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CLINDAMYCIN PASSAGE INTO HUMAN MILK

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1 The clindamycin bioactivity was measured during the dosage interval in the plasma of women with puerperal infections and in their breast milk.

2 There was a marked interindividual variation in the peak levels. The clindamycin bioactivity in the milk ranged from 1/10 to several times the corresponding bioactivity in the plasma that was collected at the same time.

3 The concentration of clindamycin in the milk (bioactivity) at the end of the dosage interval correlated with the area under the plasma concentration *v* time curve.

4 Clindamycin is thus transferred into human breast milk. Although the actual amounts secreted are small, the wellknown side effects and the lack of knowledge about the disposition and effects of clindamycin in newborn infants are strong arguments against nursing during treatment with this drug.

Introduction

Most data in humans about drug transfer to breast milk are based on fragmentary analysis in milk and plasma without consideration of the variation in drug plasma concentration during the dosage interval (for a review, see Knowles, 1965; Wilson *et al.*, 1980). The lack of quantitative information about the amount of drug transferred to the nursed infant may create problems for the physician, who has to decide whether a treated mother should nurse her child or not. A quantitative approach to study the passage of drugs into milk has been used in animal studies (Rasmussen, 1966) and recently also in man (Kampmann *et al.*, 1980; Stec *et al.*, 1980; Yurchak & Jusko, 1976; Rane & Tunell, 1981).

We are presently using the novel approach to relate drug concentrations in the milk to the area under the plasma concentration *v* time curve (AUC). The AUC should reflect drug exposure of the mammary glands over the whole dosage interval. The aim of the present study was to measure the passage of clindamycin into breast milk of women treated with this drug because of puerperal anaerobic infections.

Methods

Five women, aged 25 to 33 years, were informed about the purpose of the study and their consent was obtained. The study was approved by the Ethics Committee. Clindamycin therapy was instituted because of suspected or verified puerperal anaerobic infection. The treatment was started on the day of parturition and had been maintained at least 1 week when the study was started. The dose was 150 mg three times daily. The newborn infants were all healthy and were not nursed during the treatment. The investigation was carried out while the patients still were in hospital. Thus, the study was confined to the first 2 weeks of lactation.

On the day of study the breasts were emptied before the morning dose of clindamycin was given at 08.00 h. The milk was quantitatively collected until 14.00 h when the last plasma sample was taken. In some cases aliquots of milk were obtained in the middle of this time period. All milk concentrations refer to the average in the milk collected at the indicated time or time period. Thus possible differences between the early and the late secreted portions have not been taken into consideration.

Blood samples were taken by venepuncture at 08.00 h (before dose), 09.00 h and 10.00 h, 12.00 h and at 14.00 h after emptying the breasts. The blood was centrifuged and the plasma was refrigerated and analyzed within one day.

Clindamycin (7-deoxi-7-chlorolincomycin) hydrochloride bioactivity was assayed in serum and milk with a microbiological agar plate diffusion assay using *Staphylococcus Warneri* as indicator organism. The

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samples were assayed at the National Bacteriological Laboratory, Solna, Sweden, as soon as they were received. Standards were prepared in pooled antibiotic-free human serum and breast milk and covered the range from 1 to 16 and 0.5 to 8 μg/ml, respectively. This assay measures total bioactivity, i.e. clindamycin plus bioactive metabolites. It has been shown, however, that nearly all of the bioactivity in serum is due to clindamycin (Wagner *et al.*, 1968).

Results

The plasma concentrations of clindamycin were measured in the nursing mothers at specific times during the dosage interval. As can be seen in Figure 1 there was a fifteen-fold variation in the peak serum concentration between the mothers. In one mother (no. 1), no peak was attained during the dosage interval, probably due to slow absorption.

At the end of the dosage interval, i.e. prior to the subsequent dose breasts were emptied completely and aliquots of milk were collected. Table 1 gives the milk concentrations of clindamycin before and 6 h after the morning dose and the AUC values.

The milk concentration ranged from about 1/10 to several times the concentration in the plasma samples collected at the same time points (Table 1). There was no correlation between the milk and the plasma concentrations at the end of the dosage interval. Figure 2 illustrates the concentration profiles in one woman and shows that the curves in plasma and milk are not necessarily parallel. When the milk concentration at the end of the dosage interval was related to the AUC in plasma during the preceding dosage interval a significant correlation was obtained (Figure 3).

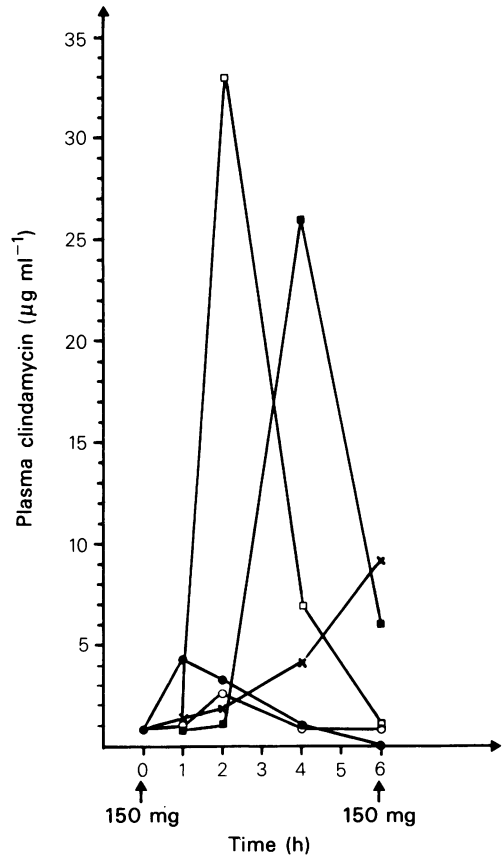

Figure 1 Plasma concentrations of clindamycin in five puerperal women during a dosage interval.

