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Cerebrospinal fluid uptake and peripheral distribution of centrally acting drugs: relation to lipid solubility

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In an anaesthetized dog model, serum kinetics and CSF entry were determined after i.v. administration of the following 8 drugs: salicylic acid (as acetylsalicylic acid), antipyrine, acetaminophen (paracetamol), lidocaine (lignocaine), trimipramine, amitriptyline, haloperidol, and imipramine. Kinetic variables were evaluated in relation to in-vitro lipophilicity, measured by the reverse-phase high-pressure liquid chromatographic (HPLC) retention index. After correction for individual values of serum binding (determined as the CSF: serum ratio at equilibrium), in-vivo volume of distribution was highly correlated with HPLC retention ($r = 0{\cdot}92$). Conversely, the time of peak CSF concentration and the CSF entry half-life were negatively correlated with HPLC retention ($r = -0{\cdot}83$ and $-0{\cdot}63$, respectively). Thus lipophilicity is a physiochemical property which has an influence on the peripheral distribution of drugs as well as their rate of entry into CSF.

For many drugs, the time-course and intensity of their pharmacodynamic action depends upon the time course of concentrations at the receptor site mediating pharmacological activity. This in turn depends not only upon the rate and extent of distribution to the tissue at which the drug is active, but also on drug uptake into other tissues which serve as storage or depot sites. For centrally acting drugs, the rate of entry into brain and the rate and extent of peripheral distribution may be determinants with as much influence on the time course of action as the rates of elimination or clearance (Coutinho et al 1970; Oldendorf et al 1972; Ramsey et al 1979; Caccia et al 1980a, b; Howerton et al 1983; Arendt et al 1983a). Alterations in physiological state, such as obesity, may profoundly influence the distribution and elimination half-life of drugs without altering total metabolic clearance (Abernethy et al 1981a, 1982a; Abernethy & Greenblatt 1982).

Extent of lipid solubility has been proposed to explain variations within and between individuals in the rate and extent of drug distribution (Arendt et al 1983a, b; Toon & Rowland 1983; Greenblatt et al 1983a). We have evaluated the rate of entry into cerebrospinal fluid (CSF), as well as the extent of peripheral distribution, of some drugs varying widely in lipid solubility. All of them have actions on the central nervous system.

Methods

Determination of lipophilicity in-vitro. The high pressure liquid chromatographic (HPLC) retention index (Arendt et al 1983a; Greenblatt et al 1983a; Arendt & Greenblatt 1984) was used to determine lipophilicity of

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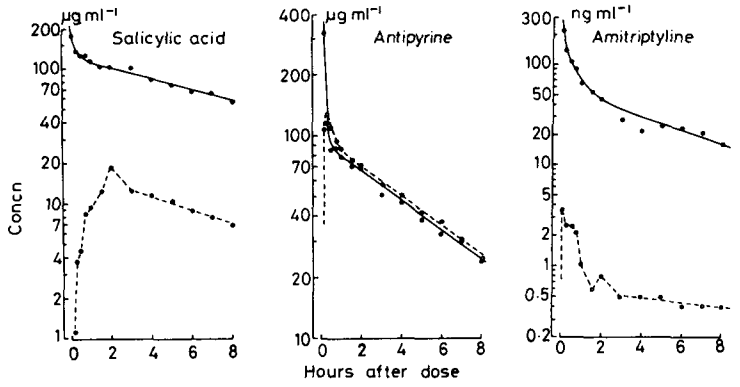

FIG. 1. Serum (●—●) and CSF (○—○) concentrations of three drugs following intravenous injection. The variable rate and extent of CSF uptake among the drugs is shown.

eight different drugs (Table 1). A Waters Associates HPLC system was used for the analysis. The mobile phase consisted of 60% phosphate buffer and 40% methanol, pH 7·4, as described by Arendt & Greenblatt (1984). The flow rate was 1·5 ml min^{-1}. The column was a 30 cm reverse-phase μBondapak C-18 stainless steel column, containing a stationary phase of octadecyl silane coated 12% with carbon and fully end-capped with trimethylsilane to remove free hydroxyl groups. All analyses were at room temperature. Pure reference standards of the eight drugs listed in Table 1 were dissolved in methanol and sequentially injected into the chromatograph. Column effluent was monitored using an ultraviolet detector operated at 254 nm.

In-vivo studies. Thirty adult mongrel dogs, mean weight 12 kg, were anaesthetized with intravenous pentobarbitone (25–30 mg kg^{-1}) with 0·5 mg i.m. propiomazine, intubated and ventilated when necessary to maintain arterial oxygen tension within normal limits (Ochs et al 1980a; Greenblatt et at 1980). Body temperature was maintained with a heating pad, and fluid losses were approximately replaced by intravenous infusion of 0·9% NaCl (saline). A 7·5 cm spinal needle was inserted into the cisternum magnum to allow repeated sampling of CSF.

