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LETTERS TO THE EDITOR

Some physico-chemical properties of amphetamine and related drugs

Pharmacokinetic studies of the amphetamine-like drugs have predominantly been made by using urinary excretion data (Beckett & others, 1968, 1969). The urinary excretion of amphetamine and related drugs depends largely on the lipid solubility of the undissociated form which amount is in turn governed by the degree of ionization of the drug at the urinary pH. The latter is measured by the pK_a value. From a search of the literature it appeared that only for some amphetamines have pK_a values been determined, whereas information on lipid solubility was even more scarce. The pK_a values of amphetamine, *N*-alkyl derivatives and related CNS stimulants were measured according to Leffler, Spencer & Burger (1954) using 0·1 mmol of the HCl salt of the drug.

The apparent partition coefficient (APC) in chloroform–water and heptane–water were measured in Teorell buffer of various pH values such that the concentration of drug in the organic and water layer was roughly the same. The concentrations of drug were measured by gas chromatography. The apparent partition coefficient at pH 7·4 and the true partition coefficient (TPC) being the partition coefficient of the

Table 1. *Partition coefficients (apparent, APC, true TPC) and* pK_a *values of a number of amphetamine-like drugs*

Drug		pK_a	% neutral at pH 7·4	APC at pH 7·4 $CHCl_3$–H_2O	TPC $CHCl_3$–H_2O	TPC Hept.–H_2O
Phenethylamine ..	b,c,e,f	9·88	0·33	0·075	20·8	0·277
Dexamphetamine ..	a,b,e	9·90	0·31	0·48	146	1·88
Methamphetamine ..	a,b	10·11	0·19	1·11	565	5·14
Ethylamphetamine ..	..	10·23	0·15	2·67	1790	38·6
Isopropylamphetamine ..	..	10·14	0·18	8·09	4460	117
Propylamphetamine ..	..	9·98	0·26	21·2	8080	312
Benzylamphetamine ..	..	7·50	44·1	1000	2250	110
Dimethylamphetamine ..	b	9·80	0·39	11·5	2890	108
Methylethylamphetamine ..		9·80	0·39	19·0	4760	166
Methylisopropylamphetamine ..		9·45	0·88	100	11300	200
Benzphetamine	..	6·55	87·2	1000	1400	74·8
Phentermine	..	10·11	0·19	1·00	514	63·2
Mephentermine	..	10·25	0·13	1·22	866	110
Chlorphentermine ..	..	9·60	0·62	4·00	797	17·5
Norephedrine	a	9·55	0·70	0·001	0·035	0·001
Ephedrine ..	a,b,d,e	9·60	0·62	0·015	2·42	0·001
Norpseudoephedrine ..	..	9·40	1·00	0·001	0·10	0·010
Pseudoephedrine.. ..	..	9·86	0·33	0·070	20·0	0·029
Methylephedrine.. ..	a,b	9·30	1·25	1·00	80·6	0·912
Phenmetrazine	..	8·45	8·20	15·60	191	2·15
Phendimetrazine	..	7·55	44·0	1000	2420	8·92
Propylhexedrine	..	10·74	0·043	1·11	2360	173
Fenfluramine	..	9·10	1·96	32·30	1640	678
4-Cl-Amphetamine	..	9·80	0·39	0·818	206	9·10
Fencamfamine	..	8·70	4·76	200	4200	110

For compounds for which pK_a values have been described the literature reference is indicated. a: Kisbye (1958); b: Leffler & others (1951); c: Tuckerman & others (1959); d: Brodie & Hogben (1957); e: Lewis (1954); f: Kappe & others (1965).

Since the error in the estimation of the pK_a and the APC is about 1%, the values are given to 3 decimal places.

neutral base were then computed. The following equation was used:

$$TPC = APC\ [1 + 10^{pK_a - pH}]$$

For a number of amphetamine-like drugs the pK_a values and partition coefficients, and also the fraction of neutral base at pH 7·4 are given in Table 1.

Ephedrine and related compounds are relatively strong bases but they have also an extremely low lipid solubility. It is therefore conceivable that these drugs are eliminated from the body mainly by urinary excretion. Dexamphetamine and a number of related drugs are relatively strong bases which implies that at the physiological pH they are more than 99% ionized. The *N*-alkyl substituted amphetamines are in general more lipid soluble than the parent compound (see Table 1).

The literature provides evidence that there is both glomerular filtration and tubular secretion but that tubular reabsorbtion of dexamphetamine under the conditions of acid urine hardly occurs (Rowland, 1969; Beckett, Salmon & Mitchard, 1969). With higher values of the urine pH the renal clearance is lower indicating that there is substantial reabsorbtion of dexamphetamine at pH 6–7.

The *N*-benzyl derivatives have less basic properties such that these drugs are to a large extent in the neutral form at the physiological pH. The renal clearance is rather low. Under slightly alkaline conditions such drugs therefore may not be detected in the urine. Illegal use of e.g. benzphetamine however can still be detected by urine analysis since these drugs are metabolized to amphetamine.

Other amphetamines such as phenmetrazine, fencamfamine and pipradrol are weak to moderately strong bases with relatively high lipid solubility. These drugs may not be excreted by the kidney under strong alkaline conditions. Indeed it has recently been shown that through the intake of sodium bicarbonate the renal excretion of fencamfamine can be suppressed completely (Vree & van Rossum, 1969). The findings have serious consequences from the standpoint of the control of doping. It is however not known what effect the level of alkalinity necessary to prevent excretion (pH 7–8 for some drugs) has on the performance of the subject taking the alkali. In general, athletes excrete acid urine so the presence of alkaline urine would certainly raise suspicion that suppression of excretion was being attempted.

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