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COMMUNICATIONS

The constitution of zinc and cerium sulphadiazines in aqueous preparation

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In 1968 Fox introduced silver sulphadiazine (AgSD, sulphadiazine is present as anion) for topical burn therapy. In particular, *Pseudomonas aeruginosa* and other gram-negative bacteria wound infections were reduced by the 1% AgSD cream. In view of the sensitization caused by topical application of sulphanilamides there was initial hesitation in its use (Bleumink & Klokke 1971), but sensitization occurred in less than ten of more than 10 000 patients (Fox 1977). Most probably the polymeric character of AgSD and the very low water solubility (0·2 mg/100 ml) accounts for this low incidence of first reactions.

In 1976, Fox et al introduced zinc sulphadiazine ($Zn(SD)_2$), zinc being essential for wound healing and a normal body constituent, and the $Zn(SD)_2$, was as effective as AgSD in burn treatment while the water solubility was enhanced (56 mg/100 ml). Then Fox et al (1978) introduced cerium sulphadiazine ($Ce(SD)_3$) with a water solubility of 83 mg/100 ml. Combination of the Ag, Zn and Ce compounds resulted in a superior topical therapy.

The literature on zinc and cerium sulphadiazine does not give exhaustive directions for their preparation (the combining of the metal salt and sodium sulphadiazine) nor analytical data, and nothing is known about the structures of the compounds (Fox et al 1978, 1979). In the zinc sulphanilamide complexes described by Narang & Gupta (1976, 1977) the sulphanilamide molecule is present as a neutral ligand; the general composition is $Zn(HS)_2X_2$ (HS = sulphanilamide, X = Cl^-, acetate).

To elucidate the nature of the complexes, we have investigated the preparation of zinc and cerium sulphadiazine. We were unable to prepare compounds that fitted the expected analytical data for $Zn(SD)_2$ and $Ce(SD)_3$, the i.r. spectra of the compounds prepared being almost identical to the spectrum of free sulphadiazine (HSD). When substitution of the acidic proton of HSD by a metal ion occurs, as was anticipated with $Zn(SD)_2$ and $Ce(SD)_3$, the i.r. spectrum would be expected to change drastically. This was found with AgSD and $Cu(SD)_2$: e.g. ν (^{1}N-H) disappeared and ν(SO) shifted to lower cm^{-1} values: $\nu(SO)_{assym}$: $1326 \rightarrow 1232\ cm^{-1}$ and $\nu(SO)_{sym}$: $1155 \rightarrow 1130\ cm^{-1}$ (Bult et al 1978, 1979), but in the zinc and cerium compounds sulphadiazine is present in its neutral form (HSD) so we made a closer examination of the reaction products.

To a solution of 0·020 mol of sodium sulphadiazine in x ml of water (x = 30–80 ml), was added a solution of 0·010 mol of zinc nitrate 6 H_2O in x ml of water. The white precipitate was filtered off after 0·5 h, washed with 25 ml of water and dried for 5 h at 120 °C.

The analytical data when x = 40 ml were: Zn: 9·99% (theor: 11·60% for $Zn(SD)_2$), HSD: 76·22% (theor: 88·40%), Na as $NaNO_3$: 9·99%, acid consumption calculated as OH: 5·13%, mole ratio HSD/Zn: 2·01 and Na/Zn: 0·76. The total percentage found by analyses: 101·3%. At higher values of x the mol ratios HSD/ZN and Na/Zn are lowered, for x = 80 ml HSD/Zn = 1·71 and Na/Zn: 0·05. For each choice of x, the total percentages found by analyses were between 100–103%. Zn was analysed by complexometric titration, HSD amperometric titration (Coenegracht et al 1973), Na by flame photometry and acid consumption by decomposition of the compound with excess of 0·1 M HCl and potentiometric back titration with 0·1 M NaOH.

The zinc compounds are therefore composed of $Zn(OH)_2$ and HSD. HSD can be present in the form of a coordination compound with, or as a physical mixture with, $Zn(OH)_2$. The i.r. spectra gave no evidence of coordination—(ν ($^4NH_2$) is expected to shift upon coordination Narang & Gupta 1977). Where a physical mixture exists, HSD would be expected to be separated by solvent extraction and this was realized by soxhlet extraction with acetone. The extract consisted of HSD and the residue of a mixture of $Zn(OH)_2$ and $NaNO_3$. Similar results were found with cerium sulphadiazine, which therefore consists also of a physical mixture of $Ce(OH)_3$ and HSD. The presence of $NaNO_3$ in the compounds was caused by coprecipitation and was greatly reduced by dilution of the reaction volume (where x = 80 ml Na/Zn is 0·05).

The formation of the physical mixture can be explained by the reaction scheme:

$$NaSD + H_2O \leftrightarrows HSD\downarrow + NaOH$$
$$Zn(NO_3)_2 + 2NaOH \leftrightarrows Zn(OH)_2\downarrow + 2NaNO_3$$

The implications of the findings concerning zinc and cerium sulphadiazine are that in topical burn therapy these mixtures containing free sulphadiazine would be

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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

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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.

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