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The Effects of Hepatic Microsomal Enzyme Inducers on the Pharmacokinetics of Ouabain after Portal and Systemic Administration to Rats

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Abstract

The microsomal enzyme inducers 3-methylcholanthrene, phenobarbitone and pregnenolone-16α-carbonitrile (PCN) are known to affect other aspects of hepato-biliary disposition in addition to metabolism. This study was designed to determine if presystemic elimination of the non-metabolized xenobiotic ouabain could be altered by these inducers.

Male Sprague-Dawley rats were pretreated with inducers or saline for four days. A day later, ouabain (0·5 mg kg^{-1}) was administered into either the ileocolic vein (portal administration) or the femoral vein (systemic administration). Blood and bile samples were collected for up to 90 min after ouabain administration. Biliary excretion rate and cumulative biliary excretion of ouabain were increased by pretreatment with PCN (75 mg kg^{-1}day^{-1}) relative to controls. Phenobarbitone pretreatment (75 mg kg^{-1}day^{-1}) also increased these parameters, but to a lesser extent than PCN. In contrast, 3-methylcholanthrene pretreatment (20 mg kg^{-1}day^{-1}) had no effect on biliary excretion. Plasma concentrations of ouabain were much lower after PCN pretreatment relative to controls, whereas neither phenobarbitone nor 3-methylcholanthrene had any effect. Similarly, clearance (both biliary and total) and volume of distribution were increased by PCN, but not by phenobarbitone or 3-methylcholanthrene pretreatment. Interestingly, the magnitude of biliary and plasma effects induced by PCN appeared to be comparable whether ouabain was administered portally or systemically.

Pretreatment of rats with PCN, but not phenobarbitone or 3-methylcholanthrene was shown to increase total clearance of ouabain, mainly via an increase in biliary clearance. Furthermore, because the enhanced clearance occurs after systemic as well as after portal administration of ouabain, a significant change in hepatic presystemic elimination was not detected.

When xenobiotics are administered orally or intraperitoneally, the amount that reaches the systemic circulation may be less than the administered dose even when absorption is complete. This reduced bioavailability is known as presystemic elimination or the first-pass effect (Routledge & Shand 1979).

While it is known that microsomal enzyme inducers can affect the disposition of chemicals by increasing their rate of biotransformation (Meikle et al 1969; Welch et al 1976; Alvan et al 1977; Stella & Chu 1980 a,b), less is known about their effect on disposition of xenobiotics resistant to metabolism. However, enzyme inducers can affect other aspects of hepato-biliary disposition in addition to metabolism. For example, phenobarbitone, pregnenolone-16α-carbonitrile (PCN) and 3-methylcholanthrene have all been shown to increase liver weight (Thompson et al 1982), and phenobarbitone and antipyrine caused an increase in blood flow to the liver (Ohnhaus et al 1971). The effects of 3-methylcholanthrene, phenobarbitone (Eaton & Klaassen 1979) and PCN (Eaton & Klaassen 1979; Stacey & Klaassen 1979) on uptake of ouabain into hepatocytes have been reported. In both studies, PCN was found to increase ouabain uptake. Biliary excretion and bile flow are also enhanced by such inducers as phenobarbitone (Klaassen 1970) and PCN or the structurally similar steroid spironolactone (Klaassen 1974). By enhancing any one of these factors, enzyme inducers can promote plasma disappearance of xenobiotics by mechanisms other than increased metabolism.

The purpose of this study was to determine if microsomal enzyme inducers could affect hepatic pre-systemic elimination for xenobiotics which are not metabolized. The cardiac glycoside ouabain was chosen for study because, in addition to being excreted unchanged (Cox & Wright 1959), it is known to undergo pre-systemic elimination (Iga & Klaassen 1979). A further reason for choosing ouabain was the observation that enzyme inducers affected the disposition of ouabain after systemic administration alone (Klaassen 1970, 1974). The inducers selected for this study were phenobarbitone, 3-methylcholanthrene and PCN, partly because of our laboratory's experience with these compounds and partly because these are three of the most widely studied inducers (Lu & West 1980).

