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Disposition of Hexobarbitone and Antipyrine in DOCA-hypertensive Rats

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Abstract—The disposition of antipyrine and hexobarbitone, and their effects on drug metabolizing hepatic enzymes have been investigated in DOCA-hypertensive rats. Antipyrine pharmacokinetic parameters were the same in hypertensive and control animals. Hexobarbitone sleeping time was longer in hypertensive rats compared with controls, while the activity of hepatic hexobarbitone hydroxylase was the same in both groups. Hepatic aminopyrine-*N*-demethylase activity was elevated in hypertensive rats while aniline hydroxylase and aryl hydrocarbon hydroxylase were lower. Glucuronyl transferase was the same in both groups. The sensitivity of the central nervous system of hypertensive rats to hexobarbitone was not altered, as determined by hexobarbitone concentration in blood and in brain. The total hepatic blood flow (arterial and portal) was significantly increased. Thus it is suggested that the difference in the disposition of the two drugs is probably not due to drug metabolizing enzyme activity. It is likely that the increase in total hepatic blood flow and rapid saturation of hepatic hexobarbitone metabolizing enzymes have significant roles in the slower metabolism and increased activity of hexobarbitone in hypertensive rats as compared with control rats.

The availability of hypertensive models such as spontaneously hypertensive rats (SHR) and renal hypertensive rats has prompted the study of pharmacokinetic and pharmacodynamic properties of drugs to understand their behaviour in man. Hypertension-induced changes in drug sensitivity and effectiveness can occur. Thus, it has been shown that pain threshold is higher in hypertensive patients (Zamir & Shuber 1980) and hypertensive rats (Zamir & Segal 1979; Maixner et al 1982).

Barbiturate sleeping time is used as an indicator for hepatic function in rodents. Shorter barbiturate sleeping times have been observed in SHR (Willis & Queener 1977; Czyzewska-Szafran et al 1979; Yates et al 1979; Ben-Zvi et al 1980; Czyzewska-Szafran & Wutkiewicz 1980; Greenspan & Baron 1981). The shorter sleeping time was accompanied by higher in-vitro specific activities of hepatic *N*-demethylase and *N*-deethylase but not of aniline hydroxylase or aryl hydrocarbon hydroxylase (Ben-Zvi et al 1980; Greenspan & Baron 1981). Induction of cytochrome P450 by phenobarbitone was greater in SHR than in control rats (Yates et al 1979). Czyzewska-Szafran et al (1979) found that the kinetic parameters of hexobarbitone were similar in SHR and normotensive rats though the threshold was higher in SHR (Czyzewska-Szafran et al 1979), while Willis & Queener (1977) found equal sensitivity for pentobarbitone in SHR and normotensive rats. Shorter hypnotic times were noted by Czyzewska-Szafran (1980) also in desoxycorticosterone acetate (DOCA)/saline hypertensive rats (DOCA-HT). In this model the sensitivity of the CNS for hypnotics was not changed by hypertension (Czyzewska-Szafran 1980; Walker & Levy 1989).

Hypertension could be accompanied by haemodynamic alterations resulting in different blood flow to the liver. Such changes of blood flow to the liver can alter the pharmacokinetics of drugs with flow-dependent elimination such as propranolol and lignocaine (Wilkinson & Branch 1984). Though no changes in blood flow to the splanchnic organs in SHR was observed (Nishiyama et al 1976; Ferrone et al 1979), such changes could occur in other models of hypertension. The purpose of the present investigation was to study the disposition of model drugs in-vivo and in-vitro, and the possible effect of blood flow on the disposition in this well-defined model of hypertension—the DOCA/saline hypertensive rat.

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Materials and Methods

Male Charles-River rats were kept at 22±1°C, 40–60% relative humidity and in 14 h light and 10 h dark, with free access to Purina chow and water. When 8 weeks old, the rats underwent right uninephrectomy under ether anaesthesia. One week later, a twice weekly subcutaneous DOCA treatment was started (5 mg/rat) and drinking water was changed to 0·9% NaCl (saline). Body weight and blood pressure were measured once weekly. The experiments with DOCA-HT rats were performed when systolic blood pressure reached 180 mm Hg about 7–8 weeks after starting the treatment.

