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A gamma scintigraphic study to compare oesophageal clearance of "Expidet" formulations, tablets and capsules in supine volunteers

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Summary

The relative rates of transit through the oesophagus of radiolabelled "Expidet" formulations, tablets, capsules or liquids were measured in 10 healthy supine male and female subjects. The movement of the formulations was followed by gamma scintigraphy. Liquids were observed to clear rapidly in a monoexponential pattern in all subjects. The transit of capsules and tablets in the same subjects was slower and more variable. In two subjects, capsules and tablets were observed to lodge in the lower third of the oesophagus. The "Expidet" formulations cleared from the mouth with several swallows and there was no evidence of oesophageal adhesion. There was no statistically significant difference in total transit time between the formulations.

Introduction

It is well recognised that tablets or capsules taken by patients in the supine position may lodge in the oesophagus, causing damage and irritation (D'Arcy, 1984; Channer and Virjee, 1985a; Drug and Therapeutics Bulletin, 1985). If tablets are taken without water, the risk is greatly increased and the units may remain lodged in the lower oesophagus until they disintegrate (Hey et al., 1982). The hydration of a sticky material against the mucosal epithelium greatly increases the chance of adhesion and has been recognised as a hazard of formulations containing gelatin or cellulose derivatives (Swisher et al., 1984).

The "Expidet" formulation is a novel solid dosage form which disperses rapidly in the mouth. It consists of a freeze-dried hydrogel matrix which rapidly absorbs moisture, dissolves and releases the drug. An important advantage of the "Expidet" formulation may be shown if the units clear from the oesophagus especially in the supine position without lodging or sticking. This would simplify the administration of solid dosage forms, there being no need to move the patient to an upright position or provide water to administer the drug. This would have a therapeutic advantage for hospitalised and non-ambulant patients since it should reduce the incidence of prolonged oesophageal retention. In addition, this would decrease nursing time for administration of the

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medication. A study was therefore carried out in which the oesophageal transit of technetium-99m (^{99m}Tc) labelled "Expidet" formulations was compared to that of tablets, hard gelatin capsules and water in normal supine volunteers in order to maximise the chances of dosage form adhesion.

Materials and Methods

Preparation of the radiolabelled dosage forms

^{99m}Tc-pertechnetate was eluted from a generator and adsorbed onto micronised Amberlite CG400 ion exchange resin (maximum size 20 μm). The resin was oven-dried for 1 h at 95 °C. The activity was calculated for each unit dose as 2–4 MBq at the time of administration.

"Expidet" formulation. The radiolabelled micronised resin (10 mg) was added to the standard "Expidet" formulation and the Expidet (12 mm diameter, 0.25 ml) was manufactured in the usual manner.

Tablet. The radiolabelled resin was added to the standard Ativan tablet formulation (Wyeth Pharmaceuticals) without an active drug. The granulate was compressed using a hand-operated tablet press to produce a tablet similar to the current Ativan formulation with a weight of 100 mg, normal convex profile and diameter of 6 mm. Hardness was measured to be in the range of 10–15 Strong Cobb units.

Capsule. The radiolabelled resin was mixed with mannitol in a mortar and pestle. The mix was hand weighed into a No. 2 hard gelatin capsules.

Liquid formulation. Ten ml of water was radiolabelled with 1–2 MBq technetium-99m DTPA.

Protocol

Ten healthy male or non-pregnant female volunteers were recruited from the University student population. Exclusion criteria included weight outside the range of $\pm 10\%$ of group mean weight, consumption of medications which could influence the results of the study, excessive tobacco consumption or participation in a similar study within the previous twelve months. Approval from the University of Nottingham Ethical Committee had been obtained and the study was performed in accordance with the guidelines for the Declaration of Helsinki (Venice Amendment) 1984. Written informed consent was obtained from the volunteers prior to entry into the trial.

The subjects were requested to refrain from drinking alcohol for 12 h before the trial and eating and drinking for 30 min before each dose was administered.

Subjects were positioned on their backs on a bed under the gamma camera and asked to swallow the radiolabelled dose form or water. No water was given with the "Expidet" formulations but 15 ml of water was given with the tablet and capsule. Continuous overhead scans for 2 min (240×0.5 s) were taken of the buccal cavity, larynx and oesophagus until the dosage form had cleared from the field of view. Additional static scans were taken at intervals where the dose form had not cleared the oesophagus by this time.

