PERITONEAL ABSORPTION OF THE ANTIBACTERIAL AND ANTIENDOTOXIN TAUROLIN IN PERITONITIS

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- 1 Taurolin metabolite plasma concentrations were measured in two groups of patients undergoing abdominal surgery, one group with peritonitis and the other without peritonitis, each group receiving taurolin by intraperitoneal instillation.
- 2 There was no significant difference in the area under the curves, for the two groups, for one of the metabolites. This would suggest that the absorption of taurolin was not modified in inflammatory conditions such as bacterial peritonitis.

Introduction

Little is known of the peritoneal absorption of drugs in humans and how it is altered in different disease states, for example in inflammatory conditions such as peritonitis, or malignant conditions short of ascites. Since peritonitis may be treated directly by intraperitoneal instillation of medicaments or by continual peritoneal lavage, it is important to know whether the substances are being absorbed and whether their absorption is modified by the condition present. The three main groups of drugs administered intraperitoneally are antibiotics (Stephen & Lowenthal, 1979), antiseptics (Sindelar & Mason, 1979) and local anaesthetics (Fomin, 1968).

Taurolin (bis-(1,1-dioxoperhydro-1,2,4-thiazinyl-4)-methane), which is on clinical trial in Great Britain, was developed as a broad spectrum bactericide and antiendotoxin (Browne, Leslie & Pfirrmann, 1976; Browne *et al.*, 1977; Pfirrmann & Leslie, 1979) and is used both as a lavage agent in peritonitis and also as an intraperitoneal instillation (Browne, MacKenzie & Doyle, 1978) both at the time of laparotomy and in the postoperative period. In solution taurolin is in equilibrium with 1,1-dioxoperhydro-1,2,4-thiadiazine (DPT) and a carbinolamine (hydroxymethyl-DPT) (Myers *et al.*, 1980; Knight, Skellern, Smail, Browne & Pfirrmann, unpublished results).

This paper, which in part was presented at the World Conference on Clinical Pharmacology and Therapeutics in London in 1980, reports the elimination of DPT and taurineamide (Figure 1), metabolites

of taurolin, in patients with bacterial peritonitis and in patients without infection, undergoing abdominal surgery. To date it has not been possible to detect free taurolin in biological fluids by the h.p.l.c. method used for this study.

Figure 1 Structural formulae of (a) taurolin, (b) DPT and (c) taurineamide.

Methods

Chemicals

Taurolin, DPT and taurineamide hydrochloride were supplied by Geistlich-Pharma, Wolhusen, Switzerland. Dansyl chloride, methanol, chloroform and heptane (reagent grade) were from BDH (Poole, Great Britain). The solvents were distilled before use. Acetonitrile (Fisons, Loughborough, GB) was analytical reagent grade.

Patients

Twenty patients of mixed ages and sex undergoing abdominal surgery were included in this study. The

patients were divided into two groups, those patients without peritonitis who were undergoing elective abdominal surgery (Table 1) and those patients with peritonitis, with free pus in the abdominal cavity, this diagnosis subsequently being confirmed bacteriologically (Table 2).

Patients received 4 g of taurolin (2×100 ml bottles of Tauroflex[®], which is a 2% solution of taurolin containing 5% polyvinylpyrrolidone-17). The taurolin solution was administered at the end of the operation by intra-abdominal instillation (over a 3 min period) through a fine umbilical catheter (No. 9F), which was then withdrawn.

An initial blood sample was taken as a control, and then eight to ten blood samples were taken at varying time intervals between 15 min and 24 h. All blood samples were stored as either serum or plasma at -18°C , at which temperature they are stable for several months.

The study was approved by the Ethical Committee of Monklands District General Hospital.

Analytical methods

The DPT and taurineamide plasma and urine concentrations were quantitatively determined by an h.p.l.c. method based on their derivatisation with dansyl chloride (Knight *et al.*, 1981). Analyses were performed in duplicate on a Spectra-Physics Model 3500B Liquid Chromatograph with u.v. detection at 254 nm. Calibration standards at five concentrations were prepared for each sample batch.

Determination of β

The data was examined graphically and the slopes of the plasma-concentration ν time curves determined by linear regression of the terminal log-linear values.

Results

In those patients where it was possible to measure plasma DPT concentrations, the maximum concentration (Tables 1 and 2) occurred between 10 and 15 min. Maximum plasma taurineamide concentrations in both non-peritonitis patients and those with peritonitis occurred between 30 min and 2 h. There were no significant differences ($P > 0.10$) in the maximum plasma concentrations of taurineamide or the area under the taurineamide concentration-time curves ($P > 0.30$) between the non-peritonitis and peritonitis groups (Tables 1 and 2). Typical semilogarithmic plots of the DPT and taurineamide plasma concentration ν time for a non-peritonitis patient and a peritonitis patient are similar (Figure 2). DPT has a half-life of less than 1 h in those patients where it was possible to measure the DPT concentrations over a period of time, whilst the semilogarithmic plot for taurineamide was biphasic in both groups (Figure 2) with an elimination half-life ($T_{1/2\beta}$) of 5.09 ± 0.58 h for the non-peritonitis group and 5.35 ± 0.79 h for the peritonitis group.

Taurineamide excreted in the urine accounted for up to 25% of the taurolin dose.

Figure 2 Typical semilogarithmic plots of plasma concentration ν time curves for DPT (▲) and taurineamide (●) assayed in duplicate from a non-peritonitis patient (a) and a peritonitis patient (b) receiving 4 g of taurolin intraperitoneally.

