ABSORPTION AND EXCRETION OF METRONIDAZOLE

PART I. SERUM CONCENTRATION AND URINARY EXCRETION AFTER ORAL ADMINISTRATION*

BY

P. O. KANE, J. A. McFADZEAN, AND S. SQUIRES

Research Laboratories, May and Baker Ltd., Dagenham, Essex

A. J. KING

Whitechapel Clinic, London

AND

C. S. NICOL

St. Thomas' Hospital, London

Metronidazole (200 mg. three times daily for 7 days) cures approximately 90 per cent. of patients infested with *Trichomonas vaginalis* (Rodin, King, Nicol, and Barrow, 1960). This paper describes the first stage of an investigation designed to determine, in the first instance, the general absorption and excretion pattern of the drug and, secondly, the cause of failure in the remaining 10 per cent. Failure to eradicate the parasite could be due to:

- (1) Failure of the patient to take the drug;
- (2) Failure of the patient to absorb the drug;
- (3) Resistance of the parasite to the drug;
- (4) Failure of the drug, having been absorbed satisfactorily, to reach the parasite;
- (5) Re-infection.

The investigations to be described concern points (2) and (3). The initial part of the investigation was an attempt to establish a normal pattern of absorption and excretion following the administration of a single tablet (200 mg.) to patients in whom treatment with a standard course of therapy (200 mg. three times daily for 7 days) was later found to be successful.

Methods

The trial was undertaken on a group of twelve female patients infested with *T. vaginalis* admitted either to St. Thomas' Hospital or to the Whitechapel Clinic, London Hospital, for a period of 24 hours. On admission, a culture was taken in a simple liver infusion broth, the bladder was emptied, and samples of blood and urine

were taken, in order to establish the absence of substances which could interfere with subsequent metronidazole determination. 200 mg. metronidazole were then administered orally; further blood samples were taken at 1, 2, 4, 8, and 24 hrs and the serum was assayed by the polarographic method (Kane, 1961), which gives comparable results to bioassay and is much quicker (Rodin and others, 1960). Urine was collected at 2 hrs, 4 hrs, and thereafter as passed, and the bladder was finally emptied at 24 hrs. The volumes were measured and again an assay of metronidazole was made on each sample by the polarographic method. These patients were then treated with the standard course of therapy and the response recorded.

One other patient was admitted to hospital for 24 hrs to follow the absorption and excretion during normal daily therapy of 3×200 mg. tablets, and estimations were made on two further in-patients while they were receiving the standard course of 200 mg. tablets three times daily for 7 days.

Results

Trichomonads were successfully grown in nine out of the twelve cultures taken from the patients admitted to hospital for 24 hrs and all showed normal sensitivity to metronidazole (0.25–1 $\mu\text{g./ml.}$).

No interfering substance was found in the baseline samples examined by polarography. Table I (overleaf) shows for the twelve patients the mean serum concentrations at successive times and the standard deviations from the mean. These data show that all patients had a similar absorption pattern, maximum values of about 5 $\mu\text{g./ml.}$ being obtained between 1 and 2 hrs after the administration of the drug, and thereafter falling off steadily to about 1 $\mu\text{g./ml.}$ after 24 hrs.

* Paper read at the M.S.S.V.D. meeting in Paris on May 12, 1961.

TABLE I

SERUM CONCENTRATIONS ($\mu\text{g./ml.}$) OF METRONIDAZOLE IN TWELVE PATIENTS AFTER 200 mg. OF THE DRUG

Time of Sample (hrs)	Patient's Reference												Mean	S.D.
	A	B	C	D	E	F	G	H	I	J	K	L		
0	0	0	0	0	0	0	0	0	0.3	0	0	0	0	0
1	7.0	4.3	4.5	6.1	5.1	5.9	2.6	4.1	4.8	4.6	4.5	4.3	4.8	1.0
2	5.8	(3.9)	3.9	5.6	4.5	4.2	3.5	4.1	4.1	5.2	4.4	4.5	4.5	0.6
4	5.1	3.3	3.5	(4.9)	4.5	3.2	2.9	3.1	3.1	4.4	3.4	3.8	3.7	0.8
8	3.8	2.3	2.5	3.9	3.3	2.8	(2.0)	2.4	2.1	3.3	2.7	(3.0)	2.9	0.5
24	1.4	0.8	0.4	1.6	1.0	0.8	0.6	1.0	0.5	1.0	0.6	0.1	0.8	0.4

() By interpolation.