The procedure was repeated with the remaining dose forms at approximately 6, 12 and 24 h.

Data evaluation

Scans were evaluated for residence time of the dose in the larynx and oesophagus by division of the image into 10 equal sections. The onset of the swallow was taken as the moment when the material passed through the glottis and the termination as the time at which the activity passed into the stomach. In two subjects (2 and 5) the "Expidet" formulation dispersed completely in the buccal cavity and the activity was cleared in a number of swallows. The oesophageal transit of the first swallow was taken as an index of the behaviour of the formulation.

Results

The data obtained were plotted as position of activity against time for each frame and examples of the traces for "Expidet" formulations and capsules are shown in Fig. 1.

Liquid. The liquid was cleared from the oesophagus with a mean total transit time of 9.1 ± 0.7 s (S.E.M.) in an exponential pattern ($r = 0.99$). A distinct delay was noted at the lower end of the oesophagus as the cardiac sphincter opened

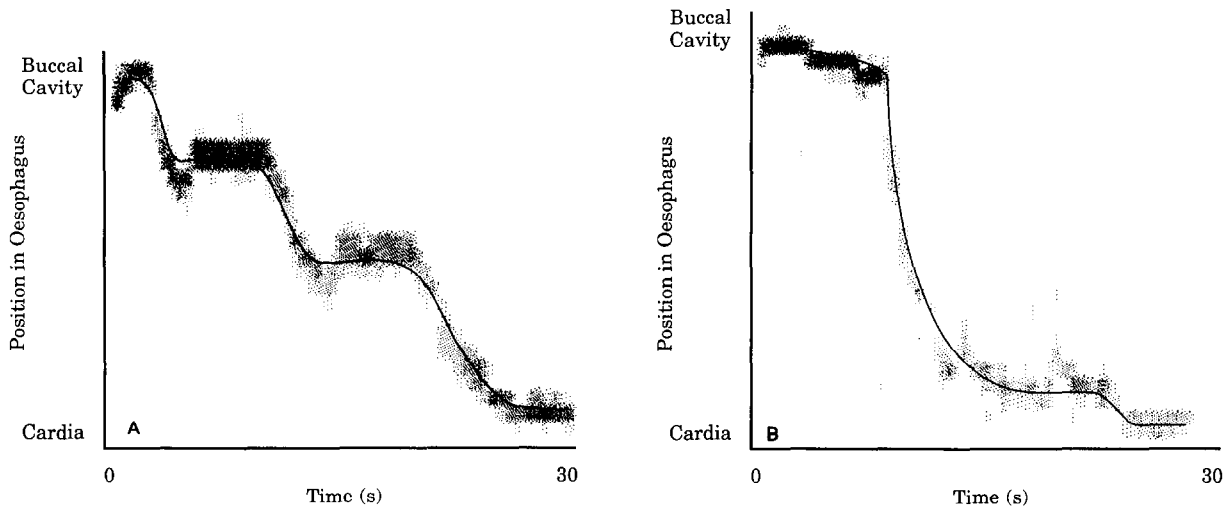

Fig. 1. Oesophageal transit of the technetium-99m labelled resin in (A) an Expidet formulation (B) a capsule.

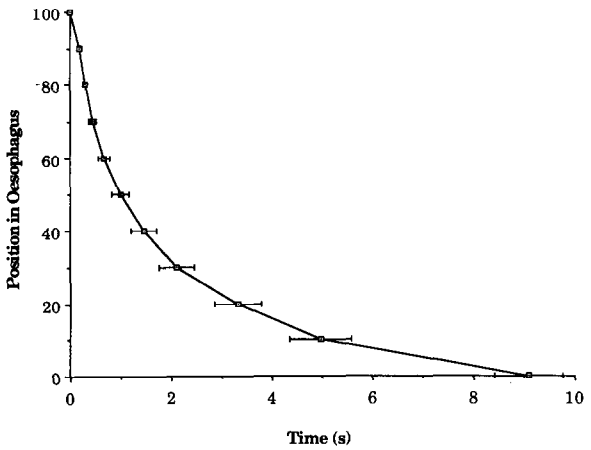

Fig. 2. Mean oesophageal clearance of liquids ($n = 10$, ± S.E.M.).

