International Journal of Pharmaceutics, 22 (1984) 99–103
Elsevier

IJP 00748

Gastric emptying and intestinal transit of non-disintegrating capsules—the influence of metoclopramide

Lydia C. Kaus [1], John T. Fell [1], Harbans Sharma [2] and David C. Taylor [3]

Department of [1] Pharmacy and [2] Medical Biophysics, University of Manchester, Manchester M13 9PL and [3] I.C.I. Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TF (U.K.)

(Received June 5th, 1984)
(Accepted July 7th, 1984)

Introduction

Metoclopramide is used as an anti-emetic to treat some forms of nausea and vomiting and also to increase gastro-intestinal motility. It can be used as an adjunct in radiographic examinations as it promotes gastric emptying and speeds up the passage of barium meals through the small intestine (Ramsbottom and Hunt, 1970; Howarth et al., 1967). A comprehensive review of its chemistry, pharmacokinetics, mode of action and uses has been written by Schulze-Delrieu (1981).

Recently, a method has been described of measuring the rate of transit of a non-disintegrating object through the intestine using gamma scintigraphy (Kaus et al., 1984). In view of the action of metoclopramide on gastric emptying and intestinal transit, it was appropriate to compare transit with and without metoclopramide.

Materials and Methods

Materials

Perspex capsules were prepared and labelled as described previously (Kaus et al., 1984). Their specific gravities were 1.03 ± 0.02.

Methods

Six informed, healthy male subjects took part in the study. The experimental procedure was as detailed previously (Kaus et al., 1984) except that each subject ingested a capsule on two separate occasions. Five minutes before the experiment, the subject was injected intravenously with either 2 ml normal saline (0.9% w/v

Correspondence: J.T. Fell, Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

sodium chloride B.P.), or metoclopramide (Maxolon, Beecham, U.K.) (10 mg/2 ml) in a random, double-blind manner. Data were recorded as detailed previously, except that the subject rotated every 15 s to obtain three-dimensional data points at effectively every half-minute.

Results

Individual plots of cumulative distance travelled with time indicated a more rapid movement during the initial stages of the capsule travelling down the small intestine after administration of metoclopramide (Fig. 1). The plots were divided into data recorded from the fifth to the twentieth-and-a-half minutes and the data from the twenty-first to the sixtieth minute. Linear regression analyses were carried out for these sections of the data. Statistical analyses of the slopes of the graphs from the first and second data group were carried out using the paired *t*-test (Table 1). Comparison of the slopes of the graphs of the first data group showed there was a significant difference between the rates of travel of the capsules, moving faster after injection of metoclopramide than after injection of saline (the control) ($P < 0.05$). Statistical analysis of the second set of data (from 21 to 60 min) and the time taken to leave the stomach showed there to be no significant difference between the two treatments (Table 1).

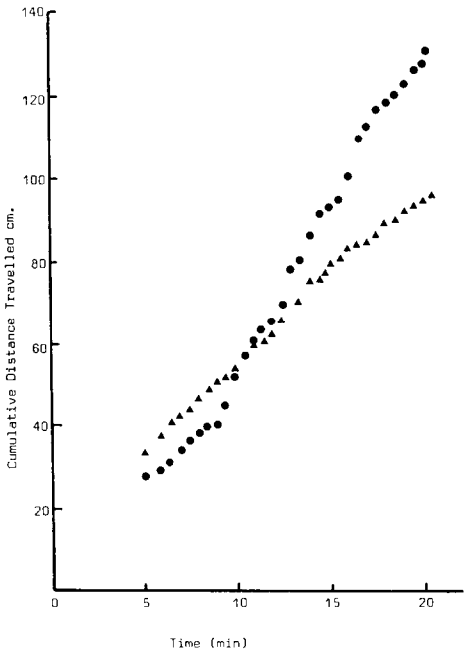

Fig. 1. Cumulative distance travelled by the capsule against time (from 5 to 20 min) after injection of saline (▲) and metoclopramide (●), Subject 1.

TABLE 1

RESULTS OF LINEAR REGRESSION ANALYSIS AND PAIRED *t*-TEST ON DATA AFTER INJECTION OF SALINE (S) AND OF METOCLOPRAMIDE (M). T.L.S. = TIME FOR THE CAPSULE TO LEAVE THE STOMACH

Subject	T.L.S. (min)		Slope (5–20.5 min)		Slope (21–60 min)	
	S	M	S	M	S	M
1	58	7	4.111	7.591	4.447	3.895
2	13	65	4.153	4.891	3.279	3.242
3	152	87	3.949	6.193	3.952	5.559
4	87	18	5.475	6.222	4.132	5.317
5	99	125	2.500	7.119	5.014	4.621
6	19	15	3.779	4.142	3.273	4.301

Normal saline vs drug—paired *t*-test		
	Observed *t*-value	Significance
Slope (5–20.5 min)	2.88	$P < 0.05$
Slope (21–60 min)	1.27	$P > 0.05$
T.L.S. (min)	0.89	$P > 0.05$

Table 2 shows the results of a paired *t*-test on the cumulative distance travelled by the capsule in saline- and metoclopramide-treated individuals. The capsule travelled significantly further after administration of metoclopramide.

