J. Pharm. Pharmacol. 1985, 37: 126–129
Communicated February 15, 1984

The effect of formulation on oesophageal transit

K. S. CHANNER, J. P. VIRJEE, *Bristol Royal Infirmary, Bristol BS2 8HW, UK*

The oesophageal transit of barium sulphate in small or large, heavy or light capsules or film coated and plain oval tablets was measured during fluoroscopy in five separate studies involving 175 subjects. Transit of large, but not small capsules was significantly faster than plain oval tablets in both erect and supine subjects ($P < 0.05$). Heavy large capsules entered the stomach in all subjects within 20 s, whereas in all other studies some subjects retained dosage forms in the oesophagus for over 5 min. The transit of heavy capsules was significantly faster than light capsules in erect subjects ($P < 0.0005$). Light capsules tended to have faster transit times than heavy capsules in the supine position. Film coating significantly enhanced oval tablet transit in erect ($P < 0.00003$) and supine subjects ($P < 0.05$). When large capsules of equal weight but less dense than film coated oval tablets were directly compared, the tablet transit was significantly superior in the erect subjects ($P < 0.0001$). In supine subjects the transit of the light capsule was significantly faster ($P < 0.005$). It is concluded that different drug formulations can have significant effects on oesophageal transit, and hence on the development of drug induced oesophageal ulceration.

When capsules and tablets are swallowed with little or no fluid and especially when the subject is supine, they frequently do not completely travel the length of the oesophagus (Praetorius & Faber 1950; Evans & Roberts 1976; Channer & Virjee 1982; Hey et al 1982). We have previously shown that the volume of drink swallowed with the capsule and the posture in which it is swallowed significantly affect transit (Channer & Virjee 1982). Tablets and capsules stick at sites of anatomical indentations in the oesophagus, for example, where the left main bronchus and aorta cross the oesophagus, at the cardiac indentation, and at the lower oesophageal sphincter. We have shown that in patients with left atrial enlargement secondary to mitral valve disease, oesophageal indentation is increased, and capsule transit significantly delayed because of this (Channer et al 1984).

Delayed oesophageal drug transit may have two effects. Firstly, since the oesophageal mucosa is a stratified squamous epithelium, drug absorption will be minimal, and delayed oesophageal transit may significantly delay the absorption of the drug (Channer & Roberts 1984). Secondly, localized ulceration may develop in the oesophagus. Over 20 drugs have been reported to be associated with this (Al-Dujaili et al 1983). Doxycycline is the drug most commonly reported upon and was originally formulated as a hard gelatin capsule. When wet, hard gelatin is sticky, and adheres to the oesophageal mucosa and it has been suggested that capsule formulations are thus more prone to delayed oesophageal transit (Carlborg et al 1978; Carlborg & Densert 1980). In Sweden the capsule formulation of doxycycline has been withdrawn and replaced by a tablet (Swedish Adverse Reaction Committee 1978).

Patients prefer to swallow capsules partly because of their smooth surface and partly because their shapes make them easier to swallow. Consequently capsule-shaped tablets (ovoids/tabloids) have been developed. In this study we have examined the effect of formulation on oesophageal transit by comparing hard gelatin capsules with plain and film-coated oval tablets.

Methods

This project was approved by the Ethics Committee of the Bristol & Weston Health Authority.

Barium sulphate tablets and capsules. Oval biconvex barium sulphate tablets 14 mm long × 9 mm wide, volume 1·7–1·9 ml and weight 0·55 g were manufactured to the following specification: barium sulphate as Baritop G powder 49·625%, microcrystalline cellulose 49·625%, magnesium stearate 0·5% and colloidal silicon dioxide 0·25% by weight. Some were film coated with a standard film coat as used in routine pharmaceutical practice comprising w/w 4% hypromellose 5, 4% hypromellose 15, 0·5% polysorbate 80, 10% Opaspray (Colorcon Ltd., Orpington, Kent), 78·5% water.

Hard gelatin capsules, size 2, 18 mm × 6 mm of volume 0·5 ml were filled with barium sulphate powder to a weight of 0·67 g. Hard gelatin capsules, size 0, 22 mm × 7·5 mm of volume 0·8 ml were filled with barium sulphate to a weight of 1·2 g ('heavy') and 0·59 g ('light').

Subjects and methods. One hundred and twelve females, mean age 52 years (17–82), and 63 males, mean age 59 years (18–82) were studied after informed consent was obtained. They had not eaten for 12 h. None complained of dysphagia.

Five separate studies were performed.