TABLE II

RENAL EXCRETION OF METRONIDAZOLE IN TWELVE PATIENTS AFTER 200 mg. OF THE DRUG

Time of Sample (hrs)	Metronidazole in Urine (mg.)												Per cent. Excreted
	A	B	C	D	E	F	G	H	I	J	K	L	
0-1	—	—	—	—	—	—	—	3.0	—	—	—	—	
1-2	4.2	14.1	9.9	7.5	9.0	3.5	13.0	7.0	7.5	9.2	8.0	3.1	
2-4	3.8	13.0	10.8	9.6	13.3	6.5	16.0	10.2	20.8	11.2	8.1	11.2	
4-8	2.6	53.8	—	23.0	21.0	16.0	37.0	12.0	39.4	4.9	18.6	16.8	
8-12	7.5	—	31.5	—	7.2	—	20.0	—	25.0	—	12.0	40.5	
12-24	8.2	10.3	1.6	35.8	19.5	29.1	3.0	31.7	22.9	30.8	26.6	19.9	
Per cent. Excreted	13	46	27	38	35	28	45	32	58	28	37	46	

The urinary excretion values are shown in Table II. There were wide variations from patient to patient, the total excretion over 24 hrs ranging from 13 to 58 per cent. of the drug administered.

These twelve patients were then given the standard course of therapy (200 mg. three times daily for 7 days), at the end of which vaginal smears and cultures were made from eleven patients, the twelfth having failed to report back. Of these eleven, ten were negative and remained so. Smears and cultures from the eleventh patient were negative for 8 to 9 weeks after treatment, after which trichomonads were again found in the vagina. These showed normal sensitivity to metronidazole in culture and it seems likely that this was a re-infection.

The estimations on the sera of these twelve patients were considered to be sufficient to give a normal standard, particularly in view of the fact that the results were so consistent and the response to therapy uniformly good.

The one patient from whom samples of serum and urine were obtained after the daily therapeutic course of three 200-mg. tablets showed a normal absorption pattern at 1 hr (Table III), and the peak serum concentration rose to 8 $\mu\text{g./ml.}$ at the end of 8 hrs, *i.e.*

4 hrs after the second dose. The serum concentration in this patient was still 3.6 $\mu\text{g./ml.}$ after 24 hrs, at which time approximately 30 per cent. of the total drug ingested had been recovered in the urine.

TABLE III

SERUM AND URINARY EXCRETION AFTER THREE 200-mg. TABLETS, TAKEN AT 0, 4, AND 8 HRS

Time of Sample (hrs)	Serum Level ($\mu\text{g./ml.}$)	Drug Recovered in Urine (mg.)
1	3.8	3
4	4.6	15
5	5.6	
8	8.0	25
9	7.4	
24	3.6	156
Total Recovered		200

Two further patients were given the standard therapeutic course of treatment (one 200-mg. tablet three times daily for 7 days) and the serum concentrations were followed as well as the urinary output. The results are given in Table IV (opposite). There was no evidence of accumulation of the drug in the serum over 7 days. In both cases the urinary excretion over the first 24 hrs was approximately the same, *i.e.* 50 per cent. of the drug ingested; after this, however, there was a wide variation in the urinary

TABLE IV

BLOOD CONCENTRATION AND URINARY OUTPUT AFTER A STANDARD COURSE OF METRONIDAZOLE (200 mg. THREE TIMES DAILY FOR 7 DAYS, *i.e.* 4.2 g.) IN TWO PATIENTS (M AND N)

Tablets were administered at 8 a.m., 2 p.m., and 8 p.m.