Three of the subjects expressed feelings of dizziness or faintness after being injected with metoclopramide without any prompting from the observer. This means

TABLE 2

CUMULATIVE DISTANCE TRAVELLED BY THE CAPSULE AND THE RESULTS OF A PAIRED *t*-TEST ON THIS DATA AFTER INJECTION OF SALINE (S) AND METOCLOPRAMIDE (M)

Subject	Cumulative distance travelled (cm)			
	1–20.5 min		1–60 min	
	S	M	S	M
1	91.9	125.8	261.8	278.6
2	91.8	98.1	216.8	228.9
3	81.2	133.2	241.3	350.3
4	100.1	124.5	279.1	352.4
5	58.8	105.5	254.2	290.2
6	80.5	90.2	221.0	265.7

Normal saline vs drug—paired *t*-test.		
Distance travelled	Observed *t*-value	Significance
1–20.5 min	3.75	$P < 0.01$
1–60 min	3.26	$P < 0.05$

that 50% of the group experienced side-effects, which have been attributed to metoclopramide in the literature. However, a lower figure of 11% is stated in the literature as being the percentage of subjects experiencing side-effects from metoclopramide. The same 3 subjects did not complain of any side-effects after being injected with saline.

Discussion

Metoclopramide has been shown in this study to have no statistically significant effect on the time taken for the capsule to leave the stomach in normal subjects. However, there was some effect on the first area of the small intestine in terms of a significant increase in the rate of travel of the capsule. This effect was profound in some subjects, showing an increase in the slope of up to 185% (Subject 5) to a slight increase of 10% (Subject 6). This was not an order effect, which might have been due to fear of having an injection (causing anxiety and leading to a rapid emptying of the capsule and increased motility) as the injections were administered in a double-blind manner. The slopes calculated from the second data group (21 to 60 min) did not show a significant difference between treatment with metoclopramide and the control, and in some cases the slope decreased after administration of metoclopramide in comparison to saline.

The effect of metoclopramide only on the transit rate in the initial part of the small intestine cannot be due to a diminishing of the pharmacological effect with time, as there was no effect on the time taken for the capsule to leave the stomach. Times of 5–30 min are quoted in the literature for the duration of the pharmacological effect of metoclopramide on the intestine or the stomach. However, the results from this study show otherwise. For instance, the largest increase in slope (Subject 5), after injection with metoclopramide as compared to normal saline, corresponded to the greatest time for the capsule to leave the stomach in the metoclopramide group. Also Subject 5 took longer to empty the capsule after administration with metoclopramide in comparison with normal saline.

Gastric emptying (in terms of the time taken for the capsule to leave the stomach) was highly variable between subjects both in the metoclopramide and the control group. There was no correlation in either group between the time taken to leave the stomach and the rate of travel in the intestine.

Metoclopramide is said to affect gastric emptying rates and hence influence the rate of absorption of drugs from the intestinal tract. For example, Nimmo et al. (1973) found that the rate of paracetamol absorption in healthy volunteers was increased after administration of metoclopramide. In the current study, metoclopramide did not affect gastric emptying, but had some effect on the rate of travel of the capsule in the small intestine. The indirect influence on the absorption of some drugs, attributed to metoclopramide, may only be important and show its greatest effect, where the gastric emptying rate is abnormally slow. The influence on the rate of absorption may also be due to the alteration in intestinal transit of the oral dosage form as shown by the current results.

The observed variability in response to the metoclopramide may have been due to a fixed dose of 10 mg being given to each subject. A dose related to the body size or weight would have ensured a similar plasma level of the drug in each subject in relation to their volume of distribution. Therefore, the dose given to some of the subjects in the study may have been too small to show the motor-stimulating effects of metoclopramide accompanied by the maximum increase in the rate of travel of the capsule.

References

Howarth, F.H., Cockel, R. and Hawkins, C.F., Effect of metoclopramide upon gastric motility and its value in barium progress meals. Gut, 8 (1967) 635–636.

Kaus, L.C., Fell, J.T., Sharma, H. and Taylor, D.C., On the intestinal transit of a single non-disintegrating object. Int. J. Pharm., in press.

Nimmo, J., Heading, R.C., Tothill, P. and Prescott, L.F., Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. Br. Med. J., 1 (1973) 587–589.

Ramsbottom, N. and Hunt, J.N., Studies of the effect of metoclopramide and apomorphine on gastric emptying and secretion in man. Gut, 11 (1970) 989–993.

Schulze-Delrieu K., Drug therapy: metoclopramide. New Engl. J. Med., 305 (1981) 28–32.