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Studies of the effect of metoclopramide and apomorphine on gastric emptying and secretion in man

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SUMMARY With oral and intravenous doses of metoclopramide there was no constant effect on the gastric emptying of test meals of glucose or sodium citrate, nor was secretion of acid by the stomach in response to test meals of glucose or sodium citrate affected. Apomorphine, in subnauseous doses (0·25 mg intravenously) slowed the gastric emptying of test meals containing sodium citrate, and 10 mg of intravenous metoclopramide abolished the slowing of gastric emptying caused by apomorphine.

There have been two convincing double-blind radiological studies which have shown that metoclopramide increases the rate of gastric emptying in man (Margieson, Sorby, and Williams, 1966; James and Hume, 1968). Metoclopramide is now used to hasten gastric emptying in the radiological assessment of the small bowel (James and Hume, 1968). Few unpleasant and no serious side effects have been noted (Trafford, Fisher, Marshall, and Douthwaite, 1967). As the main site of action of metoclopramide is still uncertain (Eisner, 1968), the following studies were made in man.

There are receptors in the duodenum which slow gastric emptying in response to the osmotic pressure of the luminal contents (Hunt and Pathak, 1960). It occurred to us that one action of metoclopramide might be to interfere with the inhibition of gastric emptying by these receptors. If this were so the gastric emptying of glucose solutions, which stimulate duodenal receptors, would be hastened. On the other hand, the gastric emptying of sodium citrate solutions would remain unchanged since they are a minimal stimulus to the duodenal receptors inhibiting gastric emptying (Hunt and Knox, 1962).

In the present paper we describe the studies which we undertook to pursue this idea.

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Methods and Technique

In all these studies the subjects were healthy male medical colleagues. Not more than one experiment on any one subject was performed on one day. Experiments involving apomorphine were separated by intervals of at least one week.

The subjects came to the laboratory in the early morning having fasted since the previous evening. Water was taken between arising and reaching the laboratory if desired. Any secretions in the stomach were washed out with 250 ml of water which was swallowed and immediately recovered through a rubber tube with a 3 mm bore with seven side holes. The position of the tube was judged from the ease of recovery of the swallowed water. The test meal at 37°C was given through the tube in about 75 seconds. The volume of the original meal in the recovered gastric contents was determined from the amount

of phenol red recovered. The gastric contents were analysed as described by Hunt (1959) and Hunt and Knox (1962). The amount of acid secreted during the test meal was calculated as ml/160 mN HCl, the supposed concentration at which it is secreted by the parietal cells.

SERIES 1

Two fasting subjects H.T. and R.M. took doses of 0-30 mg metoclopramide as syrup one hour before receiving a standard test meal. Gastric emptying was studied with 750-ml test meals containing 50 g glucose monohydrate (250 milliosmoles) and 60 mg phenol red per litre. The interval between instilling and recovering the meal was 20 minutes as it was also in the studies with glucose test meals in series 2 and 3.

SERIES 2

There were four subjects. The dose range of metoclopramide was 0-20 mg, as syrup, given two and a half hours before test meals (50 g glucose monohydrate, ie, 250 milliosmoles per litre) similar to those used in series 1.

SERIES 3

Five subjects were given metoclopramide intravenously in the dose range 0-10 mg 10 minutes before receiving a test meal (50 g glucose monohydrate, ie, 250 milliosmoles per litre) similar to those in series 1 and 2. Isotonic saline was used as a control intravenous injection. The subjects did not know whether they were receiving active or control material.

SERIES 4

This series was a repetition of series 3 using 100 mN sodium citrate (133 milliosmoles per litre) test meals instead of the glucose solution used in series 3. Because the 100 mN sodium citrate meals leave the stomach much more rapidly than the glucose meals the interval between instilling and recovering the meals was reduced to 10 minutes in series 4 and 5.

SERIES 5

In series 1 to 4 metoclopramide did not consistently increase the rate of gastric emptying. In series 5 therefore we slowed gastric emptying with apomorphine in order to provide a situation more favourable for the study of any hastening action which metoclopramide might have.

