

ABSORPTION AND EXCRETION OF METRONIDAZOLE* PART II. STUDIES ON PRIMARY FAILURES

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Part I of this paper (Kane, McFadzean, Squires, King, and Nicol, 1961) gave information on the serum concentrations obtained in twelve patients after the oral administration of a single dose of 200 mg. metronidazole. These patients were then given the standard course of therapy (200 mg. three times daily for 7 days) and responded satisfactorily. The serum concentrations were therefore considered as being those likely to be found in patients who were absorbing the drug satisfactorily.

The next stage of the investigation was to determine if patients who had failed to respond to metronidazole had an absorption defect or harboured resistant organisms. The protocol of the investigation had to remain simple as these subjects would be dealt with as out-patients.

Method

A patient was considered to be a "primary failure" when she had received a course of metronidazole of 200 mg. three times daily for 7 days and at the end of this time, *i.e.* on Day 8, continued to harbour *Trichomonas vaginalis*. When such a patient had failed to respond to therapy she was asked to return after a minimum period of 24 hrs to allow for the excretion of any residual drug, and a vaginal culture was taken. 200 mg. metronidazole was administered orally and 1 hour later a sample of blood was taken for polarographic assay.

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Results

Investigations were made on eight patients who were "primary failures", and who were attending three clinics in Britain. The parasite was successfully

cultured from seven of these patients and showed normal sensitivity to metronidazole in each case (0.25–1 $\mu\text{g./ml.}$).

The Table gives the serum concentrations of the drug in these patients 1 hour after a single dose of 200 mg. metronidazole, all results being obtained by the polarographic method (Kane, 1961).

TABLE
SERUM CONCENTRATIONS 1 HOUR AFTER ORAL
ADMINISTRATION OF 200 mg. METRONIDAZOLE TO
"PRIMARY FAILURES"

Case No.	Serum Concentration ($\mu\text{g./ml.}$)
C 1359	2.0
58936	3.1
A 4893	1.7
18491	5.6
A 6470	0.8
C 1603	4.3
AZ 3238 (male)	1.2
A 6641	3.5
Previous Observation of Twelve Patients	4.8 S.D. 1.0

Taking results differing from the mean by 2.5 times the standard deviation as significant (significance of 1 in 80), it follows that serum concentrations of 2.3 $\mu\text{g./ml.}$ or less are significantly low compared with the values found in patients responding to therapy. The Table shows this to be the case in four out of eight "primary failures".

Discussion

Four out of eight patients who were "primary failures" showed serum concentrations significantly below those obtained from a series of twelve patients in whom a satisfactory response to the drug had been obtained after the administration of 200 mg. metronidazole. No attempt was made to determine the effect of fasting on the absorption of the drug, but it is felt that, because the previous observations on twelve patients were made on a randomized basis

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and because these "primary failures" had been seen at different treatment centres, this factor does not offer a likely explanation. Röckl, Borelli, and Hardieck (1961) reported that in one of their cases several treatments were needed because, owing to a defect in the gastro-intestinal system, there was unsatisfactory absorption of the drug. Further work is being carried out to try to elucidate this problem. It is concluded that failure in a percentage of patients could well be due to poor absorption of the drug.

Summary

Investigations were made on eight patients infested with *T. vaginalis* who were found to be true "primary failures" after a standard course of treatment with metronidazole.

The parasites on culture showed normal sensitivity to the compound, but four out of eight patients showed significantly lower serum levels 1 hour after the administration of 200 mg. metronidazole. It is

concluded that poor absorption of the compound may be responsible for a percentage of failures with this drug.

REFERENCES

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Absorption et excrétion du Flagyl

II. Etudes des rechutes primaires

RÉSUMÉ

On a examiné 8 malades infectés par le *Trichomonas vaginalis* qui avaient reçu un dosage classique de 200 mg. de Flagyl trois fois par jour mais qui n'étaient pas guéris.

Les parasites étaient normalement sensibles au Flagyl, mais 4 des 8 malades avaient des taux de concentration dans le sérum beaucoup plus bas une heure après l'administration de 200 mg. du médicament. Il est probable que certaines rechutes sont causées par un taux bas d'absorption dans le sérum.