Treatment of Vincent's Stomatitis With Metronidazole

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This investigation of the treatment of Vincent's stomatitis with metronidazole (1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole ; "flagyl") was stimulated by the observation by Shinn (1962) of the beneficial effect of this compound on seven patients with Vincent's gingivitis.

Methods

The 15 patients investigated were all Africans attending the Jane Furse Memorial Hospital in Transvaal. The diagnosis of Vincent's stomatitis was made initially on clinical evidence and on the typical bacteriological findings on examination of smears from the lesions—namely, the presence of large numbers of spirochaetes with the morphology of *Borrelia vincentii* and fusiform organisms. Of the 15 patients, 14 had ulcerative gingivitis, while the other had a Vincent's lesion on the right tonsil.

Smears were taken before the beginning of treatment and thereafter twice daily at varying intervals. The initial morning smear was taken before food ; the afternoon smear was taken after food, usually porridge. The bacteriological picture was recorded as shown in the key to Table I, and the clinical progress was noted at regular intervals.

Treatment was solely by the oral administration of 200 mg. of metronidazole three times a day for seven days, except in three young children (Cases 11, 14, and 15), in whom the dose was 100 mg. three times a day for seven days.

The concentration of metronidazole in saliva was investigated in five European volunteers. One volunteer took a single dose of 1 g. of metronidazole on two separate occasions and the other four volunteers took single doses of 200 mg. At the time each sample was taken the mouth was rinsed with water and thereafter the saliva was collected in clean vessels. The samples were assayed polarographically (Kane, 1961).

Results

Table I gives the data on the 15 patients in the trial. The bacteriological findings before and after treatment are also listed, along with the final clinical assessment.

In 14 out of the 15 patients clinical resolution of the lesions was rapid and healing complete, usually by three days. It was difficult in these patients to assess the rapidity with which pain disappeared, relief of pain within a few hours being a feature noted by Shinn (1962). In every case the spirochaetes disappeared quickly, usually within 24 hours after commencement of treatment, but the fusiform organisms were in most cases slower to disappear.

A number of experiments were undertaken in which spirochaetes from the mouth were placed in different concentrations of metronidazole and the changes were observed by dark-ground microscopy. It was found that 4 μg./ml. immobilized the spirochaetes within 15 minutes. The results with lower concentrations were more difficult to interpret, as small thin spirochaetes appeared to persist for up to five hours. While it has not been found possible to isolate and maintain strains of the oral spirochaetes, the compound inhibited the growth of the Reiter strain of *Treponema pallidum* at 0.02 μg./ml. *In vitro* a strain of *Bacteroides* (*Bacteroides necrophorus* NCTC 7155) was inhibited by 4 μg. of metronidazole per ml.

Table II shows the concentrations of metronidazole obtained in the saliva of volunteers dosed with the compound.

TABLE I.—*The Bacteriological and Clinical Response of Fifteen Patients to Oral Metronidazole*

Case No.	Age	Bacterial Assessment* Before Treatment SLV	FF	OO	After Treatment SLV	FF	OO	Assessment of Treatment
1	11	2	1	2	–	–	2	No pain by 48 hours. Healed in 4 days
2	6	3	2	3	0	2	2	Healing in 48 hours. Healed in 3 days.
3	2	3	2	2				Healed when seen at 18 days
4	56	3	2	2	–	–	2	48-hour lesions clean but not healing. Lesions did not heal with metronidazole but eventually did so after course of penicillin
5	24	2	2	3				3 days raw and clean. Did not attend after
6	10	2	2	2	0	0	3	3 days, healing. Healing complete 7 days.
7	5	2	2	3	–	2	3	3 days, healed
8	3	3	2	2	–	0	2	Healed after 3rd day. Previous treatment with gentian violet —no response
9	3	2	2	2				Healed in 6 days
10	40	3	2	1	–	1	2	7 days, healing complete
11	2	2	2	2	0	0	3	4 days, healed
12	2	2	2	1	–	0	3	Healing within 48 hours. Healed in 4 days
13	32	3	1	3	–	1	2	Subjective improvement less than 24 hours. Healed in 6 days
14	2	3	1	0	–	0	2	Healing within 24 hours. Healed in 3 days
15	2	4	3	1	–	–	2	Healing 24 hours. Healed in 48 hours

Smears: SLV = Large spirochaetes (morphologically *Borrelia vincentii*). FF = Morphologically *Bacteroides fusiformis*. OO = Other organisms.
* 0 = Scanty. 1 = Few. 2 = Fair number. 3 = Large number. 4 = Masses.

