Diabetes Research and Clinical Practice, 4 (1988) 223–229
Elsevier

DRC 00181

Metformin in the digestive tract

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(Received 1 April 1987, revision received 9 September 1987, accepted 14 September 1987)

Key words: Metformin; Digestive tract

Summary

After ingestion of metformin, a drug of the biguanide class, there are gastrointestinal side effects in the form of nausea and vomiting, and about 30% of the drug is recovered in feces. The purpose of this work was to explain these two phenomena. Two sets of experiments were carried out.

Study 1 evaluated the gastroduodenal (GD) absorption in six healthy volunteers by means of an intubation method, employing a twin-lumen tube introduced into the intestine and another into the stomach. Metformin 1 g was introduced into the stomach with a homogenized meal containing a non-absorbable marker, ^{14}C-PEG 4000; another marker, PEG 4000, was perfused continuously into the duodenum at the ampulla of Vater. Samples of GD contents were collected every 15 min during 4 h. Metformin was poorly absorbed from the stomach, about 10% over a 4-h period. It did not modify the gastric emptying of a meal but induced a duodeno-gastric reflux in five out of six subjects. About 20% of the amount of drug emptied from the stomach were absorbed from the duodenum. The delivery process was the rate-limiting factor for metformin absorption from the duodenum. The AUC/24 h increased as the absorption rate from the duodenum increased.

Study 2 investigated in six healthy volunteers, using another intestinal perfusion technique, the jejunal and ileal absorption of metformin. Metformin 400 mg in saline solution was perfused, over a 2-h period, below an inflated balloon, directly into either the jejunum or the ileum. The mean amount of drug absorbed along a 25-cm segment was low, and similar from the jejunum and ileum: 10.8% and 8.8% respectively. When the drug was perfused into the jejunum, the AUC values were about 2.5 times higher than the values when the drug was perfused into the ileum. These results suggest that the whole intestine is necessary for a sufficient absorption of the drug.

Introduction

Metformin has been recommended for many years in the treatment of maturity-onset diabetes. It is now the most commonly prescribed oral hypogly-

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cemic drug of the biguanide class. In spite of its widespread use, little is known about the pharmacokinetics of this drug. Previous investigations [1–4] have shown that after ingestion of metformin, the cumulative excretion in urine over 48 h is about 50% of the ingested drug amount while the recovery in feces is about 30%. Moreover, it has been suggested that metformin could induce inhibition of gastric emptying in the rat [5] and the dog [6] and that this inhibition could be responsible for the gastrointestinal side effects of biguanides (nausea, vomiting). The purpose of this work was to study in healthy volunteers (1) the effect of metformin on gastric emptying of a meal, and (2) the gastrointestinal absorption of this drug by a direct method.

Materials and methods

Subjects

Studies were performed on 12 healthy volunteers (all men), aged 25.0 ± 1.2 years (mean ± SEM). No subject had a history of bowel disease or diabetes. All subjects gave written informed consent, the protocol having been approved by the Ethical Subcommittee of the Saint-Lazare Hospital. Their weight was 71.9 ± 1.3 kg and their height was 178.9 ± 1.4 cm. The subjects were instructed to take no drug during the 8 days preceding the study and none other than metformin during the 3 days of intubation.

General procedure

The intubation techniques facilitate investigation of the gastrointestinal absorption of drugs in man [7–9]. A complete description of the absorption of metformin from stomach to colon is given in this paper. The effect of metformin on postprandial gastric function is also reported.

Two sets of experiments were performed. In the first study (A), metformin was ingested with an homogenized meal; the gastric emptying of metformin and its gastroduodenal absorption were studied by applying the technique described by Bernier et al. [10], as improved by Malagelada et al. [11] and Vidon et al. [12]. This involved, after an intubation of the stomach and duodenum, measuring gastric functions by dilution of two aqueous non-absorbable markers, one present in the meal, the other simultaneously perfused into the duodenum.

The second study (B) involved perfusing metformin, dissolved in a saline solution, directly into the upper jejunum or the upper ileum; the drug absorption was measured from the 25-cm segment below each perfusion point.