Table 1 Milk and plasma concentrations (μg ml^{-1}) in the patients. AUC = area under the plasma concentration *v* time curve (μg ml^{-1} h)

Time	*Patient number*				
	1	*2*	*3*	*4*	*5*
	Plasma concentrations (μg ml^{-1})				
08.00 h	<1.0	<1.0	4.0	<1.0	<1
09.00 h	1.5	12	1.2	<1.0	4.6
10.00 h	2.1	33	2.4	<1.0	3.9
12.00 h	4.2	7.9	1.2	26	1.0
14.00 h	9.9	<1.0	<1.0	5.5	<1
	Milk concentration (μg ml^{-1})				
08.00 h	<0.5	0.5	<0.5	<0.5	<0.5
14.00 h	0.8	3.1	<0.5	2.0	<0.5
	AUC (μg ml^{-1} h)				
	21.1	78.5	8.0	59.5	13.2

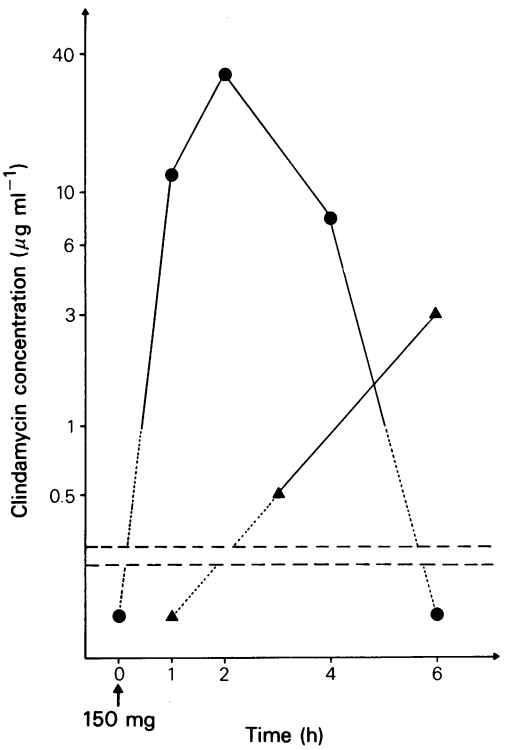

Figure 2 Plasma (●) and milk (▲) concentration in one lactating woman during a dosage interval.

Discussion

Under the assumption that the drug transfer into the mammary glands is dependent on diffusion as suggested by Rasmussen (1966), the amount of drug in unit time transferred to the breast milk is a function of the average plasma concentration during the same time. Since for clindamycin, the concentration in plasma varied extensively during the interval between the oral doses, the area under the plasma concentration *v* time curve (AUC) is a better measure of the actual exposure of the glands to clindamycin than one single concentration value. There was an excellent correlation between the AUC and the milk concentration, which supports the view that the transfer of clindamycin is a plasma concentration dependent process. The considerably higher plasma than milk concentration of clindamycin is consistent with the high plasma protein binding of this drug (Gordon *et al.*, 1973) and with the assumption that only the unbound moiety of the drug diffuses into the milk. It was difficult in these patients to get reliable data on the milk volumes during parts of the dosing interval, when the breasts were emptied by pumping.

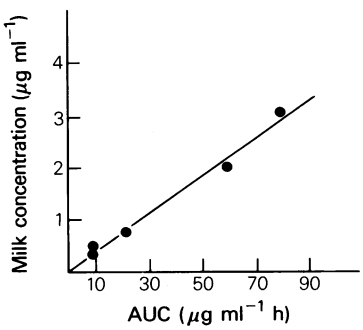

Figure 3 The milk concentration of clindamycin as a function of the area under the clindamycin plasma concentration *v* time curve in five women.

If there were no back diffusion of drug to the plasma the milk concentration *v* time profile would depend not only on the plasma concentration but also on the milk volume secreted in the mammary glands. As can be seen in Figure 2 for one patient there was a successive increase in the milk clindamycin bioactivity even during the decay phase of the plasma concentration curve. However, in another woman the drug concentration in milk decreased towards the end of the dosage interval. Our limited results do not allow any conclusions to be drawn about the mechanism of secretion.

Theoretically, a basic drug like clindamycin with a pKa value around 7.45 (Avery, 1980) would accumulate in the milk which is slightly more acid than the plasma. Such predictions hold true only if equilibrium is allowed to be established across the biological membrane. Our results show that the pH is not an important factor for the relative milk concentrations of clindamycin. Nevertheless, it is possible that slight differences in milk pH may contribute to the varying clindamycin concentration in the milk.

Our data show that it is essential to follow the plasma and milk concentration throughout the dosage interval before any conclusions about the relative concentration in the milk can be drawn.

We have no explanation for the wide differences in peak plasma concentrations of clindamycin in the different women. Intramuscular administration of clindamycin to normal individuals and renal failure patients did not yield more than a 2- to 3-fold variation in peak plasma level of clindamycin bioactivity (Roberts *et al.*, 1978). Interindividual differences in gastrointestinal absorption in the puerperium or in plasma protein binding may contribute to the varying clindamycin bioactivity levels in our patients.

In view of our findings that clindamycin is transferred into the breast milk, even though the actual amounts are small, we believe it is not advisable to nurse during treatment with clindamycin. The widely different clindamycin concentrations in the mothers make it difficult to predict the actual amounts of

clindamycin secreted into the milk. The limited knowledge about the neonatal disposition of the drug and the serious, albeit rare, gastrointestinal side effects of clindamycin hitherto reported only in adults (British Medical Journal, 1975) are further arguments against nursing during clindamycin therapy. Fortunately, other less toxic drugs can almost always be employed and replace clindamycin.

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