

FURTHER OBSERVATIONS ON METRONIDAZOLE (FLAGYL)*

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Unexpected cases of icterus gravidarum in infancy have in many instances been traced to drug absorption from the maternal circulation. After consulting with paediatricians, it was considered advisable to investigate under hospital supervision the effect, if any, of metronidazole ("Flagyl") on the foetus and later on the breast-fed infant.

In Edinburgh a "mother and baby" survey on 96 patients completed in December, 1960 (Scott Gray, 1961), suggested that there was no placental barrier to the drug. The serum concentrations in mother and child were approximately equal at the time of delivery. The drug was well absorbed during labour, and in four cases where gastric lavage had been previously carried out the serum concentrations were higher than in the remaining cases investigated.

Serum bilirubin estimations performed on mothers and babies showed no appreciable increase.

This paper presents the results of investigations into the secretion of metronidazole in breast milk and the absorption by the breast-fed infant.

Methods

The patients chosen for this project had uncomplicated ante-natal and post-natal histories. The average age of

the mother was 22.5 years and 5-day old babies were chosen, as at that age breast feeding should be well established. A delay until the seventh or tenth day was not advisable as after the initial engorgement of the breast, feeding difficulties may develop for both mother and child. All the babies were fed 4-hourly.

The ten patients were divided into two groups. Blood samples and breast milk were taken from the mother at 0, 4, and 8 hours in five patients (Group I) and also at 12 hours in the other five patients (Group II), after oral administration of one tablet of 200 mg. metronidazole. In Group I a blood sample was taken from the child at 8 hours (*i.e.* 4 hours after the first feed) and in Group II at 12 hours (*i.e.* 4 hours after the second feed). At each feed the child was test weighed. Serum and breast samples were analysed by the polarographic method (Kane, 1961).

Results

The results of the investigation (Tables I and II) showed that the serum concentrations in the mother were similar to those found in a previous series of twelve non-maternity patients (Kane, McFadzean, Squires, King, and Nicol, 1961). Concentrations of metronidazole in breast milk were comparable with those in the serum. The mean figures in $\mu\text{g./ml.}$ of breast milk concentrations at 4, 8, and 12 hours in the series were 3.4, 2.2, and 1.3, compared with

TABLE I
MOTHER AND CHILD'S SERUM LEVELS AND MILK LEVELS OF METRONIDAZOLE AFTER A SINGLE DOSE OF 200 mg. (GROUP I)

Patient's Data			Polarographic Metronidazole Estimations ($\mu\text{g./ml.}$)					
Case No.	Age Mother (yrs) Child (days)	Weight (lb.)	Serum			Breast Milk		
			0 hrs	4 hrs	8 hrs	0 hrs	4 hrs	8 hrs
1	Mother ..	26	—	3.7	2.1	0	3.6	2.7
	Male child ..	5	—	—	trace	—	70 ml. (test-weight)	—
2	Mother ..	32	—	2.6	1.6	0	3.0	3.0
	Female child ..	6	—	—	0	—	115 ml. (T.W.)	—
3	Mother ..	24	—	3.16	1.8	0	2.0	1.1
	Female child ..	6	—	—	0	—	70 ml. (T.W.)	—
4	Mother ..	18	—	3.5	1.9	0	3.0	2.0
	Male child ..	4	—	—	0.28	—	70 ml. (T.W.)	—
5	Mother ..	20	—	3.9	2.6	0	5.5	7.7
	Female child ..	6	—	—	0.4	—	60 ml. (T.W.)	—

TABLE II
MOTHER AND CHILD'S SERUM LEVELS AND MILK LEVELS OF METRONIDAZOLE AFTER A SINGLE DOSE OF 200 mg.
(GROUP 2)

Patient's Data			Polarographic Metronidazole Estimations ($\mu\text{g./ml.}$)							
			Serum				Breast Milk			
Case No.	Age Mother (yrs) Child (days)	Weight (lb.)	0 hrs	4 hrs	8 hrs	12 hrs	0 hrs	4 hrs	8 hrs	12 hrs
6	Mother	27	—	6.8	4.0	2.4	0	3.6	2.7	1.1
	Male child	5	180 9.3	—	—	—	0	115 ml.	45 ml.	—
7	Mother	21	—	6.2	4.0	2.9	0	2.7	1.6	1.1
	Male child	4	165 8.9	—	—	—	0	35 ml.	45 ml.	—
8	Mother	17	—	3.0	1.8	0.95	0	3.1	2.3	1.5
	Female child	6	165 7.9	—	—	0.2	—	90 ml.	85 ml.	—
9	Mother	23	—	2.5	1.4	1.3	0	4.2	2.6	1.8
	Male child	6	130 7.5	—	—	0.2	(Haemolysed)	90 ml.	85 ml.	—
10	Mother	18	—	3.5	2.0	1.4	0	3.1	2.0	1.0
	Male child	5	152 7.7	—	—	—	—	115 ml.	115 ml.	—

3.9, 2.3, and 1.8 serum levels. The sera of five babies contained no detectable metronidazole ($<0.05 \mu\text{g./ml.}$) and in the other five babies the amount ranged from ~ 0.05 to $0.4 \mu\text{g./ml.}$

We attempted to calculate the amount of drug ingested by the infant from the test weighings and the concentration of drug in milk. The average amount at the first feed was 0.3 mg. and at the second feed 0.17 mg. The maximum amount ingested by any one infant was 0.41 mg. There was no correlation between the amount of drug ingested by the infant and the concentrations found in the infant's serum.

Further studies will be carried out on lactating mothers receiving the standard 7-day course of metronidazole in order to ascertain whether a trichomonocidal serum concentration of the drug can be attained in the infants' serum and also to determine the total intake of drug by the infant. Such a survey will be delayed until further information is available on peak serum concentrations of metronidazole in non-maternity patients receiving a full course of therapy.

During the trials no baby developed any oral or gastro-intestinal upset.

The concentration of metronidazole has now been measured in seminal fluid, 8 hours after completion of a standard course of treatment. This was the first time such an estimation has been undertaken, and the figure of $4.8 \mu\text{g./ml.}$, though provisional, may be of some significance in the treatment of male trichomoniasis.

Summary

The excretion of orally-administered metroni-

dazole in breast milk and the blood levels obtained in both the mother and the suckling infant have been determined in a series of ten patients. Concentrations of the drug found in the breast milk were comparable with those found in the serum and were also similar to the serum concentrations found previously in a series of non-maternity cases.

The sera of five of the babies contained no detectable drug whilst in five others concentrations ranging from ~ 0.05 to $0.4 \mu\text{g./ml.}$ were found. Administration of the drug to the mother had no obvious effect on any of the babies and none of the children developed oral or gastro-intestinal upset.

REFERENCES

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Remarques nouvelles au sujet du Flagyl

RÉSUMÉ

Le taux d'excrétion du Flagyl ingéré dans le lait maternel et dans le sérum de la mère et du nourrisson a été observé chez 10 sujets. Les taux dans le lait étaient comparables à ceux dans le sérum des mères, et aussi à ceux observés auparavant dans le sérum d'une série de femmes non-parturientes.

Le sérum de cinq des enfants ne montrait aucun médicament, mais un taux de $\sim 0,05$ à $0,4 \mu\text{g./ml.}$ fut constaté chez les cinq autres. L'administration du Flagyl à la mère n'eut aucun effet visible sur l'enfant, et les enfants n'eurent aucun malaise buccal ou gastro-intestinal.