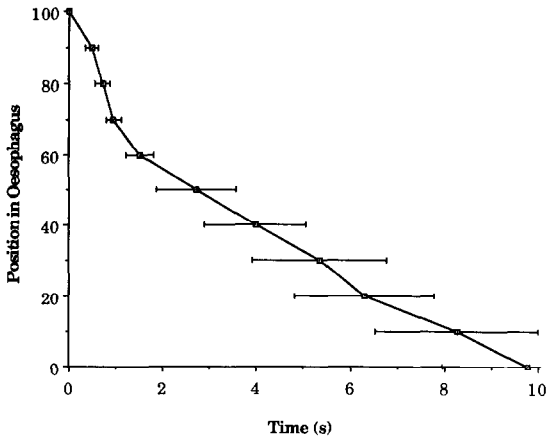

Fig. 3. Mean oesophageal clearance of capsules ($n = 8$, ± S.E.M.).

TABLE 1

Total oesophageal transit times (s) for each subject and treatment

Subject	Expidet	Capsule	Tablet	Liquid
1	11.6	6.1	**356.4**	6.3
2	7.6	12.3	15.3	9.4
3	**93.0**	7.8	16.2	9.4
4	23.9	14.2	24.4	12.2
5	5.9	**480.0**	9.7	8.8
6	20.9	2.8	2.3	12.2
7	23.9	5.6	8.0	6.9
8	7.2	**630.0**	**101.0**	7.3
9	7.6	15.8	17.2	8.8
10	19.0	13.7	9.7	9.7
Mean ± S.E.M. (excluding outliers)	14.1 ± 2.7	9.8 ± 1.8	12.9 ± 2.6	9.1 ± 0.7

Outliers are identified in bold type.

to allow passage of the formulation into the stomach. The mean data for the oesophageal transit of the liquids are shown in Fig. 2.

Capsules. The capsule lodged in the oesophagus of subjects 5 and 8 and could not be cleared by swallowing additional 15 ml aliquots of water. The capsule remained in position in subject 5 until it disintegrated. The total transit time for the remaining subjects was 9.8 ± 1.8 s (S.E.M.). The data for these subjects are shown in Fig. 3.

Tablets. In two subjects (1 and 8) the tablets became lodged in midoesophagus. The tablet took 356 s to clear in subject 1, but could not be moved in subject 8 during the study period, even when additional 15 ml aliquots of water were administered. The mean transit time, excluding subjects 1 and 8, was 12.9 ± 2.6 s (S.E.M.) and the mean data are plotted in Fig. 4.

"Expidet" formulations. The "Expidet" formulations demonstrated two distinct patterns of behaviour. Either the formulation was observed to disintegrate in the mouth, and several swallows were required to clear the activity, or the unit was swallowed whole. In subject 3 some of the activity remained in the lower third of the oesophagus until it was cleared by subsequent peristaltic waves. No water was given to clear the activity. The mean transit time excluding this subject was 14.1 ± 2.7 s (S.E.M.) and the mean data are shown in Fig. 5.

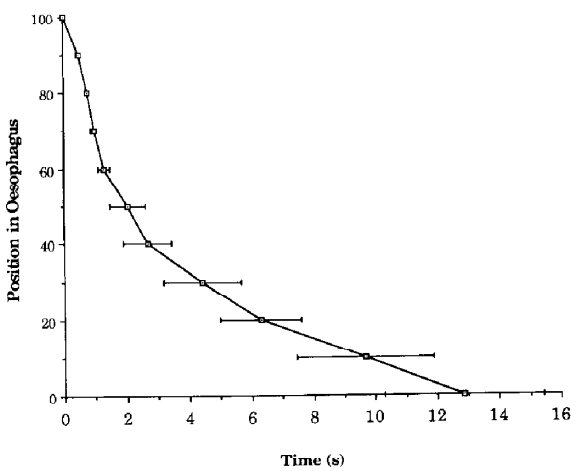

Fig. 4. Mean oesophageal clearance of tablets ($n = 8$, $\pm$S.E.M.).

