EFFECT OF CISAPRIDE ON MORPHINE ABSORPTION AFTER ORAL ADMINISTRATION OF SUSTAINED-RELEASE MORPHINE

D. J. ROWBOTHAM, K. MILLIGAN AND P. McHUGH

SUMMARY

We investigated the effect of cisapride 20 mg given orally with MST 20 mg on the absorption of morphine in a double-blind, placebo-controlled study. Cisapride increased significantly both plasma concentrations of morphine after 1 h and peak concentrations. There was no significant change in time to peak concentrations, sedation scores or percentage decrease in pupil diameters. Plasma concentrations of amylase were increased in three patients in the MST-placebo group and three in the MST-cisapride group. One patient in the MST-cisapride group developed acute pancreatitis.

KEY WORDS


MST Continus (Napp Laboratories) is a sustained-release tablet preparation releasing morphine over 12 h and is used most frequently for the treatment of pain associated with malignancy [1]. Cisapride is a new gastrointestinal prokinetic drug which increases the rate of gastric emptying, lower oesophageal sphincter pressure and small and large bowel motility [2]. Morphine delays gastric emptying and cisapride is more effective than metoclopramide in reversing this effect after i.m. administration [3].

Cisapride is now available generally and some patients may receive cisapride concomitantly with MST. Therefore, it was the purpose of this study to measure the effect of cisapride on morphine absorption after administration of MST.

PATIENTS AND METHODS

We studied 20 patients (aged 18-65 yr) undergoing minor general or orthopaedic surgery in the afternoon. Local Ethics Committee approval and written informed patient consent were obtained. Patients were excluded if they were taking any concurrent medication, had any evidence of gastrointestinal disease or were scheduled for gastrointestinal surgery.

A light breakfast was taken at 06:30 on the day of surgery and the study commenced 2 h later. Patients were allocated randomly in a double-blind design to receive either MST 20 mg and placebo or MST 20 mg and cisapride 20 mg. Tablets were taken with water 50 ml and patients rested at 45° in bed for the duration of the study. Blood 10 ml was taken from an indwelling venous cannula and visual analogue scores (VAS) for sedation were measured before and at 30-min intervals after drug administration. Plasma was separated immediately and stored at —20 °C before measurement of plasma morphine concentrations by HPLC using a technique described previously [4]. Pupil diameter was measured at 15-min intervals for 2 h and every 30 min thereafter using a pupillometer described by Asbury, Lear and Wortley [5].

The study was terminated after 5 h or when the patient left the ward for surgery.

Data were analysed using chi-square, Student's t and Mann–Whitney tests and MANOVA for repeated measures as appropriate.

RESULTS

There was a significant difference between groups in age, but not in weight, sex or type of surgery...
Table 1. Patient data (mean (range or SD)). * P < 0.05 between groups

<table>
<thead>
<tr>
<th></th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST 20 mg +</td>
<td>5/5</td>
<td>48.4 (34-62)</td>
<td>68.3 (10.1)</td>
<td>6 General</td>
</tr>
<tr>
<td>placebo (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td>4 Orthopaedic</td>
</tr>
<tr>
<td>MST 20 mg +</td>
<td>5/5</td>
<td>36.9 (18-58)</td>
<td>67.8 (12.5)</td>
<td>7 General</td>
</tr>
<tr>
<td>cisapride 20 mg (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td>3 Orthopaedic</td>
</tr>
</tbody>
</table>

(figure 1). One patient was withdrawn from the study because of an adverse reaction (see below) and data from this patient were excluded from analysis. Complete data were available for only 3.5 h because of patients leaving the ward for surgery; these therefore, are the data presented.

Mean plasma concentrations of morphine were significantly greater in the MST-cisapride group after 1 h (P < 0.05).

Mean pupil diameters at 3.5 h were significantly smaller in both groups compared with baseline values (P < 0.05 MST-placebo; P < 0.01 MST-cisapride) (figure 2); mean (SEM) percentage decreases at this time were 12.4 (4.4)% and 22.1 (5.5)%, respectively. There was no significant difference between the groups in mean pupil diameters or percentage decrease at 3.5 h.

There was no significant difference in VAS sedation scores between the groups (figure 3).