Solutions

Study A. I. Unlabelled polyethylene glycol (PEG 4000, 10 g/l) in normal saline solution was perfused into the duodenum as a duodenal recovery marker at a flow rate of 2 ml/min.

II. The homogenized meal consisted of 90 g tenderloin steak, 70 g white bread, 14.5 g olive oil, 90 g pear sherbet and 190 ml water containing 30 μCi of ^{14}C-labelled polyethylene glycol 4000 (^{14}C-PEG). The total caloric value was 490 kcal, made up of approximately 50% carbohydrates, 30% fat and 20% proteins. After homogenizing, the volume, osmolality and pH of the meal were 400 ml, 490 mOsm/kg and 5.6, respectively.

Study B. The perfused solution contained: NaCl 130 mM, KCl 5 mM, mannitol 30 mM, ^{14}C-PEG 15 μCi/l and metformin 700 mg/l.

Experimental design

Study A. Experiments were carried out over a 3-day period in six subjects aged 23.7 ± 0.2 years.

On the first day, subjects were intubated with a double-lumen tube. The meal was given on two consecutive days (days 2 and 3), with or without 1 g of metformin in a random order.

After an overnight fast, the tube was positioned under fluoroscopic control with the perfusion site of unlabelled PEG 4000 at the ampulla of Vater, the aspiration site being located 20 cm distally, near the ligament of Treitz. A gastric tube was then positioned with its tip in the antrum. The volunteers adopted a sitting position for the duration of the study.

The meal was introduced into the stomach by the gastric tube. Duodenal perfusion of PEG 4000 was started immediately before the ingestion of the

meal. The meal was introduced over a period of 164 ± 15 s. Gastric and duodenal contents were sampled every 15 min for 4 h, duodenal contents being aspirated at a rate of 1 ml/min. At the end of the experiment, the gastric contents were completely aspirated. The stomach was then rinsed with 250 ml of normal saline solution to recover all the meal marker.

Blood samples were taken at 0, 15, 30, 60, 90, 120, 150, 180, 210, 240, 360, 480 min and 24 h when the meal contained drug.

Study B. Experiments were carried out over a 3-day period in six subjects aged 25.9 ± 2.1 years.

On the first day, subjects were intubated with a four-lumen tube which also incorporated an occlusive balloon [13]. The technique has been described elsewhere [8].

The segment length was 25 cm. The solution was perfused at a rate of 5 ml/min over 2 h. After an equilibration period to obtain a hydrodynamic steady state, five successive 15-min samples were collected.

The jejunal and ileal absorption was studied on days 2 and 3, respectively.

Blood samples were taken at 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 360 and 480 min. For the jejunal study only, a blood sample was also taken at 24 h.

Analytical method

Study A. In each gastric and intestinal sample, the cold PEG concentration was measured by the turbidimetric method of Hyden [14]; ^{14}C-PEG was measured in a scintillation counter; metformin concentrations were measured by a high-performance liquid chromatography (HPLC) method.

Study B. In each intestinal sample, cold PEG and metformin concentrations were measured as in study A. In both studies, metformin plasma concentrations were measured by HPLC.

Calculations and statistical analysis

Study A. The postprandial volume of gastric contents, its fraction emptied into the duodenum, the gastric emptying of the meal and drug and the gastric secretion were measured using previously reported procedures [11]. The duodenal absorption of the drug was calculated using measured gastric and duodenal concentrations of markers and metformin. Gastric absorption of the drug was estimated from the difference between the amount given with the meal and that leaving the stomach (amount passing the pylorus + amount removed with gastric samples). Areas under the plasma concentration–time curves (AUC) were calculated by the trapezoidal rule. The peak plasma concentration of metformin (C_{max}) and times to reach the peak level (T_{max}) were determined.

Study B. The absorption of metformin along the studied segment per unit of time was calculated according to the usual formulae for perfusions [15]. Absorption was defined as the difference between the amount entering and that recovered at the sampling site.

Data are expressed as means ± SEM. Wilcoxon's *t*-test for paired or non-sequential and correlation analysis were used for statistical comparisons.