Day	Time	Blood Concentration ($\mu\text{g./ml.}$)		Urine Concentration ($\mu\text{g./ml.}$)		Total Excretion over 24 hrs to 8 a.m. (mg)	
		M	N	M	N	M	N
1	8 a.m.	0	0	0	0		
	3 p.m.	3.3					
	10 p.m.	6.1					
2	8 a.m.	3.6	4.3	88	125	327	323
	3 p.m.	6.5					
	10 p.m.	7.8					
3	8 a.m.	4.1	4.8	353	155	635	395
	3 p.m.	5.4					
	10 p.m.	9.8					
4	8 a.m.	4.7	4.5	446	153	695	289
	3 p.m.	6.3					
	10 p.m.	6.8					
5	8 a.m.	4.4	5.3	432	149	622	384
	3 p.m.	5.9					
	10 p.m.	7.8					
6	8 a.m.	3.7	5.9	159	188	157	417
	3 p.m.	3.5					
	10 p.m.	7.0					
7	8 a.m.	3.6	3.9	226	192	460	328
	3 p.m.	5.0					
	10 p.m.	7.7					
8	8 a.m.	4.1	2.2	232	124	340	257
	8 p.m.	1.0					
9	8 a.m.			68	78	120	105
10	8 a.m.				13		286
11	8 a.m.			10		13	
12	8 a.m.			1.6		1.8	
Total Recovered in Urine (g.)						3.4	2.8

excretion pattern of the two patients. Over the period of observation 81 and 67 per cent. respectively of the total drug administered was demonstrated in the urine.

Discussion

It appeared that a normal absorption pattern had been established for a single dose of 200 mg. metronidazole in patients who subsequently responded to standard therapy. This pattern could be employed to investigate patients who had failed to respond to therapy and this investigation will be described in a second paper. There was no evidence of accumulation of the drug in the serum over 7 days during standard therapy in the two patients investigated.

The excretion pattern in the urine was extremely variable.

Summary

The blood and urine concentrations in twelve patients were determined during 24 hrs after the oral administration of a single dose of 200 mg. metronidazole. Very similar serum concentrations were obtained from all patients, the concentrations falling from a maximum value of about 5 $\mu\text{g./ml.}$ between 1 and 2 hrs to about 1 $\mu\text{g./ml.}$ after 24 hrs. These patients subsequently responded satisfactorily to a standard course of treatment with metronidazole.

The urinary excretion rate appeared variable from patient to patient and it was found that after a single dose, 13–58 per cent. of the total drug was excreted within 24 hrs. In two patients, when the excretion of the drug was followed for the whole of a standard course of therapy of 200 mg. three times daily for 7 days, a marked variation in the rate of excretion was seen, although serum concentrations taken at comparable times were closely related. There was no evidence of accumulation of the drug in the serum.

We are grateful to Dr. M. Scott Gray of the Royal Infirmary, Edinburgh, for undertaking the investigations on two patients.

REFERENCES

- Kane, P. O. (1961). *J. polarographic Soc.* (In the press).
 Rodin, P., King, A. J., Nicol, C. S., and Barrow, J. (1960). *Brit. J. vener. Dis.*, **36**, 147.

Absorption et excrétion du Flagyl

I. Concentration dans le sérum et excrétion dans l'urine après dosage par voie buccale

RÉSUMÉ

La concentration du Flagyl dans le sérum et l'urine fut constatée pendant 24 heures chez 12 malades après l'ingestion de 200 mg. Les taux étaient comparables chez tous les malades, et tombaient d'un maximum d'environ 5 $\mu\text{g./ml.}$ après une ou deux heures jusqu'à environ 1 $\mu\text{g./ml.}$ après 24 heures. Ces malades furent guéris ensuite par un dosage classique de Flagyl.

Le taux d'excrétion urinaire semblait varier de personne à personne, et l'on trouva que 13 à 58 % était excrété dans les 24 heures après une seule dose. Chez deux malades l'excrétion du Flagyl fut observée pendant 7 jours, tandis qu'ils recevaient un dosage classique de 200 mg. trois fois par jour; la mesure d'excrétion variait beaucoup, bien que la concentration dans le sérum était assez constante. Il ne semblait pas que le Flagyl s'accumulât dans le sérum.