studies aimed at elucidating the clearance kinetics of metronidazole and its major metabolites.

Such studies have been performed, and will be reported in a subsequent publication.

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A STUDY OF THE TRANSFER OF α-METHYLDOPA TO THE HUMAN FOETUS AND NEWBORN INFANT

Methyldopa (Aldomet) has been used for many years for the treatment of hypertension and the main features of its disposition and metabolism in normal and hypertensive adults have been established (Buhs, Beck, Speth, Smith, Trenner, Cannon & Laragh, 1964; Au, Dring, Grahame-Smith, Isaac & Williams, 1972). This antihypertensive agent has also been used for the control of hypertension in pregnancy (Redman, Beilin, Bonnas & Ounsted, 1976), but there appear to be no reports indicating the extent of placental transfer of methyldopa to the foetus or of the levels in the milk of mothers receiving this drug.

This letter describes the results of preliminary studies conducted around the time of delivery, of the concentration of methyldopa in maternal and foetal blood, amniotic fluid and early milk samples from women who have received treatment with the drug during their pregnancy. These investigations were carried out with the approval of the Northwick Park Hospital Ethical Committee and under its rules.

Samples of blood, amniotic fluid and milk were obtained from pregnant women who had received continuous treatment with methyldopa for at least 4 weeks to the time of delivery; the doses ranged from 0.75–2.0 g per day. Maternal and umbilical cord blood samples (10 ml) were collected into heparinized tubes at delivery. The plasma was separated, and after the addition of sodium metabisulphite (0.5 mg/ml), the samples were kept at −20°C until analysed. Samples of amniotic fluid were treated in the same way as plasma. Milk samples, collected between 30 and 60 h after delivery, from three women, were analysed on the day of collection when possible, or refrigerated at +4°C overnight.

The concentration of free and conjugated methyldopa in these fluids was determined with a fluorimetric method of assay essentially the same as that described by Kwan, Foltz, Breault, Baer & Totaro (1976). No blank samples of these fluids were available, but a correction for background fluorescence was made as described by Saavedra, Reid, Jordan, Rawlins & Dollery (1975). The milk was analysed in the same way as plasma except that at the protein precipitation stage, the solution was shaken with 10 ml of ether before centrifuging, to remove lipids. Fluorimetric measurements were made at 330 nm activating and 380 nm emission wavelengths.

Table 1 The concentration of free (F) and conjugated (C) α-methyldopa in maternal plasma at delivery, umbilical cord plasma, amniotic fluid and milk

Patient	*Dose (mg)*	*Time of delivery (h after last dose)*	*α-Methyldopa concentration (μg/ml)*							
			Maternal plasma		*Cord plasma*		*Amniotic fluid*		*Milk**	
			F	*C*	*F*	*C*	*F*	*C*	*F*	*C*
1	500/12 h	14	0.31	0.40	0.43	0.38	–	–	–	–
2	250/8 h	2	0.20	0.30	0.2	0.2	–	–	–	–
3	250/8 h	7	0.72	0.44	1.0	0.5	0.4	1.2	–	–
4	250/8 h	7	0.3	0.5	0.3	0.2	0.4	1.0	–	–
5	250/6 h	6	0.66	0.75	0.87	0.50	0.82	1.34	0.1	0.7
			–	–	–	–	–	–	0.1	0.4
			–	–	–	–	–	–	0	0.3
			–	–	–	–	–	–	0	0.2
6	250/8 h	15	0.08	0.12	0.13	0.12	–	–	0	>0.1
7	250/8 h	2	0.24	0.21	0.41	0.24	–	–	0.1	0.15
8	250/8 h	8	1.2	1.2	1.26	1.39	–	–	–	–
9	500/6 h	4	0.7	0.6	0.80	0.50†	0.9	2.7	–	–
					0.50	0.40				
10	250/8 h	10	0.70	1.30	1.30	1.40	–	–	–	–
11	500/6 h	12	0.2	0.50	0.5	0.3	0.7	1.8	0.2	0.9
12	250/6 h	5	0.34	0.11	0.18	0.10	0.1	0.1	–	–

* Collected between 30 and 60 h after delivery; dosage continued unchanged during this period.
† Venous and arterial cord blood respectively.

The results detailed in Table 1 show the methyldopa concentration in the maternal and umbilical cord plasma to be similar in almost all cases and also the ratios of free to conjugated drug do not differ markedly.

The total methyldopa concentration in the amniotic fluid samples examined was, with one exception, higher than the corresponding plasma concentration and the proportion of the drug which was conjugated was also higher than in the plasma.

The levels of methyldopa in the few milk samples which were analysed were very low, and most of the drug in the milk was conjugated.

