Cancer Chemother Pharmacol (1982) 8: 133–135

Cancer Chemotherapy and Pharmacology

Metoclopramide in the Reduction of Nausea and Vomiting Associated with Combined Chemotherapy

Robert Cox, Christopher E. Newman*, and Michael J. Leyland

Departments of Medicine and Thoracic Surgery, East Birmingham Hospital, Birmingham B9 5ST, Great Britain

Summary. *The nausea and vomiting associated with combination chemotherapy is a serious cause of morbidity. Though widely used, metoclopramide has not previously been shown, in controlled studies, to be of benefit in reducing these side-effects.*

A double blind placebo-controlled randomized trial of IV and oral metoclopramide is reported, based on 117 courses of chemotherapy. Of 59 courses in which metoclopramide was given, vomiting was prevented in 28 (47%), compared with only 10 of 58 (17%) in the control group, a highly significant ($P < 0.001$) improvement.

The importance of adequate dosage of metoclopramide and the role of IV metoclopramide are emphasized.

Introduction

Although large numbers of anti-emetics are prescribed for patients undergoing chemotherapy, there have been few reports of their effectiveness compared with a placebo. Metoclopramide is commonly used to reduce the nausea and vomiting associated with chemotherapy, and was the standard drug in one recent trial [7]. However, to date there has been no evidence from controlled trials of its usefulness. Indeed, in two studies [3, 4] it was found to be no better than a placebo.

Patients may feel nauseous or actually vomit prior to their chemotherapy [9], and it is reasonable to suppose that in these patients only a parenterally administered drug is likely to have any effect. There has been no previously reported trial of the effectiveness of parenteral and oral metoclopramide compared with a placebo.

It was therefore decided to conduct a placebo-controlled trial of parenteral and oral metoclopramide.

Reprint requests should be addressed to M. J. Leyland, Consultant Physician, Dept. of Clinical Haematology

* *Present position:* Medical Director, Newfoundland Cancer Research Centre

Materials and Methods

Patients receiving chemotherapy for small cell carcinoma of the bronchus under the auspices of the West Midlands Lung Cancer Study Group were entered into the trial. Combination chemotherapy consisting of either cyclophosphamide, VP 16, and methotrexate or vincristine, adriamycin, and procarbazine was used. Patients were admitted to hospital for IV chemotherapy. For each pulse of chemotherapy patients were allocated to receive either metoclopramide or a placebo according to a grouped randomization method [6]. Identical packs containing 8 ampoules for IV administration and 15 tablets, and distinguished only by a code number, were available for each patient for each pulse of chemotherapy. The ampoules and tablets contained 10 mg metoclopramide or placebo.

One ampoule was given IV immediately prior to chemotherapy. The ward staff were then instructed to give metoclopramide/placebo every 4 h for the next 48 h and 4-h thereafter if the patient continued to experience nausea or vomiting. If the patient was suffering nausea or vomiting it was requested that the IV preparation be given, the oral preparation being reserved for patients without symptoms.

Each course of treatment was assessed separately for both severity and duration of symptoms. Patients were placed into one of five symptom groups according to the worst symptom they suffered during the course, viz. no nausea, nausea only, vomiting, severe vomiting, and uncontrollable vomiting. Patients in the last category were withdrawn from that course, though they were included in the assessment. The duration of symptoms was taken as the time from the pretreatment injection of metoclopramide to the time of the last recorded symptom. For the purposes of analysis the durations were considered in the following intervals $0- < 4$ h, $4- < 8$ h, $8- < 12$ h, $12- < 24$ h, $24- < 48$ h, and > 48 h.

Differences in the results of treatment in the metoclopramide and placebo groups were tested for statistical significance with the χ^2-test.

0344-5704/82/0008/0133/$ 01.00

Results

Thirty-seven patients were entered in the trial and 164 courses of chemotherapy were issued. No patient received more than ten courses (mean 4.4). Thirteen (8%) courses were not assessable (assessment form inadequately filled in 8; metoclopramide/placebo not given 2; patients given other anti-emetic 2; patient died during chemotherapy 1). In 34 (21%) courses an inadequate amount of medication was given for the duration of symptoms. Thus there were 117 (71%) courses available for analysis. These were well matched both in the chemotherapy (Table 1) and in the amount of metoclopramide or placebo they received (mean 2.03 ampoules and 5.25 tablets for metoclopramide; 2.7 ampoules and 5.01 tablets for placebo).

Of the 59 courses in which satisfactory amounts of metoclopramide were given vomiting did not occur in 28 (47%), compared with only 10 of 58 (17%) of the courses in which the placebo was given. This result is highly significant (X^2 12.17 with 1 d.f., $P < 0.001$). In addition, overall analysis of the subgroups shows a significant reduction in the incidence of courses in which the more severe symptoms were experienced when metoclopramide was given with placebo ($P < 0.01$) (Fig. 1).

Treatment with metoclopramide, however, did not significantly reduce the duration of symptoms (Fig. 2).

There were no side-effects attributable to metoclopramide in any patient.

