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Further studies on nitrofurantoin excretion in dog hepatic bile

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Summary

1. Results obtained with a dog donor-recipient model indicate that following intravenous administration of nitrofurantoin sodium, nitrofurantoin is subjected to enterohepatic cycling. At least one-third of the nitrofurantoin originally excreted in the donors' bile after a nitrofurantoin dose of 3 mg/kg is re-absorbed intestinally in the recipients within 3 hours.

2. After intraduodenal administration of a nitrofurantoin suspension to dogs at doses ranging from 2 to 12 mg/kg, about 10% of the dose is recovered in bile as nitrofurantoin within 6 hours. A hydrocholeretic effect was also observed which correlated with the amount of drug administered. Both biliary drug excretion and the related hydrocholeresis appeared linearly related over the drug dose range.

3. The hydrocholeresis observed in dogs within 3 h after intravenously administered nitrofurantoin sodium, equivalent to 3 mg/kg nitrofurantoin, was at least ten times that seen following the intravenous administration of an equimolar dose of dehydrocholic acid given as its sodium salt.

Introduction

Nitrofurantoin, 1-(5-nitrofurfurylideneamino)hydantoin, is a drug effective in the treatment of urinary tract infections in man and animals (Paul & Paul, 1964, 1966). Recently it was reported that after intravenous administration of nitrofurantoin sodium to dogs, about 20% of the dose was excreted in hepatic bile and a related hydrocholeretic effect observed (Conklin & Wagner, 1971). As a result of this, further studies were carried out to obtain additional information on biliary nitrofurantoin excretion and the hydrocholeresis. Some of these results were presented previously at a FASEB Meeting (Conklin, 1970).

Methods

Experimental

Adult male Beagles (10–16 kg) were anaesthetized with aqueous pentobarbitone sodium (35 mg/kg i.v.). Each animal was prepared for the collection of hepatic bile and ureteral urine as described previously (Conklin & Wagner, 1971). In the donor-recipient experiments, dogs of nearly equal weight were prepared in pairs for the collection of hepatic bile and ureteral urine. The bile cannula of the donor was inserted into the duodenum of the recipient about 10 cm below the pylorus and secured in place.

Blood, bile and urine were collected before each drug administration. Nitrofurantoin (Furadantin, Eaton Labs., N.Y.) as a suspension in 1% sodium carboxymethyl cellulose (CMC) gum was administered intraduodenally by a gavage tube. For intravenous drug administration, a nitrofurantoin sodium (Furadantin Sodium, Eaton Labs., N.Y.) solution in 5% dextrose was administered by a single intravenous injection. All drug doses are presented as mg/kg of nitrofurantoin. Sodium dehydrocholate (Nutritional Biochemicals Corp.) was dissolved in 5% dextrose and administered by a single intravenous injection.

After a 1 h control period to stabilize bile and urine flow, drug was administered. Bile and pooled urine from both kidneys were collected at 0·5 h intervals, for a period of 3 or 6 h, and the volumes recorded. Blood samples were obtained by venipuncture in heparinized syringes. Hydration was maintained by an intravenous infusion (Harvard Apparatus) of 5% dextrose at a constant rate of 0·764 ml/min throughout each experiment, including the control period.

Assays

Urine (1·0 ml) and blood (0·5 ml) were analysed for nitrofurantoin by the nitromethane-Hyamine procedure (Conklin & Hollifield, 1965, 1966) and bile (0·5 ml) by a modification of this procedure (Conklin & Wagner, 1971).

Total bile solids were determined as described previously (Conklin & Wagner, 1971) and used as the criterion to verify the hydrocholeresis. To obtain a reasonable estimate of the effect, all of the values representing it were adjusted, by deducting the bile flow in each animal for the 0·5 h interval just before drug administration from the bile flow encountered for each 0·5 h after drug administration.

Results

Donor–recipient study

Since a substantial amount of nitrofurantoin is excreted in dog bile (Conklin & Wagner, 1971), a study was performed to ascertain if nitrofurantoin is subjected to enterohepatic circulation. Stewart & Harrison (1961) described a technique for investigating biliary excretion, reabsorption, and re-excretion of drugs in the rat. This donor–recipient model was slightly modified to investigate the possible intestinal reabsorption of nitrofurantoin in dogs after its initial biliary excretion.

Following intravenous administration of nitrofurantoin to the donors at 3 mg/kg, nitrofurantoin was recovered in both the bile and urine of the recipients (Table 1).

