SHORT REPORTS

Effect of posture and drink volume on the swallowing of capsules

Drug-induced oesophageal ulceration is an increasingly recognised problem.[1 2] Since ulceration is due to a direct irritant effect the passage of the drug must first be delayed. Tablets have been found[3] to stick in the oesophagus. This study shows the effect of posture and drink volume on the oesophageal transit of capsules.

Patients, methods, and results

After barium meal and swallow examinations in which normal oesophageal motility was found 50 patients (22 men, 28 women, aged 20-87 years) swallowed four standard hard gelatin capsules (Farillon Lok-Cap) filled with 97% barium sulphate while standing and lying supine with 15 ml and 60 ml water. The time for the capsule to pass from the oropharynx to stomach was measured during screening. If after 10 minutes the capsule remained in the oesophagus, it was washed out with water before proceeding to the next swallow.

Four patterns of capsule movement were seen.

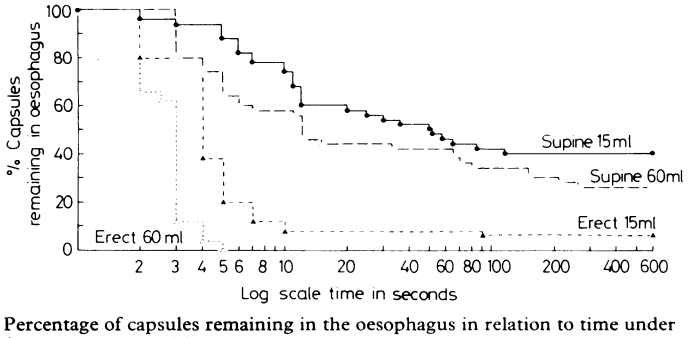
Normal transit—In 28% of patients all capsules passed into the stomach in < 15 seconds.

Delayed transit—In 20% of patients the capsule passed into the stomach in >20 seconds without dispersal. Delay occurred at the level of the left main bronchus on one occasion, above the lower oesophageal sphincter on six, and at both sites on eight. All these patients had gastro-oesophageal reflux with or without hiatus hernia. No other consistent relation between radiological diagnosis and pattern of capsule movement was found. Five of 22 (23%) patients complained that tablets tended to stick, and three of 14 (21%) normally swallowed tablets without water.

Arrested transit—In 52% of patients the capsule disintegrated. Capsules lodged at the level of the left main bronchus on seven occasions or above the lower oesophageal sphincter on 29. Disintegration occurred between two and three minutes and the remnants remained adherent for 10 minutes until washed off. This group included eight of 10 (80%) patients with dysphagia for food, five of eight (62·5%) who complained of difficulty in swallowing tablets, 14 of 22 (64%) who complained of tablets sticking, and seven of 14 who took tablets without liquid. Most (68%) patients said tablets stuck in the throat but this was never shown. Three patients were aware that the capsule had stuck and two localised it correctly.

Delayed by gastro-oesophageal reflux—A capsule was delayed on a column of refluxed barium on 10 occasions and lodged and distintegrated on three. No capsule was seen to reflux from stomach to oesophagus.

The figure shows the clearance of capsules from the oesophagus. All capsules swallowed while standing with 60 ml water entered the stomach within 5 seconds. The four groups were significantly different at the $p < 0.01$ level (Friedman).[4] Analysed independently the erect position and 60 ml volume had highly significant effects on capsule transit (both $p < 0.001$, Wilcoxon).[4]



Percentage of capsules remaining in the oesophagus in relation to time under four different conditions.

Comment

Barium sulphate tablets have been found[3] by fluoroscopy to stick in the oesophagus. In our study the effect of posture and drink volume on capsule transit in patients with normal oesophageal motility (as assessed by barium swallow) was highly significant. This has not previously been shown. Evans and Roberts[3] found a positive correlation between the presence of hiatus hernia reflux and disordered peristalsis and tablet sticking. This was not found in our study although delayed passage was always associated with gastro-oesophageal reflux.

Hard gelatin capsules absorb water and become adherent to the moist mucosa of the oesophagus if their passage is delayed for longer than two minutes. Once adherent disintegration occurs and the contents are released on to the non-absorptive stratified squamous mucosa. Variations in drug absorption are possibly related to oesophageal disintegration rather than to gastric or intestinal drug malabsorption. Evans and Roberts[5] also compared hard and soft gelatin capsules but found no significant difference between the sticking rates of either. In only 22% of their patients did capsules stick. Our rate of 52% was similar to their tablet sticking rate of 58%.

