production in each group as a result of stimulation with PGE_1. Maximum mean increases, again at 10^{-5} M were 16.8 ± 2.2 and 11.2 ± 1.3 pmol cyclic AMP/10^6 cells in the young and elderly people respectively ($P < 0.05$).

The mean increase over baseline produced by isoprenaline 10^{-6} M was 8.3 ± 1.4 pmol/10^6 cells in the young group and 4.3 ± 0.7 pmol/10^6 cells in the elderly group ($P < 0.001$). No sex differences were observed in either group in any of the studies.

A striking feature of this study was the markedly lower cyclic AMP production by lymphocytes from elderly people in the absence of any stimulation. Previous findings (Dillon *et al.*, 1980) suggested this but the differences in that study were not statistically significant. Stimulation of cyclic AMP production by isoprenaline 10^{-6}M gave similar results to those reported previously by us (Dillon *et al.*, 1980).

Our results also clearly demonstrate a decrease in lymphocyte adenylate cyclase system responsiveness to PGE_1 in the elderly. The differences appear larger when absolute values of cyclic AMP production are plotted (Figure 1), because of a difference in baseline responsiveness. However, the differences in baselines are effectively corrected for when *increases* in cyclic AMP production are presented and here again lymphocytes from old people showed a decreased cyclic AMP response (Figure 2).

What are the implications of the present findings for cyclic AMP mediated responses? If a particular physiological response depends on a critical intracellular concentration of cyclic AMP being reached or on a critical increment in cyclic AMP over baseline, then cells from elderly people would be expected to demonstrate a reduced responsiveness to PGE_1. This would be in keeping with previous findings of decreased responsiveness of tissues to β-adrenoceptor induced adenylate cyclase stimulation. However, stimulation of adenylate cyclase by PGE_1 is independent of the β-adrenoceptor (Bourne & Melmon, 1971). Thus there is a decreased response to two different stimulating agents acting on different primary receptors. These results suggest that a possible basis for the age related alteration in lymphocyte cyclic AMP responsiveness is the translation of the receptor-drug interaction into an effect. This could occur either at the level of the regulatory proteins or as a result of qualitative or quantitative alterations in adenylate cyclase. An attractive hypothesis would be that alterations in cell membrane structure in old age (Kohn, 1978) have a restricting effect on one or more of these systems.

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DISPOSITION OF METOPROLOL IN THE NEWBORN

The use of β-adrenoceptor blockers in the treatment of hypertension during pregnancy, either alone or in combination with hydralazine, has received increasing attention over the last few years. Among factors adding to this interest are the documented good tolerance to β-adrenoceptor blockers in the treatment of hypertension, increasing experience with β-adrenoceptor blocker treatment during pregnancy

without alarming adverse effects and the availability of relatively β_1-adrenoceptor selective blockers which have very little pharmacological effect on the uterus.

β-adrenoceptor blockers have been shown to pass the placental membranes and exist in an equilibrium between maternal blood and foetal blood in the steady-state situation (Cottrill *et al.*, 1977; Melander *et al.*, 1978; Sandström, 1978; Bianchetti *et al.*, 1981). With the β_1-adrenoceptor selective blocker metoprolol, Sandström (1978) has recently reported a significant correlation at birth between drug concentrations in maternal blood and cord blood after prenatal treatment of hypertensive mothers with metoprolol.

This report is here followed up with studies on the fate of metoprolol in the newborn child. For this purpose a selective and highly sensitive method for the determination of metoprolol in small blood samples has been developed.

The study, which was approved by the Ethical Committee of the Örebro region, initially included eight women and was later extended to a second group of nine women. They had all been treated with metoprolol, 50–100 mg twice daily. The children were in general delivered in the 38th gestational week. All the mothers gave oral informed consent to the study.

Immediately after delivery 10 ml blood samples were taken from the mother's ante-cubital vein and from the cord (mixed cord blood) for the analysis of metoprolol in plasma.

In addition, at 2 h, 5 h and 20 h after birth a 100 μl sample of capillary blood was taken from the heel of the child. Variations in this schedule were sometimes necessary because of practical clinical problems. The blood was immediately transferred into preweighed test tubes containing 10 ml of 0.9% saline. The tubes were then weighed again and stored at −20°C until analysis.

The cord and maternal blood was analysed for metoprolol content by the method of Ervik (1975). The capillary blood samples from the infants were analysed for metoprolol by means of a selective and sensitive method based on gas chromatography and mass spectrometry (Ervik, unpublished observations).

A significant correlation ($P < 0.001$) was found between metoprolol levels in plasma from maternal and cord blood (Figure 1). In 5 of the 17 cases (mother + child) no metoprolol was found in either the maternal or the umbilical plasma. An additional group of 8 cases had levels below 50 nmol/l. In three cases the plasma levels were above 200 nmol/l.

Blood levels of metoprolol during the first postnatal day are shown in Figure 2. In two infants with measurable levels in the umbilical plasma, no metoprolol was found in the blood samples taken 2–3 h after birth. In all other infants an increase in metoprolol concentrations was observed. All five infants with unmeasurable levels in the umbilical plasma showed significant blood levels 3–5 h after birth, in one case as high as 755 nmol/l and 820 nmol/l after 2 and 5 h, respectively. In the remaining infants the metoprolol levels increased up to fourfold over the first 2–5 h, in general followed by a gradual decrease over the following 15 h.

