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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2 W.L. Pacha, Experientia *25*, 802 (1969).
3 G. Johnsson and C.G. Regardh, Clin. Pharmacokin. *1*, 233 (1976).
4 R. Gugler, G. Bodem and J.J. Dengler, Gesellschaft für innere Medizin (in press), quoted by J. Meler, Curr. med. Res. Opinion *4*, 65 (1977).
5 D. Lavene, Y.A. Weiss, M.E. Safar, Y. Loria, D. Georges and P.L. Milliez, J. clin. Pharmac. *17*, 501 (1977).
6 E.E. Ohnhaus, E. Nuesch, J. Meler and F. Kalberer, Eur. J. clin. Pharmac. *7*, 25 (1974).
7 L.A. Salako, A.O. Falase, A. Ragon and Risquat A. Adio, Niger. J. med. Sci. (in press).

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.

Effect of sulpiride on cumulative volume of urine excreted in control and hypophysectomized rats

Treatment	n	Hours after dosing (ml urine/kg b.wt) 1	2	3	4	5	6	7
Normal control	5	1.3±2.0	5.5±3.8	6.2±4.2	8.6±3.1	9.6±1.6	11.4±3.0	14.1± 6.0
Normal+sulpiride	4	0	0	0	0	2.6±5.3	11.7±9.3	17.5±10.9
Hypophysectomized control	5	0	4.0±5.6	13.2±5.5	15.7±4.5*	19.0±6.0**	21.3±6.7*	22.5± 5.2
Hypophysectomized sulpiride	5	0	0	0	0	0	0	0

Data means± SD. * $p<0.02$ compared to normal control. ** $p<0.01$ compared to normal control.

Urine volume was expressed in ml/kg. Significance of the differences between means was determined by Student's t-test.

Results and discussion. Initial studies in rats which were not saline-loaded showed that either the oral or parenteral administration of sulpiride caused a reduction in urine volume for up to 6 h depending upon the dose. However, the urine volumes in the untreated nonhydrated rat were too low to permit any quantitative evaluation of a drug effect. Thus, in subsequent studies we used the saline-loaded rat. The inhibitory effect of sulpiride in this model was observed with doses greater than 120 mg/kg orally and at 40 mg/kg i.m. or i.p., doses which are considerably below the acute LD_{50} of sulpiride in the rat[9]. The pharmacologic effect observed with sulpiride is referred to herein as an antidiuretic effect since the measured effect was antagonism of saline-induced diuresis. Moreover, rats which failed to excrete urine during the test period were found to have empty urinary bladders at necropsy indicating that sulpiride inhibited urine formation and not micturition.

An i.p. dose of 120 mg sulpiride/kg inhibited urine excretion completely for up to 5 h in normal rats (table). The period during which there was essentially complete absence of urine excretion was followed by a period of marked diuresis so that by the 7th h the cumulative urine output by the sulpiride-treated rats was similar to that of the controls. Urine excretion was inhibited for at least 7 h in hypophysectomized rats. The seemingly greater inhibitory effect in the hypophysectomized rats occurred despite the fact that the untreated hypophysectomized rats excreted significantly more urine than did the untreated normal rats the first 6 h of the test.

In order to determine whether the antidiuretic effect observed with sulpiride was a nonspecific effect of high doses of antipsychotic drugs, haloperidol, clozapine, pimozide and chlorpromazine were tested at doses of 120 mg/kg i.p. None of these antipsychotic drugs inhibited the saline-induced diuresis.

Although it is not possible to conclude on the basis of the present studies that the mechanism of the sulpiride-induced antidiuretic response observed in humans and rats is the same, demonstration of the antidiuretic effect in the hypophysectomized rat indicates that the effect is not prolactin-mediated. Kohli et al.[3] have shown recently that sulpiride is a potent antagonist of dopamine stimulated renal vasodilation in the dog. Thus, the antidiuretic effect of sulpiride may be due to a direct effect on the renal vasculature.

Although we are not aware of any toxic manifestations attributable to the transient antidiuretic effect of sulpiride in the rat, the fact that this response has been observed in healthy women[8] and the report of hypertensive attacks occurring in some hypertensive patients receiving sulpiride[10], suggest that additional studies on the renal effects of sulpiride are warranted.

1 A. Tagliamonte, G. DeMontis, M. Olianas, L. Vargin, G.U. Corsini and G.L. Gessa, J. Neurochem. *24*, 707 (1975).
2 A. Restelli, C. Lucchini and A. Glasser, Pharmac. Res. Commun. *7*, 409 (1975).
3 J.D. Kohli, P.H. Volkman, D. Glock and L.I. Goldberg, Fed. Proc. *37*, 792 (1978).
4 L. Debeljuk, H. Daskal, R. Rozados and A. Guitelman, Experientia *30*, 1355 (1974).
5 A.M. Mancini, A. Guitelman, C.A. Vargas, L. Debeljuk and N.J. Aparicio, J. clin. Endocr. Metab. *42*, 181 (1976).
6 H. Chimeses, Presse méd. *78*, 1844 (1970).
7 B. Marchandise, Ann. Endocr., Paris *32*, 746 (1971).
8 P.T. Männistö, K. Korttila and T. Seppala, Arzneimittel-Forsch. *28*, 76 (1978).
9 C. Laville, Lille méd. *17* (suppl.), 4 (1972).
10 P. Corvol, F. Bisseliches and J.M. Alexandre, Ann. Med. intern., Paris *124*, 647 (1973).

Penetration barrier to sodium fluorescein and fluorescein-labelled dextrans of various molecular sizes in brain capillaries[1]

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Summary. The permeability of the blood-brain barrier to sodium fluorescein, or fluorescein-labelled dextrans of various molecular weights, was investigated. Unlike the capillaries in both the area postrema and the eminentia mediana, the capillaries of the cerebral cortex were impermeable to all the intravenous tracer substances used.

In most brain regions, including the cerebral cortex, the blood-brain barrier (BBB) prevents diffusion of lipid-insoluble particles from the blood stream into the brain parenchyma. This barrier has been localized histologically mainly in the capillary endothelium[2-4].

The transcapillary transport of lipid-insoluble particles takes place through small pores or channels of the capillary endothelium in most tissues of the body[5]. On the basis of theoretical calculations from physiological data, Fenstermacher and Johnson[6] proposed that pores with a diameter