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Domperidone as an Antiemetic in Paediatric Oncology

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Summary. *Domperidone was evaluated as an antiemetic in the control of nausea and vomiting associated with the administration of cytotoxic chemotherapy for various malignancies in a paediatric population. The results indicate that it is an effective agent for this purpose, control having been reasonable or good in 47 of 58 drug trials. The optimum dose would appear to be 0.7 mg/kg per dose. The only toxicity noted was of pain at the site of intravenous administration if domperidone was not adequately diluted.*

Introduction

Chemotherapy for malignant disease often results in nausea and vomiting, which can be severe and incapacitating. Control of this complication of treatment is not always satisfactory. Children with cancer who are destined to receive chemotherapy for 1–3 years are in need of more effective antiemetic regimens than are available at present.

Domperidone is a peripheral dopamine antagonist, which has been shown to be effective in the control of nausea and vomiting associated with a variety of conditions (nonspecific vomiting in the paediatric age group [1, 2], treatment of postoperative nausea and vomiting [4], and control of chemotherapeutically induced nausea and vomiting in adults [3, 5, 6] and children [7]). We have evaluated the use of domperidone as an antiemetic in children receiving cytotoxic treatment for a variety of malignant diseases in terms of its efficacy, toxicity, and patient acceptability. A placebo comparison was considered unethical, and comparison with metoclopramide has already been documented [7]. A single or double blind trial with phenothiazines was not possible because of the sedative effects of the latter. Domperidone was therefore investigated as a single agent in escalating dosages determined by efficacy and by side-effects.

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Patients and Methods

Fifty-eight trials were conducted in 27 patients. There were 19 boys and eight girls, with an age range from 1 year 10 months to 13 years. The malignancies being treated included leukaemia, lymphoma (Hodgkin's and non-Hodgkin's), nephroblastoma, neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma. The chemotherapy schedules and dosages are almost invariably associated with severe nausea and vomiting for several hours unless vigorous treatment with effective antiemetics is given.

Preliminary investigations with oral domperidone were unsuccessful in controlling vomiting, and a few patients actually reported nausea due to the drug. For the trial, therefore, the IV route was chosen. Domperidone was given IV immediately prior to cytotoxic treatment and repeated 4 h later. If an IV solution continued for more than 6 h a further dose of domperidone was given IV 4 h from the last dose. As IV fluids were usually discontinued 6 h after cytotoxic therapy, only two IV injections were normally given. Domperidone suppositories were provided, to be given if required 4-hourly for up to 24 h from the administration of cytotoxic therapy. The starting dose was 0.3 mg/kg IV (two trials), increased to 0.5 mg/kg (20 trials), with a further and final increase in dosage of domperidone to 0.7 mg/kg (36 trials). As only 10-mg or 30-mg suppositories were available, the dosage was approximated as nearly as possible to 1 mg/kg.

Control of nausea and vomiting was graded on a scale from 1 to 3 as detailed below:

1) Poor. Inadequate control of nausea and/or vomiting;

2) Reasonable. A few small vomits. Little nausea. Patient generally feeling satisfactory;

3) Good. Less than three vomits.

Assessment in the younger children was carried out by a parent or nurse who was constantly in attendance for up to 24 h after administration of chemotherapy. Vomits were accurately recorded on fluid balance charts and nausea was interpreted as failure to participate in meals and snacks at normal intervals for each patient. Older children, who had often considerable experience of the same chemotherapy regimens given with our previous combination of phenothiazines (usually promethazine and chlorpromazine up to 25 mg 2 hourly alternately IV, via burette), recorded nausea and vomiting themselves.

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Results

Effectiveness of domperidone was assessed as follows:

1) Good: 17 trials;
2) Reasonable: 30 trials;
3) Poor: 11 trials.

Reasonable or good control was achieved in 14 of 20 patients who received 0.5 mg/kg per dose (70%) and 32 of 36 who received 0.7 mg/kg per dose (89%).