Table 1. Distribution of courses of metoclopramide and placebo between the two combinations of chemotherapy

Combination chemotherapy	No. of courses	
	Metoclopramide	Placebo
Cyclophosphamide, methotrexate, VP 16	34	32
Vincristine, adriamycin, procarbazine	25	26

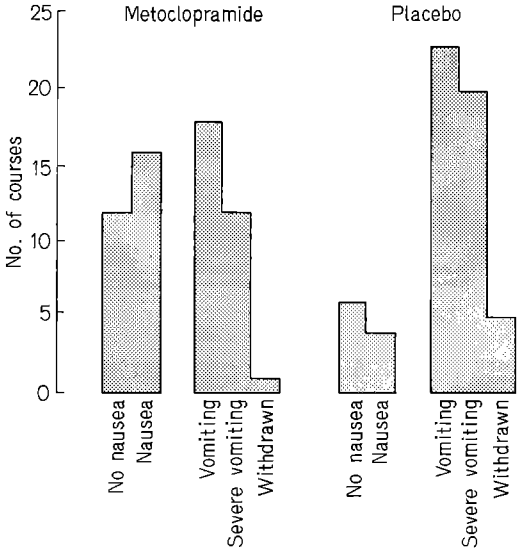

Fig. 1. Incidence of nausea and vomiting with metoclopramide and placebo. Note that all patients with vomiting also have nausea. This explains the apparent increase in the incidence of nausea in the metoclopramide-treated group. The reduction in the incidence of vomiting is highly significant $P < 0.001$

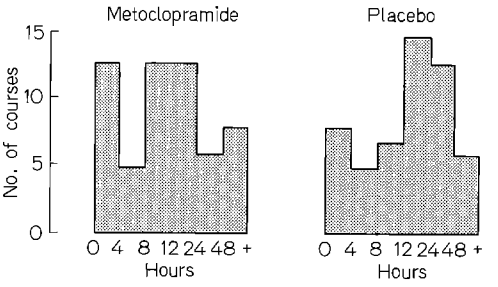

Fig. 2. Duration of symptoms

Discussion

Chemotherapy is being increasingly widely used. For the patient, nausea and vomiting are often the most unpleasant side-effects, and may cause refusal of further treatment. Clearly there is a need for effective methods to control these side-effects.

There have been few reported placebo-controlled trials of anti-emetic agents used in the prevention of nausea and vomiting associated with chemotherapy, and none at all of parenterally administered metoclopramide. Moertel and Reitmeier [3] performed a series of studies on various agents and found that thiopropazate and thiethylperazine had significant activity. However, the clinical improvement compared with placebo was sufficiently small for them to feel justified in retaining a placebo in a further investigation, in which they found oral metoclopramide to be ineffective. Morran et al. [4] conducted a placebo-controlled trial of several orally administered drugs, including metoclopramide, but found that only a combination of fluphenazine and nortriptyline had a significant anti-emetic action. However, there is considerable evidence from uncontrolled trials [2, 5], and also anecdotal evidence, that metoclopramide is an effective agent. Thus it was felt not only justifiable but essential to conduct a further trial of metoclopramide.

In the present trial there was a highly significant ($P < 0.001$) reduction in the number of courses in which vomiting occurred when metoclopramide was administered. Vomiting occurred in 87% of placebo-treated patients but in only 53% of the group receiving metoclopramide. Although nausea appears to be more frequent in the treated groups than the placebo group (Fig. 1), this reflects the overall reduction in the incidence of the more severe symptoms, and it should be remembered that all patients who vomited also had nausea.

Why has metoclopramide not been shown to be an effective anti-emetic previously? One explanation is the higher dosage used in the present trial, with the emphasis on the IV route. Bioavailability of orally administered metoclopramide in normal volunteers varies between 32% and 97% (mean 61%) [1], but is likely to be lower in patients who are nauseous or vomiting. Further improvement might be obtained by increasing the dose of metoclopramide, particularly as no patient experienced side-effects due to metoclopramide. To achieve this, probably the major component of treatment should be given IV.

Regular frequent IV therapy is associated with problems of administration. In this study all the patients assessed received their pretreatment IV metoclopramide/placebo. It had been intended that nauseous patients would continue to receive IV metoclopramide. This was not always practical. Intravenous administration of drugs requires more nursing time than oral administration. Often a suitably qualified nurse will have to be specially called to the ward to administer the drug. Our patients were all treated on busy thoracic medical or surgical wards. Better co-operation would presumably be obtained in a specialized oncology ward where nursing staff are readily available to give IV medication. It also proved difficult to encourage an attitude of prophylactic anti-emetic therapy. Although we have no direct evidence it is possible that the situation may be analagous to analgesia administration. Once the symptom is well established a greater dose of the pharmacological agent is required for its relief than if the agent is given prior to development of the symptoms [8]. This was the basis for giving an IV bolus of metoclopramide prior to chemotherapy.

Realization that metoclopramide does work, allied with greater readiness to give it IV, should allow a reduction in the incidence of vomiting amongst patients receiving chemotherapy.

Acknowledgements. The authors wish to acknowledge the assistance of Beecham Research Laboratories in preparing the metoclopramide (Maxolon) and placebo packs used in the trial.

The co-operation of the nursing staff of East Birmingham Hospital, without which the trial could not have been conducted, is gratefully acknowledged.

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Received October 12/Accepted November 12, 1981