Methods

Ouabain and urethane were obtained from Sigma Chemicals (St Louis, MO). [^{3}H] Ouabain (10–20 mCi mmol^{-1}) from New

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England Nuclear (Boston, MA), 3-methylcholanthrene from Eastman Chemicals (Rochester, NY) and phenobarbitone from Merck (Rahway, NJ). PCN was a gift from the Upjohn Co. (Kalamazoo, MI). All other chemicals used were obtained of the highest quality available.

Pretreatment of Animals

Male, Sprague-Dawley rats, 220–300 g (Sasco, Omaha, NE), were pretreated for four days with the following daily doses: phenobarbitone 75 mg kg^{-1} in saline; PCN, 75 mg kg^{-1} in two percent Tween 80 in saline; 3-methylcholanthrene, 20 mg kg^{-1} in corn oil. Saline served as the vehicle control. All compounds were administered in a volume of 5 mL kg^{-1}.

Collection of Blood and Bile

Rats were anaesthetized with urethane (1·0 g kg^{-1}) and for the femoral vein and artery were cannulated with polyethylene tubing (PE-50) for systemic drug administration and blood sampling.The common bile duct was cannulated with PE-10 tubing for bile collection. A middle ileocolic vein was isolated and cannulated with PE-10 tubing attached to a 30-gauge needle for portal administration (Thompson & Klaassen 1982). The rectal temperature of the anaesthetized rats was maintained at 37°C with a heat lamp to prevent hypothermia-induced changes in hepatic function (Roberts et al 1967). Ouabain was dissolved in saline, mixed with [^{3}H]ouabain in a concentration sufficient to deliver 0·5 mg kg^{-1} (12 μCi kg^{-1}) and administered (2 mL kg^{-1}) over a 60-s period. For each pretreatment, the animals were divided into two groups. One group received ouabain in the ileocolic vein and saline in the femoral vein (portal administration), whereas in the other group the administration was reversed (systemic administration). Blood was collected (50–250 μL) into heparinized tubes at 0, 1, 2, 3, 4, 5, 10, 15, 20, 30, 45, 60, 75, and 90 min after ouabain administration. Bile was collected 5 min before dosing, and at 5, 10, 15, 20, 30, 45, 60, 75 and 90 min after the dose. Bile volume was measured gravimetrically, assuming a density of 1·0 g mL^{-1}.

Determination of Ouabain in Plasma and Bile

Because ouabain is not biotransformed (Cox & Wright 1959) plasma (50–150 μL) and bile (25–50 μL) were analysed directly. Total radioactivity in plasma and bile was determined by liquid scintillation spectrometry using Complete Scintillation Cocktail 3a70 (Research Products International, Elk Grove, IL) in a Packard Tri-Carb Spectrometer (La Grange, IL). Correction for quenching was made by automatic external standardization.

Pharmacokinetics

The area under the plasma concentration versus time curve (AUC) was determined for the first 90 min by the trapezoidal rule (Gibaldi & Perrier 1975) and extrapolated to infinity according to the following equation (Levy & Gibaldi 1975):

$$AUC = AUC_{0-90} + \frac{C}{\beta} \quad (1)$$

where C is the plasma concentration of ouabain at the last collected time (90 min) and β is a pharmacokinetic parameter which was calculated after plasma concentration versus time data were fitted to a bi-exponential equation by the CSTRIP program of Sedman & Wagner (1976):

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

where A and α are, respectively, the y intercept and elimination rate constant of the distributive phase and B and β are the y intercept and elimination rate constant of the terminal phase. After the initial parameters were determined, a more rigorous treatment of the data was obtained using NONLIN (Metzler et al 1974). Total body clearance (CL) and apparent volume of distribution (V_β) were calculated according to the following equations:

$$CL = \frac{D}{AUC} \quad (3)$$

$$V_\beta = \frac{D}{AUC \cdot \beta} \quad (4)$$

where D = the dose of drug administered in μg kg^{-1} and the AUC used was that after systemic administration. Systemic availability (f) and hepatic extraction (E_h) were determined according to equations five and six, respectively.