1. *Large capsule (heavy) vs plain oval tablet.* These were given to 9 males, mean 63 years (50–82) and 16 females, mean 49 years (21–71).
2. *Small capsules (size 2) vs plain oval tablet.* These were given to 8 males, mean 60 years (38–77) and 17 females mean 54 years (24–77).

* Correspondence.

3. *Heavy capsules (size 0) vs light capsule (size 0).* These were given to 10 males, mean 61 years (42–82) and 15 females, mean 51 years (30–72).
4. *Film coated oval vs plain oval tablet.* These were given to 21 males, mean 59 years (34–82) and 29 females, mean 54 years (22–79).
5. *Film coated oval tablets vs light large capsule (size 0).* These were given to 15 males, mean 53·5 years (18–79) and 35 females mean 51 years (17–82).

Subjects were given a 15–30 ml drink and then asked to swallow in the erect, and later in the supine position, two of the tablets or capsules to be compared, with 15 ml water each. The order of administration of tablet/capsule was random. The time taken for the tablet/capsule to descend the oesophagus was measured with a stopwatch during X-ray fluoroscopy. The oesophagus was screened continually for up to 30 s. If the tablet or capsule remained in the oesophagus, the area of field exposure was narrowed to include only the tablet or capsule. The position of the dose form was then checked by spot screening approximately every 30 s, up to a maximum of 5 min. If a tablet or capsule remained in the oesophagus for 5 min, its position was noted and the subject stood up and took a further drink to clear the oesophagus, before proceeding to the next dosage. Such subjects were designated 'stickers'. Subjects in which all four tablets/capsules entered the stomach in <5 min, were designated 'non-stickers'.

Subjects were questioned about the presence of upper gastrointestinal symptoms and were asked if they experienced difficulty swallowing tablets normally, and if they were aware of tablets sticking in the oesophagus during the study.

The results were analysed using non-parametric statistical methods.

Previous estimations have shown that the average radiation exposure during the study is 0·07 mSv whole body dose equivalent, compared with an exposure during a barium enema of greater than 30 mSv.

Results

Fig. 1A–D shows the oesophageal clearance of the formulations.

Large capsules have significantly faster oesophageal transit than plain oval tablets in both erect ($P = 0·05$ Wilcoxon matched pairs signed ranks test) and supine subjects ($P < 0·05$; Fig. 1A). There was no significant difference between the oesophageal transit of plain oval tablets and small capsules. Heavy large capsules descended the oesophagus significantly faster than light large capsules in erect subjects ($P < 0·0005$) (Fig. 1B). Film coating of oval tablets significantly improved oesophageal transit in both erect ($P < 0·00003$) and supine subjects ($P < 0·05$; Fig. 1C). When light large capsules and film coated oval tablets of similar weight were compared, the oesophageal transit of the film coated tablet was significantly superior in the erect subjects ($P < 0·0001$) but significantly inferior in supine subjects ($P < 0·005$; Fig. 1D).

In all five studies supine posture was associated with delayed oesophageal transit of capsules and tablets.

Table 1 lists the responses of the 175 subjects to specific questions relating to their manner of swallowing dosage forms. Delayed oesophageal transit of dosage forms was found less frequently in subjects who were in the habit of swallowing tablets or capsules without a drink.

In some patients barium tablets and capsules were seen to move up and down in the oesophagus on X-ray fluoroscopy and this movement was seen more frequently in patients in whom one or more pills remained in the oesophagus for 5 min [59 (43%) stickers: 4 (11%) nonstickers; $P < 0·005$ Chi-squared test].

The anatomical sites at which tablets and capsules stopped within the oesophagus were (occurrence with %): upper third oesophagus 5 (2), level of left main bronchus 35 (14), behind heart 73 (30), above lower oesophageal sphincter 126 (51) and more than one site 6 (2).

Table 1. Subject characteristics.

	Stickers (%)	Non-stickers (%)
Total subjects	138	37
Smokers	47 (34)	14 (38)
Upper gastro-intestinal symptoms	87 (63)	24 (65)
Previous abdominal surgery	81 (59)	19 (51)
Taking drugs regularly	79 (57)	17 (46)
History of difficulty swallowing tablets	38 (28)	11 (30)
History of tablets sticking	66 (48)	17 (46)
History of taking tablets without a drink	26 (19)	13 (35)*

'Stickers' = One or more capsules or tablets remained in the oesophagus for 5 min.
'Non-stickers' = All tablets/capsules swallowed entered the stomach in <5 min.
* $P < 0·05$ (Chi-squared test).

