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A pharmacokinetic comparison of two delayed-release peppermint oil preparations, Colpermin and Mintec, for treatment of the irritable bowel syndrome

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Summary

Urinary excretion of menthol and its glucuronide metabolites was used to compare the pharmacokinetic profile of peppermint oil (0.6 ml) given as Colpermin or Mintec preparations to 13 normal subjects. Peak concentrations of menthol occurred 3 h after administration of the Mintec preparation, thereafter the concentrations rapidly decreased. In contrast, the urinary concentration – time profile of menthol after Colpermin showed lower concentrations which were maintained for up to 9 h after dosing. This data indicates that the Colpermin preparation delivers peppermint oil more effectively to the distal small intestine and ascending colon than the Mintec formulation.

Introduction

For centuries, it has been known that plant essential oils such as those from peppermint, dill and fennel have marked carminative and antispasmodic properties (Guenther, 1949). These preparations directly inhibit gastrointestinal smooth muscle (Gunn, 1920; Plant and Miller, 1926). Peppermint oil (a major constituent of which is menthol) may act by reducing the influx of calcium ions into intestinal muscle (Taylor et al., 1985). Menthol and other cyclical mono-terpenes in the peppermint oil are highly fat-soluble and are therefore rapidly absorbed from the proximal small intestine when taken orally. The topical effects are almost exclusively confined to the upper gastrointestinal tract, and include relaxation of the lower oesophageal sphincter (Creamer, 1955, Sigmund and McNally, 1969).

Peppermint oil injected directly into the large intestine during colonoscopy reduces colonic motility (Duthie, 1981) and spasm (Leicester and Hunt, 1982). Orally administered peppermint oil must be contained in a delayed-release preparation to produce a similar topical effect in the colon or distal small intestine. The delayed-release peppermint oil preparation (Colpermin, Tillotts Laboratories) effectively treats spastic colon and the irritable bowel syndrome (Rees et al., 1979, Evans et al., 1982).

A second delayed release formulation of pep-

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permint oil (Mintec, SK&F Ltd.) has recently been marketed in the U.K. and unpublished "in house" data suggest that it is also useful in treating the irritable bowel syndrome (SK&F data on file). Pharmacokinetic data show that both Colpermin (Somerville et al 1984) and Mintec (SK&F data on file) are delayed-release preparations but since the formulations differ, we have compared the pharmacokinetics of the two products in 13 volunteers.

Materials and Methods

The menthol content of 0.2 mls of peppermint oil from each preparation was estimated by gas chromatography following extraction into diethyl ether as described by Bell et al. (1981). 13 Volunteers (6 male and 7 female) mean age 35 years (range 18–70 years) and mean b. wt. 67.5 kg, range 47–76 kg, gave their informed consent to take part in the study. They were asked to refrain from ingesting any menthol-containing sweets, cough pastilles, toothpaste etc. during and for at least 24 h before commencing the study.

At 08.00 h, after an overnight fast, each of the 13 subjects took, in random order, 0.6 ml of peppermint oil, as capsules of Colpermin (Tillots Laboratories) or Mintec (SK&F Ltd.).

To ensure adequate urinary production the subjects were encouraged to drink liberal amounts of non-alcoholic fluid throughout the study. Urine was collected at 2-h intervals for 14 h and then the rest of the first 24-h output was collected as a single overnight 10-h collection. The subjects were permitted to eat normally 2 h after ingesting the capsules.