This series was divided into three parts, and the tests were performed in four subjects. In the first part the rate of gastric emptying of sodium citrate in test meals (100 mN) was measured. In the second part the effect of 0·2-0·25 mg intravenous apomorphine given 10 minutes before instilling the sodium citrate meals (100 mN) was measured. In the third part the effect of 10 mg intravenous metoclopramide on the emptying of sodium citrate test meals (100 mN) was measured following previous intravenous injection of apomorphine. The metoclopramide was given five minutes after the apomorphine and five minutes before the test meal.

PRESENTATION OF RESULTS (SERIES 1-4)

As the doses required to produce effects with metoclopramide under our conditions were not known, subjects were given a series of doses of increasing magnitude starting with a dummy dose. The results for the zero dose and for subthreshold doses thus serve as controls for the doses that were large enough to give effects. The doses were unknown to the subjects. In order to determine the relationship between dose and effect, the measured response, say volume of meal recovered, was plotted on the ordinate against dose on the abscissa. By eye the relationship was rectilinear in all instances. Regression lines were fitted by least squares with dose as independent variable.

Results

SERIES 1

Table I shows that for six oral doses varying between 0 and 20 mg, R.M. showed a mean

Subject	*n*	*Intercept (a)*	*Slope (b)*	*SE Slope*	P
Series 1					
H.T.	6	396	0·80	1·09	0·5
R.M.	5	373	−4·70	1·29	0·05
Series 2					
H.T.	5	421	−0·54	1·10	0·7
K.X.	5	295	4·14	4·03	0·35
P.R.	5	352	6·32	3·38	0·25
R.M.	5	423	−0·54	2·64	0·85
Series 3					
H.T.	5	445	−2·44	6·42	0·7
K.X.	5	342	3·20	6·48	0·7
M.N.	5	297	−1·64	6·57	0·8
P.R.	5	427	2·00	5·21	0·7
R.M.	5	385	−0·44	5·93	0·9
Series 4					
H.T.	7	239	2·57	6·91	0·75
K.X.	7	238	7·89	6·07	0·25
M.N.	7	341	−3·42	10·49	0·75
P.R.	7	304	−6·32	7·55	0·45
R.M.	7	262	−15·85	3·70	0·01

Table I *Volume of meal recovered in series 1-4*

The coefficients are for regression equations of volume of test meal recovered (y ml) against dose of metoclopramide (x mg independent variable): a is the value of the extrapolated regression line at zero dose. The regression equations include values obtained with zero dose: n is the number of tests per subject. The null hypothesis is that the volume of meal recovered is independent of dose of drug. P is obtained by 't' test of the slope.

reduction in volume recovered of 4·7 ml per mg. Thus overall, a 20 mg dose reduced the volume of glucose meal recovered from 373 to 279 ml (373-94), which was significant at the 1 in 20 level. Subject H.T. showed an insignificant increase in volume recovered over the dose range 0-30 mg. Parietal secretion was unchanged by the drug (Table II).

SERIES 2

Table I shows that when the drug was given orally two and a half hours before the test there were no significant increases or decreases in the volume of the meal recovered. In one subject there was a small but statistically significant increase in parietal secretion with dose (Table II).

SERIES 3

Table I shows that with a glucose test meal and the drug given intravenously there was no significant change in volume of meal recovered. Parietal secretion was unchanged (Table II).

SERIES 4

Table I shows that using rapidly emptying sodium citrate test meals intravenous metoclopramide gave a highly significant reduction in the volume of meal recovered in R.M.; the volume recovered at 10 minutes falling from 268 ml with zero dose to 104 ml with 10 mg given intravenously. No other subjects showed any change. Parietal secretion was unchanged (Table II).

