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The surface activity and self-association of some β-adrenoceptor blocking agents in aqueous solution

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The surface activity at the air-solution interface of a series of β-adrenoceptor blocking agents has been determined. The drugs investigated included, propranolol, sotalol, oxprenolol, labetolol, timolol, metoprolol and acebutolol. Correlation between surface activity and local anaesthetic potency of the drugs is examined. Light scattering measurements have indicated self-association of sotalol, oxprenolol, acebutolol and metoprolol in 0·5 mol kg^{-1} sodium chloride. Critical micelle concentrations and aggregation numbers are reported.

Many of the β-adrenoceptor blocking agents exhibit a range of pharmacological effects which are independent of their β-blocking activity and which arise as a result of modification of the cell membrane. These effects, collectively referred to as the membrane stabilizing activity, include non-specific cardiac depression, depression of myocardial conduction velocity and local anaesthetic activity. Hellenbrecht et al (1973) have correlated the magnitude of the membrane effects with the hydrophobicity of the drug molecules as indicated by partitioning characteristics and surface activity. A similar parallelism between surface activity and local anaesthetic potency was established by Levy (1968). In the present study the surface activity of a series of β-adrenoceptor blocking agents, including several compounds not available to previous workers, has been examined and correlations with their reported local anaesthetic activity have been examined. Surface tension measurements have also been used to detect any self-association of the drugs in water and electrolyte solutions.

The β-adrenoceptor blocking agent, propranolol hydrochloride, has been reported to form micelles in aqueous solution (Elliott et al 1973). Other pharmacological classes of drugs including the tranquillizers (Attwood et al 1974), the antihistamines (Attwood 1972; Attwood & Udeala 1975a), the anti-acetylcholine drugs (Attwood 1976a, b) and the antidepressants (Attwood & Gibson 1978) also exhibit this property. Aqueous solutions of the β-adrenoceptor blocking agents have been examined by light scattering techniques and the extent of association is reported.

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MATERIALS AND METHODS

Materials. The following drugs were sufficiently well purified by the manufacturers to be used as supplied; the hydrochlorides of sotalol (4′-(1-hydroxy-2-isopropyl-aminoethyl)methanesulphonanilide) (Duncan, Flockhart); labetolol [5-(1-hydroxy-2-(1-methyl-3-phenyl-propylamino)ethyl) salicylamide] (Allen and Hanburys); acebutolol {(±)-3′-acetyl-4′-(2-hydroxy-3-isopropylaminopropoxy)-butyranilide} (May and Baker); propranolol {(±)-1-isopropylamino-3-naphth-1′-yloxypropan-2-ol} (ICI) and oxprenolol {(±)-1-(*o*-allyloxyphenoxy)-3-isopropylaminopropan-2-ol} (Ciba); timolol maleate {(−)-1-butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate} (Merck, Sharp and Dohme); metoprolol tartrate {(±)-1-isopropylamino 3-*p*-(2-methoxyethyl) phenoxypropan-2-ol tartrate} (Geigy Pharmaceuticals).

Water was distilled from alkaline permanganate in a glass apparatus and its surface tension was checked against the literature value before use. Sodium chloride was of Analar grade.

Surface tension measurements. Measurements were made at 303K by the Wilhelmy plate method using a Cahn Electrobalance Model R.G. Solutions were aged until an equilibrium surface tension was established.

Light scattering measurements. A Fica 42000 photogoniodiffusometer (A.R.L. Ltd) was used to measure the light scattered by the compounds in electrolyte-free solution and in the presence of 0·5 mol kg^{-1} sodium chloride. Measurements were made at 303K using light of wavelength 546 nm. Solutions were clarified by ultrafiltration through 0·1 μm Millipore filters until the ratio of the light scattering at angles

of 30° and 150° did not exceed 1·10. The refractive index increments, dn/dm, of the micellar species were measured at 546 nm using a differential refractometer.