The volume of each urine sample was recorded and 25 ml were retained for analysis. The menthol content of each sample was measured after hydrolysis of the major metabolite, menthyl glucuronide. Sodium acetate buffer pH 4.8 (1 ml; 0.2 M) and 5000 units of β-glucuronidase were added to duplicate aliquots (5 ml) of urine and the mixture was incubated overnight at 37 °C in a water bath. After cooling the samples to ambient temperature, cineole (1.5 mg) was added as a solution in ether (15 mg/ml) as a recovery standard and terpenes were extracted with diethylether (5 ml). The ether extract was reduced to ca. 1 ml by evaporation under nitrogen and 1 μl of each reduced extract was analysed on a Perkin Elmer Model 8310 gas chromatograph using a 3% SE 30 column with nitrogen as the carrier gas (40 ml/min). The temperature programme used an initial oven temperature of 50 °C with a 2 °C/min gradient to a final temperature of 250 °C. Under these conditions the retention times of cineole and menthol were 5.32 min and 6.47 min, respectively.

The rate of excretion (mg menthol h^{-1}) at the mid-point of each urine collection was calculated and the data were analysed using a microcomputer-based pharmacokinetic programma (MAC-LSNR) using two-or 3-compartment models as appropriate. Nine sets of data were unsuitable for analysis, leaving data for 7 subjects in the Colpermin group and 10 subjects in the Mintec group.

Results

The mean total menthol content, measured as free menthol plus menthyl acetate, was 117 ± 5 mg for the Mintec preparation and 110 ± 5 mg for the Colpermin preparation ($n = 4$ determinations). The duplicate analyses of the urines by gas-liquid chromatography (GLC) agreed within $\pm 5\%$.

The total urinary excretion over the 24-h period following administration of Colpermin or Mintec is shown in Table 1. The menthol metabolite recovery was approximately 50% greater in the Mintec-treated group although the differences were not significant.

The rates of menthol excretion are shown in Fig. 1. Following Mintec administration, the peak urinary excretion occurred at 3 h post-dosing and the profile indicates that release of the menthol occurred high in the gastrointestinal tract. In contrast, after Colpermin administration the urinary menthol excretion occurred over a sustained period from 3 to 9 h. Peak concentrations were approximately one quarter of those in the Mintec-treated group.

Analysis of the mean sets of data for both treatment groups showed that a two-compartment model was valid for the Colpermin-treated group

TABLE 1

Total urinary recovery of menthol and metabolites following Colpermin and Mintec administration

Subject	Sex	Age	Weight (kg)	Menthol recovered (mg)	
				Colpermin	Mintec
1	F	30	56	110.6	137.5
2	F	40	67	100.5	99.3
3	M	38	86	83.0	158.0
4	F	45	67	77.7	171.2
5	F	18	52	68.3	112.7
6	F	18	47	71.6	229.9
7	M	46	73	82.8	199.4
8	M	40	72	147.1	133.3
9	M	42	91	95.5	91.1
10	M	18	64	60.8	74.6
11	M	19	67	18.8	81.1
12	F	30	59	275.5	117.6
13	F	70	76	49.5	95.9
Mean		34.9	67.5	95.5	130.9
S.D.		±15.1	±12.6	±62.2	±47.3
Paired *t*-test				$P = 0.123$ (n.s.)	

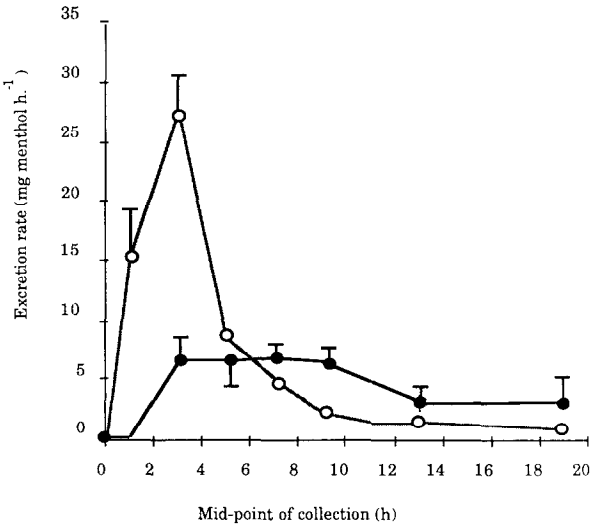

Fig. 1. Mean excretion of menthol (in the form of its glucuronide metabolite), following ingestion of 0.6 mls of peppermint oil, either as Colpermin (●) or Mintec (○). Error bars indicate S.E.M.; $n = 13$ per group.