TABLE 1. *Biliary re-excretion of nitrofurantoin in dogs after an intravenous dose of nitrofurantoin*

Source	Donor dose excreted bile (0–3 h)	Donor dose excreted urine (0–3 h)
Donor	13·9% ± 2·3*	21·5% ± 3·7†
Recipient	1·5% ± 0·4†	3·4% ± 1·2†
Drug re-excreted‡	11·1% ± 3·9	24·0% ± 6·6

Conditions: nitrofurantoin sodium as a solution in 5% dextrose (pH 9·0) was administered by a single i.v. injection at a nitrofurantoin dose of 3 mg/kg to the donors. *Based on an average factor of 0·65 ± S.D. 0·11, obtained from a ratio of total drug in bile: total drug in urine in 6 dogs, and the amount of drug recovered in the donors' urine, from 0–3 h after intravenous drug administration at 3 mg/kg. Average value ± S.D. †Average value ± S.D., based on 4 pairs of dogs, and the dose administered to the donors. ‡Average value ± S.D., based on 4 pairs of dogs, and the donors' dose estimated in the donors' bile.

Although nitrofurantoin concentrations ranging from 2 to 5 μg/ml were detectable in the donors' blood within 30 min after administration of the drug to the donors, the drug was not detected in the blood of recipients. The recipients exhibited an average hydrocholeresis of 2·6 ml ± S.D. 1·8 for the 0–3 h interval after the donors received the drug.

It was established from previously reported results (Conklin & Wagner, 1971) that during the first 3 h after intravenous administration of nitrofurantoin at 3 mg/kg, the average ratio for total drug in bile: total drug in urine is 0·65 ± S.D. 0·11, based on 6 dogs. Using this value, and the amount of drug recovered in the urine of the donors and in the bile and urine of the recipients, an *estimate* was obtained regarding the recipients' intestinal absorption of nitrofurantoin from the donors' bile. The results (Table 1) indicate that at least one-third of the nitrofurantoin originally excreted in the donors' hepatic bile, or about 5% of the donors' dose, is reabsorbed intestinally.

Intraduodenal study

In relation to the observed enterohepatic cycling of nitrofurantoin, a study was conducted to determine biliary drug excretion and the hydrocholeresis after intraduodenal administration of nitrofurantoin. As shown by the results in Table 2, substantial biliary nitrofurantoin excretion and a related hydrocholeretic effect were noted in dogs following the intraduodenal administration of a nitrofurantoin suspension at 2 mg/kg.

TABLE 2. *Biliary excretion of nitrofurantoin in dogs after an intraduodenal dose of nitrofurantoin*

	Hepatic bile (0–3 h)
Hydrocholeresis*	10·2 ml ±3·6
Total drug*	3·5 mg±1·6
Dose excreted*	12·5% ±4·4

Conditions: nitrofurantoin as a suspension in 1% sodium carboxymethyl cellulose gum was administered intraduodenally at 2 mg/kg. *Average value±S.D., based on three dogs. Hydrocholeretic effect adjusted for the control bile flow obtained for the 0·5 h just before drug administration, 1·6 ml±S.D. 0·3.

TABLE 3. *Hepatic bile excretion of nitrofurantoin in dogs* (0–6 *h*) *after intraduodenal doses of nitrofurantoin*

Dose (mg/kg)	Hydrocholeresis* (ml)	Total drug* (mg)	Dose excreted* (%)
2	10·6±1·6	2·0±0·2	8·9±1·2
6	22·9±4·5	8·3±0·7	10·0±2·9
12	47·9±6·7	17·6±5·1	12·6±3·8

Conditions: nitrofurantoin as a suspension in 1% sodium carboxymethyl cellulose gum was administered intraduodenally. *Average value±S.D., based on three dogs. Hydrocholeretic effect adjusted for the control bile flow obtained for the 0·5 h just before drug administration, 2 mg/kg–1·1 ml±S.D. 0·1, 6 mg/kg–1·8 ml±S.D. 0·2, and 12 mg/kg–1·4 ml±S.D. 0·7.

A drug-dose relationship was apparent in dog bile for the 6 h period after intraduodenal administration of nitrofurantoin as a suspension at doses ranging from 2 to 12 mg/kg (Table 3). Both the biliary drug excretion and the related hydrocholeresis encountered appeared linearly related to the dose level over the range investigated. Maximum drug excretion in bile and the maximum hydrocholeretic effect occurred within 2 h after each dose. The excretion patterns for total bile

solids encountered after nitrofurantoin administration agreed well with corresponding patterns reported previously for this drug in dogs (Conklin & Wagner, 1971).

