Antipyrine absorption after delayed oesophageal capsule transit

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Twenty fasted patients were given hard gelatin capsules containing antipyrine and barium, and in ten patients the capsule arrested and disintegrated in the oesophagus. Plasma antipyrine was assayed at 10 min intervals for 1 h, then 30 min intervals for a further 3 h. The plasma concentration-time curves for the patients in whom the capsule entered the stomach rapidly, and for those in whom the capsule lodged in the oesophagus, were compared. The absorption in the first hour was calculated from the area under the plasma concentration-time curve and found to be significantly lower if the capsule disintegrated in the oesophagus ($P < 0.0005$). The time to peak plasma concentration was delayed by an average of 46 min ($P < 0.01$) and the peak plasma concentration was significantly lower ($P < 0.05$) if delayed capsule transit occurred. Delayed capsule transit through the oesophagus significantly changed the pharmacokinetic profile of antipyrine.

Keywords antipyrine transit time absorption

Introduction

Oesophageal transit of capsules and tablets is commonly delayed if they are swallowed with only small volumes of water in the supine position (Channer & Virjee, 1982; Hey *et al.*, 1982) and less commonly whilst standing or sitting (Fisher *et al.*, 1982). Capsules may then disintegrate within the oesophagus releasing their contents onto the oesophageal mucosa and local ulceration may result (Collins *et al.*, 1979). The oesophageal mucosa is a stratified squamous epithelium and so drug absorption is likely to be minimal. We have studied the effect of delayed oesophageal transit on the absorption profile of antipyrine administered in capsule form. Antipyrine is a highly soluble agent which is known to be rapidly absorbed into the blood after oral administration (Stevenson, 1977).

Methods

Twenty in-patients awaiting cardiac catheterisation gave informed, signed consent to take part in this study which was approved by the Ethics

Committee of Bristol and Weston Health Authority. All patients were starved overnight and an intravenous cannula was inserted. The first fifteen patients were asked to swallow a single hard gelatine capsule, size 0, containing 300 mg antipyrine powder and 256 mg barium sulphate powder in the supine position with 15 ml of water or less. The position of the capsule was assessed by fluoroscopy. In ten of these fifteen patients (Group 1) the capsule remained and disintegrated in the oesophagus (defined as delayed oesophageal transit). In the remainder the capsule entered the stomach within a few seconds before capsule disintegration (Group 2a). Five patients were given a single capsule in the erect position with 15 ml of water and immediately lay down. In all these five patients the capsule entered the stomach within seconds before disintegration (Group 2b). All patients remained supine for 1 h and thereafter were freely mobile. The position of the capsule and its remnants was checked at 10 min intervals until all the barium remnants could be seen in the stomach. The estimated radiation dose attributable to the study was no more than 0.1 mSv whole body dose equivalent.

Venous blood samples were taken at 10 min intervals for 1 h and then 30 min intervals for a further 3 h. Plasma was immediately separated and stored frozen for subsequent analysis.

No patient had dysphagia nor previous upper gastrointestinal surgery. Group 1 comprised ten male patients of average age 47 years (range 32–57). Eight had angina, one an atrial septal defect and one constrictive pericarditis. Group 2 comprised one female and nine male patients, all with angina, of average age 50 years (range 32–60). In Group 1 six of the patients and in Group 2 all 10 patients were taking either a β -adrenoceptor blocker, nifedipine or a long-acting nitrate, drugs known to decrease oesophageal motility.

Antipyrine was assayed in the serum using high performance liquid chromatography (Danhof *et al.*, 1979). Results were analysed using Student's *t*-test, and Mann Whitney U test.

Results

Group 1

Direct questioning revealed that seven of the 10 patients had upper gastrointestinal symptoms (heartburn 4, flatulence 5, acid regurgitation 1, post-prandial epigastric pain 3). Seven patients had previously noticed tablets sticking after swallowing; five in the throat and two retrosternally. Six patients swallowed tablets regularly without a drink. Four smoked cigarettes.