RESULTS AND DISCUSSION

Association characteristics. In the absence of added electrolyte, only acebutolol hydrochloride showed any significant departure from the theoretical light scattering line calculated for unassociated monomers (see Fig. 1). The extent of deviation could be accounted for by assuming a monomer-dimer equilibrium. In the presence of 0·5 mol kg^{-1} NaCl, self-association was noted for acebutolol, oxprenolol, sotalol and metoprolol (Fig. 1). The extent of association was

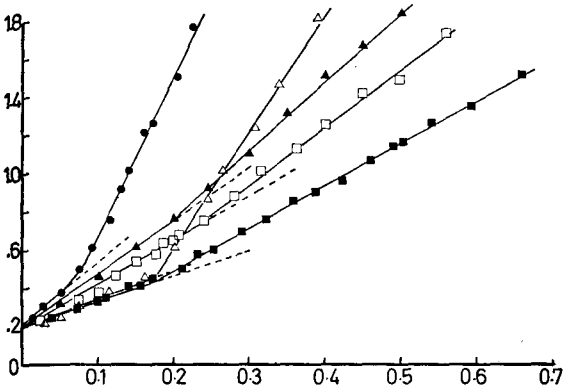

FIG. 1. Variation of the scattering ratio, S_{90} (ordinate), with concentration (abscissa: mol kg^{-1}) for ●, acebutolol HCl; △, oxprenolol HCl; □, metoprolol tartrate, and ■, sotalol HCl in 0·5 mol kg^{-1} NaCl and ▲, acebutolol HCl in H_2O. - - - - theoretical light scattering from unassociated monomers.

determined from plots of $Km_{mic}/\triangle R_{90}$ against the molal concentration of micelles, m_{mic}, according to eqn 1.

$$Km_{mic}/\triangle R_{90} = A + Bm_{mic} \quad .. \quad (1)$$

K is the optical constant and $\triangle R_{90}$ is the Rayleigh ratio of the solution at an angle of 90° to the incident beam, in excess of that of a solution at the critical micelle concentration (cmc). The scattering intensity was too low to allow reliable estimation of the second virial coefficients, B, from which micellar charge is normally calculated. Aggregation numbers, N, were equated with the reciprocal of the intercept, A, and are given in Table 1. Previous workers (Elliott et al 1973) have reported an aggregation number of 36 for propranolol hydrochloride in 0·2 mol kg^{-1} KCl. The considerable difference in association characteristics between this compound and those of Table 1 is indicative of the greater hydrophobicity conferred by the naphthalene ring of propranolol. No association could be detected for timolol and labetolol, although determinations on both compounds were restricted by their limited solubility.

Table 1. Light scattering data for β-blocking agents in the presence of 0·5 mol kg^{-1} NaCl.

Compound	dn/dm kg mol^{-1}	cmc mol kg^{-1}	Aggregation number N
Oxprenolol HCl	0·0555	0·175	4
Acebutolol HCl	0·0734	0·075	3
Sotalol HCl	0·0479	—	1–2
Metoprolol HCl	0·0650	—	1–2

Surface activity. Plots of surface tension, σ, as a function of log molal concentration, m, are presented in Figs 2 and 3. Areas per molecule were determined

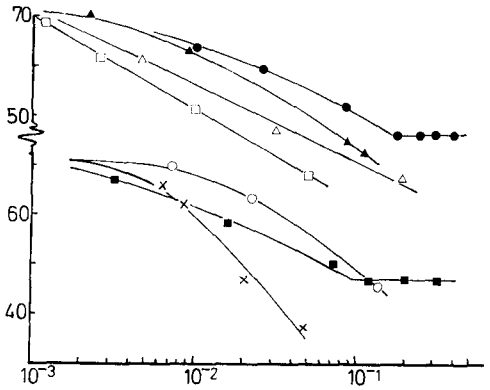

FIG. 2. Surface tension, σ (ordinate: mN m^{-1}), as a function of log molal concentration for ■, propranolol HCl; ○, sotalol HCl; ×, timolol maleate; ●, acebutolol HCl; ▲, oxprenolol HCl; △, metoprolol tartrate; and □, labetolol HCl, in aqueous solution at 303K. Abscissa: concentration (mol kg^{-1}).

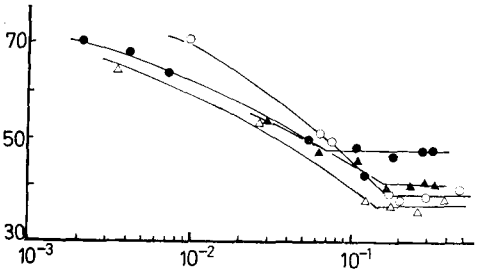

FIG. 3. Surface tension, σ (ordinate: mN m^{-1}), as a function of log molal concentration for ●, acebutolol HCl; ▲, oxprenolol HCl; ○, sotalol HCl and △, metoprolol tartrate in 0·5 mol kg^{-1} NaCl at 303K. Abscissa: concentration (mol kg^{-1}).

from the surface excess concentration, Γ, calculated using the Gibb's adsorption equation

$$\Gamma = -\frac{1}{x2{\cdot}303RT}\left[\frac{d\sigma}{d\log m}\right] \quad \ldots \quad (2)$$

x has a numerical value varying from 1 for ionic surfactants in dilute electrolyte-free solution to 2 for ionic surfactants in concentrated electrolyte-free solution (Pethica 1954). In view of the uncertainty in the value of x, calculations were made using x = 1. It is realized that these values (see Table 2) may underestimate the true area per molecule.

