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STUDIES ON THE MICROENCAPSULATION OF DEXTROPROPOXYPHENE HYDROCHLORIDE. PART 2. THE IN VIVO URINARY EXCRETION IN MAN.

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ABSTRACT

In this study, the spectrophotometric method suggested by Amundson et al (1) was used for the quantitation of dextropropoxyphene hydrochloride (D-PRX·HCl) (free drug plus metabolite) in urine after the oral administration of powder drug and microcapsules.

INTRODUCTION

D-PRX·HCl is a centerally acting analgesic (2). It does not have the antiinflammatory activity of aspirin and antipyretic activity of aspirin and acetaminophene (3).The usual dose is 65 mg, three or four times a day (4). The daily dose is agreed to be 260 mg (4,5). The analgesic activity develops rapidly.

It is metabolized during the first pass through the liver, therefore its systemic availability is low after oral administration (6). Only 18 % of a 65 mg dose enters the systemic circulation, unchanged (7). The major biotransformation route is the mono-N-demethylation to a seconder amino, norpropoxyphene. The pharmacological activity of norpropoxyphene is uncertain even though it is present in serum for a long period of time (1,8).

About 7 % of D-PRX·HCl is excreted unchanged in 48 hours; this leads to the fact that most of the drug is excreted as metabolites (7). Seven other metabolites were determined in urine which were in negligible amounts (9). It was shown that the unchanged drug is mainly excreted in the first 0-6 hours, while the metabolite is excreted in 6-48 hours (1).

MATERIALS

D-PRX·HCl with <63 μm particle size (E_1), microcapsules prepared with this particle size and with a core-shell ratio of 1:1 (M_1) and 1:2 (M_2) were filled in hard gelatin capsules (Elanco, Size 0, Opaque white).

The pH 7.8 phosphate buffer used in the extraction of urine was freshly prepared for each volunteer and 16 mg of bromthymol blue was added to 400 ml of the buffer prior to use.

METHOD

The volunteers started fasting 12 hours before the oral administration. The capsules were administered along with 200 ml of water to five healthy people. The food intake was permitted after 1 hour following administration. Total urine was collected at 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-36, and 36-48 hours. Each volunteer received the capsule at 7:30 a.m. The capsules contained 65 mg D-PRX·HCl.

A 10 ml aliquot of the urine collected at each time period was pipetted into a 250 ml-separating funnel and acidified with the addition of 4 drops of 6 N HCl. It was extracted with 50 ml chloroform. The chloroform extract was first washed with 25 ml of 0.1 N NaON and then with 25 ml of water. 25 ml of pH 7.8 buffer solution was added. After agitation for 2-3 minutes, the yellow chloroform layer was drained into a separating funnel containing 10 ml of 0.1 N NaOH. The absorbance of the blue aqueous layer was then determined at 620 nm on a Schimadzu-UV-240 Graphicord.

Extraction was repeated twice for each sample.

In order to avoid the interference of other substances present in urine, blank values were determined for each volunteer prior to

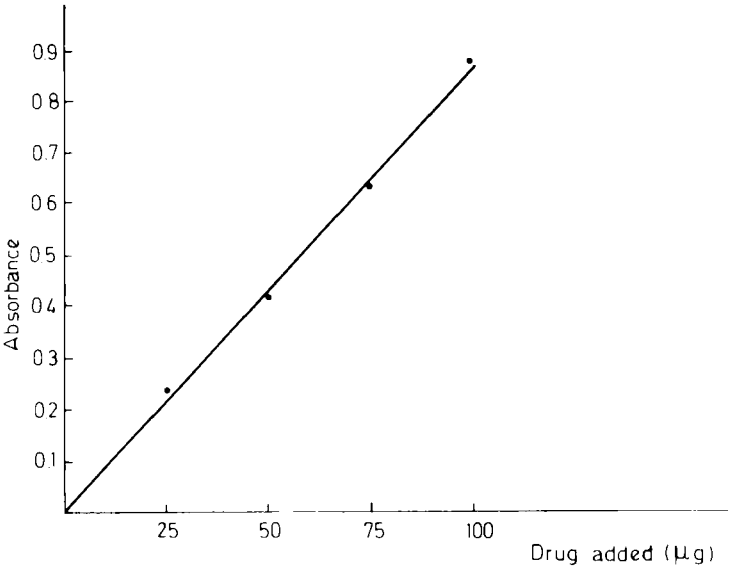

FIGURE 1
Standard Curve For D-PRX·HCl Added To Urine. (r^2= 0.995)

drug administration and subtracted from the values obtained after dosage.

Using the stock solution, 10 ml of control urine solutions containing 25, 50, 75 and 100 μg drug were prepared and treated in a like manner. The standard curve (Figure 1) was drawn and used for the quantitation of drug in urine after oral administration.

RESULTS AND DISCUSSION

The average amount of total D-PRX·HCl, ie the unchanged drug and the metabolites, excreted in urine within 48 hours after the oral administration of 65 mg of D-PRX·HCl as powder drug and microcapsules are given in Table 1.

The accumulative D-PRX·HCl amount excreted in urine after the dosage was plotted versus time and illustrated in Figure 2.

As illustrated in Figure 2, the amount excreted after the administration of microcapsules is lower than the amount excreted by

TABLE 1

Mean Amounts Of D-PRX·HCl Excreted In Urine.