Each drug was given to three or four animals, and no dog received more than one drug. Antipyrine was administered as an aqueous solution (200 mg ml^{-1}) and acetaminophen was administered as a solution of propylene glycol–ethanol–5% dextrose (40:10:50 by volume) 50 mg ml^{-1}. Salicylic acid was administered as an aqueous solution of the lysine salt of acetylsalicylic acid. All other drugs were given as their commercially available parenteral preparations. Medications were administered rapidly by direct intravenous injection.

Venous blood samples were drawn from an indwelling cannula placed in a peripheral vein before each dose and at the following post-dosage times: 5, 15, 30, 45 min, 1, 1·5, 2, 3, 4, 5, 6, 7, and 8 h. CSF samples were similarly drawn from the indwelling cisternal cannula before the dose and at the times described above.

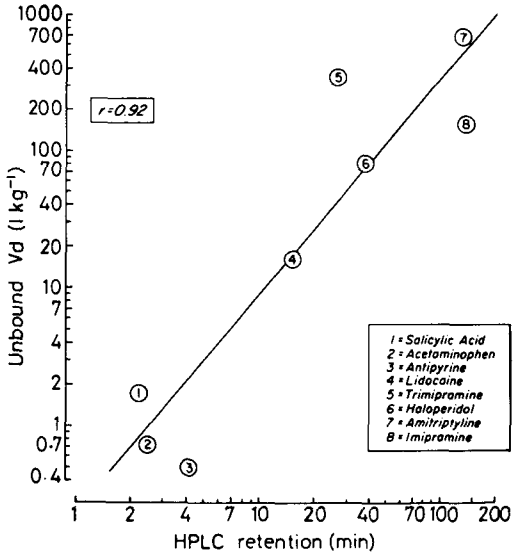

FIG. 2. Relation of HPLC retention to in-vivo volume of distribution of unbound drug. Each point represents the mean value for all animals that received that drug. The solid line was determined by a linear regression analysis.

Analyses. Concentrations of salicylic acid, acetaminophen, and antipyrine in all serum and CSF samples were determined by HPLC (Ameer et al 1981; Greenblatt et al 1983b, c). Concentrations of the five other drugs were determined by gas chromatography with nitrogen phosphorous detection (Abernethy et al 1981b, 1982b, 1984a, b). Demethylated metabolites of the three tricyclic antidepressants (desmethyltrimipramine, nortriptyline, desipramine) were also measured in animals receiving those drugs, but concentrations were not high enough for formal kinetic analysis.

Serum drug concentrations after intravenous dosage were analysed by iterative non-linear least squares

regression techniques described by Ochs et al (1978). Concentrations were fitted to a linear sum of exponential terms. Coefficients and exponents from the function of best fit were used to determine total volume of distribution using the area method, apparent elimination half-life and total clearance. CSF concentrations were similarly analysed. Fitted functions were used to determine the apparent half-life of CSF entry and the CSF disappearance half-life. Based on prior studies showing that the CSF: total serum concentration ratio after attainment of distribution equilibrium is closely related to the free fraction of drug in plasma (Lund et al 1972; Freil & Troupin 1975; Muscettola et al 1978; Greenblatt et al 1980; Ochs et al 1980b), volume of distribution of total drug was divided by the CSF: serum ratio to yield the apparent volume of distribution of unbound drug.

Linear regression analysis was used to assess the relation among kinetic variables and in-vitro lipophilicity. We did not evaluate more complex mathematical relationships, since the number of data points was relatively small.

Results

Drugs disappearance from serum in all cases was described by a sum of exponential terms (Fig. 1). There was wide variability among drugs in volume of distribution, elimination half-life, and total clearance (Table 1). Likewise the drugs were different in lipophilicity based on HPLC retention, with retention times ranging from 2·3 min for salicylic acid to 140 min for imipramine. In-vivo distribution was highly associated with lipophilicity. Increasing lipid solubility based on HPLC retention was highly correlated with unbound volume of distribution after logarithmic transformation ($r = 0·92$, $P<0·002$) (Fig. 2). HPLC retention was positively, although not significantly, correlated with total clearance ($r = 0·59$), and was not significantly correlated with elimination half-life ($r = 0·01$).

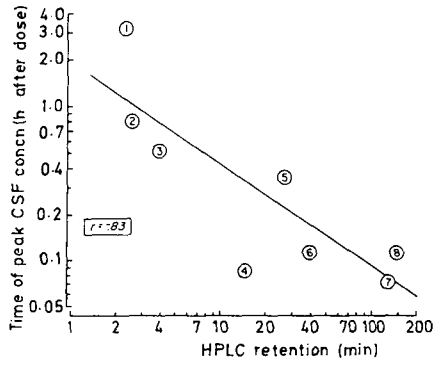

FIG. 3. Relation of HPLC retention to the rate of entry into CSF, based on the time of peak CSF concentration. Each point represents the mean value for all animals that received that drug. The solid line was determined by linear regression analysis. Key as for Fig. 2.