There was a positive correlation between history of dysphagia, difficulty in swallowing tablets and sensation of tablets sticking (mainly in the throat), and delayed capsule transit; yet only three of 26 (11·5%) patients were aware that a trial capsule had lodged in their oesophagus. It is even more important, therefore, for the prescribing doctor to be aware of the potential problem and to advise patients to take drugs with a drink while standing. This should avoid any local irritant effect of drug contact and ensure more regular absorption.

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Different interactions of indomethacin and sulindac with thiazides in hypertension

Treatment with anti-inflammatory drugs has caused problems when administered with loop diuretics in the treatment of congestive heart failure.[1] Attenuated hypotensive effect of thiazides has recently been described during concomitant treatment with indomethacin.[2] It was concluded that products formed by the arachidonic acid cyclo-oxygenase contribute to the regulation of blood pressure, as indomethacin inhibits the cyclo-oxygenase. Sulindac inhibits exclusively the extrarenal prostaglandin synthesis both in vitro and in vivo,[3] while indomethacin inhibits the prostaglandin synthesis in all organs. To elucidate the influence of renal prostaglandins on the antihypertensive effects of thiazides we investigated the effect of thiazides during treatment with indomethacin and sulindac.

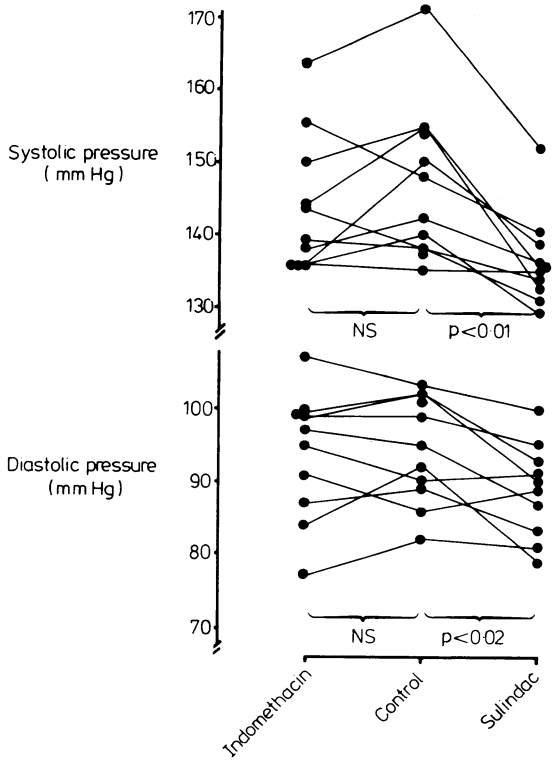
Patients, methods, and results

Ten men (median age 50 years) with essential hypertension (WHO classification I) with supine diastolic pressure higher than 100 mm Hg before drug treatment were selected for the study. All patients were in good health and had no history of dyspeptic symptoms. Serum concentrations of electrolytes and creatinine were within normal ranges. The protocol was approved by the local ethical committee and the patients gave informed consent to the study.

The patients were treated with thiazide (five with 10 mg bendrofluazide (Centyl) and five 100 mg hydrochlorothiazide and 10 mg amiloride (Moduretic)). After a four-week run-in period all patients received either indomethacin capsules, 100 mg daily, or sulindac tablets, 400 mg daily, for four

weeks in addition to the thiazide treatment. Compliance was determined by weekly pill counts. Blood pressure, heart rate, and body weight were measured weekly in the outpatient clinic after 15 minutes recumbent in standard conditions in the late afternoon. Duplicate measurements of blood pressure were performed weekly using a random zero sphygmomanometer (Hawksley and Sons Ltd, Lancing). Measurements, including body weight, taken during the second, third, and fourth week of the indomethacin treatment were compared with those obtained during treatment with sulindac and with similar data from the run-in period. Statistical significance was determined by the Wilcoxon test for paired differences.

Body weight increased by 1 kg during treatment with indomethacin when compared with during sulindac treatment or the run-in period ($p < 0.02$). No changes were observed during treatment with sulindac. Supine and erect blood pressure increased significantly during treatment with indomethacin as compared to during treatment with sulindac (figure). Sulindac, however, significantly enhanced the antihypertensive effect of thiazides when blood pressure during treatment is compared with that during the run-in period: indomethacin tended to attenuate this antihypertensive effect in the same patients (figure).