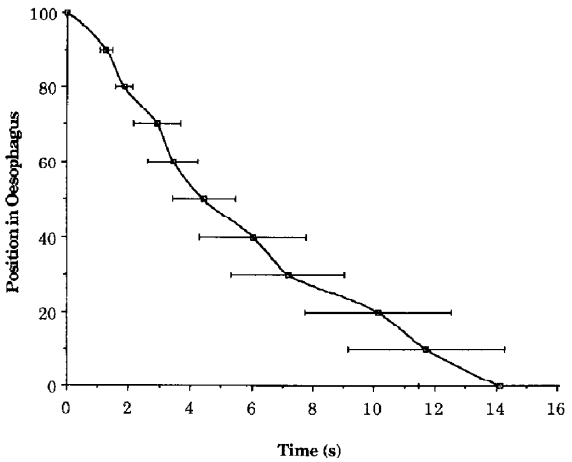

Fig. 5. Mean oesophageal clearance of Expidets ($n = 9$, $\pm$S.E.M.).

The total oesophageal transit times for the individual subjects for each dosage form is shown in Table 1. The data were averaged and the S.E.M. calculated, both for all the subjects and omitting the subjects with abnormal profiles.

Discussion

There have been many papers and reviews outlining the problems of oesophageal transit of various dosage forms (Channer and Virjee, 1982; Heller et al., 1982; Al-Dujaili et al., 1983; Fell, 1983) and it is now generally accepted that oesophageal transit is markedly affected by the posture of the subject and the amount of water used to swallow the dosage form. Oesophageal retention of a formulation containing an irritant drug can lead to damage to the mucosa, ulceration and even stricture or perforation. Oesophageal ulceration has been reported for many drugs including emepronium bromide (Fellows et al., 1982), some antibiotics (Collins et al., 1979) and non-steroidal anti-inflammatory drugs (Heller et al., 1982). Retention of the dosage form in the oesophagus has been demonstrated to delay drug absorption, as drugs cannot easily pass through the stratified squamous epithelium of the oesophageal mucosa (Channer and Roberts, 1985).

Hey et al. (1982) and Channer and Virjee (1985a, 1986) have previously examined the effect of size, shape and density of the dosage form, and position of the subject on oesophageal transit. In the present study, capsules and tablets were observed to lodge in the oesophagus in 2/10 (20%) of the subjects. This compares with 37 capsules lodging in 175 subjects (21%) in the Channer and Virjee study and 160 out of 726 (22%) swallows in the study by Hey et al. Oesophageal transit was reported to be slower in supine patients than in upright ones (Channer and Virjee, 1982, 1985a).

The effect of coating of the formulation on the oesophageal adherence has been studied extensively and gelatin capsules and some cellulose films have been implicated as the materials most likely to form sticky surfaces. The tendency of hydroxymethylcellulose to adhere can be adjusted by incorporation of sucrose which reduces surface stickiness; conversely addition of lactose or titanium oxide and talc increases the tendency to adhere (Marvola et al., 1983). Fell (1983) has challenged the belief that gelatin capsules are more likely to stick than tablets, and concluded that both dosage forms should be regarded as having equal potential to adhere.

Channer and Virjee (1985b) showed that, although coated tablets had significantly shorter oesophageal transit times than plain tablets, the coated tablets were slower to disintegrate if they become lodged in the oesophagus. The interior surface of the oesophagus is moist rather than wet and a dosage form in contact with the mucosa will cause partial dehydration at the site of contact as the unit hydrates, resulting in formation of a gel between the formulation and the mucosa. The unit then disintegrates from its non-contact side. Disintegration of the lodged formulation is slow, first because the amount of dissolution fluid available is low, being dependent on the volume of swallowed saliva and secondly due to the reduced surface area available for dissolution.

The general pattern of buccal clearance of the "Expidet" formulation is either to dissolve rapidly in the mouth and hence is cleared with several swallows, or to pass through into the oesophagus as a single unit (Wilson et al., 1987). Prolonged oesophageal retention of "Expidet" formulations if swallowed as an intact unit is unlikely since this formulation requires only a small volume of liquid to disperse. If the unit is retained in the lower oesophagus due to pathologies affecting structure or motility, it will disintegrate rapidly as seen in subject 3. The data from the present study suggest that the "Expidet" formulation is a solid dosage form which can be taken without water and avoids the problems of oesophageal retention associated with conventional formulations.

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