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LACK OF EVIDENCE FOR POLYMORPHISM IN METOPROLOL METABOLISM

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The claim for polymorphism in the metabolism of metoprolol is based on a logical fallacy. A frequency distribution of metoprolol AUC data is presented and, although highly skewed, no evidence of more than a single population is apparent. Plasma and urine metoprolol and metabolite data are also presented to support this.

Keywords polymorphism metoprolol α-hydroxymetoprolol

Introduction

The phenomenon of polymorphism in the metabolism of a number of drugs is now well documented and, although still somewhat of a rarity, the number of examples is growing slowly (Sloan *et al.*, 1978; Eichelbaum *et al.*, 1979). Recently there have been several reports describing poor metabolisers of metoprolol and an attempt has been made to establish a correlation between the metabolism of metoprolol and debrisoquine. In a study on eight volunteers Lennard *et al.* (1982a) were able to demonstrate that subjects phenotyped as poor metabolisers of debrisoquine displayed greater AUC values of metoprolol than the corresponding extensive metabolisers of debrisoquine. The authors took this as being evidence of a polymorphism in metoprolol metabolism and, in a more recent study (Lennard *et al.*, 1982b), have reiterated this claiming in addition that this 'oxidation phenotype' is a major factor in determining the metabolism of and response to metoprolol.

Setting aside, for the moment, our belief that their claim for metoprolol polymorphism is logically fallacious it is difficult to accept the argument that the pathway shared by debrisoquine and metoprolol, namely alicyclic hydroxylation, is critical in the case of the latter drug. Hydroxylation, although the major metabolic pathway for debrisoquine, accounts for only 10% of the dose eliminated in the urine following oral metoprolol. The major metabolic route for metoprolol is *o*-demethylation followed by oxidation to a carboxylic acid, H 117/04 (Borg *et al.*, 1975); even if the conversion to α-hydroxymetoprolol were shown to be polymorphic this would be relatively insignificant in determining the overall elimination of metoprolol. Lennard and his colleagues acknowledge this difficulty (1982b) but assert that the other pathways *must* be under genetic influence to explain their findings. We wish to present here data we have collected showing that there is no evidence that the overall elimination of metoprolol is polymorphic.

Methods

Metoprolol and α-hydroxymetoprolol plasma and urine concentrations together with urine concentrations of the major, but pharmacologically inactive metabolite H 117/04 have been measured after administration of a single oral dose of 100 mg metoprolol as a film-coated tablet (Lopresor®) to eight young, healthy volunteers. We have also collected metoprolol AUC data in 113 young, healthy subjects following a single 100 mg oral dose of the film-coated tablet: this data is from our own published work and the published papers and research reports of others (Regårdh *et al.*, 1975; Kendall *et al.*, 1977; Melander *et al.*, 1977; Quarterman *et al.*, 1979; Kendall *et al.*, 1980; Quarterman *et al.*, 1981; Jack *et al.*, 1982b). Similar data on acebutolol following a single oral dose of 400 mg (Sectral®) in 34 young, healthy volunteers have also been collected for comparison since this drug is eliminated by a different pathway and no suggestion of polymorphism has ever been made (Gulaid *et al.*, 1981; Jack *et al.*, 1982a,b).

Results

The data relating to plasma and urine concentrations of metoprolol and its metabolites are presented in Table 1. The mean values calculated from this data

Table 1 Metoprolol (M), α-hydroxymetoprolol (αHM) and major metabolite (H 117/04) data in eight young, healthy volunteers following a single 100 mg oral dose of the film-coated tablet.

	Plasma AUC (ng ml⁻¹ h)		*Half-life (h)*	*Urine ratio*	
Volunteer	*M*	*αHM*	*M*	*M/αHM*	*M/H 117/04*
1	1426	698	3.6	0.76	0.13
2	1789	544	6.2	20.21	0.13
3	573	614	3.7	0.38	0.12
4	391	807	4.3	0.37	0.06
5	1084	662	3.8	0.83	0.14
6	358	933	3.4	0.14	0.03
7	516	554	3.9	0.53	0.10
8	361	514	4.6	0.38	0.11

have been published previously (Quarterman *et al.*, 1981). Of the eight volunteers studied only one would be classified by Lennard *et al.* (1982a,b) as a poor metaboliser: this is subject 2 with a metoprolol/α-hydroxymetoprolol urine ratio of 20.21 and an elimination half-life of 6.2 h. There is, however, nothing else to distinguish this volunteer from the others and the plasma metoprolol and α-hydroxymetoprolol AUC values and urinary metoprolol/H117/04 ratios are very similar to subject 1 who would be classified as an extensive metaboliser. In addition there is no correlation between metoprolol and α-hydroxymetoprolol AUC values ($r = -0.30$).

