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Delayed release peppermint oil capsules (Colpermin) for the spastic colon syndrome: a pharmacokinetic study

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Excretion of menthol (as glucuronide) from orally ingested peppermint oil contained in Colpermin was compared with oil contained in two soft gelatine capsules. Total 24 h urinary excretion of menthol was similar in the two formulations in healthy volunteers, but peak menthol excretion levels were lower and excretion delayed with Colpermin. Menthol excretion was reduced in ileostomy patients who took Colpermin and moderate amounts of unmetabolised menthol were recovered from the ileostomy effluent. This is consistent with Colpermin being a delayed-release form of peppermint oil.

Keywords Colpermin pharmacokinetics spastic colon

Introduction

Peppermint oil, a major constituent of which is menthol, inhibits gastrointestinal smooth muscle, both in laboratory animal preparations (Gunn, 1920; Plant & Miller, 1926; Muirhead & Gerald, 1916; Forster *et al.*, 1980; Taylor *et al.*, 1983) and in man (Sigmund & McNally, 1969), possibly by interfering with mobilisation of calcium ions (Taylor *et al.*, 1983). When injected *directly* into the large intestine during colonoscopy peppermint oil reduces colonic spasm induced by the procedure (Leicester & Hunt, 1982) and reduces colonic motility (Duthie, 1981). However, topical pharmacological effects, when taken orally, such as relaxation of the lower oesophageal sphincter (Sigmund & McNally, 1969) are predominantly upper gastrointestinal; menthol and other plant monoterpenes in peppermint oil are rapidly absorbed from the proximal gut.

Colpermin (Tillotts Laboratories Ltd) is an enteric coated peppermint oil formulation designed to delay peppermint oil release and which appears useful in the treatment of the irritable bowel/spastic colon syndrome (Rees *et al.*, 1979). We have used a specific g.l.c. assay for menthol and its metabolites (Bell *et al.*, 1981) in studying menthol metabolism to determine if Colpermin does indeed retard drug release.

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Methods

We performed pharmacokinetic studies in six volunteers (four male and two female of age range 17–37 years) who ingested in the fasting state at 08.00 h in random order, 0.4 ml of peppermint oil, either as two Colpermin capsules or contained in two soft gelatine capsules without enteric coating and known to dissolve readily in the stomach. Urine was collected for 24 h; in 2 hourly aliquots for the first 14 h. The volunteers were encouraged to drink to ensure adequate 2 hourly urine samples. The menthol content of the ingested peppermint oil ranged from 91 to 97 mg per capsule. The amount of menthol excreted (in the form of its major metabolite, menthol glucuronide) was then determined.

The study was repeated in six patients, each with an ileostomy (three female and three male—age range 22–49 years) except that urine collection was a single 24 h sample. Five of the six ileostomy patients simultaneously collected their ileostomy effluent for the 24 h period of study, following the ingestion of Colpermin. The 24 h excretion of menthol in urine, as the glucuronide metabolite, and in the ileostomy effluent, as unmetabolised menthol, was then determined.

Approval for the study was granted by the Ethics Committee of the City Hospital, Nottingham, and informed consent given by each subject.

