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ATENOLOL ELIMINATION IN THE NEONATE

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1 The elimination of the cardioselective β-adrenoceptor antagonist atenolol has been studied in 35 neonates by measuring drug concentration in cord blood and in blood obtained at 24 h by heel stab.

2 Elimination rate was assessed by calculating the slopes of lines joining these two concentration points.

3 The slopes had a mean of 0.043 h^{-1} (equivalent to a half-life of 16 h) and were normally distributed with 95% of values being in the range 0.02–0.066.

4 There was no relationship between slope and neonatal weight or skinfold thickness, but most babies were at term and the range of these indices was narrow.

5 Babies who developed a bradycardia had cord atenolol concentrations and slopes which did not differ significantly from those in babies without bradycardia.

6 We conclude that atenolol elimination in the neonate is reduced when compared to adults. This prolonged elimination is consistent with the physiological characteristics of this age group and with previous observations on drugs eliminated by renal excretion.

Keywords atenolol neonate elimination

Introduction

It is now well recognised that drug disposition in the first few weeks of life often differs substantially from that seen in the adult (Assael, 1982). Differences in body composition and immaturity of drug elimination pathways are largely responsible for these changes in disposition. In the full term neonate plasma proteins are qualitatively and quantitatively different to the adult (Wallace, 1977), water constitutes a greater proportion of body weight (Friis-Hansen, 1961; Maclaurin, 1966) and both glomerular filtration and liver metabolism are reduced (Aperia *et al.*, 1981; Short *et al.*, 1976). The major consequence of these differences is that drugs are generally eliminated more slowly in the neonate compared to the adult. Preterm babies tend to show more exaggerated changes in drug elimination (Morselli & Thiercelin, 1983). We have recently reported the results of a study designed to assess the possible role of atenolol in women with pregnancy associated hypertension (Rubin *et al.*, 1983). The neonatal assessment which this study involved presented an opportunity to gain information on the elimination of atenolol from the neonate and to investigate whether certain factors could influence the rate of elimination.

Methods

The study protocol was approved by the Research and Ethical Committee of the Glasgow Northern District and has been described in detail elsewhere (Rubin *et al.*, 1983). One hundred and twenty women with pregnancy associated hypertension were randomly allocated in double-blind manner to treatment with atenolol or placebo. The dose of atenolol was initially 100 mg/day and was increased to 200 mg/day if blood pressure control was inadequate, but no other drugs were used. Blood for atenolol analysis was obtained at the time of delivery (mixed cord blood) and 24 h following birth when 0.5 ml was collected from the babies by heel stab. All samples were subsequently stored at −70°C and analysed within 4 months using the high pressure liquid chromatography assay of atenolol in whole blood as previously described (Yee *et al.*, 1979). In our laboratory this method has a lower limit of sensitivity of 10 ng ml^{-1} with a coefficient of variation which did not exceed 10% over the concentration range observed in these studies. In order to maintain the double-blind nature of the study, laboratory staff did not disclose the results of the atenolol determinations to the investigators until the trial had been completed.

All babies were admitted for at least 24 h to the special care unit and had a detailed clinical examination in addition to extensive biochemical and haemodynamic monitoring.

Data analysis

The cord blood atenolol concentration represents the concentration of drug in the baby's blood at the beginning of extrauterine life. The difference between this concentration and that at 24 h provides an indication of the rate at which atenolol is being eliminated from the baby. For ease of presentation and analysis the slope (h^{-1}) of the line joining each of these points was calculated by linear regression. Relationships were then sought using multiple regression analysis between the rate at which atenolol concentration declined and neonatal weight, triceps skinfold thickness and subscapular skinfold thickness. Data are presented as mean ± s.d. and statistical comparisons are by unpaired, two tailed *t*-test.

Results

Among the 60 women who received atenolol, five were withdrawn from the study before delivery and one had an intrauterine death. In another 20 either cord or neonatal blood were not obtained. The remaining 34 women gave birth to 35 babies (one set of twins). The cord and 24 h atenolol concentrations are shown in Figure 1 and a histogram showing the distribution of the slopes of lines joining these points is shown in Figure 2. The slopes had a mean of 0.043 h^{-1} and were normally distributed. Expressed in terms of half-life, the mean was 16.1 h and 95% of values were in the range: 10.5–34.6 h.

The regression of slope on neonatal weight and skinfold thickness (both triceps and subscapular) as assessed by multiple regression analysis demonstrated that these three variables accounted for only 23% of the variance in slope. The relationship was:

$$y = 0.039 - 0.006x_1 + 0.024x_2 - 0.017x_3$$

where y = slope, x_1 = neonatal weight and x_2 and x_3 = triceps and subscapular skinfold thickness respectively.

Fourteen babies whose mothers had received atenolol developed a heart rate below 120 beats min, though this was usually transient and in no case required pharmacological intervention. Twenty one babies from the atenolol group had no bradycardia. The cord blood atenolol concentrations were the same in each of these groups: 129 ± 69 ng ml^{-1} in those babies who developed bradycardia and 124 ± 97 ng ml^{-1} in those who did not ($P > 0.8$). However, there was a tendency for the drug to be eliminated more slowly in the group who developed a bradycardia: the

