

Secretion of prednisolone into breast milk

Many drugs are secreted into breast milk (Knowles, 1965; Catz and Giacoia, 1972) but only a few in quantities sufficient to affect the suckling infant—for instance, thiouracil, bromides, alcohol, and ergot. Little is known of the secretion of steroids, perhaps because of the problems of estimating these compounds in milk. This communication reports measurements of the secretion of radioactive (tritium-labelled) prednisolone and its radioactive metabolites in the breast milk of seven healthy women. An oxidation technique was used to prepare the tritium in the milk in a suitable form for liquid scintillation counting.

Subjects and methods

Seven healthy lactating volunteers were chosen for the study. Three were mothers who had been lactating for several months and were about to wean their infants. Four were mothers, recently delivered, who had elected to bottle-feed their infants but who were willing to lactate for the duration of the study; lactation was well established before the study commenced. The study was sanctioned by the Ethics Committee of the Royal Free Hospital and permission for the radioactive dosage used was given by the Isotope Panel of the Medical Research Council. No infants went to the breast after the mothers had entered the study.

Each subject was given orally 5 mg prednisolone incorporating $10 \mu\text{Ci } ^3\text{H}$ -prednisolone. The radioactive prednisolone, supplied by the Radiochemical Centre, Amersham, was labelled at positions 1, 2, 4, and 6 of the steroid nucleus. The dose for each subject was dissolved in 5 ml ethanol and then added to 25 ml of orange juice. Each subject expressed milk with the assistance of a breast-pump at varying intervals over a period of about 48 hours after taking the radioactive dose. The times of expression were not rigidly controlled but were left to the convenience of the individual. In two subjects urine was collected for 48 hours.

Quadruplicate 0.5 ml aliquots of each milk sample were prepared for liquid scintillation counting by oxidation using a Packard Model 306 Sample Oxidiser (Packard Instrument Company, Illinois). Packard Combustaid 0.3 ml was added to each sample to ensure a sufficiently high temperature for complete combustion. The recovery obtained with this oxidation technique was found by experiment to be better than 98%. The mean background (using polyethylene counting vials)

was about 14 counts/min with a standard deviation of less than ± 2 counts/min.

Results

The concentration of radioactivity in each sample of milk is shown in the Table. For each subject the highest level of radioactivity was recorded in the first sample obtained. The level then fell rapidly, typically reaching an approximate plateau after 24 to 36 hours (Fig.). The mean plateau level was

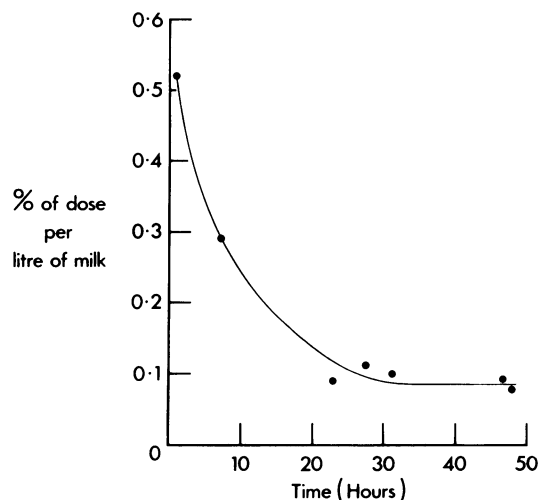


FIG.—Variation with time of radioactivity in milk (Case 4).

$0.09 \pm 0.04\%$ of administered radioactivity per litre of milk (mean \pm SD). The mean total recovery of the radioactive dose in breast milk over the period of the study normalized to a milk volume of 1 litre was 0.14% (range 0.07 – 0.23).

Urine was collected from two subjects (Nos. 3 and 5) for 48 hours. The total recoveries of the radioactive dose were 30 and 32% respectively.

Discussion

Only low levels of naturally occurring steroids have been found in human and cow's milk (Harkness and Darling, 1971). Nevertheless, the secretion of pregnane- 3α , 20β -diol in breast milk is thought to contribute to prolonged neonatal jaundice either by inhibiting glucuronyl transferase

