TERBUTALINE IN BREAST MILK

Nursing mothers with chronic bronchial asthma or obstructive lung disease may require treatment with bronchodilating drugs and the question then arises whether or not these drugs are present in breast milk in concentrations that entail risk for adverse effects in the infants. Theophylline kinetics in breast milk have been studied (Yurchak & Jusko, 1976; Stec *et al.*, 1980), and it was concluded that the risk for toxic effects in the baby was low. To our knowledge, no information is available about the appearance in milk of β_2-adrenoceptor agonists, such as fenoterol, salbutamol, or terbutaline. A sensitive mass-spectrometric technique for the determination of terbutaline in plasma has recently been presented (Jacobsson *et al.*, 1980), and the pharmacokinetics of the drug can therefore now be clarified in more detail. This method has been utilized in the present study, which reports the terbutaline concentrations in breast milk and plasma from nursing mothers who were on continuous treatment with terbutaline because of obstructive lung disease.

The two mothers (H.B. 27 years, 66 kg body weight and A.W. 30 years, 75 kg body weight) were treated with a dose of 2.5 mg terbutaline sulphate three times a day. No other drugs were given. Both mothers were in good general condition with their asthma well controlled. The infants, approximately 3 weeks of age, were healthy and had a normal development. The investigation was performed after at least 2 weeks' treatment of the mothers with terbutaline. Nursing had proceeded normally. Blood from an antecubital vein and milk were sampled from the mothers during a period of up to 8 h after the morning dose of terbutaline. No milk was taken from the left breast until 4 h after tablet intake. Milk was collected with a pump at the early phase of the meal. For comparison, on one occasion in each mother, milk from the late phase of the meal was also sampled. Plasma and milk samples were frozen and later analysed for terbutaline. In the last sample from each mother, also the concentration of terbutaline in skimmed milk was determined. After nursing any remaining milk in the breasts was removed with the pump.

The results are shown in Table 1. Despite the same dose, patient H.B. reached only about half the terbutaline concentration of patient A.W. Milk samples from the left and right breast showed similar concentrations, except for the last sampling in patient A.W. Thus, delaying the sampling from the left breast did not influence the concentration of terbutaline in the milk. The terbutaline concentrations in milk were always higher than in plasma. This is in agreement with the principle of non-ionic diffusion, which predicts a higher concentration in milk of substances that are more ionized at the pH of human milk

Table 1 Concentration of terbutaline in plasma and breast milk during maintenance therapy (2.5 mg three times a day). Milk was sampled from the early phase of the meal unless otherwise stated.

Patient	*Time after last dose (h)*	*Terbutaline concentration (ng/ml)*				*Ratio milk:plasma**
		Plasma	*Breast milk*			
			Left breast	*Right breast*	*Mean*	
H.B.	0	1.11				
27 years	1.2			3.56		
66 kg	1.5			4.10 (late)		
	4.3		2.90	3.55	3.23	2.0
	4.6	1.64				
	7.8	0.97	3.02	2.50	2.76	2.9
			2.77 (skimmed)			
A.W.	1.3	3.07				
30 years	2.3			3.94		1.5
75 kg	2.5	2.61		4.11 (late)		
	4.2	2.72	4.06	3.75	3.91	1.4
	7.3	1.98	2.52	4.61	3.57	1.8
				3.97 (skimmed)		

*Calculation of the ratio milk:plasma is based on the underlined values.

(usually 7.0) than at the pH of plasma (7.4) (Rasmussen, 1971). Terbutaline is such a substance, having pK_a values of 8.8, 10.1 and 11.2. As seen in Table 1, the milk:plasma concentration ratios increased with decreasing plasma concentration. Patient H.B. had a higher ratio (2.0–2.9) than patient A.W. (1.4–1.8). The reason for this difference is not known, but such a situation could arise if the milk from patient H.B. had a lower pH. Another possibility is a difference in fat content of the milk from the two mothers. Assay of skimmed milk showed a lower concentration of terbutaline than in whole milk (Table 1). Thus, in milk, terbutaline appears to be concentrated in the fat fraction. This finding, somewhat surprising in light of the hydrophilic nature of the terbutaline molecule, is further supported by the result from analysis of terbutaline in milk from the late phase of the meal (measured at 1.5 h in patient H.B. and at 2.5 h in patient A.W.). The late milk, known to be high in fat content, showed in both mothers a higher concentration of terbutaline than the early milk. The larger concentration difference between early and late milk in patient H.B. might have been due to a simultaneous rise of the plasma concentration.

In the present study, the average concentration of terbutaline in early milk was 3.50 ng/ml. As a mean estimate of the daily milk intake a figure of 165 ml kg^{-1} day^{-1} has been given (Anderson, 1979). This suggests that the infants would have ingested about 0.58 μg kg^{-1} day^{-1} of terbutaline base, which corresponds to 0.70 μg kg^{-1} day^{-1} of the sulphate salt. This is only 0.7% of the mean daily dose of the mothers (107 μg kg^{-1} day^{-1}). Late milk had a slightly higher concentration of terbutaline than early milk, but the difference would add but little to the estimate of ingested amount.

It appears, as a consequence of the relatively stable milk levels of terbutaline during maintenance therapy, that the infant would receive similar amounts of terbutaline irrespective of how the tablet intake of the mother is spaced in relation to nursing.

Even if the oral bioavailability and elimination kinetics of terbutaline in newborn infants are unknown, it seems unlikely that the amount of terbutaline ingested via milk by these infants would lead to plasma levels with noticeable pharmacological effects. Unfortunately, we did not have the possibility to check the plasma concentrations in the babies, but no symptoms of β-adrenoceptor stimulation could be found at routine clinical examination and both children have had a normal development.

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DISTRIBUTION OF UDP-GLUCURONYLTRANSFERASE IN DIFFERENT HUMAN FOETAL TISSUES

The literature about conjugation of xenobiotics with glucuronic acid has recently been the subject of extensive reviews (see e.g. Dutton & Burchell, 1976; Dutton 1978). Extrahepatic glucuronidation is well documented. Aitio (1973) compared the uridine diphosphoglucuronyltransferase activities towards 4-methylumbelliferone in the liver, intestine, adrenals, kidneys, spleen, thymus, heart and brain in the rat. He concluded that the liver is the most important organ of glucuronide synthesis in this species.

The hepatic capacity to conjugate morphine with glucuronic acid does not develop until after birth in