expected to have a higher incidence of sensitization and allergies. Such products are therefore less suitable for topical application. The zinc and cerium sulphadiazine samples used by Fox et al (1976, 1978) are identical to our products. In accordance with our conclusions is the finding of Fox et al (1976) that zinc sulphadiazine was partially blocked by *p*-aminobenzoic acid (sulphadiazine is blocked) in contrast with silver sulphadiazine which is not blocked. In non-aqueous media it is possible to prepare $Zn(SD)_2$ separately.

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An investigation of the comparative liposolubilities of β-adrenoceptor blocking agents

P. B. Woods*, M. L. Robinson, *E. R. Squibb & Sons Ltd, International Development Laboratories Moreton, Wirral, Merseyside, U.K.*

Currently there are nine β-adrenoceptor blocking drugs and one α/β-blocker available for clinical use in the U.K. The pharmacokinetics of the group vary significantly from one member to another. β-Blockers can be highly or only minimally bound to plasma proteins, their distribution varies from one drug to another and plasma half-life can be as little as 2 h (oxprenolol) or as long as 24 h (nadolol). They can be almost entirely metabolized (propranolol) or be excreted unchanged (nadolol). One of the major determinants of the pharmacokinetic profile of a drug is its liposolubility (Kubinyi 1979). Highly liposoluble β-blockers undergo a high degree of first pass metabolism in the liver, are highly bound to plasma proteins and concentrate in the central nervous system.

Only incomplete and fragmented partition coefficient data is available for β-blockers and the current work is aimed at obtaining directly comparable data. We have investigated their comparative liposolubilities by determination of their distribution between n-octanol and aqueous buffer (distribution coefficients).

The drugs used were: nadolol, propranolol hydrochloride, oxprenolol hydrochloride, sotalol hydrochloride, acebutolol hydrochloride, labetalol hydrochloride, metoprolol tartrate, pindolol, atenolol, timolol maleate.

The n-octanol was washed with water and 1 M sodium hydroxide solution and then washed 3 times with distilled water.

The phosphate buffers 0·1 M, pH 7·0 and pH 7·4 were prepared from sodium dihydrogen orthophosphate and di-sodium hydrogen orthophosphate.

The n-octanol and the phosphate buffer were pre-equilibrated by shaking together, separating and storing until required.

The drug sample was dissolved in the phosphate buffer at an appropriate level and an aliquot (5 ml) of the buffer was shaken with a suitable volume of the saturated n-octanol (250 ml for atenolol; 50 ml for sotalol and nadolol; 2·5 ml for propranolol and labetalol; 5 ml for all other compounds) for 1 h. The mixture was then left to separate for 30 min, centrifuged for 1 min and the layers separated. The u.v. absorption of the aqueous layer was measured at an appropriate wavelength, and compared with the original aqueous solution before partition.

The β-adrenoceptor blocking drugs tested varied widely in their lipophilic characteristics. Results at room temperature (20 °C), pH 7 and at 37 °C, pH 7 and pH 7·4 are presented in Table 1.

Table 1. Distribution coefficients n-octanol/buffer.

Drug	Previously published* distribution coefficients		Distribution coefficients at: pH 7·0 and 20 °C	pH 7·0 and 37 °C	pH 7·4 and 37 °C
Atenolol	—		0·003	0·008	0·015
Nadolol	—		0·008	0·022	0·066
Sotalol	0·011		0·011	0·012	0·039
Pindolol	0·12		0·20	0·29	0·82
Acebutolol	0·62	(pH 7·4)	0·17	0·35	0·68
Metoprolol	0·18		0·15	0·37	0·98
Timolol	—		0·28	0·51	1·16
Oxprenolol	0·43		0·51	1·01	2·28
Labetalol	—		4·6	8·3	11·5
Propranolol	5·4		5·4	8·6	20·2

* Coombs et al 1980; Hellenbrecht et al 1973; Appelgren et al 1974.

* Correspondence.

It is apparent that these drugs fall into three groups with regard to their distribution coefficients. Propranolol and labetalol are highly lipophilic, nadolol, sotalol and atenolol are lipophobic, the remaining compounds being intermediate in the range. The highly lipophilic drugs had distribution coefficients up to 2 000 times those of the least lipid soluble drugs.

Generally, the 37 °C figure is approximately double the room temperature result and it can be concluded that temperature can significantly affect the distribution coefficients of the drugs. It has previously been shown that small changes in pH result in large changes in distribution coefficients (Hellenbrecht 1973). Our results support this finding. Increasing the pH from 7·0 to 7·4 generally caused up to a threefold difference in the distribution coefficient. For most compounds our results at room temperature, pH 7, correspond well with previous workers. Differences can be explained by variations in experimental parameters, particularly temperature and pH. We have carefully standardized temperature, pH and experimental procedure to establish comparative liposolubilities.

The blood-brain barrier acts like a lipid membrane (Mayer et al 1959) and lipid-soluble drugs penetrate the central nervous system to a greater extent than water-soluble drugs.

Propranolol is highly concentrated in the brain, and brain plasma ratios in the region of 15:1 have been demonstrated in animal and human studies (Myers et al 1975); less lipophilic drugs such as atenolol and practolol penetrate the c.n.s. to a much lesser degree (Day et al 1977). β-Blockers are relatively free of troublesome side-effects, but c.n.s. effects can cause problems in some patients (Fleminger 1978; Stephen 1966; Sanders 1978; Steinert & Pugh 1979). Clinically, therefore, patients who have experienced adverse central effects with propranolol or the other relatively lipophilic β-blockers might benefit by a change of therapy to a drug with a low lipophilicity. Double blind clinical comparisons of β-blockers are required to confirm the advantage of the lipophobic compounds in terms of central side effects.

The liposolubility of β-blockers is also correlated with the extent to which they are metabolized, highly lipophilic drugs such as propranolol being almost completely metabolized and lipophobic drugs such as nadolol, sotalol and atenolol being little or completely unaffected by liver metabolism. A high degree of metabolism during first pass through the liver has disadvantages, since this introduces a variable which can affect plasma concentrations (Johnsson & Regardh 1976).

A high affinity for lipids also coincides with a high degree of plasma protein binding (Johnsson & Regardh 1976). The high protein binding of the lipophilic blockers is an additional theoretical adverse factor in terms of a predictable response since small changes in plasma proteins, during for instance, illness, could significantly affect the concentrations of free drug in the blood. Recently, it has been suggested that blood concentrations of highly protein bound β-blockers may be altered in inflammatory disease (Bishop et al 1980) and that increased plasma propranolol binding can occur in myocardial infarction (Routledge et al 1980).

Ideally, the pharmacokinetic profile of a β-blocker should comprise of long plasma half-life, no metabolism, low protein binding and low c.n.s. penetration. A low distribution coefficient is associated with these favourable pharmacokinetics. We have been able to classify β-blockers according to their lipophilicity and have established that three drugs, nadolol, atenolol and sotalol are much less lipophilic than the other seven tested.

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