TABLE II.—*Metronidazole Concentration (μg./ml.) in Saliva After Oral Administration*

Time of Sampling Saliva	200 mg. Metronidazole Volunteer No. 1	2	3	4	1 g. Metronidazole 5a	5b
0	0	0	0	0	0	0
Half hour	0	0	0	0	0·5	
1 hour	1·2	1·3	2·9	1·4	0·5	
2 hours	1·5	1·4	5·0		3·8	
3 „					8·5	
4 „	2·3	2·3	3·5	2·9		
5 „					18·3	12·6
6 „					19·8	14·1
7 „	1·6	1·2	3·5	2·4		12·1
8 „						7·1

Discussion

The treatment of Vincent's stomatitis is at present unsatisfactory, and while it is universally accepted that the condition is associated with the presence of large numbers of spirochaetes and fusiform organisms (normal commensals in the mouth) the pathogenesis remains obscure. However, it is clear that removal of the spirochaetes and fusiform organisms coincides with

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resolution of the lesions. It has been reported (Emslie, Cross, and Blake, 1962) that penicillin chewing-gum is the treatment of choice and that this therapy results in rapid resolution of the lesions. However, there are many who would condemn the use of penicillin in such a fashion (Anderson, 1961), particularly because of the dangers of sensitization to penicillin and possibly of producing resistance in other organisms in the mouth. Recently, objections to systemic penicillin in dental practice have also been pointed out (*Canad. med. Ass. J.*, 1962).

It was an incidental observation that directed attention to the use of metronidazole for this condition, and there is little doubt that this compound when given orally is effective clinically and active against the organisms of Vincent's infection. It is not yet clear whether it is the presence of the compound in the saliva or the presence of the compound in the serum, the concentration of which reaches 4.8 μg./ml. one hour after the oral administration of 200 mg. (Kane, McFadzean, Squires, King, and Nicol, 1961), or both, that is responsible for the clinical effect.

Metronidazole is a well-tolerated compound which has now been administered to tens of thousands of patients for the treatment of trichomoniasis without side-effects, and it would appear to provide a simple and safe therapy for Vincent's infections.

Summary

Fifteen patients with Vincent's stomatitis were treated with metronidazole. In 14 of the 15, clinical resolution of the lesions was rapid, and healing was usually complete within three days. The spirochaetes disappeared within 24 hours, but the disappearance of the fusiform organisms was slower.

Metronidazole is active *in vitro* against the spirochaetes and against one strain of *Bacteroides*.

It is not clear if the compound acts by virtue of its presence in the serum or in the saliva, or in both.

It is suggested that it provides an effective form of therapy without the disadvantages of penicillin.

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Maximal Tubular Resorptive Rate for Inorganic Phosphate in Hyperparathyroidism

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Primary hyperparathyroidism is difficult to recognize when the increased plasma-calcium concentration varies so that it may be within the normal range at times though a tumour is present. Similarly, hypercalciuria is not always found because of renal failure. Moreover, some patients with normal renal function and a raised concentration of calcium in the plasma do not have hypercalciuria. The result is that there is often a need for additional biochemical support before the diagnosis can be established.

In the earlier studies of primary hyperparathyroidism, hyperphosphaturia and hypophosphataemia were found to be characteristic in the absence of renal failure. Albright and Ellsworth (1929) thought the reduced renal resorption of phosphate was the prime effect of parathyroid hormone, changes in calcium metabolism following it. This view was challenged when Collip, Pugsley, Selye, and Thomson (1934) injected parathormone into nephrectomized rats and found a rise in serum-calcium concentration. From this time evidence has accumulated that the main function of the hormone is to raise the ionized-calcium concentration in the plasma by acting directly on bone, and by reversing the protein binding of the ionic calcium (Lloyd, Rose, and Smeenk, 1962). When parathormone is present in excess, whether experimentally or clinically, changes in renal-phosphate excretion must be interpreted against this background of its primary action on the concentration of ionized-calcium in the plasma. Because this is difficult to measure accurately and also because there are many other causes of hypercalcaemia, we have studied the effects of hyperparathyroidism on phosphate excretion with the aim of providing a supplementary method of diagnosis.

In primary hyperparathyroidism Sirota (1953) found in two patients that the maximal resorptive rate for phosphate was depressed, returning to normal after the adenomas were removed. He attributed the alteration mainly to changes in glomerular filtration rate. Anderson (1955a) reported four more patients who had their TmP determined before and after removal of their tumours, in whom the elevation of the TmP to normal values could not be explained by changes in filtration rate and appeared to be due to removal of the tumour. Hiatt and Thompson (1957) confirmed these findings in another patient and also demonstrated a lowered TmP in normal subjects on giving parathormone intravenously. Hyde, Vaughan Jones, McSwiney, and Prunty (1960), however, reported a further series from which they felt that estimation of the TmP was not a reliable way of confirming a diagnosis of hyperparathyroidism because the values fluctuated widely, tending also to change as the test proceeded, possibly because of the high concentration of inorganic phosphorus in the plasma reached during their infusions.

A group of patients with proved hyperparathyroidism were investigated to show the possible usefulness in diagnosis of phosphate clearances under intravenous phosphate loading. The method of determining the TmP has been improved by doing clearances at two raised constant plasma-phosphate concentrations so that a statistical determination of the error could be made and the effect of raising the plasma-phosphate concentration in two steps could be determined.

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