Mean concentration of 2-PAM.Cl in blood (μg/ml) ± SE and its biological half-life with and without thiamine HCl

Time after injection of oxime (min)	2-PAM.Cl (30 mg/kg i.m.)		Thiamine (10 mg/kg i.m.)+ 2-PAM.Cl (30 mg/kg i.m.)					
	Male*	Female	Male	Female	Pa	Pb	Pc	Pd
3	4.23±0.96	4.27±0.25	5.15±0.98	3.28±0.70	NS	NS	NS	NS
15	4.56±0.44	4.60±0.75	4.49±0.69	4.76±0.32	NS	NS	NS	NS
30	5.09±0.49	5.48±0.42	5.98±0.38	4.46±0.31	NS	<0.05	NS	<0.05
45	4.64±0.46	4.67±0.47	5.45±0.60	5.50±0.50	NS	NS	NS	NS
120	2.48±0.41	1.67±0.38	2.68±0.58	3.77±0.65	NS	NS	NS	<0.01
150	2.12±0.23	0.75±0.33	2.40±0.44	3.10±0.29	<0.01	<0.01	NS	<0.001
180	1.58±0.18	0.28±0.19	1.60±0.10	3.08±0.48	<0.001	<0.05	NS	<0.001
Biological half-life 2-PAM.Cl (min)	124	88	130	212				

*5 rats were used in each case. Pa: Tests for significance on the sex difference in rats receiving only 2-PAM.Cl. Pb: Tests for significance on the sex difference in rats receiving only 2-PAM.Cl + thiamine HCl. Pc: Tests for significance for the effect of thiamine HCl in male rats. Pd: Tests for significance for the effect of thiamine HCl in female rats. NS: Not significant.

that thiamine HCl is secreted as an organic base in the renal tubules and that it competes with other weak base compounds for the secretory mechanism[10]. From this study it was seen that thiamine HCl had an overall effect on the female rats and retention of 2-PAM.Cl was highly significant at 150 and 180 min. The male rats did not respond to this effect. Little is known on influence of the sex of the animal on the retention of oximes. The results show a significant sex difference on the retention of 2-PAM.Cl, and it is well-established that the rat has an apparent distinction of showing more variation between the sexes in its response to chemicals than any other species[11].

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Pharmacokinetics of pindolol in Africans

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Summary. The pharmacokinetics of pindolol were determined in 12 hypertensive African subjects after a single oral dose of the drug. The estimated pharmacokinetic parameters do not differ significantly in Africans from the values which have been obtained in other races.

Pindolol is one of the beta-adrenoceptor blockers now widely used all over the world. In Africa it finds its greatest use as an antihypertensive agent, and we have therefore determined certain of its pharmacokinetic parameters in this group of patients. The clinical pharmacokinetics of beta-adrenoceptor blockers have not been previously reported in Africans, although it is generally agreed that the pharmacokinetics of drugs need to be studied among each geographical or racial group in which the drugs are being used, since the pharmacokinetics may be affected by genetic or environmental factors and such effects may have important bearings on the clinical uses of the drugs.

Materials and methods. 12 patients, 4 males and 8 females, all Africans and aged between 30 and 64 years, were studied. They all had uncomplicated essential hypertension of mild to moderate severity. They were taken off all drugs for 2 weeks before the study to eliminate the possibility of any interaction between the beta-blocker and other drugs. Clinical examination and laboratory investigations did not reveal the presence of any significant impairment of renal or hepatic function in any of the patients.

On the experimental day, the patients reported at the clinical pharmacology laboratory at 10 a.m. after having had breakfast at 7 a.m. Pindolol was administered orally in a dose of 20 mg using the commercial preparation, Visken (Sandoz). One 10-ml sample of blood was withdrawn from an antecubital vein before the administration of the drug, and 6 further samples were drawn 0.5, 1, 2, 4, 6 and 8 h after the drug. Blood samples were collected into heparinized bottles and immediately centrifuged to separate the plasma which was then stored frozen until used.

Pindolol was determined in plasma using the fluorimetric method of Pacha[2]. The pharmacokinetic parameters were calculated from the experimental data for each individual, a one-compartment model being assumed. Means are given ± SE of mean.