Results

Study A

Gastric absorption of metformin. Total ^{14}C-PEG recovery was measured by adding ^{14}C-PEG contained in gastric samples, the final aspiration, the gastric lavage and the amount passing the ligament of Treitz. Recovery was nearly complete, being 95.1 ± 2.7 and 95.7 ± 1.4% with and without metformin, respectively. The amount of drug lost from the stomach by gastric emptying and sampling over the study was 81.9% of the amount ingested. The metformin to ^{14}C-PEG ratio in each gastric sample over 4 h postprandially also reflects gastric absorption of the drug; it was 86.7 ± 1.0%. These results indicate that about 13% of metformin were absorbed from the stomach over a 4-h period.

Gastric emptying. Gastric emptying of the meal

TABLE I

INTRAGASTRIC VOLUME OF MEAL EXPRESSED AS PERCENT OF INGESTED MEAL VOLUME IN RELATION TO TIME

	Intragastric volume of meal			
Time after meal ingestion	1 h	2 h	3 h	4 h
With metformin	66.5 ± 1.6	36.9 ± 3.4	12.9 ± 3.3	1.6 ± 0.9
Without metformin	67.2 ± 2.5	37.4 ± 3.0	13.9 ± 4.8	5.5 ± 5.0

varied little between subjects, the intragastric volume of meal in relation to time was not statistically different with or without metformin (Table 1). At the end of the 4 h, almost all of the initial meal had left the stomach.

Gastric secretion. Total gastric volume is made up of the volume of the meal present in the stomach plus the volume of salivary and gastric secretions. These salivary and gastric secretions varied considerably between subjects but were not significantly modified by metformin. Their values were 1040 ± 230 and 977 ± 154 ml with and without metformin, respectively.

Duodenogastric reflux. In five subjects out of six, there was a duodenogastric reflux when the meal contained metformin. Indeed, gastric juice was stained yellow by bile acids as early as 20 min after ingestion of the meal in four subjects and continued so over more than 2 h. Cold PEG was detected in three gastric samples from five subjects. When metformin was not ingested, gastric juice was never stained by bile acids. In one subject, cold PEG was detected during 3 h and 45 min after ingesting the meal with and without drug respectively; no side effects were associated with duodenogastric reflux.

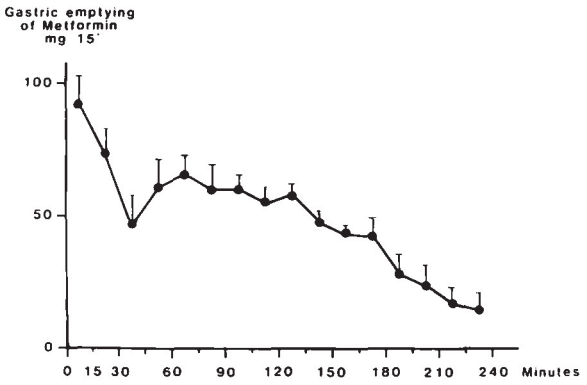

Fig. 1. Gastric emptying of drug in relation to time over a 4-h period after ingestion with a meal (mean ± SEM).

Gastric emptying and duodenal absorption of metformin. Gastric emptying of metformin did not vary between subjects. The amount of drug emptied within a period of 4 h was 78.4 ± 2.2% of the total amount that could have been emptied, i.e., the amount ingested minus the amounts sampled over 4 h.

The amount of drug emptied every 15 min varied considerably during the study (Fig. 1). The duodenal absorption of this drug (Y) is closely related to the gastric emptying rate (X) (Fig. 2). The relation is linear ($r = 0.73$): $Y_{mg/15\ min/20\ cm} = 0.22X_{mg/15\ min} - 1.1$; the slope of 0.22 for the regression line indicates that only 22% of the drug emptied from the stomach was absorbed from the duodenum. Individual absorptive capacities for this segment ranged from 11 to 31% of that delivered at the pylorus over 4 h.