Volunteer \ Time (hr)		0–2	2–4	4–6	6–8	8–10	10–12	12–24	24–36	36–48	Total	% of dose
E_1	A	3.29	5.30	1.9	2.49	1.66	0.31	5.04	1.81	1.82	23.62	36.34
	B	0.14	1.74	1.62	0.90	0.04	0.15	2.25	2.21	0	9.05	13.92
	C	2.99	5.03	4.97	5.32	1.91	4.96	5.45	5.66	4.84	41.13	63.28
	D	1.85	0.38	1.22	0	0.35	0.09	2.0	3.18	0	9.07	13.95
	E	0.15	0.27	1.96	0.44	0.81	1.19	6.11	3.0	5.06	18.99	29.21
	Mean	1.68	2.54	2.33	1.83	0.95	1.34	4.17	3.17	2.34	20.37	31.34
M_1	A	0.25	0.32	0.04	0.02	0.16	0.28	0.63	0	0.02	1.72	2.65
	B	0.64	1.47	1.0	0.03	0.56	0.56	2.70	0.05	0.82	7.83	12.05
	C	0.31	0.43	0.62	0.69	0.60	0.69	1.74	0.84	0.93	6.85	10.54
	D	0.68	0.76	1.10	1.10	0.51	0.63	2.60	2.39	1.65	11.42	17.57
	E	0.51	0.54	0.53	0.79	0.76	0.69	2.32	0.71	1.13	7.98	12.28
	Mean	0.48	0.70	0.66	0.52	0.52	0.57	1.99	0.80	0.91	7.16	11.02
M_2	A	0.06	0.07	1.16	0.28	0.03	0.03	0	0.13	0.09	1.85	2.85
	B	0.03	0.12	0.27	0.18	0.05	0	2.69	0.34	1.79	5.47	8.42
	C	0.82	1.56	0.34	0.41	0.45	0.44	4.23	1.07	0.91	10.23	15.74
	D	0	0	0	0.06	0.44	1.41	1.48	1.28	1.91	6.58	10.12
	E	0.09	0.64	0.21	0.16	0.05	0.69	0.15	1.86	0.14	3.99	6.14
	Mean	0.20	0.59	0.39	0.22	0.20	0.51	1.71	0.94	0.97	5.62	8.65

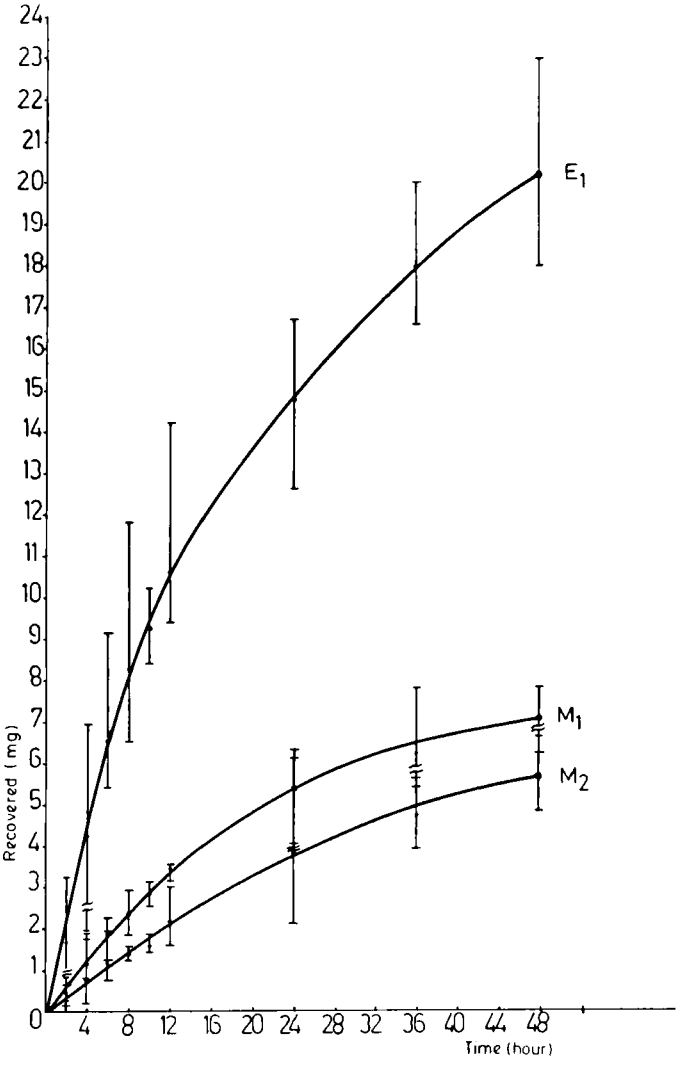

FIGURE 2

Mean Accumulative Urinary Excretion Of D-PRX·HCl.

the powder drug. This proves that the absorption from the microcapsules is slower than D-PRX·HCl powder. Since the first step in the absorption of a drug is the release from the dosage form, and the release of D-PRX·HCl from the microcapsules is slow, it can be predicted that the absorption rate will be low as well.

The excretion rate of D-PRX·HCl from the microcapsules with a core-shell ratio of 1:2, is slower than those with a core-shell ratio of 1:1 as seen in Figure 2.

To decide on a certain core-shell ratio for use in theurapeutics, an unencapsulated D-PRX·HCl to provide the initial theurapeutic blood level should be determined and then combined with the microcapsules. The amount and time of absorption should then be determined. The capsules prepared serve as a promising first step in the development of a clinically useful sustained-release preparation.

In conclusion, this study demonstrates that microcapsules capable of providing prolonged effective in vivo release of D-PRX·HCl can be prepared. The capsules used so far have defect-filled coatings and show in vitro and in vivo release more rapidly than predicted. Further study has to be done for improving capsule quality.

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