$$f = \frac{AUC_{(portal)}}{AUC_{(systemic)}} \quad (5)$$

$$E_h = 1 - f \quad (6)$$

Because ouabain is not metabolized, the non-renal component of clearance (CL_{NR}) is essentially biliary clearance. Insofar as AUC_{0-90} accounted for $\geqslant$90% of AUC, CL_{NR} was calculated as follows:

$$CL_{NR} = \frac{\text{Cumulative biliary excretion}_{0-90}}{AUC_{0-90}} \quad (7)$$

Statistical Analysis

AUC values after portal and systemic administration of ouabain were compared by Student's *t*-test. Comparison of AUC between pretreatment groups was performed by a one-way analysis of variance. Where significant variance occurred, the means were compared by Duncan's new

Table 1. Effect of inducers on liver weight (% body weight) and bile flow (μL min^{-1} kg^{-1}).

	Saline	3-Methylcholanthrene	Treatment Phenobarbitone	PCN
Liver weight[a]	4·18 ± 0·16	5·13 ± 0·07*	5·45 ± 0·21	5·24 ± 0·13*
Bile flow	70·4 ± 6·32	73·9 ± 3·4	75·7 ± 3·4	74·7 ± 5·6

[a] Data for liver weights from Thompson et al (1982). * $P < 0·05$, compared with controls.

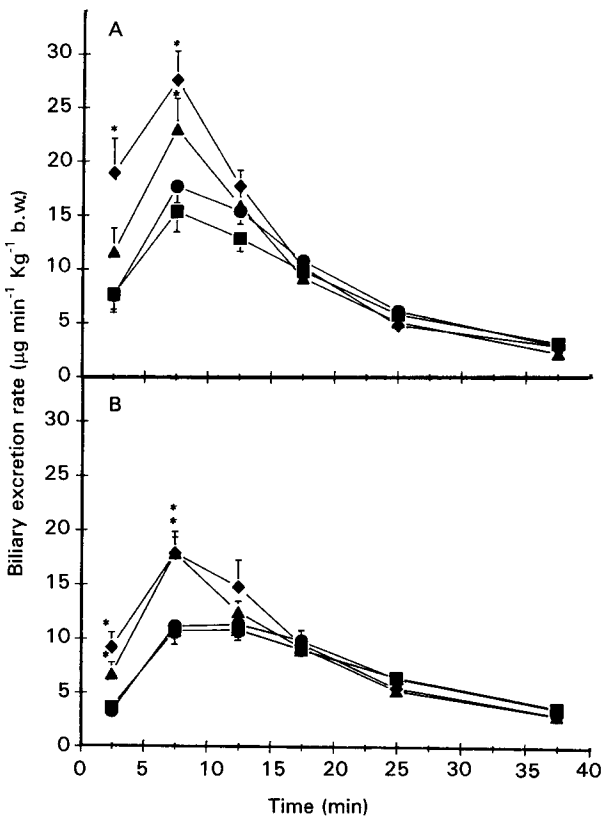

FIG. 1. Effect of inducers on the biliary excretion rate of ouabain after A. portal or B. systemic administration to rats at 0·5 mg kg^{-1}. Each symbol and bar represents the mean ± s.e.m. (n = 5–7). * P <0·05 compared with controls. ● Control; ■ 3-methylcholanthrene; ▲ phenobarbitone, ◆ PCN.

multiple range test. In all cases, a P value of <0·05 was considered statistically significant.

Results

The effects of microsomal inducers on liver weight and bile flow are summarized in Table 1. Previous work has shown that pretreatment with any of the three inducers caused significant (23–31) increases in liver weight, relative to controls (Thompson et al 1982). In contrast, bile flow, collected in this study just before dosing with ouabain, was unaffected by any of the inducers.

