamycin 40 mg/m² (CAP). The patient with uterine cancer was also treated with the CAP regimen. The man with testicular cancer received cisplatin 20 mg/m² on Days 1-5, vinblastin 6 mg/m² on Days 1 and 2 and bleomycin 15 mg/m² on Days 2, 9, and 16, repeated every 3 weeks (PVB). At the time of inclusion in Study 1 the patients were receiving chemotherapy course Number 1 to 12 (median 5). Three patients received chemotherapy for the first time.

The Cr-EDTA clearances of all the patients were normal or were only slightly reduced.