TABLE
Radioactivity in milk samples

Case no.	Sample time (hours after dose)	Volume (ml)	Radioactivity concentration (% of dose/l)	Total percentage output normalized to volume of 1 l
1	5	30	0.42	0.23
	10	28	0.33	
	20	20	0.23	
	30	20	0.20	
	35	30	0.14	
	47	26	0.13	
	50	30	0.15	
2	6	57	0.23	0.11
	12	62	0.12	
	22	66	0.12	
	37	54	0.06	
	50	62	0.06	
	58	100	0.07	
	3	4	48	
18		92	0.14	
24		66	0.12	
30		90	0.11	
44		110	0.13	
4	48	64	0.10	0.21
	1	100	0.52	
	8	74	0.29	
	23	83	0.09	
	28	88	0.11	
	31	78	0.10	
	47	59	0.09	
	48	10	0.08	
5	3	12	0.41	0.08
	7	15	0.27	
	14	8	0.14	
	19	25	0.10	
	23	110	0.07	
	27	130	0.07	
	31	90	0.09	
	39	30	0.09	
	43	200	0.02	
	47	140	0.10	
6	10	16	0.33	0.07
	24	31	0.02	
	34	14	0.03	
	58	16	0.02	
7	61	20	0.01	0.15
	4	123	0.35	
	10	96	0.22	
	23	138	0.09	
	29	132	0.10	
	33	116	0.10	
48	154	0.09		

(Arias *et al.*, 1964) or by inhibiting the secretion of bilirubin glucuronide from the liver (Hargreaves and Piper, 1971). Studies on lactating rats given cortisone 20 mg/day showed a significant retardation of growth and development in the sucklings. Most of them died and the survivors weighed 50–60% less than the controls, had lustreless pelts, and greatly retarded sexual development (Mercier-Parot, 1955). Gynaecomastia has been reported in a male infant when his mother inadvertently doubled the dose of her oral contraceptives (Curtis, 1964). Clinical side effects in infants who have been breast-fed by mothers receiving prednisolone

have not been recorded but such mothers desiring to breast feed their babies may have been discouraged.

The secretion of ^3H in human breast milk has previously been studied after the administration of labelled oral contraceptives. Pincus *et al.* (1966) found the recovery of radioactivity over a four-day period from administration of ^3H -norethynodiol or ^3H -ethynodiol diacetate was less than 0.15% of the administered dose. In contrast, Laumas *et al.* (1967) found a mean recovery of 1.1% over a five-day period after administration of ^3H -norethynodiol. One possible reason for the difference between these

results may have been the difficulties in preparing low-activity milk samples for liquid scintillation counting. Laumas *et al.* (1967) precipitated milk protein with tri-chloroacetic acid and then separately counted the supernatant and the precipitate, the latter after digestion in hyamine hydroxide. The more-recently available method of sample preparation used in this study—automatic sample oxidation—is both simpler than chemical digestion and more accurate. Both backgrounds and counting efficiencies were found to be closely reproducible from run to run.

The results of this study show that in seven subjects a mean of 0.14% of the radioactivity from a 5-mg dose of ^3H -prednisolone was recovered per litre of breast milk secreted over 48–61 hours from oral administration of the steroid. This may represent radioactivity bound to the unaltered drug and to its biologically inactive metabolites. If these results can be related to a realistic clinical situation—say, that of a mother taking 30 mg of prednisolone daily (for whatever reason)—the amount of steroid which might be received by a suckling infant through the breast milk would be extremely small.

Summary

The secretion of ^3H in the breast milk of seven volunteers was studied over a period of about 48 hours after the oral administration of 5 mg of ^3H -prednisolone. A range of 0.07 to 0.23% of the dose per litre was recovered.

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Watery diarrhoea and ganglioneuroma with secretion of vasoactive intestinal peptide

The association between a functioning adrenal ganglioneuroma and persistent watery diarrhoea was reported in 1952 by Hawfield and Daisley. Other neural crest tumours, including neuroblastomas, have since been described in patients with severe diarrhoea. Many of these tumours secrete large amounts of catecholamines and metabolites into the urine. A pheochromocytoma may also secrete a large excess of catecholamines but diarrhoea is not an associated symptom. The aetiology of watery diarrhoea in neural tumours is speculative. Several humoral factors have been incriminated, such as prostaglandins (Sandler, Karim, and Williams, 1968). A high tissue level of prostaglandin $F_{2\alpha}$ has been detected in a single case of ganglioneuroma with diarrhoea but also in neuroblastomas and pheochromocytomas without diarrhoea.

In 1970 a vasoactive intestinal peptide (VIP) was isolated in the pig, and it is now known to provoke increased fluid secretion into the bowel and diarrhoea (Bloom, Polak, and Pearse, 1973). Bloom *et al.* (1973) found high levels of VIP in six patients with severe watery diarrhoea reminiscent of cases described by Verner and Morrison (1958). In one of these patients the tumour was not pancreatic in origin but was "a complex ganglioneuroblastoma". It therefore seemed germane to investigate the case of watery diarrhoea reported here for the presence of excess VIP production.

Case report

A 5-year-old girl presented with a 30-month history of persistent watery diarrhoea. The constant soiling worried the parents, especially as she was about to start school. Her motions, 2–5 a day, were brown, non-offensive, and watery and did not contain blood, mucus,