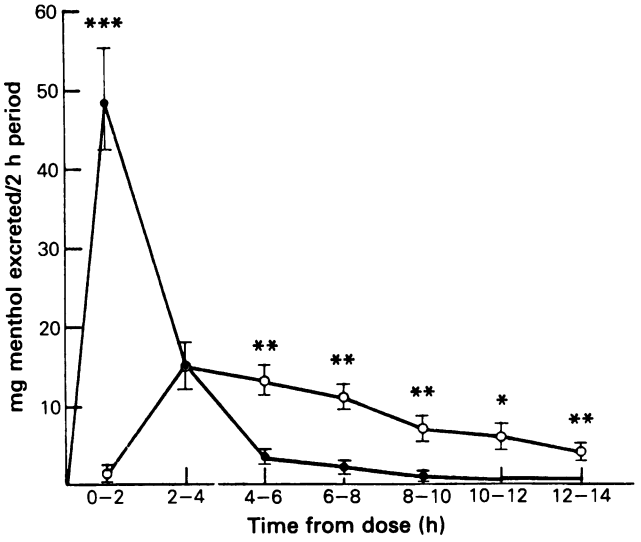

Figure 1 Urinary excretion of menthol in six volunteers ingesting either two Colpermin capsules (○) or the equivalent amount of peppermint oil in soft gelatine capsules (●). ***$P < 0.001$, **$P < 0.01$, *$P < 0.02$.

Results

In the normal volunteers the mean percentage recovery of the ingested menthol in the pooled 24 h samples was similar; 35% (64 mg) and 40% (74 mg) respectively for the Colpermin and gelatine capsule groups. However, the peak menthol excretion levels were lower and were delayed in individuals taking Colpermin capsules and excretion prolonged (Figure 1). The 24 h urine excretion of menthol (as the glucuronide) in the six ileostomy patients following ingestion of two Colpermin capsules were considerably reduced, 17% (31 mg) of the dose ingested, compared with the 35% (55 mg) recovery figure obtained in the normal volunteers (Table 1). By contrast, 29% of ingested menthol was excreted when the ileostomy patients took peppermint oil in two soft gelatine capsules. The 24 h recovery of unmetabolised menthol from ileostomy effluent ranged from 11–187 mg, and total recovery from urine + ileostomy fluid 24 h following ingestion of Colpermin in five of the six ileostomy subjects was variable. Total recovery was 64, 72, 77 and 100% in four patients, but only 22% in the fifth. One patient spontaneously noted a strong peppermint oil odour in the ileostomy fluid: virtually 100% of the drug was recovered in the ileostomy fluid with excretion of only 1% of the menthol in the urine.

Discussion

In order for peppermint oil to be of use in the spastic colon syndrome, the oils contained in it must reach the colon in an unmetabolised state. Our results show clearly that when peppermint oil is given orally in the form of Colpermin the appearance of menthol metabolites in the urine is much delayed. These results, taken in conjunction with the finding of reduced urinary metabolite quantities and high ileostomy effluent levels in four of the five ileostomy patients studied, strongly suggest that the capsule does effectively delay menthol delivery. This is consistent with a radiological study of

Table 1 24 h urine excretion of menthol: results expressed as mean and range

	Menthol excreted (mg)	
	Gelatine capsules	*Colpermin capsules*
Normal subjects (6)	74 (46–91)	64 (45–75)
Ileostomists (6)	55 (41–72)	31 (2–44)

the disintegration of barium filled enteric coated capsules in a small number of volunteer patients undergoing a Barium follow-through examination (Evans, 1980).

The reason for the very low recovery of menthol from the ileostomy fluid of one subject is not explained. The lower urinary recovery of menthol in the ileostomy patients compared with the normal volunteers suggests that some peppermint oil reaches the large bowel, even when ingested in the form of soft gelatine capsules.

Our observations that much of the peppermint oil, a natural carminative contained in Colpermin, is released in the colon, plus the previous findings that peppermint oil directly instilled into the colon of man reduces colonic spasm (Leicester & Hunt, 1982) and reduces colonic motility (Duthie, 1981), supports the small clinical study of Rees *et al.* (1979) that Colpermin is useful in the treatment of the irritable bowel/spastic colon syndrome.

When peppermint oil is ingested in the form of Colpermin capsules the common side effects, such as oesophageal reflux and heartburn, secondary to relaxation of the cardio-oesophageal sphincter (Sigmund & McNally, 1969) should be minimal. However, a transient hot burning sensation in the back passage during defaecation, due to unabsorbed menthol reaching the rectum, has been noted in a small number of patients taking Colpermin at high doses, but this can be mitigated by reducing the dose.

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