The ratio of the free methyldopa concentration in the maternal and the foetal plasma was about one (0.85 ± 0.39 s.d.) in these studies. This is the expected result after a prolonged period of therapy with a drug which is not appreciably bound to the plasma proteins and which is fairly slowly eliminated by excretion and metabolism. Thus, both the mother and the foetus have a concentration of methyldopa in their plasma which is within the therapeutic range in the adult, but there appears to be no reports of an adverse effect of this treatment in the newborn: Redman *et al.* (1976) observed no apparent effect on the birth weight of infants of mothers receiving methyldopa.

The finding that the proportion of conjugated methyldopa in the maternal and umbilical cord plasma are also similar (ratio 1.34 ± 0.48 s.d.) requires some comment. Kwan *et al.* (1976) have shown considerable differences in the extent of conjugation to occur depending upon the route of administration. After the intravenous administration of methyldopa relatively little conjugated drug was found in the plasma and urine compared with that found after oral dosage. Saavedra *et al.* (1975) reported similar results in the plasma of a smaller group of subjects. The implication of these reports is that in the adult most of the conjugation of methyldopa occurs during its absorption from the gastrointestinal tract. The work of Buhs *et al.* (1964) suggests that the conjugate is an *o*-sulphate. Conjugation with sulphate is the most developed of the drug conjugation processes at birth (Gladtke & Heimann, 1975), but if the pattern of conjugation is similar to that in the adult, little conjugation of methyldopa would seem likely to occur in the foetus. Thus it seems probable that the sulphate conjugated drug in the umbilical plasma is mainly the result of its placental transfer from the maternal blood. The effect of the considerable sulphatase activity in the placenta (Guiot & Dzialoszynski, 1964) is not known.

The fact that free and conjugated methyldopa are present in plasma in approximately equal concentrations, suggests that the two forms of the drug have similar membrane transfer characteristics. However, the higher concentration of conjugated methyldopa compared to free methyldopa in amniotic fluid suggests that the former may be excreted the more readily in foetal urine, or is the less readily

reabsorbed. It is of interest that the relatively high concentration of methyldopa in the amniotic fluid means that this fluid constitutes an appreciable reservoir of the drug in the foetal environment; the amniotic fluid can contain more methyldopa than is present in the total body water of the infant.

The results of the milk analyses indicate that methyldopa can be secreted in the milk of lactating women receiving the drug. The few results obtained suggest that the concentration of methyldopa in milk will be very low and unlikely to be sufficient to affect the infant. However, further studies are required to establish the extent of secretion in the milk and its relationship to methyldopa dosage.

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DRUG INTERACTIONS WITH WARFARIN ENANTIOMERS – A DIFFERENT PERSPECTIVE

Since the two enantiomers of warfarin differ in pharmacokinetic characteristics and metabolic fate (Breckenridge & Orme, 1972; Breckenridge, Orme, Wesseling, Lewis & Gibbons, 1974; Chan, Lewis & Trager, 1972; Hewick, 1972; Hewick & McEwen, 1973; O'Reilly, 1974; Yacobi & Levy, 1974), it is not surprising that they differ also with respect to their interaction with certain drugs (Lewis, Trager, Chan, Breckenridge, Orme, Rowland & Schary, 1974; O'Reilly, 1976). It has been suggested that biotransformation interactions between warfarin and certain other drugs can be prevented by using one of the enantiomers instead of the commonly used racemic mixture. For example, O'Reilly (1976) has found a stereoselective interaction between metronidazole and S(−)-warfarin and has suggested that the use of R(+)-warfarin in place of racemic warfarin may be an advantageous therapeutic strategy for preventing interactions between the anticoagulant and metronidazole or certain other drugs.

There are other clinical aspects of drug interactions with warfarin than those related to stereoselectivity. R(+)-warfarin exhibits a considerably steeper anticoagulant effect-log drug concentration in plasma relationship in humans than does S(−)-warfarin (Wingard, O'Reilly & Levy, 1978). Consequently, if other variables remain constant, the same relative change in total clearance of each enantiomer caused by inhibition or induction of warfarin metabolizing enzyme systems, resulting in the same relative change in their steady state concentrations in plasma, should have a more pronounced effect on the anticoagulant activity of the enantiomer with the steeper effect-log concentration curve, i.e. R(+)-warfarin. However, one additional factor must be taken into consideration: the biological half-life of R(+)-warfarin is longer than that of S(−)-warfarin in humans so that the differences between maximum and minimum plasma concentrations during the usual 24 h dosing interval are larger for S(−)-warfarin than for the other enantiomer. To clarify the problem, the effects of changes in the elimination kinetics of the two enantiomers of warfarin on their anticoagulant effect have been determined by computer simulation.

Details of the computer simulation procedures have been described previously (Wingard & Levy, 1977).