Table 2. Surface activity of β-blocking agents in water and 0·5 mol kg^{-1} NaCl

Compound	Solv.	cmc mol kg^{-1}	concn (mol kg^{-1} $\times 10^3$) for π = 10 mNm^{-1}	area per molecule m^2 $\times 10^{20}$
Propranolol HCl	H_2O	0·095	11	62
Oxprenolol HCl	H_2O	—	12	54
	NaCl	0·170	9	54
Acebutolol HCl	H_2O	0·170	20	51
	NaCl	0·070	11	51
Sotalol HCl	H_2O	—	30	42
	NaCl	0·180	25	35
Metoprolol tartrate	H_2O	—	5	57
	NaCl	0·140	7	44
Labetolol HCl	H_2O	—	3	51
Timolol maleate	H_2O	—	8	33

Inflections in the surface tension plots obtained in electrolyte-free solution were noted for acebutolol and propranolol indicating self-association (Fig. 2). The cmc value for propranolol was in reasonable agreement with the value (0·108 mol litre^{-1}) previously obtained by light scattering. (Elliott et al 1973).

The surface tension of several of these compounds has previously been reported and correlated with their local anaesthetic activity (Levy 1968; Hellenbrecht et al 1973). Some of the more recently introduced β-blocking agents including labetolol, acebutolol, timolol and metoprolol are not included in such studies and it is of interest to see how their surface tension correlates with their reported local anaesthetic potency. Many of the previously reported surface tension measurements were made in buffered solutions. In view of the effect which buffer components can have on the surface activity of drug molecules (Zografi & Zarenda 1966) it was necessary to repeat these measurements under standardized conditions so that comparisons of surface activity could be made. The differing curvatures of the surface tension plots of Figs 2 and 3 give rise to problems in comparing relative surface activity and indeed raise some doubts as to the validity of such comparisons. Thus sotalol, which causes an insignificant lowering of surface tension at concentrations <0·01 mol kg^{-1}, has an equivalent surface activity to propranolol at 0·1 mol kg^{-1}. In their study of correlations between surface activity and local anaesthetic potency, Hellenbrecht et al (1973) compared the drug concentrations required to produce a surface pressure, π (surface tension of solvent–surface tension of solution) of 10 mN m^{-1}. This procedure was adopted in this present investigation. The relative concentrations are given in Table 2.

A detailed comparison of the local anaesthetic potency of the more recent compounds is not available. Acebutolol has a reported activity of about one-fifth that of propranolol (Basil et al 1973). It is therefore less effective as a local anaesthetic than oxprenolol, which is about one half as active as propranolol (Vaughan Williams & Papp 1970), but much more active than sotalol which has a reported potency of 1/16 that of propranolol (Davis 1970). The relative surface activity of acebutolol is thus in the same ranking order as its local anaesthetic potency. Labetolol is reported to resemble propranolol in being a potent local anaesthetic (Farmer et al 1972). It is, however, much more surface active than propranolol and it is unfortunate that further details of its local anaesthetic potency are not available. Timolol and metoprolol are considered to be practically devoid of local anaesthetic activity (Dollery et al 1969; Åblad et al 1973) and hence might be expected to have a surface activity similar to that of sotalol. The surface activities of these compounds are however much higher than sotalol and this anomalous behaviour is due to the organic counterions associated with these compounds. It has been noted previously (Attwood & Udeala 1975b) that replacement of a simple inorganic counterion such as a Cl^- ion with an organic counterion such as a maleate ion causes a greatly increased surface activity. For example the antihistamine, tripelennamine will cause a lowering of the surface tension of water by 10 mN m^{-1} at a concentration of 0·01 mol kg^{-1} when present as the hydrochloride salt, whereas the same surface tension lowering is achieved by only 0·0025 mol kg^{-1} of this drug in the form of the maleate salt.

Fig. 3 shows the σ-log m plots in the presence of 0·5 mol kg^{-1} NaCl for those drugs which, from light scattering, were shown to associate in solution. Reasonable agreement between cmc values from the two techniques was obtained.

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