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Evaluation of the gastric absorption and emptying of drugs under various pH conditions using a simple intubation method: application to diclofenac

N. VIDON[1], A. PFEIFFER[1], J. GODBILLON[2], M. RONGIER[1], S. GAURON[2], J. HIRTZ[2], J. J. BERNIER[1] & J. P. DUBOIS[2]

[1]INSERM U290, Hôpital Saint-Lazare, 107 bis rue du Faubourg Saint Denis, 75010 Paris and [2]Laboratoires CIBA-GEIGY, Biopharmaceutical Research Center, B.P. 308, 92506 Rueil-Malmaison Cedex, France

Sodium diclofenac (50 mg) together with [^{14}C]-PEG as a non-absorbable marker were dissolved in 400 ml of water (A), phosphate buffer pH 7.5 (B) or a homogenized meal (C). Each of these was ingested in random order by six volunteers on 3 consecutive days. Some gastric absorption of the drug was established with C but the plasma drug concentration-time profiles mainly reflected the process of gastric emptying.

Keywords diclofenac gastric absorption gastric emptying intubation method

Introduction

When sodium diclofenac is administered in aqueous solution to fasting subjects, the unchanged drug appears rapidly in the plasma (C_{max} at 10 to 15 min after ingestion; Riess *et al.*, 1976). However, the pH of the solution appears to influence the reproducibility of the plasma drug concentration-time profile. Thus, the occurrence of double peaks was greater with unbuffered (17 out of 36 observations) than with buffered (none out of 32 observations) solution, although the amount of drug absorbed was similar (unpublished data). The double peaks may be explained by significant gastric absorption of the drug and/or a delayed gastric emptying of a part of the dose followed by subsequent absorption from the small intestine. As diclofenac is partially (10%) transformed into an indolinone derivative when incubated at 37°C in artificial gastric juice (unpublished data), a possible degradation of the drug within the stomach might be an additional factor.

To understand better the fate of diclofenac (an acidic drug) in the stomach, a simple intubation method was applied to evaluate the effects of solution pH and gastric absorption, emptying and degradation on the time-course of plasma diclofenac in man.

Methods

Subjects

The study was approved by the ethics sub-Committee of the hospital. It was performed in six healthy male volunteers. None had a history of bowel or cardiovascular disease and the results of liver and renal function were normal. The subjects signed an informed consent form.

Ingested solutions

Sodium diclofenac (50 mg) was ingested on separate occasions dissolved in the following media:

- Solution A (400 ml): distilled water (mean pH 5.8).
- Solution B (400 ml): phosphate buffer (mean pH 7.6).
- Homogenized meal (400 ml): caloric value 490 kCal, made up of 50% carbohydrate, 30% lipid, 20% protein (osmolality 490 mosm kg^{-1}, pH 5.6).

^{14}C-labelled polyethylene glycol (PEG, 30 μCi, 50 mg in 3 ml water) was added to the solutions and the meal. Radioactive rather than unlabelled PEG was used since it provides more precise and accurate measurements at low concentrations.

Correspondence: Miss N Vidon, INSERM U290, Hôpital Saint-Lazare, 107 bis rue du Faubourg St Denis, 75010 Paris, France

Protocol

The experiments were carried out over a 3 day period. On the morning of each day, after an overnight fast, a nasogastric tube was positioned under radiological control with its tip in the antrum. The stomach contents were aspirated after which either solution A, B or C (in a random order) was introduced into the stomach through the gastric tube. Immediately after introduction, a sample was taken for analysis. Further samples were aspirated every 10 min for 50 min after A and B, every 20 min for 2 h after C. Before each sampling, the gastric contents were mixed by aspiration and re-introduction.

Immediately after the last sample, 50 ml of a solution of phenol red (5 g l^{-1}), used as recovery marker, were introduced into the stomach, and the gastric contents were aspirated as completely as possible. The stomach was rinsed with 100 ml of buffer pH 7.5 and the gastric contents were again aspirated.

Serial blood samples for drug assay were collected over 8 h after each drug administration.

Analytical methods

Unchanged diclofenac in plasma was measured by h.p.l.c. (Godbillon *et al.*, 1985).

In each gastric sample, [^{14}C]-PEG was measured by liquid scintillation counting and diclofenac and its indolinone derivative were measured by h.p.l.c. Phenol red in the last two gastric samples was measured by a colorimetric method (McLeod *et al.*, 1968).

Data analysis

Since the gastric contents were mixed before each sampling, it was assumed that diclofenac (as soluble salt or insoluble free acid) would remain homogeneously distributed in the gastric contents irrespective of their pH.

Gastric emptying, absorption and degradation were considered as factors responsible for the disappearance of diclofenac from the stomach.

Assuming a first-order process for gastric emptying of liquid meals (Hunt *et al.*, 1967), the half-life was calculated from a semi-log plot of the final and initial volumes of A, B or C *vs* time. The final volume of solution or meal left in the stomach was calculated from the total ^{14}C-radioactivity in the stomach at 50 min or 2 h, corrected for the recovery of phenol red. The intragastric volumes of A or B every 10 min, of C every 20 min, were calculated by interpolation.

The amount of diclofenac disappearing from the stomach by emptying and absorption (or precipitation or degradation) was estimated from measured concentrations of diclofenac and PEG.