Fig. 1 depicts the rate of biliary excretion after either portal administration (A) or systemic administration (B) for each of the four groups. In all cases, the rate of excretion after portal administration was greater than after systemic administration within the same treatment group. Pretreatment of rats with PCN caused a marked increase in the rate of biliary excretion relative to the control group. This difference was noted after both portal (A) and systemic (B) administration, being somewhat greater after the portal route. However, this difference was transient and did not persist beyond 20 min after the dose. A similar effect, but of lower magnitude, was noted for phenobarbitone pretreatment, while 3-methylcholanthrene pretreatment was without effect.

The cumulative excretion of ouabain after portal (A) or systemic (B) administration for each treatment group is shown in Fig. 2. As was seen for the rate of biliary excretion, there tended to be greater cumulative excretion after portal administration than after systemic within most of the treatment groups. For example, for control rats, cumulative biliary excretion of ouabain after portal administration exceeded that after systemic administration for up to 60 min after ouabain was given to control animals, up to 45 min after being given to PCN-treated animals and up to 10 min after being given to 3-methylcholanthrene-treated animals. Only the phenobarbitone treatment group failed to show this effect.

In addition to comparison by route of administration, comparisons were also made between inducer groups for a given route of administration. For example, after portal administration PCN caused a 25% increase and phenobarbitone a 10% increase in cumulative excretion relative to the control group (495 and 439 versus 399 μg kg^{-1}, $P < 0{\cdot}05$). After systemic administration, the PCN-pretreatment group excreted 16% and the phenobarbitone group 6% more ouabain in bile than did the controls (408 and 373 versus 351 μg kg^{-1}), but this was not statistically significant. The disappearance of ouabain from plasma is depicted in Figs 3 and 4. In Fig. 3, plasma disappearance curves are arranged to emphasize the difference between portal and systemic administration within each treatment group. Regardless of pretreatment group, plasma concentrations of ouabain were

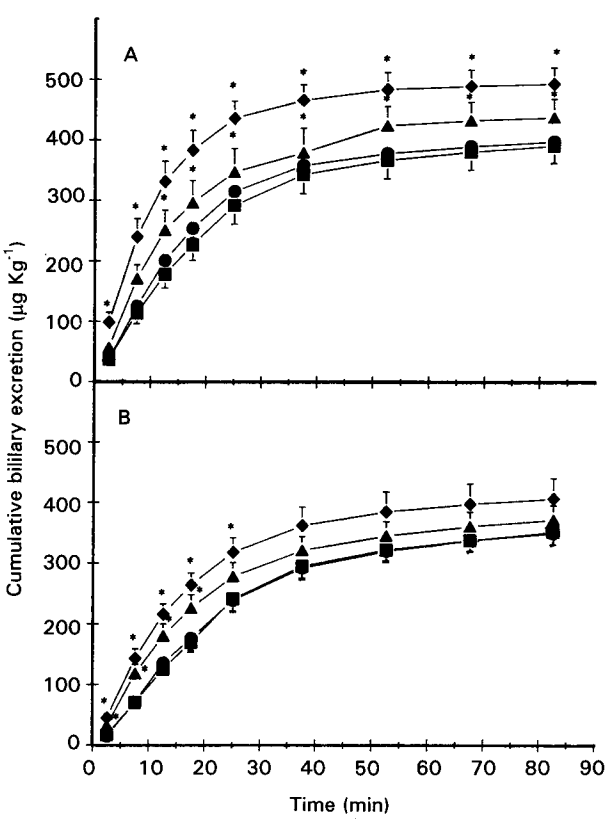

FIG.2. Effect of inducers on cumulative biliary excretion of ouabain after A. portal or B. systemic administration to rats at 0·5 mg kg^{-1}. Each symbol and bar represents the mean ± s.e.m. (n = 5–7). * P < 0·05 compared with controls. ● Control; ■ 3-methylcholanthrene; ▲ phenobarbitone, ◆ PCN.