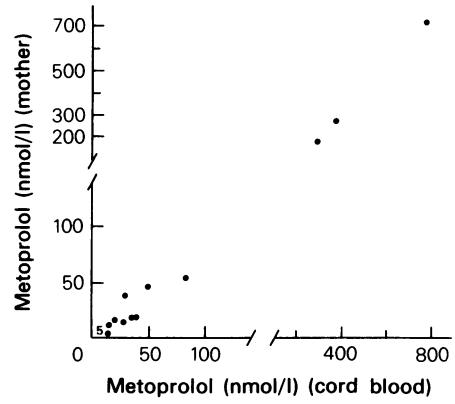

Figure 1 Concentration of metoprolol in maternal and umbilical plasma. Note that the upper portion of each scale is contracted. $n = 17$, $r = 0.995$, $P < 0.001$. Zero values, $n = 5$.

The aim of this investigation was primarily to study the rate of elimination of metoprolol in the newborn infant. A decreased elimination rate as compared to adult values was expected, because of the relative immaturity of the newborn liver and the fact that in adults metoprolol is eliminated exclusively by hepatic metabolism (Regardh *et al.*, 1974).

Although an elimination process must be present

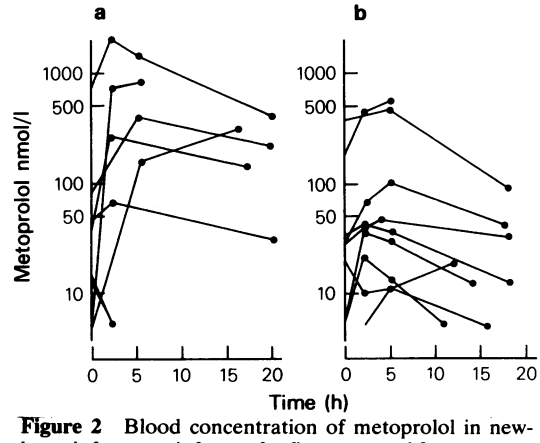

Figure 2 Blood concentration of metoprolol in newborn infants. **a**, infants of a first group of 8 women; **b**, infants of a second group of 9 women. 0 time indicates concentration of metoprolol in umbilical plasma at the time of birth.

during the first postnatal day, as indicated by the decrease in metoprolol levels between 5 and 20 h, this process might be partly masked by another process, tending to increase the blood levels of metoprolol during the first postnatal hours.

Our tentative explanation for this phenomenon is a redistribution of metoprolol from various tissue sites as a consequence of the dramatic haemodynamic changes occuring at birth. Transfusion of blood from the placenta may also, to a small extent, contribute since it increases the total amount of metoprolol present in the child.

The fact that plasma was used for cord blood analysis and whole blood for the subsequent analysis is probably of minor significance, since the distribution of metoprolol between erythrocytes and plasma has been found to be 1:1.

The phenomenon observed does not seem to be unique for metoprolol since a similar tendency has been described in one case after treatment of the pregnant mother with propranolol (Cottrill *et al.*, 1977).

Hence, pharmacologically significant blood levels of metoprolol occur during the early postnatal period in infants of mothers treated with metoprolol. No adverse effects of β-adrenoceptor blockade as measured by means of the Apgar score, or the production of neonatal bradycardia or symptoms of hypoglycaemia were observed over the first 24 h.

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A PHARMACOKINETIC COMPARISON BETWEEN DIFFERENT SLOW-RELEASE FORMULATIONS OF METOPROLOL (LOPRESOR SR AND BETALOC SA)

Two slow-release formulations of metoprolol tartrate (Lopresor SR, Ciba-Geigy Pharmaceuticals & Betaloc SA, Astra) are currently marketed in the United Kingdom for once-daily treatment of hypertension and angina. Although both forms have been evaluated against conventional metoprolol in clinical and volunteer studies, no direct comparison of the two slow-release dosage forms has been reported. We present here the results of such a study in which plasma level profiles were measured following single oral administration of 200 mg metoprolol tartrate in the form of Lopresor SR and Betaloc SA tablets to six healthy volunteers.

The volunteers were aged 25–48 years and their weights ranged from 62–82 kg. Each volunteer agreed not to take any other medication for 8 days prior to, and during the study period. They were given single doses of 200 mg metoprolol tartrate in the form of Lopresor SR tablets (Batch No. 04/992/2) and Betaloc SA/Selokeen tablets (Batch No. 7504.78D 11) on two separate occasions. The tablets were administered in random order with 1 week between treatments. Each dose of metoprolol was administered with 100 ml of water following an overnight fast. Light standardised meals were given at 2 and 4 h after dosing.

Blood samples (10 ml) for drug estimation were drawn immediately before and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. The samples were heparinised and centrifuged immediately. The plasma was collected and stored at −20°C until analysed. Metoprolol was estimated using a double radio-isotope derivative (DRID) technique which is capable of detecting drug concen-