Since vomiting preceded administration of cytotoxic therapy in 22 trials, the results were stratified according to the prechemotherapeutic presence or absence of vomiting. It was shown that the control of emesis was significantly better ($P = 0.01$; Mann-Whitney U-test applied to the distribution of the 1, 2, 3 ratings) in the 36 trials where vomiting did not precede chemotherapy, as compared with the 22 trials where it did. In the former group the result was good (score 3) in 15 of 36 trials (42%) and in the latter group in only two of 22 trials (9%), which is a significant difference ($P = 0.02$) according to the χ^2-test (Fig. 1).

The duration of effectiveness appeared to be 3–4 h. Alternative antiemetics were given in only three trials: in the first a phenothiazine was added because of a hysterical reaction in a 4-year-old boy. In the second metoclopramide was substituted after 6 h when three injections of domperidone (0.5 mg/kg) had failed to control vomiting. The same child had reasonable control of nausea and vomiting with domperidone at a dose of 0.7 mg/kg on two subsequent trials. In the third trial prochlorperazine suppositories were given when vomiting persisted after 18 h from cytotoxic therapy when four injections of domperidone (0.7 mg/kg) had been ineffective. Two children asked to opt out of the trial: both had previously been controlled with a promethazine/chlorpromazine combination and preferred to revert to that as they wanted to 'sleep through their sickness'. The principal side effect was soreness at the injection site after direct administration IV. This was noted in the majority of trials but not recorded at the time so that accurate assessment could not be made. When the drug was given in 10–15 ml solution and run in over 5–10 min this was abolished. One child reported disorientation for up to 18 h after administration of domperidone. This child had received liberal IV fluids after cyclophosphamide and this disorientation might have been related to dilutional hyponatraemia. There was no somnolence associated with administration of domperidone.

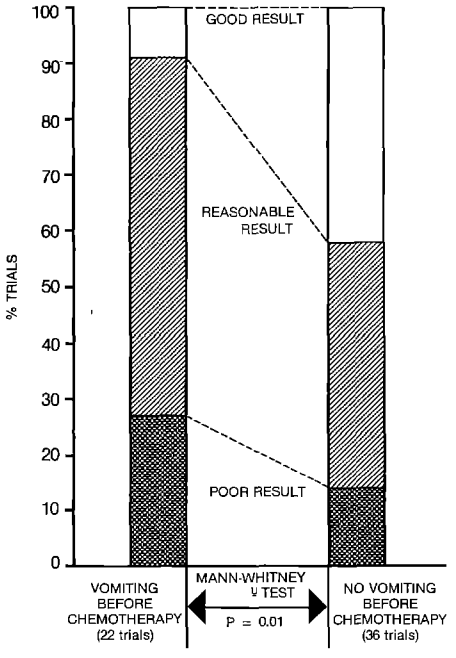

Fig. 1. Relevance of prechemotherapeutic vomiting to antiemetic effect of domperidone

Discussion

It was the overall impression of physicians, nursing staff, parents, and patients that domperidone was superior to any of our other previously used antiemetic regimens. The main advantage was the lack of side-effects encountered. The most pronounced difference from our previous experience was the complete absence of somnolence encountered. For children undergoing intensive chemotherapy for malignancy there are advantages and disadvantages to sedation as a side-effect of antiemetics. There is often a considerable psychological element to their drug-induced nausea and vomiting. This was borne out in 22 trials where vomiting was recorded prior to the start of the cytostatic infusion and where the antiemetic effect of domperidone appeared to be limited. In such cases sedation up to 1 h prior to chemotherapy may be beneficial. On the other hand the pronounced lack of sedation after chemotherapy administration enables the patients to participate in ward activities and to co-operate with fluid balance, which is important particularly after administration of cyclosphosphamide. Of 17 patients who had previously experienced control of emesis with a promethazine/chlorpromazine combination following chemotherapy, 15 preferred domperidone when given the option to choose.

In those children who received domperidone suppositories, control of nausea and vomiting was

maintained if there had been initial control with IV domperidone.

In conclusion, domperidone is an effective antiemetic in the management of chemotherapy-induced nausea and vomiting in children at a dose of 0.7 mg/kg and appears to lack toxicity.

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