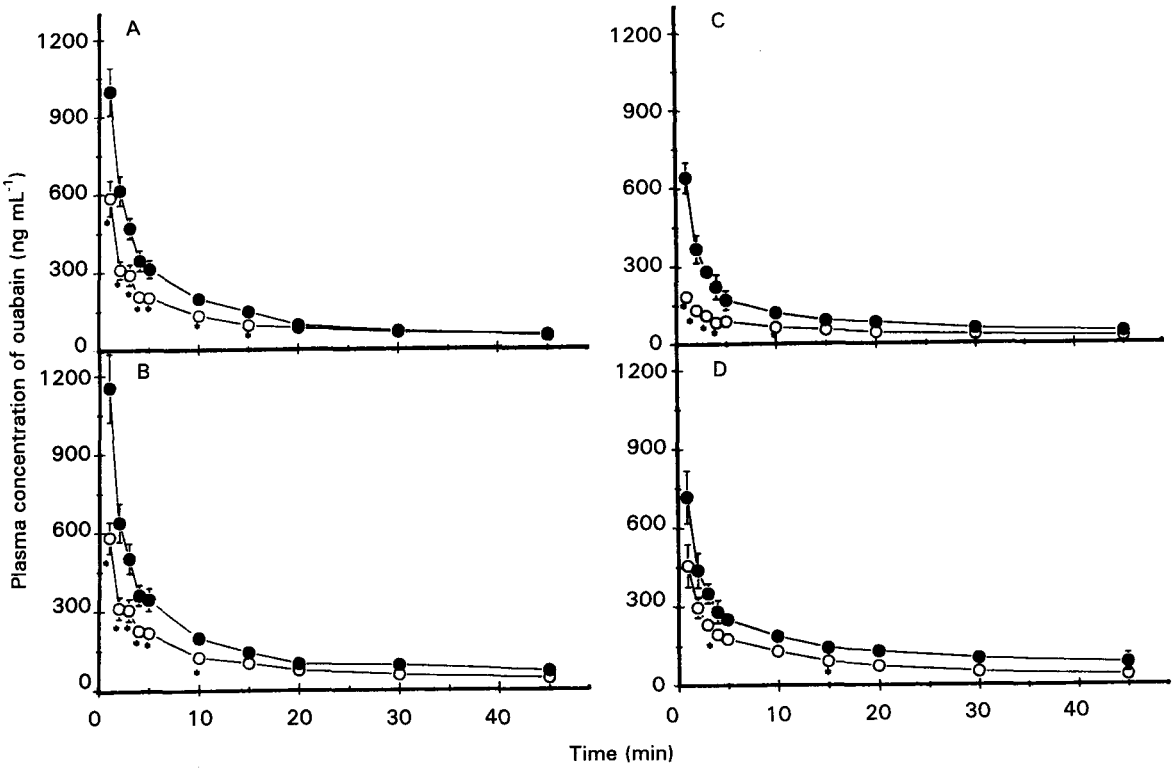

FIG. 3. Plasma disappearance of ouabain against time after portal (○) or systemic (●) administration at 0·5 mg kg^{-1} to control rats (B) and 3-methylcholanthrene (A), PCN-(C) phenobarbitone-(D) pretreated rats. Each symbol and bar represents the mean ± s.e.m. (n = 5–7). * $P < 0.05$ compared with corresponding systemic value.

lower after portal than after systemic administration. However, as was the case for the rate of biliary excretion, this difference was transient and tended to disappear by about 20 min after the dose. In Fig. 4, the effects of the inducers on plasma disappearance when given by the same route of administration are depicted for both portal (A) and systemic (B) administration. Regardless of the route of administration, plasma concentrations of ouabain in the PCN group were lower than controls, at least for the first 20 min after the dose. However, none of the other inducers had a similar effect.