Group 2

Seven of the 10 patients had upper gastrointestinal symptoms (heartburn 3, flatulence 5, acid regurgitation 4, post-prandial epigastric pain 1). One patient complained of dysphagia for big tablets. Six admitted to a sensation of tablets

Figure 1 Plasma antipyrine concentrations (mean $\pm$ s.e. mean) in 10 patients after normal oesophageal capsule transit (●) and in 10 patients after delayed oesophageal capsule transit (○). * $P < 0.01$, ** $P < 0.0001$.

sticking, in the throat in four and retrosternally in two. Four patients swallowed tablets regularly without a drink. There were four smokers.

Figure 1 shows the plasma antipyrine profile for the two groups. No antipyrine was found in the first 10 min plasma sample of any of the patients in Group 1. Thereafter antipyrine concentrations were significantly different from those in Group 2 at 20 min ($P < 0.001$) and 30 min ($P < 0.01$). Mean time to peak concentration in Group 1 was 76 min (range 30–180) and 30 (range 10–90) in Group 2 and these were significantly different at the $P < 0.01$ level (Mann Whitney). The peak plasma concentration was significantly lower in Group 1 ($7.94 \pm 0.46 \mu\text{g/ml}$; mean $\pm$ s.e. mean) than in Group 2 ($10.6 \pm 0.90 \mu\text{g/ml}$) ($P < 0.05$). The area under the plasma concentration time curve was calculated for the period 0–60 min (AUC 0–60) and compared in the two groups. It was significantly lower in Group 1 ($212 \pm 67 \mu\text{g ml}^{-1} \text{min}$) than in Group 2 ($403 \pm 33 \mu\text{g ml}^{-1} \text{min}$) ($P < 0.0005$). No significant difference was found between the AUC_{0–60} in the two subsets of Group 2.

Disintegration of capsules was seen on X-ray at 10 min in all cases. In Group 1 the position of the initial capsule arrest was at the level of the left main bronchus in nine subjects and in the lower third of the oesophagus in one. Barium first appeared in the stomach by 20 min in seven, by 30 min in one and by 40 min in two subjects. All barium remnants were in the stomach by 20 min in two, 30 min in four, 50 min in one, 60 min in one and 90 min in two.

Discussion

This study has shown that variability in the time course of absorption of antipyrine when administered orally in capsule form can result from delayed transit in the oesophagus.

We chose to study patients attending for planned cardiac catheterisation because they formed a representative sample of the tablet taking population and could be studied conveniently. They were fasted and fluoroscopy was required as part of their investigation. From previous experience (Channer & Virjee, 1982) it had been predicted that approximately 40% of patients taking capsules in a supine position with small drink volumes would have delayed transit of capsules through the oesophagus. It was there-

fore planned to classify patients into two groups according to the position of the capsules when they disintegrated (previously shown to occur consistently between 2 and 4 min (Channer & Virjee, 1982)). In practice in 10 of 15 patients the capsule remained in the oesophagus and disintegrated when swallowed supine with a small drink. In order to achieve balanced groups it was therefore necessary to study five more patients with normal oesophageal capsule transit. To achieve this they swallowed a capsule standing and then returned to the supine position. This provided two groups of patients who were matched in respect of disease severity, gastrointestinal symptoms, smoking habits, age and sex.

In the groups in whom oesophageal transit was fast the rapid rise in antipyrine plasma levels was consistent with the known rapid absorption of antipyrine. In the group in whom the capsule lodged in the oesophagus there was clear evidence of delayed drug absorption. Capsules disintegrated consistently and always by 10 min, releasing barium and antipyrine onto the oesophageal mucosa. The delay in absorption approximately matched the delay in transit of barium from the oesophagus into the stomach. This would suggest that antipyrine is not absorbed through oesophageal mucosa.

The slower rate of absorption was associated with a significantly lower peak plasma level and the time to peak level was prolonged by over 45 min on average. We were unable to determine if total absorption was affected but we believe this to be unlikely. The changes in the pharmacokinetic profile that we have demonstrated from delayed oesophageal transit are most important for drugs whose response is related to peak plasma level, for example, hypnotics and analgesics.

For hypnotics especially, delayed oesophageal transit is a real risk. Many patients take their night sedation just before retiring with little or no water and, in these circumstances, the probability of oesophageal arrest is high. Factors which influence oesophageal transit should be added to those which influence gastric emptying as causes of altered drug absorption (Nimmo, 1979).

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