Discussion

In subjects in the supine position when the effects of gravity are eliminated, intrinsic peristaltic action must clear the oesophagus of swallowed boluses. When peristaltic activity is decreased by drugs e.g. anticholinergics, oesophageal clearance is delayed (Channer et al 1983). Previous studies have demonstrated that gastro-oesophageal reflux is associated with delayed transit of dosage forms (Evans & Roberts 1976; Channer & Virjee 1982). Using barium swallow and radionuclide oesophageal transit studies we have shown that inco-ordinated oesophageal peristalsis is associated with the repeated up and down motion of capsules when swallowed in the supine position (unpublished observations). This 'intra-oesophageal reflux' was seen in 36% of subjects. It is not associated with dysphagia but is

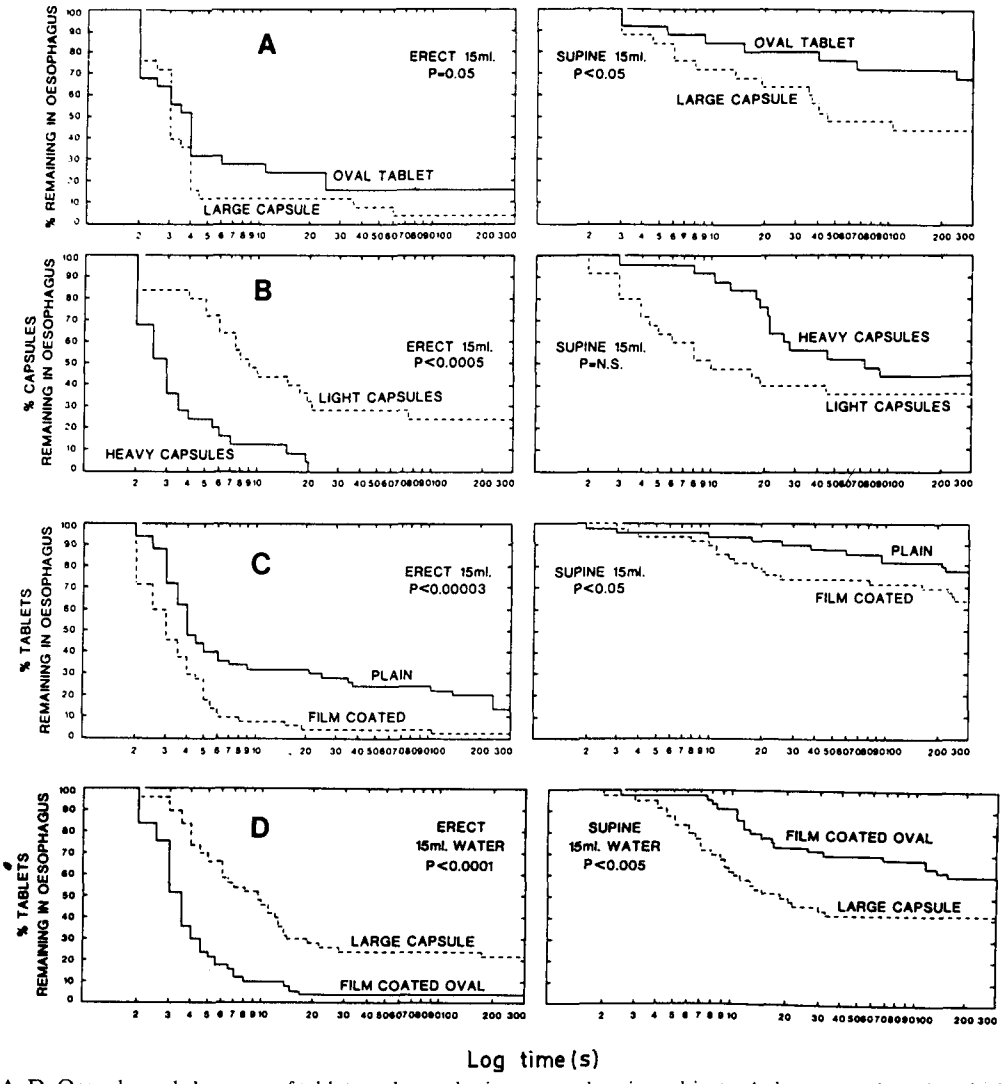

FIG. 1. A–D, Oesophageal clearance of tablets and capsules in erect and supine subjects: A, large capsule and oval tablets; B, heavy and light capsules; C, film-coated and plain oval tablets; D, large capsules and film-coated oval tablets.

significantly correlated with failure of oesophageal capsule or tablet clearance.