The effects of inducers on the pharmacokinetics of ouabain after portal and systemic administration are summarized in Table 2. For each pretreatment group, total body clearance (CL) and volume of distribution (V_β) were higher and AUC was lower after portal administration of ouabain than after systemic administration. When comparisons were made between treatment groups after the same route of administration, PCN resulted in an increased CL and V_β and a lower AUC, regardless of how ouabain was administered. Neither phenobarbitone nor 3-methylcholanthrene had any effect on these parameters. Apparent systemic availability, the ratio of AUC(portal) to AUC(systemic), was about the same (50–63%), regardless of which pretreatment group was considered. The same held true

Table 2. Pharmacokinetic parameters of ouabain after systemic and portal administration.

		Control	3-Methylcholanthrene	Phenobarbitone	PCN
CL	Systemic	45·00 ± 6·0	44·1 ± 6·8	38·8 ± 6·9	75·7 ± 10·7†
(mL min^{-1} kg^{-1})	Portal	76·0 ± 7·5*	71·3 ± 11·4*	70·1 ± 9·5*	152·7 ± 40·0†*
V_β	Systemic	1·45 ± 0·22	1·81 ± 0·38	1·31 ± 0·13	2·31 ± 0·32
(L kg^{-1})	Portal	2·13 ± 0·30*	2·36 ± 0·27*	2·94 ± 0·50*	5·62 ± 0·83†*
$t_{\frac{1}{2}}$	Systemic	22·3 ± 1·8	25·8 ± 4·5	21·9 ± 3·4	29·5 ± 6·6
(min)	Portal	20·1 ± 2·8	21·2 ± 3·5	25·3 ± 5·5	23·8 ± 2·8
AUC	Systemic	12·1 ± 1·5	11·2 ± 1·6	10·5 ± 1·8	6·17 ± 0·57†
(μg mL^{-1} min)	Portal	7·00 ± 0·88*	6·72 ± 0·97*	6·58 ± 0·61	3·07 ± 0·73†*
Apparent systemic availability		57·8	60·0	62·7	49·7
Apparent hepatic extraction		42·2	40·0	37·3	50·3

Mean ± s.e.m of five to seven rats. * $P < 0.05$ compared with systemic administration, † $P < 0.05$ compared with controls with the same route of administration.

Table 3. Effect of inducers on total body and biliary clearance of ouabain after portal and systemic administration.

Parameter	Ouabain administration route	Saline	Treatment		
			3-Methylcholanthrene	Phenobarbitone	PCN
CL_{NR} ($mL\,min^{-1}\,kg^{-1}$)	Systemic	34·6 ± 4·1	38·4 ± 5·1	31·6 ± 4·1	72·7 ± 11·9
	Portal	68·3 ± 7·9*	65·4 ± 11·2	77·3 ± 11·9*	176 ± 46·1†*
	Systemic/portal	0·51	0·59	0·41	0·41
CL_{NR}/CL (%)	Systemic	70·2 ± 3·7	69·8 ± 3·5	74·6 ± 4·8	75·5 ± 3·5
	Portal	79·9 ± 3·0	78·3 ± 5·9	87·8 ± 6·2	96·9 ± 5·0†*
	Systemic/portal	0·88	0·89	0·82	0·78

Mean ± s.e.m. of five to seven rats. CL_{NR} is non-renal clearance which for ouabain is essentially biliary clearance, CL_{NR}/CL is the ratio of non-renal (i.e. biliary) clearance to total body clearance. * $P < 0·05$ compared with systemic administration, † $P < 0·05$ compared with controls with the same route of administration.

for apparent hepatic extraction (i.e., presystemic availability), which ranged from 37 to 50 percent.

Table 3 summarizes biliary clearance (CL_{NR}) and its role in total clearance as affected by inducers and route of administration. As was the case for total clearance, biliary clearance was always much higher after portal administration of ouabain than after systemic administration, regardless of treatment group. Also, like total clearance, biliary clearance was markedly increased by PCN pretreatment (but not by phenobarbitone or 3-methylcholanthrene, regardless of the route of administration. The ratio of biliary to total clearance in control animals was about 80% after portal administration of ouabain, increasing to about 97 and 88%, after PCN and phenobarbitone, respectively, but was unchanged by 3-methylcholanthrene. After systemic administration of ouabain, the ratio of biliary to total body clearance ranged from 70–75% regardless of pretreatment.