Table 1 Details of the non-peritonitis patients with the DPT and taurineamide parameters obtained following intraperitoneal instillation of taurolin (4 g)

Patient	Sex	Pathology	Operative treatment	Weight (kg)	Age (years)	DPT $C_{p\max}$ ($\mu\text{g ml}^{-1}$)	$C_{p\max}$ ($\mu\text{g ml}^{-1}$)	Taurineamide $T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	AUC ($\mu\text{g ml}^{-1} \cdot \text{h}$)
1	F	Duodenal ulcer	Total vagotomy and pyloroplasty	53	29	NQ	28	Insufficient data		
2	M	RMF pain	Appendicectomy	65	23	NQ	34	1.3	5.1	236
3	F	Gallstones	Cholecystectomy	69	64	10	50	2.5	2.5	242
4	F	Carcinoma of oesophagus	Insertion of celestin tube	53	45	NQ	71	1.6	3.9	252
5	F	Pancreatic abscess	Drainage	63	74	NQ	76	1.7	7.9	684
6	M	Gallstones	Cholecystectomy	90	32	NQ	33	1.6	5.1	139
7	F	Duodenal ulcer	Total vagotomy and pyloroplasty	55	21	NQ	40	1.2	3.9	219
8	F	Duodenal ulcer	Total vagotomy and pyloroplasty	36	37	NQ	80	1.2	5.0	372
9	F	Gallstones	Cholecystectomy	58	60	NQ	46	Insufficient data		
10	F	Duodenal ulcer	Total vagotomy and pyloroplasty	53	40	20	86	1.4	4.7	402
11	M	Duodenal ulcer	Total vagotomy and pyloroplasty	56	30	NQ	27	1.5	7.7	216
Mean $\pm$ s.e. mean				59.2 $\pm$ 4	41.4 $\pm$ 5.3	17.5 $\pm$ 2.5	51.9 $\pm$ 6.7	1.56 $\pm$ 0.13	5.09 $\pm$ 0.58	307 $\pm$ 54

$C_{p\max}$ Maximum plasma concentration of metabolite
 AUC Area under the taurineamide plasma concentration v time curve
 NQ not quantifiable

Table 2 Details of the peritonitis patients with the DPT and taurineamide parameters obtained following intraperitoneal instillation of taurolin (4 g)

Patient	Sex	Pathology	Operative treatment	Weight (kg)	Age (years)	DPT C_{pmax} ($\mu\text{g ml}^{-1}$)	C_{pmax} ($\mu\text{g ml}^{-1}$)	Taurineamide $T_{1/2\alpha}$ (h)	Taurineamide $T_{1/2\beta}$ (h)	AUC ($\mu\text{g ml}^{-1}\text{h}$)
12	F	Perforated appendicitis	Appendicectomy	60	20	18	53	1.6	5.7	295
13	F	Perforated appendicitis	Appendicectomy	82	41	NQ	59	1.4	6.4	391
14†	M	Perforated appendicitis	Appendicectomy	52	15	NQ	27	0.6	3.3	73†
15	F	Perforated appendicitis	Appendicectomy	48	16	25	74	1.4	2.7	270
16	M	Perforated appendicitis	Appendicectomy	35	11	NQ	55	—	5.1	361
17	M	Perforated duodenal ulcer*	Repair of perforation	51	65	NQ	66	2.3	7.7	571
18	M	Perforated Crohn's disease	Ileo-caecal resection	51	30	—	54	1.4	6.3	286
19	M	Perforated ulcerated colitis	Panproctocolectomy with ileostomy	50	19	—	65	Insufficient data		
20	M	Perforated Crohn's disease	Ileo-caecal resection	55	25	15	40	Insufficient data		
Mean $\pm$ s.e. mean				53.8 $\pm$ 4.1	27 $\pm$ 5.6	19.3 $\pm$ 2.97	54.8 $\pm$ 4.73	1.45 $\pm$ 0.22	5.35 $\pm$ 0.79	362 $\pm$ 46
C_{pmax}	Maximum plasma concentration of metabolite									
AUC	Area under the taurineamide plasma concentration v time curve									
NQ	not quantifiable									
†	Taurin dose (2 g)									
*	Chemical peritonitis									

Discussion

In many of the patients studied the plasma concentrations of DPT were below the detection limit of the h.p.l.c. method, and in the remaining patients plasma DPT concentrations could only be measured up to about 2 h because of the rapid metabolism of DPT.

There is no appreciable change in the absorption of taurolin/DPT in patients with peritonitis as reflected by the values of the area under the taurineamide concentration-time curve for both groups of patients (Tables 1 and 2). However the absorption of taurolin/DPT from the peritoneal cavity, in part directly into the systemic circulation and partly into the portal vein, is so rapid (DPT_{max} occurs at 10–15 min) that the difference in the rate of absorption would have to be very large to be of any clinical importance.

The results also show that DPT is rapidly metabolised ($T_{1/2} < 1$ h) to taurineamide, which has an elimination half-life of about 5 h in both groups.

Both taurolin and DPT have been shown effectively to inhibit the growth of a variety of pathogenic organisms (Browne *et al.*, 1977). Their antibacterial activity is thought to be dependent upon the formation of hydroxymethyl derivatives, which subsequently interact with lipopolysaccharides present in the bacterial cell wall (Wicki & Pfirrmann, 1979).

The patients with peritonitis did not receive any other antibiotic. Wound healing was unimpaired and there were no residual abscesses.

Thus in conclusion the absorption of taurolin would not appear to be modified in inflammatory conditions such as bacterial peritonitis.

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