This study shows that drug formulations differ in their oesophageal transit characteristics. Patients prefer to swallow capsules and the oesophageal transit of capsules was superior to plain oval shaped tablets in both erect and supine subjects. Film coating of oval tablets significantly improved their transit compared with plain tablets and compared with large capsules of equal weight, but only in erect subjects. In supine subjects the capsule transit was significantly faster than a film coated tablet.

These results are at variance with those of Carlborg et al (1978) and Carlborg & Densert (1980) who suggest that capsule formulations are more prone to delayed oesophageal transit. Hey et al (1982) also showed that capsule transit was superior to that of large oval and round tablets but they preferred not to give capsules, because of the risk of persistent mucosal adherence and subsequent ulceration. In fact, of the drugs known to cause oesophageal ulceration (Al-Dujaili et al 1983) most are tablet formulations.

It is clear that to ensure complete oesophageal transit the formulation must be swallowed with a large volume of water with the subject upright. Film coated oval tablets and light large capsules may minimize oesophageal delay, in supine subjects.

We would like to thank Mr Lewis (Pharmacist) for manufacturing the capsules and Mr Sendall of Cox

Pharmaceuticals Ltd for manufacturing the oval tablets. Jill Wilkinson (Superintendent Radiographer) gave us her continued support.

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J. Pharm. Pharmacol. 1985, 37: 129–130
Communicated 29 May, 1984

Effect of sodium azide and sodium selenite on prostaglandin synthesis in rabbit kidney medulla slices

YOHKO FUJIMOTO*, TAKU YAMAMOTO, NOBUYUKI NIWASE, TADASHI FUJITA, *Department of Hygienic Chemistry, Osaka College of Pharmacy, Matsubara, Osaka 850, Japan*

Sodium azide, a catalase inhibitor, stimulated the generation of medullary prostaglandin E_2, while the glutathione peroxidase activator sodium selenite inhibited it. These results suggest that hydroperoxides play an important role in the control of prostaglandin synthesis.

Lipid peroxidation can modulate arachidonate turnover and prostaglandin synthesis in rabbit kidney medulla slices (Fujimoto et al 1983). Cyclooxygenase activity can be enhanced or inhibited by antioxidants depending on their type and concentration (Fujita et al 1982). On the other hand, prostaglandin cyclooxygenase activity has been shown to be inhibited by added glutathione peroxidase (Lands et al 1971; Smith & Lands 1972). The sensitivity of the cyclooxygenase to inhibition by added glutathione peroxidase has been taken as an indication of a continuous requirement for some peroxide for activation (Smith & Lands 1972; Hemler & Lands 1980). This paper deals with the effects of sodium azide and sodium selenite on the in-vitro production of prostaglandin E_2, in order to investigate the possible involvement of hydroperoxides in regulation of prostaglandin synthesis.

Materials and methods

Male rabbits (2–2·5 kg) were anaesthetized (sodium pentobarbitone, 30 mg kg^{-1}) and the kidneys were removed and rapidly chilled in ice-cold 0·9% NaCl. Slices of medulla were prepared as described by Fujimoto & Fujita (1982). In all experiments the slices (0·4 g) were preincubated in 4·0 ml of 0·15 M KCl/0·02 M Tris-HCl buffer, pH 7·4, at 4 °C for 5 min. Following preincubation, the medium was discarded, the slices rinsed twice with the Tris-HCl buffer and incubated with various concentrations of drugs at 37 °C for 30 min. After incubation, the medium was assayed for prostaglandin E_2 content by a high-pressure liquid chromatographic method (Fujimoto et al 1983). Briefly, prostaglandin E_2 extracted with ethyl acetate (approximately pH 3) was measured after its base-catalyzed conversion to prostaglandin B_2 (Jouvenaz et al 1970). Peak heights were measured for the quantification of the extracted prostaglandin B_2 relative to a prostaglandin B_2 standard prepared from authentic prostaglandin E_2.

The values are the mean ± standard error. Statistical significance was calculated using Student's paired *t*-test.

* Correspondence.

Results and discussion

Azide has been reported to inhibit the endogenous catalase activity (Morehouse et al 1983). The biochemical mechanism by which selenium acts as an antioxidant remained obscure until Rotruck et al (1973) presented some experimental evidence for the involvement of selenium in the glutathione-dependent metabolism of hydroperoxides. Those authors described an incorporation of intraperitoneally injected ^{75}Se into a protein fraction which after partial purification showed glutathione peroxidase activity. It was assumed that selenium might function as a constituent of glutathione peroxidase. To assess the potential involvement of hydroper-