In-vivo experiments

(a) Sleeping times were recorded following intraperitoneal (i.p.) administration of 100 mg kg^{-1} hexobarbitone. Hexobarbitone concentrations in blood and brain were determined in one set of experiments at 15 min after the animals lost righting reflex and in a second set of experiments when righting reflex was regained. Hexobarbitone was assayed according to Cooper & Brodie (1955) as modified by Valentovic & Bachmann (1980). (b) Antipyrine was injected into DOCA-HT and control rats i.p. at a dose of 15 mg kg^{-1} (containing 5 μCi of [^{14}C]antipyrine). Blood samples were withdrawn from the tail at 30 min intervals up to 210

min. Blood antipyrine concentration was determined according to Bakke et al (1974). The pharmacokinetic parameters were calculated from the plot of log concentration of antipyrine vs time.

In-vitro assays

DOCA-HT and control rats were killed by cervical dislocation. Hepatic microsomes were prepared according to Cinti et al (1972) by calcium aggregation. Aniline hydroxylase and aminopyrine *N*-demethylase were determined according to Mazel (1971), hexobarbitone hydroxylase according to Valentovic & Bachmann (1980), aryl hydrocarbon hydroxylase according to Wattenberg et al (1962) and UDP-glucuronyl transferase with 4-methylumbelliferone as substrate according to Mulder (1971). Microsomal protein was determined according to Lowry et al (1951), and BUN according to Valentovic & Bachmann (1980).

Systemic haemodynamics

Surgical preparation (femoral artery and left ventricle cannulation) was carried out under ether anaesthesia. The rats were allowed to recover in restraining cages for 2 h. Studies were performed in conscious rats. Arterial blood pressure was monitored with a pressure transducer connected to a recorder (Electronic for medicine, VR-6). Cardiac output and organ blood flow were determined by the radioactive microsphere technique (Bonaccorsi et al 1978), using ^{57}Co-labelled microspheres (NEN, 15 ± 3 μm, specific activity 8·31 mCi g^{-1}). Haemodynamic parameters were computed as follows:

$$F_o = (R_o \cdot F_r)/R_r;\ CO = (R_t \cdot F_r)/R_r;\ SVR = MAP/CO$$

where F_o is the organ blood flow, R_r is the blood sample radioactivity, R_o is the organ-radioactivity, R_t is the total radioactivity injected, F_r is the withdrawal blood flow rate (0·3 mL min^{-1}), CO is the cardiac output, SVR is the systemic vascular resistance and MAP is the mean arterial pressure.

The radioactivity found in the liver represents only the hepatic arterial flow since the radioactive microspheres are trapped in the capillaries during their first pass (Nies et al 1976). Portal (venous) blood flow was calculated as the sum of flows to the spleen, stomach and small intestine.

Statistical comparisons were by Student's *t*-test.

Results

The pharmacokinetic parameters of antipyrine in DOCA-HT animals were similar to those of controls (Table 1). Hexobarbitone sleeping time was longer in DOCA-HT compared with control rats (Table 2). Hexobarbitone concentrations in blood and brain of DOCA-HT rats were the same as in normotensive animals at awakening. Hexobarbitone concentration was higher than in controls, both in blood and brains of DOCA-HT rats, 15 min after righting reflex was lost (Table 2). There was no difference in the ratio of concentrations of hexobarbitone in blood and brain at either time.

Table 1. Pharmacokinetics parameters of antipyrine in DOCA-HT and control rats.

	Control	DOCA-HT
$t_{\frac{1}{2}}$ (h)	2·67 ± 0·24	2·98 ± 0·14
C_o (μg mL^{-1})	15·92 ± 0·71	15·85 ± 0·66
Vd (L kg^{-1})	0·95 ± 0·04	0·96 ± 0·04
K_{el} (h^{-1})	0·26 ± 0·02	0·23 ± 0·01
CL (L kg^{-1} h^{-1})	0·25 ± 0·02	0·22 ± 0·01

Results are expressed as mean ± s.e.m. (n = 6).

Table 2. Hexobarbitone blood and brain concentrations and sleeping time in DOCA-HT rats.

Hexobarbitone	Control	DOCA-HT
15 min after losing righting reflex		
blood (μg mL^{-1})	78·3 ± 2·5 (12)	104·3 ± 5·3 (10)*
brain (μg g^{-1})	57·9 ± 8·0 (12)	86·5 ± 10·4 (10)*
On awakening		
blood (μg mL^{-1})	29·9 ± 2·7 (10)	32·4 ± 3·1 (10)
brain (μg g^{-1})	33·1 ± 5·6 (10)	34·2 ± 4·2 (10)
Sleeping time (min)	38·0 ± 2·7 (10)	57·5 ± 4·0 (8)*

Results are presented as mean ± s.e.m. (n). * $P < 0·05$ compared with controls.