Subject	*n*	*Intercept (a)*	*Slope (b)*	*SE Slope*	P
Series 1					
H.T.	6	8·3	0·54	0·37	0·2
R.M.	5	20·8	−0·42	0·31	0·3
Series 2					
H.T.	5	15·0	−0·06	0·08	0·5
K.X.	5	17·4	0·06	0·36	0·9
P.R.	5	29·4	0·52	0·09	0·01
R.M.	5	28	0·20	0·34	0·9
Series 3					
H.T.	5	13·8	−0·40	0·39	0·9
K.X.	5	22·6	−0·36	0·84	0·7
M.N.	5	18·2	−1·16	0·73	0·2
P.R.	5	31·6	0·00	0·99	—
R.M.	5	23·6	−1·12	0·74	0·2
Series 4					
H.T.	7	11·8	−0·19	0·16	0·3
K.X.	7	10·5	−0·37	0·19	0·1
M.N.	7	21·5	−0·31	0·30	0·3
P.R.	7	19·8	0·13	0·44	0·3
R.M.	7	19·1	0·11	0·55	0·9

Table II *Volume of parietal secretion recovered in series 1-4*

The coefficients are for regression equations of volume of parietal secretion recovered (y ml) against dose of metoclopramide (x mg independent variable): a is the value of the extrapolated regression line at zero dose. The regression equations include values obtained with zero dose: n is the number of tests per subject. The null hypothesis is that the volume of parietal secretion is independent of dose of drug. P is obtained by a 't' test of the slope.

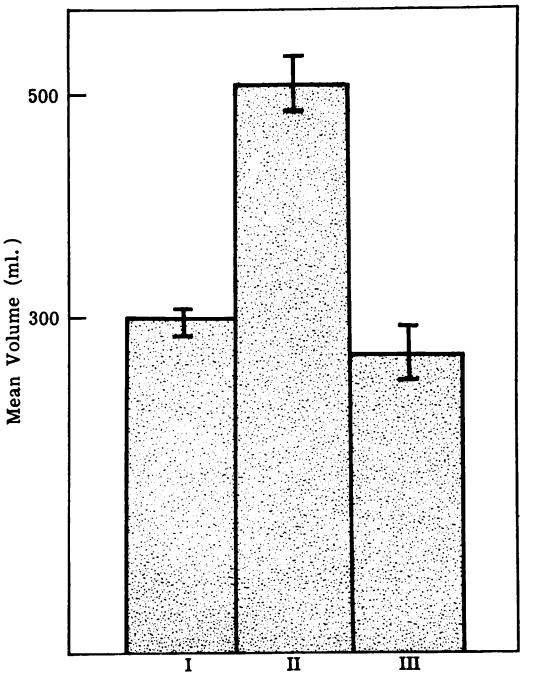

Fig. 1 *Mean volume of sodium citrate test meal recovered after 10 minutes in four subjects. I—with sodium citrate alone (control). II—10 minutes after intravenous apomorphine. III—10 minutes after apomorphine and five minutes after metoclopramide. Vertical bars represent the standard error of the mean.*

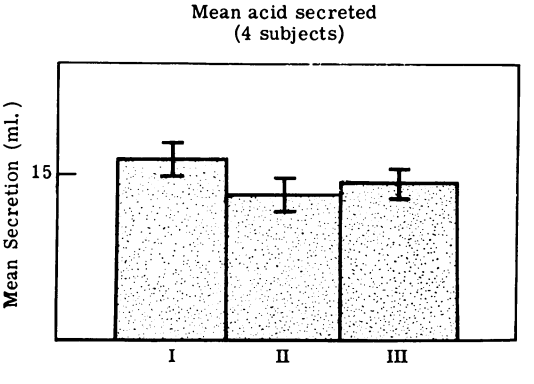

Fig. 2 *Mean acid secreted in response to sodium citrate test meals recovered after 10 minutes in four subjects. I—with sodium citrate alone (control). II—10 minutes after intravenous apomorphine. III—10 minutes after apomorphine and five minutes after metoclopramide. Vertical bars represent the standard error of the mean (ml 0·16 NHCl).*

SERIES 5

The effects of apomorphine on the volume of sodium citrate meal recovered are shown in Figure 1. In the control series, a mean of 299 ml (SE ± 17·4) of the original meal was recovered. When apomorphine was given 10 minutes before the test meal the mean recovery increased to 509 ml (SE ± 19·9). When metoclopramide was given five minutes after the apomorphine and five minutes before the test meal, the mean volume recovered was 265 ml (SE ± 26·4). This volume is not significantly less than the 299 ml obtained for the control citrate test meals in this series (paired 't' test). Figure 2 shows that the parietal secretion was little changed after either apomorphine or apomorphine plus metoclopramide. There was no evidence of significant regurgitation of bile in any of the recovered gastric contents.