Adverse reactions

One patient in the MST-cisapride group was withdrawn from the study because of an adverse reaction. He was a healthy 50-yr-old male scheduled for haemorrhoidectomy, with no significant medical history or findings on examination. Preoperative white cell count and haemoglobin,
CISAPRIDE AND MST

TABLE II. Increased plasma concentrations of amylase at 4 h (normal range 10-82 u litre\(^{-1}\)). Only patient No. 8 developed symptomatic pancreatitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Group</th>
<th>Plasma amylase conc (u litre(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>MST-placebo</td>
<td>46</td>
</tr>
<tr>
<td>15</td>
<td>MST-placebo</td>
<td>41</td>
</tr>
<tr>
<td>17</td>
<td>MST-placebo</td>
<td>98</td>
</tr>
<tr>
<td>1</td>
<td>MST-cisapride</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>MST-cisapride</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>MST-cisapride</td>
<td>53</td>
</tr>
</tbody>
</table>

At the end of the study, plasma concentrations of amylase were measured in plasma samples taken at 0 and 4 h in every patient (table II). Three patients in the MST-placebo group and three patients (including the one with pancreatitis) in the MST-cisapride group had increased concentrations of amylase at 4 h. No other patient complained of abdominal symptoms.

DISCUSSION

Cisapride increased plasma morphine C\(_{\text{max}}\) and concentrations after 1 h significantly when taken simultaneously with MST 20 mg in patients before surgery. Plasma morphine C\(_{\text{max}}\) was unchanged. Pupil diameters decreased significantly in both groups after MST, but there was no significant difference between the groups. MST produced little preoperative sedation and there was no difference between the groups.

Plasma concentrations of morphine were similar to those found in other studies after MST [6-8]. Manara and others [7] investigated the effect of oral metoclopramide 10 mg on plasma concentrations of morphine and its effects after MST 20 mg. In contrast to cisapride in this study, metoclopramide had no effect on plasma morphine C\(_{\text{max}}\). However, metoclopramide was associated with a change in median (range) plasma morphine C\(_{\text{max}}\) values from 2.25 (0.5-5) h to 1.25 (0.5-2.5) h, respectively (\(P < 0.05\)). Corresponding values in this study were 1.25 (0.5-2.5) h and 1.5 (1-3) h. The findings of Manara and others are consistent with metoclopramide increasing the rate of absorption of morphine, presumably by enhancing gastric emptying.

The conclusions of the present study are less clear, as plasma C\(_{\text{max}}\) was unaffected. Increased
plasma concentrations of morphine associated with cisapride may be caused by changes in volume of distribution, elimination rate constant, absorption rate and morphine release from the tablet. At present, there are no data to suggest that cisapride would affect any of these factors other than rate of absorption resulting from enhanced gastric emptying. However, this is speculative, as data from this study do not indicate which of these mechanisms is involved.

The effect of morphine on pupil diameter was demonstrated in both groups, but there was no significant difference between groups. Both groups in the present study showed little evidence of sedation. This is consistent with the findings of Kay and Healy [9] who demonstrated a mean preoperative 10-point VAS sedation score of 0.6 after MST 30 mg, compared with 0.3 after placebo. However, Manara and colleagues demonstrated higher sedation scores which were significantly greater during the first 90 min after MST 20 mg taken with metoclopramide. Differences in sedation may be caused by the earlier tCmax in the metoclopramide group or the possible analgesic effect of metoclopramide [10].

Cisapride increased plasma concentrations of morphine after administration of MST in this study, but no differences in pupil diameter or sedation were demonstrated, possibly because plasma concentrations or morphine were too small to show an effect. The effect of cisapride on the absorption of larger doses of morphine is not known but, if it is consistent with the findings of this study, then it may be associated with a significant increase in morphine effects.

One patient in the MST-cisapride group developed acute pancreatitis. Plasma concentrations of amylase, measured at the end of the study, were increased significantly in three (30%) patients in the MST-placebo group and three (30%) patients in the MST-cisapride group (including the patient who developed pancreatitis). Bogoch, Roth and Bockus [11] described a similar incidence of increased serum concentrations of amylase. I.m. morphine was administered to 39 medical patients with normal serum concentrations of amylase and blood samples were taken frequently over 24 h. Serum concentrations of amylase were increased in 11 (28%) patients. These findings were confirmed by Gould, Van Kley and Knight [12], who demonstrated increased serum concentrations of pancreatic amylase iso-enzyme in seven of 17 patients (41%).

It is likely that increased plasma concentrations of amylase in this study were caused by morphine-induced spasm of the biliary tract and sphincter of Oddi—a side effect which has been recognized for some time [13]. However, cisapride was found also to increase contractions of the biliary tract and sphincter of Oddi in dogs, but decreased their resting tone [14]. No data are available as yet in man and no case of increased concentrations of amylase or pancreatitis has been reported with administration of cisapride alone. However, the number of patients exposed to cisapride is still relatively low.

ACKNOWLEDGEMENT
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REFERENCES
11. Bogoch A, Roth JLA, Bockus HL. The effects of
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