Plasma concentrations of pindolol (ng/ml), half-life (h) and elimination constant K_{el} (h^{-1}), in individual subjects after a single oral dose of 20 mg pindolol

Subject No.	0.5 h	1 h	2 h	4 h	6 h	8 h	$t_{1/2}$ (h)	K_{el} (h^{-1})
1	60	63	71	60	54	42	8.0	0.09
2	7	110	95	52	44	47	3.4	0.21
3	59	88	74	68	63	52	7.3	0.10
4	42	69	54	52	14	9	1.6	0.43
5	20	63	105	56	52	34	3.3	0.21
6	10	42	88	116	66	38	2.5	0.28
7	14	62	69	90	57	45	3.8	0.18
8	6	51	81	64	54	40	4.3	0.16
9	72	115	100	95	90	48	4.4	0.16
10	15	33	67	46	23	18	3.0	0.23
11	9.5	18	58	43	36	32	4.8	0.14
12	8	14	73	66	53	36	3.9	0.18
Mean	26.9	60.7	77.9	67.3	50.5	35.1	4.2	0.20
SE	7.0	9.3	4.7	6.4	5.8	3.4	0.5	0.03

Results and discussion. The table shows the plasma concentrations of pindolol at various time intervals in each of the 12 patients studied. The peak level varied between 58 and 116 ng/ml. Time to peak level was 1 h in 4 patients, 2 h in 6, and 4 hours in 2, the mean time to peak level being 1.9±0.3 h. The half-life for disappearance from the blood estimated graphically from the straight portion of the semilogarithm plot of pindolol concentration against time varied between 2.3 and 7.8 h with a mean of 4.2±0.5 h.

It is well-known that the beta-adrenoceptor blockers are mostly rapidly and completely absorbed after oral administration but differ in their degree of metabolism, urinary excretion of unchanged drug, potency and oral bioavailability. Thus, pindolol which is 60% metabolized and has no significant first-pass effect[3], has a half-life intermediate between that of alprenolol, which is almost completely metabolized and has a high first-pass effect[3], and practolol, which is excreted unchanged in the urine[3]. The half-life of 4.2±0.5 h obtained in this series does not differ significantly from data available in the literature. Thus, Gugler, Bodem and Dengler[4] obtained a half-life of 4.7±0.8 h; Pacha[2] had a half-life of 3.2±1.2 h and Johnsson and Regardh from a review of the literature up to 1976 found an average half-life of 3–4 h. Similarly, the time to peak level of 1–4 h in the individual patients in this study is similar to the results obtained in earlier studies[2,3,5]. The elimination rate constant (K_{el}) determined using the expression $K_{el} = \ln 2/t_{1/2}$, gave a mean value of 0.20±0.03 h^{-1}. This value is similar to the values obtained by previous investigators[5,6]. One of the features which have been held to be of clinical advantage in the use of pindolol is the small interindividual variation in blood levels. This has also been demonstrated in the African patients studied here, for, whereas there is only a 2-fold difference between the lowest and the highest peak levels in the group, a similar study with propranolol showed a 5-fold difference[6].

It is therefore concluded that on the basis of this study the pharmacokinetics of pindolol in Africans do not differ significantly from those found in other areas.

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Inhibition of saline-induced diuresis in the rat by sulpiride

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Summary. Sulpiride (120 mg/kg, i.p.) inhibited saline-induced diuresis in the rat, an effect not observed with haloperidol, clozapine, pimozide or chlorpromazine. The antidiuretic effect of sulpiride also occurred in hypophysectomized rats suggesting that the response was not prolactin-mediated.

Sulpiride is a neuroleptic agent with central[1,2] and peripheral[3] dopamine antagonist activity. It is a potent stimulant of prolactin secretion in animals[4] and man[5] which accounts, at least in part, for its mammotrophic and galactorrheic side effects[6,7]. Männistö et al.[8] have recently reported that sulpiride inhibits urine excretion in humans and suggested that this too may be a prolactin-mediated response. In order to assess the importance of prolactin in this response, we determined the effect of sulpiride on urine excretion in hypophysectomized rats.

Methods. Hypophysectomized female rats weighing approximately 150 g were purchased from Charles River. Absence of the pituitary was verified at necropsy upon completion of the experiments. The rats were fasted overnight and were then given 0.9% NaCl (25 ml/kg) orally followed immediately by i.p. dosages of either sulpiride · SO_4 (120 mg/kg) or the vehicle control (1.5 ml H_2O/kg). The rats were housed individually in metabolism cages without access to food or water and urine was collected at hourly intervals after palpating the bladder.