Supine diastolic and systolic blood pressure in hypertensive patients receiving thiazide before (control period) and during concomitant treatment with indomethacin or sulindac.
NS = Not significant.

Comment

Sulindac and indomethacin are both anti-inflammatory drugs and inhibit the synthesis of prostaglandins by inhibiting the cyclo-oxygenase. Their effects are different in respect of renal prostaglandins, however, since indomethacin decreases the urinary excretion of prostaglandin E_2 while sulindac does not afflict this excretion at all, thereby suggesting no effect on renal prostaglandins.[3] It has recently been argued that prostaglandins may contribute to the regulation of blood pressure, since indomethacin-induced inhibition of the prostaglandin synthesis possibly attenuates the antihypertensive effects of drugs with different modes of action—for example, thiazides and beta-blockers.[2] In contrast, sulindac enhances the antihypertensive effect of thiazides, and since sulindac is distinguishable from indomethacin in that it does not influence the renal prostaglandins, two different hypotheses may be suggested. Firstly, regulation of the arterial blood pressure may entail renal prostaglandins, and antihypertensive effect of diuretics may be caused by an inhibition of the renal prostaglandin degradation. Secondly, our findings suggest that inhibition of the extrarenal prostaglandin synthesis decreases the blood pressure, indicating that prostaglandins may contribute to the regulation of the blood pressure, as suggested by Watkins *et al.*[2]

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Chloroquine-associated pruritus in a European

Pruritus occurring after ingestion of chloroquine for chemotherapy or chemoprophylaxis of malaria is a toxic reaction commonly encountered in Africans.[1-3] To our knowledge this reaction has not previously been described in a European.

Case report

A 23-year-old white British nurse who was working in a rural, holoendemically malarious area of Kenya was taking dapsone 100 mg and pyrimethamine 12·5 mg (Maloprim) weekly on an irregular basis for malaria chemoprophylaxis. She developed a high temperature and shaking chills. Because of the history of exposure to malaria, the absence of diagnostic facilities, the lack of signs or symptoms suggestive of other diagnoses, and the fact that she had previously had a similar attack, when malaria had been confirmed, presumptive treatment with chloroquine phosphate was begun. She was given chloroquine by mouth, 600 mg base initially and then 300 mg base at eight, 24, and 48 hours. The first tablets were ingested at about 10 00 and the second dose at 1800 the same day. Early next morning she awoke with severe itching over her entire body, particularly her palms and the soles of her feet. She was unable to sleep and described the itching as being deep "under the skin" and that "there was no way to relieve it."

She was examined that morning, when there were no abnormal physical signs except scratch marks. The temperature and chills disappeared within 24 hours and did not recur. Although itching continued for about 55 hours, it did not increase after the dose of chloroquine at 24 hours and it lessened before the last dose at 48 hours. Antihistamines were given without apparent effect. She felt nauseated throughout the treatment but did not vomit; she was not taking any other drugs. Tablets from the tin from which her course had been taken were not analysed; however, randomly selected chloroquine phosphate tablets from other tins purchased from the same manufacturer at the same time were examined by Dr F C Churchill, at the Centers for Disease Control, Atlanta, Georgia, USA, using high-pressure liquid chromatography. The tablets contained the expected amount of chloroquine phosphate and had no obvious impurities. One of us was taking tablets for malaria chemoprophylaxis from the same tin without untoward effects. In 1974 the patient had taken 600 mg chloroquine phosphate base for malaria without itching.

Comment

The symptoms observed in this European patient were identical with those previously reported in chloroquine-associated pruritus in Africans.[1-3] Generally, the patient has taken chloroquine before; symptoms begin six to 48 hours after ingestion of the drug; and pruritus affects the entire body but particularly the palms, soles, and scalp. A rash is not present, and there are no other associated signs or symptoms. There is no relation between the occurrence of itching and the presence of malaria parasites in the blood. The sensation is often severe enough to be incapacitating, and frank psychosis may develop. Patients are generally unwilling to take chloroquine again. Itching has been reported after ingestion of other chloroquine salts as well as chloroquine phosphate and occurs after intramuscular injection as well as oral administration. The syndrome has been reported after ingestion of chloroquine for chemoprophylaxis and for