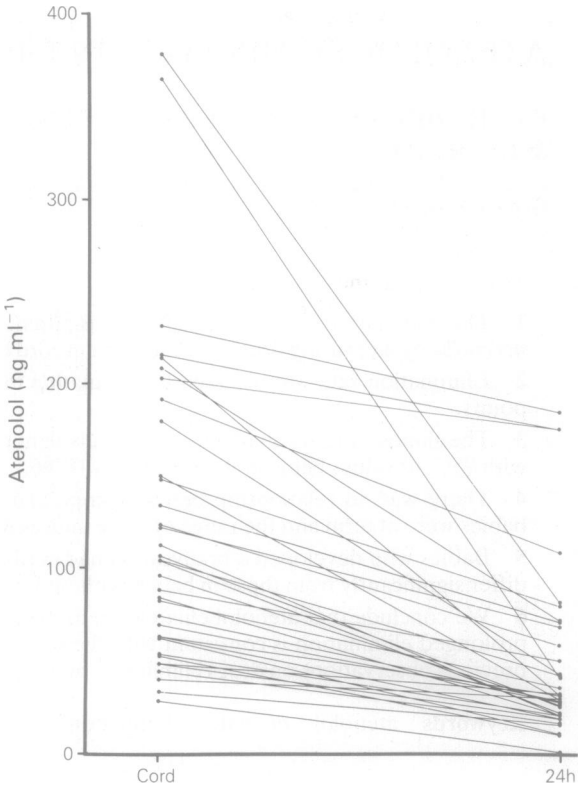

Figure 1 Atenolol concentration (ng ml^{-1}) in cord blood and in neonatal blood 24 h following delivery. Data points from the same individual are joined for ease of interpretation.

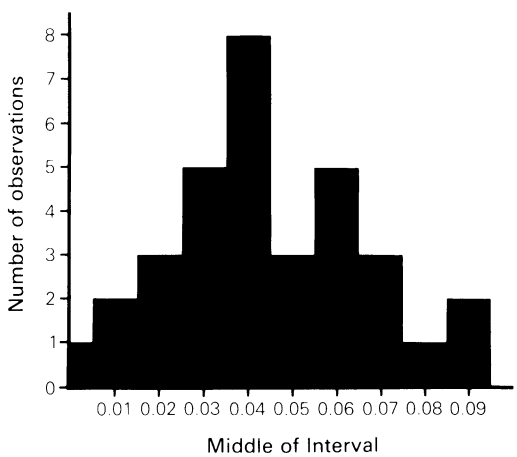

Figure 2 Histogram of slopes of lines connecting concentrations at $t = 0$ and $t = 24$. The distribution was found not to differ significantly from a normal distribution when tested by Chi squared ($\chi^2 = 1.22$, d.f. = 4, $P > 0.8$).

slope of atenolol disappearance was 0.0348 ± 0.0212 in the babies with bradycardia and 0.0485 ± 0.0226 in those without ($P < 0.08$).

Discussion

Pharmacokinetic studies in the neonate are difficult for obvious practical reasons. When a drug is being administered regularly and parenterally it is possible to estimate clearance from a knowledge of steady state concentrations (Thomson *et al.*, 1983). However, in this study we were able to observe only the decline in atenolol concentration following delivery and only one blood sample was obtained from each baby except in two cases where additional samples were drawn for further electrolyte determination. While this limits the extent of data interpretation which is possible, a useful estimate of the rate at which atenolol is eliminated from the neonate can nonetheless be obtained.

Atenolol is a hydrophilic drug which is excreted largely unchanged by the kidney. In healthy young adults its elimination half-life has been reported to be in the 3–8 h range (Mason *et al.*, 1979; Rubin *et al.*, 1982). The range of elimination rates which we observed in the neonates was therefore approximately 4 times slower than in the adult. This delayed excretion was expected and is consistent with the differences between neonatal and adult elimination rates observed for other drugs which are excreted mainly by the kidney (Morselli & Thiercelin, 1983). It is assumed that immaturity of renal function is primarily responsible for these differences although an increased volume of distribution in the neonate could also be a contributing factor.

There is only limited information available on the disposition of β-adrenoceptor blockers in the human neonate. Metoprolol and propranolol, which undergo liver metabolism, have also been found to have delayed elimination in the neonate (Cottrill *et al.*, 1977; Lundborg *et al.*, 1981). However, the blood concentration of both metoprolol and propranolol actually appeared to rise in the first few hours of life before beginning to decline. Only two of the babies in our study had blood sampling at an intermediate time point and they showed a progressive decline with time.

There was no correlation between neonatal weight, skinfold thickness and rate of atenolol elimination. Since weight and skinfold thickness are indication of maturity, this lack of correlation might seem surprising. However, all except five of these babies had a gestational age at or above 38 weeks and the range of maturity being assessed was consequently rather narrow. The spectrum of elimination rate constants was normally distributed (Figure 2) and the approximate threefold variation from lowest to highest is very similar to that seen in the adult (Mason *et al.*, 1979; Rubin *et al.*, 1982). Since none of these babies was seriously ill (Rubin *et al.*, 1983) it can be inferred that the range of elimination rates seen in this study simply reflects the normal variation seen in the human, scaled down to neonatal proportions. We are therefore unable to comment on the possible influence of prematurity or major neonatal pathology on atenolol elimination. Interestingly, the rate of elimination of atenolol in two babies was in the range normally seen in young adults. However, there were no characteristics with respect to gestation, general state of health or cord atenolol concentrations which could differentiate these babies from the remainder.

There was no apparent relationship between atenolol concentration in cord blood and subsequent development of bradycardia. The rate of drug elimination tended to be slower in those babies who developed a bradycardia but the difference failed to achieve significance at the 5% level. It is likely that the influence of atenolol on heart rate in the neonate, as in the adult, will be the result of a combination of pharmacokinetic and pharmacodynamic factors.

In conclusion, we have demonstrated that the elimination of atenolol in neonates at term is delayed in a manner which would be expected on the basis of the known physiological characteristics of this age group.

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