The specific activities of hepatic mixed function oxidase enzymes with various substrates are presented in Table 3. While the specific activities of aniline hydroxylase and aryl hydrocarbon hydroxylase were lower in DOCA-HT compared with control rats, aminopyrine *N*-demethylase was elevated in DOCA-HT animals, while hexobarbitone hydroxylase was unaffected. The activity of UDP-glucoronyl transferase with 4-methylumbelliferone was not significantly different between the two groups. BUN in the DOCA-HT rats was 0·47 ± 0·018 mg mL^{-1} compared with 0·49 ± 0·016 mg mL^{-1} in controls.

Table 4 summarizes the haemodynamic variables of the two groups. There were marked and significant changes in systemic haemodynamic parameters in DOCA-HT compared with control rats. Systolic pressure was increased by 65%, diastolic pressure by 100%, MAP by 80%, and SVR was increased by 80% compared with normotensive rats; the rats in both groups were not different in their cardiac output.

Liver and left kidney weights were significantly higher ($P < 0·01$) in DOCA-HT animals compared with controls.

Blood flow to different organs is presented in Table 5. Inducing hypertension in DOCA-HT rats caused a 40% drop in the hepatic arterial blood flow while a significant increment in blood flow to the splanchnic area (spleen, stomach,

Table 3. Specific activities of hepatic drug metabolizing enzymes in DOCA-HT and control.

Enzyme	Control	DOCA-HT
Aniline hydroxylase	0·31 ± 0·001	0·17 ± 0·03*
Aryl hydrocarbon hydroxylase	47·24 ± 2·44	17·33 ± 7·54*
Hexobarbitone hydroxylase	6·44 ± 0·22	6·85 ± 0·39
Aminopyrine *N*-demethylase	0·79 ± 0·09	2·23 ± 0·46*
Glucuronyl transferase	25·68 ± 0·87	27·95 ± 1·08

Specific activities are expressed in nmol product formed (mg protein)$^{-1}$ min^{-1}, except for aryl hydrocarbon hydroxylase which is in fluorimetric units (mg protein)$^{-1}$/20 min. Results are expressed as mean ± s.e.m. (n = 8). * $P < 0·01$ compared with control.

Table 4. Organ weights and haemodynamic parameters of DOCA-HT and control rats.

	Control	DOCA-HT
Body weight (g)	390·8 ± 4·2	399·2 ± 9·0
Liver weight (g)	11·4 ± 0·42	15·3 ± 0·9*
Left kidney weight (g)	1·7 ± 0·1	3·6 ± 0·2*
Systolic pressure (mm Hg)	111·7 ± 3·5	184·3 ± 5·7*
Diastolic pressure (mm Hg)	67·0 ± 2·9	123·2 ± 6·1*
Mean arterial pressure (mm Hg)	84·1 ± 3·2	143·6 ± 5·6*
Cardiac output (mL min^{-1})	82·2 ± 6·4	81·1 ± 8·1
Heart rate (beats min^{-1})	351·7 ± 4·0	353·3 ± 5·6
Systemic vascular resistance (mm Hg min mL^{-1})	1·05 ± 0·01	1·82 ± 0·11*

Results are expressed as mean ± s.e.m. (n = 6). * $P < 0.01$ compared with control.

Table 5. Blood flow distribution in DOCA-HT and control rats.

	Blood flow (mL min^{-1})	
	Control	DOCA-HT
Heart	6·28 ± 0·64	7·04 ± 0·72
Lung	1·89 ± 0·17	1·92 ± 0·22
Diaphragm	0·65 ± 0·05	0·62 ± 0·13
Brain	1·10 ± 0·09	1·09 ± 0·17
Testis	0·39 ± 0·09	0·40 ± 0·09
Right kidney	5·50 ± 0·25	—
Left kidney	5·47 ± 0·36	12·59 ± 1·92**
Right adrenal	0·22 ± 0·03	—
Left adrenal	0·21 ± 0·02	0·14 ± 0·02*
Spleen	0·92 ± 0·10	0·99 ± 0·18
Stomach	1·10 ± 0·17	1·27 ± 0·07
Small intestine	9·64 ± 0·73	16·07 ± 1·03*
Portal (venous)	11·66 ± 0·79	18·33 ± 1·10*
Liver (arterial)	3·83 ± 0·41	2·47 ± 0·19*
Hepatic (total)	15·48 ± 0·68	20·80 ± 1·00*

Results are expressed as mean ± s.e.m. (n = 6). * $P < 0.05$ compared with control, ** $P > 0.05$ compared with the left and right kidneys of control.

and small intestine), which constitutes the hepatic portal flow, was observed. The total hepatic blood flow in DOCA-HT was 34% higher compared with control rats. The blood flow to the left kidney in DOCA-HT uninephrectomized rats was comparable to the flow of both kidneys in control rats. There was no difference between the two groups in blood flow to the brain.