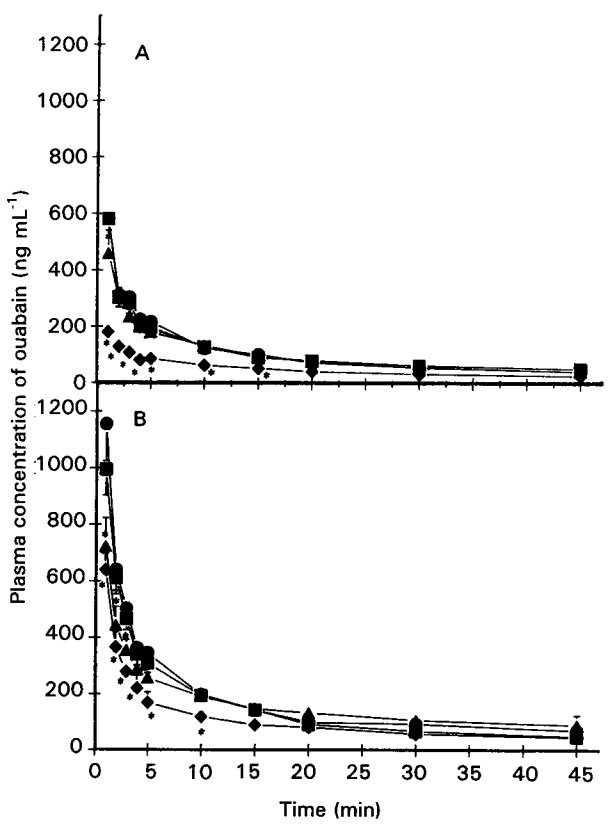

FIG. 4. Effect of inducers on plasma disappearance of ouabain after A. portal or B. systemic administration to rats at 0·5 mg kg^{-1}. Each symbol and bar represents the mean ± s.e.m. (n = 5–7). * $P < 0·05$ compared with controls. ● Control; ■ 3-methylcholanthrene; ▲ phenobarbitone, ◆ PCN.

Discussion

Earlier studies demonstrated that microsomal enzyme inducers influence the biliary excretion and plasma disappearance of ouabain (Klaassen 1970, 1974). However, these studies did not give any indication as to whether the presystemic elimination of ouabain would be altered, because ouabain was administered only by the systemic route. The present study was undertaken to compare the effects of inducers on biliary excretion and plasma pharmacokinetics after both portal and systemic administration.

In agreement with earlier work (Klaassen 1970), when ouabain was administered systemically to rats pretreated with inducers, PCN produced a significant increase in biliary excretion and plasma disappearance relative to the group pretreated with vehicle alone, whereas 3-methylcholanthrene and phenobarbitone had little or no effect. These effects of ouabain on plasma disappearance were reflected in a lower AUC, higher clearance (both biliary and total), and larger volume of distribution. However, unlike previous work, the data derived from the portal administration of ouabain to pretreated rats in this study permits assessment of presystemic elimination. As expected, vehicle-pretreated rats had a lower AUC after portal administration than that after systemic administration (Iga & Klaassen 1979). Accordingly, systemic availability and hepatic presystemic elimination were about 60% and 40%, respectively. Pretreatment with 3-methylcholanthrene or phenobarbitone had no effect, whereas PCN pretreatment caused a significant decrease in the portal AUC relative to that of controls. However, the decrease was comparable with that observed after systemic administration and therefore, systemic availability changed relatively little, to about 51%.

It is interesting that PCN could have such a significant effect on total clearance and volume of distribution, but have little effect on systemic availability. Some insight as to

why this is true might come from the definition of clearance. Total body clearance is defined as the amount of blood cleared of unchanged drug by all processes per unit time (Gibaldi & Perrier 1975). Usually, hepatic clearance and renal clearance are the most significant processes. In the case of ouabain, hepatic clearance is much more significant than renal clearance, accounting for roughly 70% of total clearance after systemic and about 80% after portal administration. Furthermore, since ouabain is not metabolized (Cox & Wright 1959), its hepatic clearance is due entirely to biliary clearance, i.e., to hepatic uptake and excretion into bile.