Discussion

There is clear evidence from two double-blind radiological trials that metoclopramide in intravenous doses of 10 mg increases the rate of gastric emptying (Margieson *et al*, 1966; James and Hume, 1968). We expected our test meal techniques to give similar results. Initially test meals containing 50 g glucose/l were used on the assumption that metoclopramide might block the effect of glucose on the duodenal osmoreceptors. In our first series R.M. showed a significant increase in gastric emptying. Because the drug had produced no such effect in H.T. it seemed desirable to have a longer period for absorption of the metoclopramide before giving the glucose test meal. Four subjects therefore took varying doses of syrup 150 minutes before the test. There was evidence of absorption since all the subjects were sleepy after higher doses, but in spite of this, none of the subjects, not even R.M., showed an increase in gastric emptying. At this stage it seemed that we should have used an intravenous form of metoclopramide to ensure that the administered dose was effective at the time of the test. The previous four subjects and M.N. were given doses of metoclopramide intravenously 10 minutes before the test meal of glucose. There was no significant change in gastric emptying. Four out of five subjects became drowsy with the larger doses.

It seemed that in using glucose we had chosen the wrong type of test meal to demonstrate the effect. It occurred to us that metoclopramide might increase gastric emptying by changing glucose metabolism either generally or locally. A fall in blood sugar is a known stimulus of gastric motility (Bachrach, 1953). Alternatively, because glucose slows gastric emptying by stimulating duodenal receptors, metoclopramide might not be able to overcome such an effect. For this reason we now used test meals of sodium citrate solution which have a minimal effect on the duodenal osmoreceptors slowing gastric emptying (Hunt and Knox, 1962). With these citrate meals only one subject (R.M.) out of five showed a significant increase in gastric emptying. In summary only two out of 16 studies (Table I) in five subjects showed any consistent increase in gastric emptying with increase in dose of metoclopramide.

At this point it seemed that the barium sulphate in the previous radiological studies might be the critical factor but a few experiments with barium in the laboratory established that the gastric emptying of barium sulphate suspensions was similar to that of water (to be published). From casual observations on H.T., it was known that gastric emptying in the *x*-ray room could on occasion be much less quickly established than it was in the laboratory. It occurred to us that patients having barium meals are under some degree of stress which can reduce gastric peristalsis (Jungmann and Venning, 1955). It seemed possible that metoclopramide might only increase the rate of gastric emptying when it was already reduced by central nervous action. We therefore wished to test the effect of metoclopramide during slowed gastric emptying. Having shown that apomorphine slowed gastric emptying we had a model in which to study the effect of metoclopramide. Ten milligrams of metoclopramide abolished the very considerable slowing of gastric emptying produced by 0·2-0·25 mg apomorphine, the molar ratio being about 50:1.

The doses of apomorphine used produced either no nausea or only very transient nausea. Thus at the time apomorphine was slowing gastric emptying, presumably by acting on the area postrema (Borison and Wang, 1953), it was causing no other signs or symptoms. This raises the question as to whether gastric emptying may be slowed by naturally occurring substances, say adrenaline, in the circulation acting on the area postrema.

This investigation is an interesting example of the difficulties which may arise in replicating in the laboratory results obtained in clinical work. The unstressed state of our healthy trained subjects was apparently responsible for the ineffectiveness of metoclopramide in hastening their gastric emptying. This presumably accounts for the difference between our results and the proven effectiveness of metoclopramide in clinical circumstances.

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