In this study, we found significant increases in time to arrhythmia in the treatments with amperozide, melperone and bretylium compared with saline, indicating an antiarrhythmic effect of approximately the same magnitude by the doses used in guinea-pigs against digoxin-induced arrhythmias. These drugs share class III antiarrhythmic properties. As for the treatments with thioridazine and lignocaine the time to arrhythmia was increased but did not reach statistical significance.

The results of the present in-vivo study are in agreement with the recent findings (Arlock, unpublished observations) that amperozide has antiarrhythmic properties, and thus warrants further investigation in other models.

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Letter to the Editor

Bioavailability of sustained release acetazolamide

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A paper presented at the 1985 British Pharmaceutical Conference compared the bioavailability of two formulations of acetazolamide (Diamox 250 mg tablets and Diamox Sustets 500 mg capsules) (Ledger-Scott & Hurst 1985). Based on 0–24 h concentrations of acetazolamide in plasma after single doses, the authors concluded that the sustained release product was absorbed only 50% compared with the tablet. I would like to present a different interpretation of the reported information based on unique properties of acetazolamide.

Pharmacokinetic studies of drugs usually employ plasma concentration determinations to characterize the rate and extent of absorption of an administered dose. It is implied by this usage that a linear relationship exists between plasma values and concentrations of the drug in whole blood, the latter being a more definitive measurement of amounts absorbed. For acetazolamide, or any of the unsubstituted aromatic sulphonamides, this relationship does not hold because of a preferential uptake of these drugs by red blood cells (Maren 1967; Lehmann et al 1969; Wallace & Riegelman 1977). This phenomenon is well documented as due to an association of the drug with carbonic anhydrase to form an enzyme-inhibitor complex. What has apparently not been addressed, however, is the effect of this phenomenon on a comparison of two formulations having differing rates of absorption.

Lehmann et al (1969) have reported the mean concentrations of the two carbonic anhydrase isoenzymes in human red cells and their acetazolamide dissociation constants and used these values to describe the overall distribution of acetazolamide in the body. Using the Lehmann values, the concentration of acetazolamide in red cells in equilibrium with plasma can be determined as:

$$C_{rbc} = C_f + \frac{C_f \times C_{m(b)}}{K_b + C_f} + \frac{C_f \times C_{m(c)}}{K_c + C_f} \qquad (1)$$

where: C_{rbc} is the concentration in red blood cells, C_f is the concentration of free (unbound) acetazolamide in plasma, $C_{m(b)}$ and $C_{m(c)}$ are the maximum concentrations of acetazolamide which can be bound to carbonic anhydrases B and C (136 μm ml^{-1} and 20 μm ml^{-1},

respectively), K_b and K_c are the dissociation constants of acetazolamide-carbonic anhydrases B and C (1 and 0·1 μM), respectively.

Using this method of calculation, a plot of plasma concentration versus red blood cell concentration was derived which matched the experimentally determined curve reported by Wallace & Riegelman (1977) over the concentration range 0 to 10 μg ml^{-1}, acetazolamide in plasma when a protein binding value of 93% (Shah et al 1974) was used. Above 10 μg ml^{-1} red cell values rose more rapidly than predicted by the formula presumably because of a decrease in the degree of plasma protein binding with higher concentrations. The concentration of acetazolamide in whole blood may be determined as:

$$C_b = C_{rbc} \times H + C_p \times (1\text{-}H) \qquad (2)$$

where: C_b is the concentration in whole blood, C_p is the concentration in plasma, H is the relative packed red blood cell volume (haematocrit).

Although sufficiently detailed data were not included in the Ledger-Scott & Hurst (1985) paper to make the determination of whole blood concentrations, a report was issued a few years ago (Schoenwald et al 1978) which did provide such data. This study employed 18 subjects in a crossover comparison of three formulations, two of which were identical (or nearly so) with the formulations under consideration. The two studies differed in that the earlier one involved two doses of the 250 mg tablet 4 h apart whereas the new study compares single doses of each formulation. The two studies demonstrated similar peak concentrations, times to peak and areas under plasma concentration-time curves when corrections are made for the dosage difference of the tablet. The authors of the earlier study arrived at the same conclusion that the sustained release formulation was not as bioavailable as the rapidly released tablet. They claimed a 64% availability as compared with a 50% availability reported in the more recent study. The 1978 study contained data over a 36 h rather than 24 h period. Had it stopped at the 25 h sampling time, the conclusion to be drawn would have been 53% available compared with the tablet rather than that reported (64%).

Table 1. Mean concentrations of acetazolamide in the plasma (Schoenwald et al 1978) and calculated concentrations in the whole blood of 18 subjects receiving either 2–250 mg Diamox tablets or 1–500 mg Diamox Sequel*.

	Acetazolamide concentrations expressed in μg ml^{-1} after:			
	Diamox 250 mg tablets		Diamox Sequels 500 mg	
Time (h)	Plasma	Whole blood	Plasma	Whole blood
1	13·57	20·79	3·35	10·72
2	11·18	18·96	5·02	13·08
4	7·30	15·58	7·04	15·32
6	14·23	29·87	6·80	15·08
8	15·09	21·89	5·79	14·00
11	10·51	18·43	4·82	12·83
21	3·13	10·36	2·71	9·60
25	2·18	8·53	2·64	9·47
30	1·35	6·45	2·25	8·68
36	0·89	4·96	1·87	7·82
$AUC†_{0-25}$	205·7	387·3	108·6	295·6
$AUC†_{0-36}$	221·3	458·7	120·8	390·6

* Diamox Sequel, the product name used for sustained release capsules in the USA have almost the identical composition as Diamox Sustets, the product name used in the UK.

† AUC = Area under the concentration-time curve.

Using the calculations described above, with K_b = 0·22 μg ml^{-1}, K_c = 0·022 μg ml^{-1}, $C_{m(b)}$ = 30 μg ml^{-1}, $C_{m(c)}$ = 4·4 μg ml^{-1} (Lehmann et al 1969) along with 93% plasma protein binding and a haematocrit of 0·45, the data of this study are shown in Table 1 in which a comparison of 0–36 h areas under the whole blood concentration-time curves indicates similar absorptions for the two formulations. Extrapolation of the blood level curves to infinity would lead to even closer correspondence since concentrations of acetazolamide were higher for the sustained release product than for the tablet at the last sampling time. On the other hand, the comparison of plasma concentration-time curves for the two preparations will never indicate equivalence even after extrapolation to infinity.

It can be concluded that the pharmacokinetics of acetazolamide cannot be determined using only plasma concentrations after single oral dosage. In addition, one cannot evaluate the bioavailability of a sustained release acetazolamide product without regard for the non-linear plasma to blood concentration relationship. This led to the inappropriately designed comparison of the sustained release products with the rapid-release formulation by Ledger-Scott & Hurst (1985).

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