Because of the relative contribution of biliary clearance to overall clearance, it seemed reasonable to assume that any factors that promoted biliary excretion of ouabain would also increase its clearance. As summarized in the results section, PCN pretreatment caused a modest increase relative to saline controls in cumulative excretion of ouabain, by 25% if ouabain was administered portally and 16% if administered systemically. Phenobarbitone caused a much smaller enhancement of biliary excretion while 3-methylcholanthrene pretreatment had no effect. This increase in cumulative biliary excretion is apparently due to a transient increase in the rate of biliary excretion of ouabain and not due to increased bile flow. However, in contrast to this relatively modest increase in biliary excretion, biliary clearance was more than doubled by PCN pretreatment, whereas phenobarbitone and 3-methylcholanthrene had no effect. Thus, ouabain was being eliminated from plasma at a greater rate than could be accounted for by its excretion into bile.

The current study was not designed to measure tissue levels of ouabain, so it is not possible to account directly for the organ or compartment responsible for this increased disappearance of ouabain from plasma. However, previous in-vitro studies (Eaton & Klaassen 1979) indicated that PCN but not phenobarbitone or 3-methylcholanthrene pretreatment of rats selectively increased the uptake of ouabain into isolated hepatocytes. These authors postulated that the carrier-mediated process responsible for uptake of ouabain into hepatocytes was selectively stimulated by PCN pretreatment (Eaton & Klaassen 1978). It is therefore plausible that enhanced uptake into liver promoted by PCN was the factor which accounted for the increased rate of disappearance of ouabain from plasma observed in the present study.

Given the marked increase caused by PCN on the clearance of ouabain (both biliary as well as total), the lack of effect on presystemic elimination is curious. Again, a closer inspection of the definition of clearance may offer some explanation. It is known that hepatic clearance is determined not only by intrinsic clearance (CL_{int}, in this case, hepatic uptake and biliary excretion), but by hepatic blood flow (Gibaldi & Perrier 1975). According to Routledge & Shand (1979), an increase in CL_{int} of a highly extracted drug will result in a more noticeable decrease in AUC after portal than after systemic administration. In contrast, an increase in hepatic blood flow has the opposite effect, i.e. a more noticeable decrease in AUC after systemic administration. PCN caused a definite enhancement of CL_{int} as seen by the marked decrease in $AUC_{(portal)}$. If PCN were to cause an increase in liver blood flow as well, this would contribute to the decreased AUC observed after systemic administration. Because the decrease in AUC would, therefore, be independent of route of administration, little overall effect on systemic availability and its converse, hepatic extraction (i.e., presystemic elimination), would be expected. This possibility cannot be directly addressed because liver blood flow was not measured here. However, a survey of the literature does not indicate any reports of a PCN-induced alteration of liver blood flow, so this explanation does not seem likely.

Alternatively, the fact that AUC is decreased regardless of route of administration may simply reflect the finding that ouabain is not a highly extracted drug. The hepatic extraction ratio for ouabain in untreated animals determined here and elsewhere ranges from 0·4 to 0·5. Thus, trends which apply to highly extracted drugs may not be applicable to ouabain and other drugs of intermediate extraction. Apparently, for this class of drug, it is difficult to predict what effect a change in intrinsic clearance or a change in hepatic blood flow might have on systemic availability.

In summary, pretreatment of rats with PCN, but not 3-methylcholanthrene or phenobarbitone, was shown to increase total clearance of ouabain, mainly via an increase in its biliary clearance. Although the precise mechanism by which PCN could exert this effect was not determined here, it is possibly due to a selective increase in a mechanism which transports ouabain from blood to liver. Furthermore, since this enhanced clearance occurs after systemic as well as after portal administration, a significant change in hepatic presystemic elimination was not detected.

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