The rate of drug entry into CSF was highly variable. Lipophilicity was inversely related to the rate of CSF entry. There was a negative correlation between HPLC retention and the time of peak CSF concentration ($r = -0·82$, $P<0·02$) (Fig. 3) and with CSF entry half-life ($r = -0·63$, $P < 0·1$). The extent of CSF entry was variable, with CSF: serum ratios as high as 1·0 for acetaminophen and as low as 0·04–0·05 for the tricyclic antidepressants trimipramine, amitriptyline, and imipramine. After attainment of distribution equilibrium, disappearance of drug from CSF and plasma occurred with similar half-lives ($r = 0·65$, $P<0·08$).

Discussion

The present study is consistent with prior reports indicating that lipophilicity is a determinant of peri-

Table 1. In-vitro lipophilicity and in-vivo kinetic variables (values are mean ± s.e.).

	Salicylic acid	Acetaminophen	Antipyrine	Lidocaine	Trimipramine	Haloperidol	Amitriptyline	Imipramine
Number of animals	4	3	4	4	4	4	3	4
Weight (kg)	11·0(±1·7)	14·2(±1·7)	16·0(±5·1)	9·3(±1·4)	12·5(±1·0)	12·4(1·8)	9·3(±1·4)	12·5(±1·5)
Dose (mg)	250[a]	500	500	25	25	5	25	25
HPLC Retention (minutes)	2·32	2·53	4·17	14·7	25·6	38·1	124·0	140·0
Serum kinetics								
Total Vd (litres kg^{-1})	0·24(±0·03)	0·75(±0·1)	0·54(±0·06)	9·0(±1·5)	13·1(±2·1)	16·2(±2·6)	26·3(±9·3)	7·3(±1·4)
Elimination half-life (h)	7·8(±0·65)	1·01(±0·14)	2·8(±0·43)	1·5(±0·11)	4·0(±0·4)	5·2(±0·5)	3·4(±0·9)	4·0(±1·3)
Total clearance (ml min^{-1} kg^{-1})	0·36(±0·02)	32·9(±8·0)	2·3(±0·38)	70·4(±7·9)	39·4(±8·5)	35·8(±2·4)	85·6(±22·7)	27·8(±10·0)
CSF kinetics								
Peak CSF concn[b]	11·7(±2·8)	32·8(±3·2)	73·6(±26·1)	0·63(±0·7)	27·2(±14·8)	6·9(±1·0)	6·5(±1·5)	29·7(±9·1)
Time of peak (h after i.v. dose)	3·3(±0·5)	0·83(±0·08)	0·56(±0·16)	0·083(±0)	0·36(±0·14)	0·12(±0·04)	0·063(±0)	0·12(±0·04)
Entry half-life (min)	60·6(±8·0)	19·3(±2·1)	4·1(±1·8)	0·58(±0·5)	5·5(±3·0)	0·55(±0·6)	2·0(±1·3)	2·8(1·6)
Disappearance half-life (h)	5·3(±0·7)	1·13(±0·08)	2·9(±0·5)	2·0(±0·3)	7·4(±2·5)	7·9(±1·3)	6·4(±0·8)	4·1(±1·4)
CSF/Serum ratio	0·13(±0·01)	1·00(±0)	0·98(±0·03)	0·55(±0·06)	0·041(±0·01)	0·20(±0·03)	0·048(±0·017)	0·045(±0·01)

[a] Given as 500 mg of the lysine salt of acetyl salicylic acid.
[b] In μg ml^{-1} for salicylic acid, acetaminophen, antipyrine, and lidocaine; in ng ml^{-1} for trimipramine, haloperidol, amitriptyline, and imipramine.

pheral distribution of drugs and their rate of entry into CSF (Arendt et al 1983a, b; Toon & Rowland, 1983). If drug distribution occurs by passive diffusion alone, then the extent of distribution into peripheral tissues, of which adipose tissue is a major component, should be determined in large part by the extent of drug uptake into such tissues. In the present study, peripheral distribution of eight drugs varying widely in lipid solubility was highly correlated with their in-vitro lipophilicity based on the HPLC retention index. Similar findings have been reported for other classes of drugs such as benzodiazepines, (Arendt et al 1983a; Greenblatt et al 1983a), β-adrenoceptor antagonists (Arendt et al 1983b) and barbiturates (Toon & Rowland 1983). Correction of pharmacokinetic volume of distribution for the apparent extent of drug protein binding should be made in elucidating this relationship. Since only the unbound or free drug is available for diffusion to peripheral tissues, unbound volume of distribution more closely reflects the actual extent of drug uptake into tissues than does total volume of distribution (Arendt et al 1983a; Greenblatt et al 1982).

Lipophilicity similarly was a determinant of the rate of drug appearance in CSF, suggesting that the drug entry into CSF is determined in large part by the capacity to diffuse across the lipoidal blood brain barrier (Brodie et al 1960; Oldendorf, 1974a, b; Arendt et al 1983b). Thus the lipophilicity of drugs may have a useful predictive value for some in-vivo pharmacokinetic properties. Furthermore the HPLC retention index holds promise as a rapid and reproducible means of quantitating lipid solubility that does not require radioactively labelled drug (Henry et al 1976; Hulshoff & Perrin 1976; Lins et al 1982; Arendt et al 1983a; Arendt & Greenblatt 1984; Haky & Young 1984).

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