TABLE 2

Pharmacokinetic parameters from 17 subjects

Subject	Lag time (h)	t_{max} (h)	Absorption $t_{1/2}$ (h)	Terminal elimination $t_{1/2}$ (h)	AUC 0–19 h (mg)	AUC 0–inf. (mg)
Copermin						
2	0.98	3	0.5	3.1	98.9	101.8
7	1.94	7	1.7	3.7	83.8	90.3
8	0.98	5	0.9	3.0	147.7	151.2
9	0.88	7	2.8	4.7	95.2	106.3
10	0.88	3	0.5	4.6	64.5	70.8
11	0.96	3	0.6	3.3	18.6	19.0
13	0.88	7	1.1	2.8	47.0	48.4
Mean ±S.D.	1.07 ± 0.39	5 ± 2	1.2 ± 0.9	3.6 ± 0.8	79.5 ± 41.3	84.0 ± 42.9
Mintec						
1	0.96	3	0.4	5.2	164.2	166.0
2	0.36	3	0.8	1.4	142.7	143.0
3	0.88	3	1.0	5.8	131.3	137.4
4	0.82	3	0.7	0.9	98.4	98.5
5	0	3	0.4	9.0	234.6	264.8
7	0	3	0.5	2.9	78.5	78.9
8	0.96	3	0.4	3.7	118.1	119.7
10	0.24	1	0.8	2.8	72.9	74.2
11	0	3	1.0	3.1	89.6	91.3
12	0.98	3	0.4	3.7	99.0	98.2
Mean ±S.D.	0.5 ± 0.4	2.8 ± 0.6	0.7 ± 0.3	3.8 ± 2.4	122.9 ± 48.8	127.2 ± 56.7
Unpaired *t*-test	$P = 0.017$	$P = 0.047$	$P = 0.097$	$P = 0.284$	$P = 0.074$	$P = 0.110$

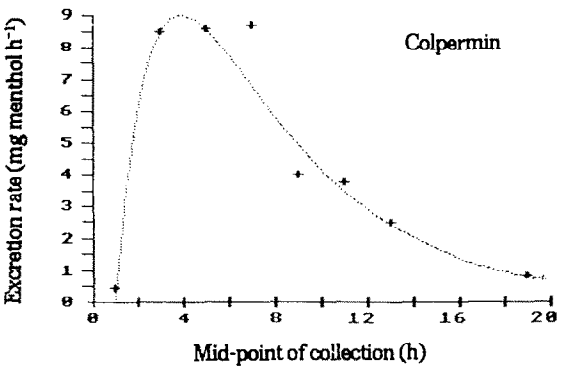

Fig. 2. Computer-generated line of best fit (two-compartment model) for the mean menthol excretion following Colpermin.

(Fig. 2), whereas in the Mintec-dosed group a 3-compartment model was needed to fit the data adequately (Fig. 3). Individual sets of data from each group were analysed to see whether the models derived from the mean data were suitable. It was confirmed that the two- and 3-compartment models were needed to characterise the individual Colpermin and Mintec data, respectively. There was a significant lag time in the appearance of methol and its metabolites in the urine ($P < 0.017$, unpaired t-test) after Colpermin, although differences in rate of menthol absorption following Mintec or Colpermin were not significant (Table 2). Terminal half-life for menthol excretion was calculated to be 3.6 h following Colpermin, and 3.8 h following Mintec administration.