Nitrofurantoin blood concentrations were detectable only in the dogs which received the 12 mg/kg dose. These drug concentrations ranged from 1 to 2 μg/ml for the 2 h period after drug administration. Bile:blood drug concentration ratios of about 200 were estimated for this interval. These ratios agree reasonably with those observed previously in the dog within 0·5 h after the intravenous administration of nitrofurantoin at 3 mg/kg (Conklin & Wagner, 1971).

Dehydrocholic acid study

The bile salt, dehydrocholic acid (DHCA), is administered clinically as a hydrocholeretic drug (Grollman, 1965). For comparison, a study was performed to determine hydrocholeresis in dogs after administration of DHCA alone and concomitantly with nitrofurantoin. A much greater hydrocholeresis was evident in dogs after the intravenous administration of nitrofurantoin at 3 mg/kg than after a DHCA dose (5·1 mg/kg) equimolar to the nitrofurantoin dose (Table 4). When

TABLE 4. *Hepatic bile flow in dogs after an intravenous dose of nitrofurantoin or dehydrocholic acid (DHCA)*

Compound	Control flow before dose* (ml/0·5 h)	Hydrocholeresis after dose* (ml/0·5 h)	Total hydrocholeresis after dose* (ml/3·0 h)
DHCA	1·6±0·5	1·3±0·7	1·4±0·9
Nitrofurantoin	1·4±0·7	8·6±3·4	20·6±1·7
DHCA+nitrofurantoin†	1·5±0·6	9·5±3·1	22·4±4·5

Conditions: each compound as a sodium salt in a solution of 5% dextrose (pH 9·0) was administered by a single intravenous injection. Nitrofurantoin was administered at 3 mg/kg and DHCA at 5·1 mg/kg, a dose equimolar to the nitrofurantoin dose. *Average value±S.D., based on three dogs. Hydrocholeretic effect for the first 0·5 h or the 3·0 h after dose, adjusted for the control bile flow obtained for the 0·5 h just before drug administration. †Administered concomitantly.

DHCA was administered intravenously to dogs at higher doses of 10·2 and 20·4 mg/kg, doses equimolar to nitrofurantoin doses of 6 and 12 mg/kg, respectively, a corresponding increase in the hydrocholeretic effect was observed which appeared linear from 5·1 to 20·4 mg/kg.

As reported by Cook, Bianchi, Hambourger & Green (1950), a hepatic bile flow of about 0·9 (ml/kg)/h was obtained in anaesthetized dogs within 1 h following an intravenous dose of DHCA at 20 mg/kg. In agreement with this, an average hepatic bile flow of 1·1 (ml/kg)/h was obtained in dogs during the present study within 1 h after DHCA was administered intravenously at 20·4 mg/kg. The excretion pattern of total bile solids observed under these conditions with DHCA agreed well with corresponding patterns obtained with this drug in dogs by Cook *et al.* (1950).

The results encountered when nitrofurantoin and DHCA were administered concomitantly to dogs by individual intravenous injections indicate that DHCA administration did not reduce the nitrofurantoin-related hydrocholeresis anticipated for an equivalent intravenous dose of nitrofurantoin alone (Table 4). Also, in agreement, an average biliary dose recovery for nitrofurantoin of 28·6% ±S.D. 4·2 was obtained from 0–3 h after the concomitant administration of the two drugs, in comparison to an average nitrofurantoin biliary dose recovery of 20·5% ±S.D. 6·2, for the same interval after the administration of nitrofurantoin alone (Table 4).

Discussion

The biliary and urinary drug recoveries from the donor–recipient experiments indicate that at least one-third of the nitrofurantoin originally excreted in bile is absorbed intestinally before its subsequent biliary re-excretion. However, it is not possible to determine the exact amount of intestinal drug absorption by relying solely on these two routes of drug excretion. Nitrofurantoin is well absorbed, quickly distributed into most body fluids, and a primary mechanism of elimination is enzymatic degradation (Paul & Paul, 1964, 1966). This suggests that additional drug was distributed into other body fluids and degraded by body tissues following drug absorption in the intestine. It therefore seems reasonable to assume that there is greater intestinal absorption of nitrofurantoin from hepatic bile than that shown by just the biliary and urinary drug excretion in the recipients.

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