The frequency distributions of the metoprolol and acebutolol AUC data are presented in Figure 1 and, although the metoprolol data are highly skewed in contrast to the normally distributed acebutolol data, there is no evidence of two populations.

Discussion

The argument put forward by the protagonists of metoprolol polymorphism may be summed up as follows: poor metabolisers of debrisoquine display larger metoprolol AUC values than do extensive metabolisers therefore, since debrisoquine exhibits polymorphism, the metabolism of metoprolol must also be polymorphic. This is a fallacious argument which can be refuted on the grounds of logic alone. There may, of course, be a relationship between metoprolol and debrisoquine metabolism but the exact nature of this is, as yet unclear. Our data in eight young, healthy volunteers give no grounds for the claim that polymorphism is a major determinant of the metabolism of metoprolol. It is certainly a possibility that the metabolic pathway leading to α-hydroxymetoprolol may be under genetic control but this has yet to be established in a group of reasonable size. Even if this pathway were genetically controlled its overall contribution to elimination is likely to be small.

We believe we are justified in using AUC data from our own studies and from those of others since we have collected only data from single dose studies of the film-coated tablet and metoprolol is well absorbed following oral administration (Regårdh & Johnsson, 1980). Although we ourselves have shown that females taking an oral contraceptive have significantly greater AUC values than control females (Kendall *et al.*,

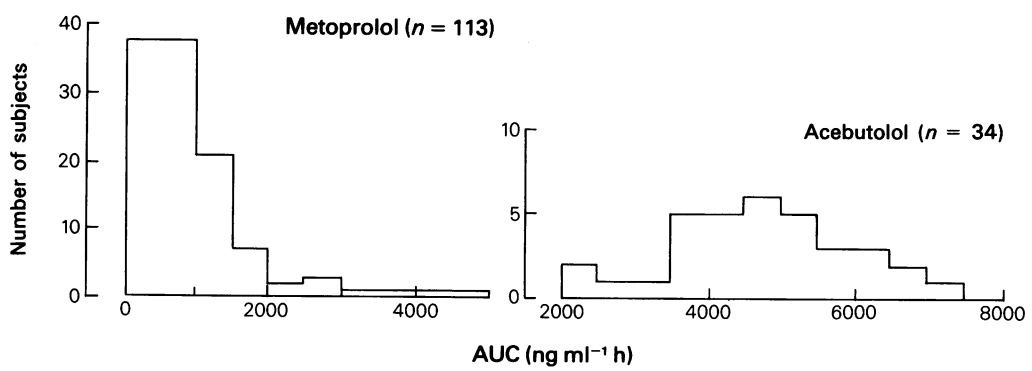

Figure 1 Frequency histogram for area under the curve values.

1982) we believe that the grouping of the data in intervals of 500 ng ml^{-1} h reduces any effect this phenomenon is likely to have. If the frequency of poor metabolisers of debrisoquine is about 9% of the population (Shah *et al.*, 1982) we would expect about 10 poor metabolisers of metoprolol in our population, assuming a similar frequency. Although, as we have seen, the distribution was highly skewed no distinct sub-group was apparent.

Skewed distributions such as this are not new: Koch-Weser (1981) has discussed this phenomenon and noted that drugs such as phenytoin, hydralazine, phenothiazines, tricyclic antidepressants and others all show wide variations in blood drug concentrations following fixed doses in different individuals. Indeed our own work on the inter- and intra-subject variability of β-adrenoceptor blocker pharmacokinetics suggests that the AUC distribution of propranolol is also highly skewed (Jack *et al.*, 1982b).

Although it is possible to claim that AUC values alone may not reveal polymorphism if a decreased conversion to α-hydroxymetoprolol were compensated for by an increased metabolism to the dealkylated compound, H 117/04, examination of the data in Table 1 does not support this. Admittedly the data are from only eight volunteers but this is exactly the number used by Lennard *et al.* (1982a) to put forward their original claim for metoprolol polymorphism. Also we must emphasise again that conversion to α-hydroxymetoprolol accounts for only 10% of the administered dose. What is needed is a study of metoprolol and its metabolites in a larger number of subjects and, until this is done, it would surely be prudent to refrain from claims of polymorphism.

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