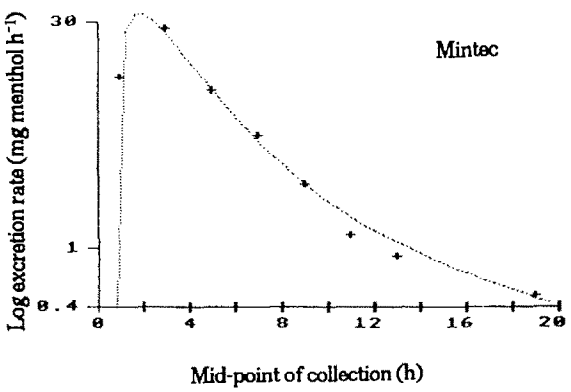

Fig. 3. Computer-generated line of best fit (three-compartment model) for the mean menthol excretion following Mintec.

No subject noted any side effects with Colpermin capsules, but 5 subjects had symptoms variously described as nausea, and vague abdominal pain some time during the first 4 h after taking Mintec capsules.

Discussion

Previous studies have shown that Colpermin (Somerville et al., 1984) or Mintec (SK & F Ltd. data on file) delay the absorption of menthol from peppermint oil when compared with the same quantity of peppermint oil contained in uncoated soft gelatin capsules. However, menthol (and hence peppermint oil) is released more quickly from Mintec capsules than from Colpermin.

Measurement of relative bioavailability based on manufacturers' estimates of menthol content of 0.2 ml peppermint oil differ widely. The menthol content of Mintec is approximately 85 mg (SK & F, data on file), whereas that of Colpermin is 108 mg (Tillotts Laboratories, personal communication). This discrepancy is presumably due to methodological differences employed by the manufacturers. The menthol derivatives present in peppermint oil include the isovalerate and the acetate esters. Our estimates of total menthol content (including derivatives), using the same procedure for capsule menthol content and urine samples, show the preparations to be equivalent. The apparent lower bioavailability of the Colpermin may be related to the slow release of the product over a period longer than the 24-h collection.

Assuming the mouth-to-caecum transit time is unaffected by the two preparations, the topical smooth muscle relaxant effect of the peppermint oil in Mintec is likely to occur higher up the gastrointestinal tract than with Colpermin. The average mouth-to-caecum transit time for capsules is estimated to be 4 h (Read et al., 1980; Wilson & Hardy, 1985). Colonic transit time of capsules is highly variable, particularly for the terminal bowel; measurements of transit time of similar capsules indicate a caecum-to-splenic flexure time of 6.9 ± 2.9 h ($n = 12$) in healthly individuals (Wilson, unpublished observations).

The prolonged period over which the pepper-

mint oil is released from the Colpermin capsule (once the protective coating has been removed) may be due to the hydrophobic excipient (Francois et al., 1982), present in the Colpermin formulation. Such oil-paste formulations enable a sustained in vivo release of the active constituent. Thus in contrast to the Mintec preparation, Colpermin capsules seem likely to release the peppermint oil in the distal small intestine and colon.

In patients with the irritable bowel syndrome, mouth-to-caecum transit time may be shorter than in normals (Corbett et al., 1981) which indirectly implicates abnormality of the small as well as the large bowel in this condition. Nevertheless, many gastroenterologists believe that most of the symptoms of the irritable bowel syndrome probably arise from altered colonic motility (Holdstock, 1969; Sullivan et al., 1978). When peppermint oil is given either orally (Creamer, 1955) or by gavage (Sigmund and McNally, 1969) relaxation of the cardiooesophageal sphincter occurs within 1–15 min and rarely lasts for more than 5 min. Similarly, 0.2 ml of peppermint oil instilled directly into the colon began inhibiting motor activity within two min and the effect lasted, on average, about 12 min (Duthie, 1981). Since whole-gut transit times are usually more than 24 h (Edwards et al., 1987), and motor activity in the left colon may be particularly marked soon after meals and on wakening in the morning (Narducci et al. 1987), preparations which release peppermint oil into the colon over longer periods may be desirable. The oil would then be likely to reach the left iliac fossa, which is the major site of muscle spasm.

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