Results and discussion

The data are expressed as means ± s.d. The formation of the indolinone derivative occurring *in vitro* was not observed *in vivo*. Therefore, degradation of diclofenac did not contribute to its disappearance from the stomach.

As early as 1 min after A, at 20 min after B but

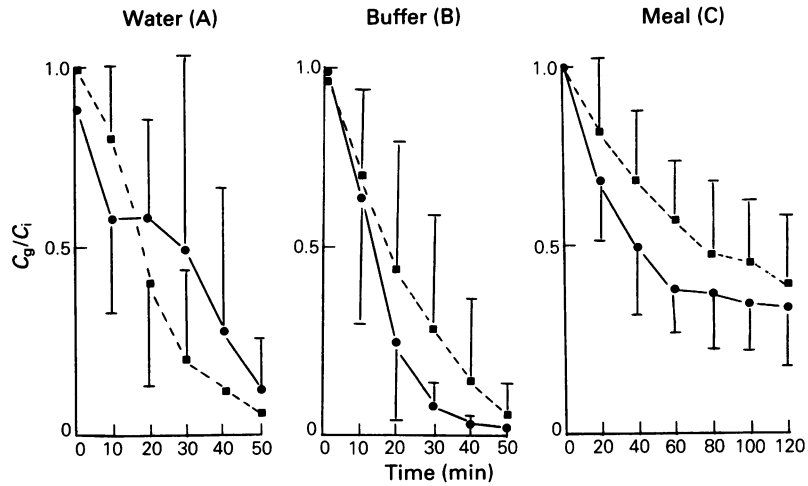

Figure 1 Disappearance of diclofenac (●) and PEG (■) from the gastric contents: mean ratio of the concentration in each gastric sample (C_g) to the initial concentration (C_i) as a function of time.

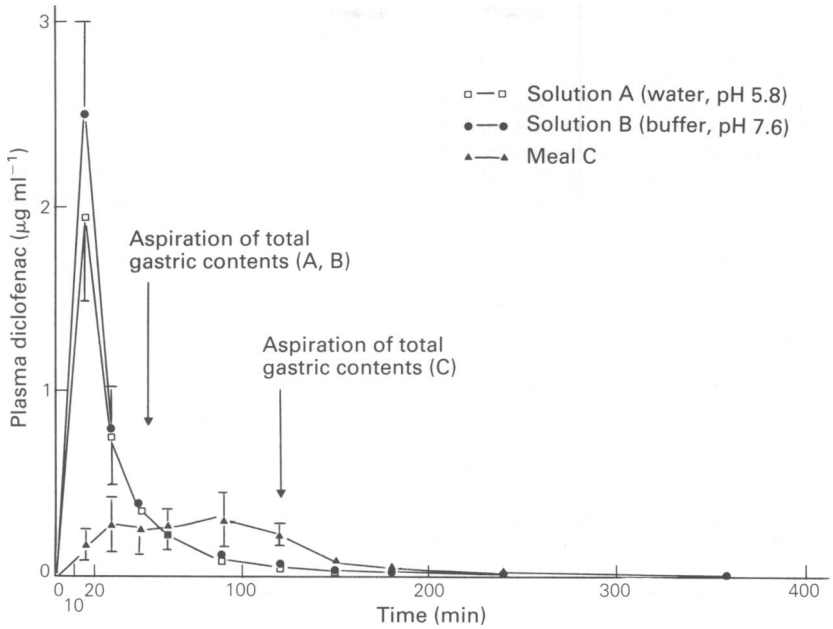

Figure 2 Mean plasma diclofenac concentrations ($\mu g\ ml^{-1}$) after ingestion of solutions A and B and meal C, each containing 50 mg sodium diclofenac.

only at 2 h after C, the pH of the gastric contents was below the pKa of diclofenac (3.9).

Buffered and unbuffered solutions were emptied similarly from the stomach. With an emptying half-life of 5 ± 1 min, about 75% of the marker for solutions A and B and about 70% of the diclofenac were delivered into the small intestine during the first 10 min (Figure 1). The gastric absorption of diclofenac was estimated to be negligible.

With a gastric emptying half-life of 52 ± 21 min, about 50% of the marker and 36% of the diclofenac were emptied from the stomach in the first 40 min after ingestion of the meal (Figure 1). A moderate gastric absorption was estimated (about 10 mg in the first 40 min).

In contrast to previous findings, double peaks were not observed in the plasma drug concentration-time profile in any subject after administration of the unbuffered solution A (Figure 2). Since in the present study, the gastric contents were mixed before each sampling, insoluble free acid formed was probably emptied with the liquids (Malagelada *et al.*, 1976). In the previous studies, undissolved diclofenac was possibly left in the stomach and emptied later, causing a subsequent increase in plasma drug concentration.

The plasma concentration-time profiles of diclofenac (Figure 2) reflected the gastric emptying of the solutions and meal. Owing to the slow emptying rate of the meal, small amounts of drug were delivered into the intestine over time resulting in much lower plasma concentrations of diclofenac.

Conclusions

Degradation of diclofenac did not occur within the stomach after administration of a solution or a meal. Some gastric absorption was established with the meal, but the plasma drug concentration-time profiles mainly reflected the process of gastric emptying.

Using a simple intubation method, it was possible to delineate gastric absorption, gastric emptying and gastric degradation of an acidic drug.

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