Discussion

In the present study the specific activities of both aniline hydroxylase and aryl hydrocarbon hydroxylase were significantly reduced in DOCA-HT rats unlike the findings in SHR in which these enzymes were unaffected (Vainionpaa et al 1974; Ben-Zvi et al 1980; Greenspan & Baron 1981); *N*-demethylase activity was induced in both hypertensive models at a certain age (Greenspan & Baron 1981; Merrick et al 1985). Glucuronyl transferase activity was unaltered in DOCA-HT rats, while Ben-Zvi et al (1980) found it to be inhibited in SHR. The existence of multiple isozymes of cytochrome P450 and of UDP-glucuronyl transferase is well documented (Black & Coon 1987; Burchell & Coughtrie 1989; Tephly et al 1989; Guengerich 1990); it is thus conceivable that these hepatic isozyme families are differently induced in various models of hypertension.

Antipyrine and hexobarbitone are examples of model drugs frequently used for the assessment of hepatic oxidative capacity. While the kinetic profile of antipyrine can be assessed, hexobarbitone sleeping time is an accepted bioassay for hepatic oxidative function, assuming an inverse relationship between sleeping time and oxidative capacity. It is also usually accepted that these two drugs are metabolized by the same cytochrome P450 isozymes. Breimer et al (1977), however, showed that rifampicin shortened the elimination half-life time and increased clearance of hexobarbitone, whereas no change in pharmacokinetic parameters of antipyrine was observed. 3-Methylcholanthrene increased intrinsic clearance of antipyrine whereas that of hexobarbitone was decreased (Van der Graaff et al 1983). From those studies it may be concluded that the two model drugs are not detoxified by the same isoenzyme of cytochrome P450. Our results, showing prolonged hexobarbitone sleeping time in DOCA-HT rats compared with controls, without any change in the kinetic parameters of antipyrine, could have been explained on the basis of different isoenzymes of cytochrome P450; however, the equal in-vitro activity of hexobarbitone hydroxylase in both groups excludes this possibility of differential cytochrome P450 isoenzyme induction as a result of hypertension. Valentovic & Bachmann (1980) showed prolonged sleeping time and lower clearance of hexobarbitone in uraemic rats. The possibility of high urea levels in DOCA-HT rats was considered because the hypertension induced is a renal hypertension model; this possibility was ruled out, however, because BUN was the same in both groups.

Hexobarbitone is a drug with a high hepatic extraction ratio (0·65) (Vermeulen et al 1983; Van der Graaff et al 1985) and hence its hepatic elimination is dependent on hepatic blood flow. Thus in DOCA-HT rats, in which hepatic blood flow is significantly higher than in controls in spite of decreased hepatic arterial flow, sleeping time should have been shorter than in controls. However, hexobarbitone sleeping time in the DOCA-HT rats was, surprisingly, longer than in controls. This contradiction may be reconciled by the observation that hexobarbitone first pass metabolism is saturable at comparatively low doses (Vermeulen et al 1983; Van der Graaff et al 1985). Thus, in our study, absorption of hexobarbitone may be faster in DOCA-HT rats (because of increased intestinal blood flow, and because of saturation of hepatic oxidative pathways for hexobarbitone, higher concentrations of intact hexobarbitone escape the liver and reach the CNS, causing longer sleeping time compared with control rats. Antipyrine metabolic elimination is independent of hepatic blood flow because of its low hepatic extraction ratio (Rane et al 1977).

The increase in portal blood flow found in the DOCA-HT model (compared with the control group) is close to the observation made in another model of renal hypertension (Flohr et al 1976), but different from those observed in SHR (Nishiyama et al 1976; Tsuchiya et al 1978; Ferrone et al 1979). The sensitivity of the central nervous system to hexobarbitone in this model of hypertension was not impeded (based on hexobarbitone levels in blood and brain) as was also shown by Walker & Levy (1989) for phenobarbitone.

In conclusion we have shown that induction of hyperten-

sion by uninephrectomy followed by DOCA treatment induces changes in the oxidative disposition of model drugs both in-vivo and in-vitro. These changes are different from those shown in SHR, which may indicate that various kinds of hypertension may induce different changes in drug disposition.

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