Plasma metformin concentrations. The highest maximum plasma concentrations of metformin (Table 2) were recorded for subjects 5 and 6 who exhibited the highest mean duodenal absorption of

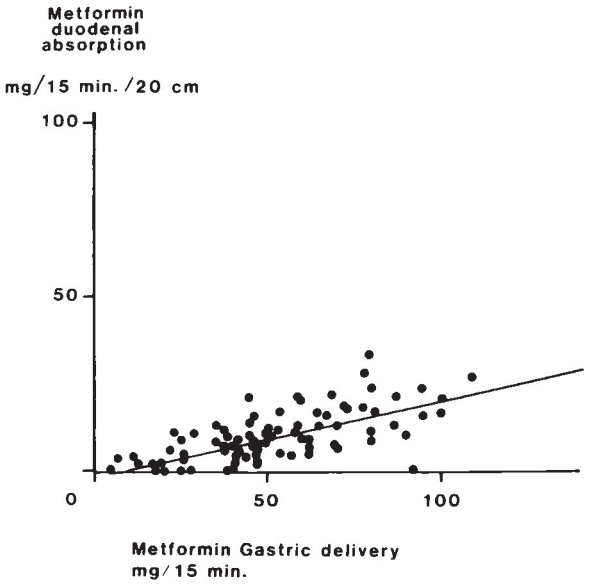

Fig. 2. Duodenal absorption of metformin. Relationship between gastric delivery and duodenal absorption rate. 'y' is the duodenal absorption rate, 'x' the delivery rate from the stomach (mean of six subjects).

drug over 4 h, 27 and 31% respectively. Low C_{max} and low AUC values were associated with low rates of absorption. Interindividual differences in C_{max} and bioavailability (Fig. 3) were related to the amount of metformin absorbed in the duodenum. A minimum of 50 mg of metformin must be absorbed in the duodenum over 4 h, i.e., 3 mg/15 min in order that sufficient metformin can be detected in the plasma to give an AUC value.

TABLE 2

INDIVIDUAL VALUES OF C_{max}, T_{max} AND AUC/24 h AFTER INGESTION OF METFORMIN WITH A MEAL (STUDY A)

Subject	C_{max} (mg/l)	T_{max} (h)	AUC/24 h (mg·min·l^{-1})
1	1.17	3	478
2	0.96	3	253
3	0.62	4	422
4	1.18	4	656
5	1.70	3.5	1062
6	1.71	6	1141
Mean	1.22		669
SEM	0.17		147

Study B

The difference between absorption rates of metformin measured in a 25-cm segment of the jejunum and ileum was not statistically significant. The absorption rates were 10.8 ± 2.6 and 8.8 ± 1.1% of the amount of drug perfused into the jejunum and ileum, respectively.

The peak plasma concentration of metformin (Fig. 4) and the AUC/24 h (Table 3) when the drug was perfused into the jejunum were significantly ($P < 0.05$) higher than the values when the drug was perfused into the ileum. The respective AUC values were 280 ± 24 mg · min · l^{-1} and 123 ± 14 mg · min · l^{-1}.

In subject 3, on day 3, the perfusion point was in the transverse colon. Metformin was not detected in plasma over 8 h except at 150 min; at that time the drug plasma concentration was only 0.15 mg/l which is the minimum detectable level by this method of analysis.

Discussion

The first study showed that metformin did not modify the rate of gastric emptying in healthy

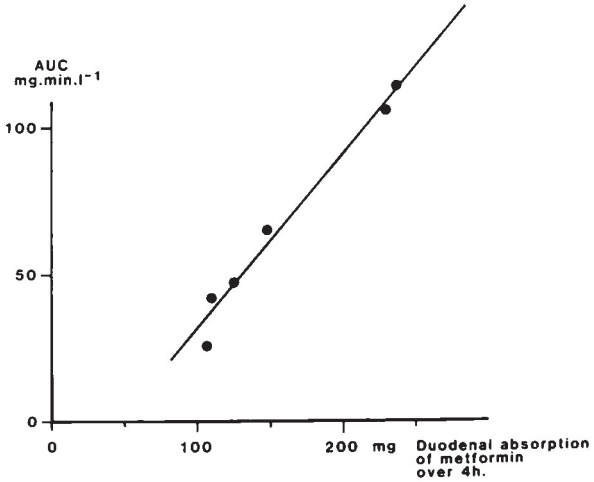

Fig. 3. Duodenal absorption of metformin. Relationship between AUC/24 h and duodenal absorption rates over 4 h after ingestion with a meal. $r = 0.989$.

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