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Radiological abnormalities of the ileum associated with the use of clofazimine (Lamprene; B663) in the treatment of skin ulceration due to *Mycobacterium ulcerans*

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Summary During the course of treatment with clofazimine (Lamprene; B663) for skin ulceration due to *Mycobacterium ulcerans*, a female patient aged 38 developed severe and persistent gastro-intestinal symptoms, with diarrhoea. These became most intense 9 months after starting the drug, during which period the dosage had been 100 mg three times daily.

Barium meal examination of the gastro-intestinal tract showed striking abnormalities of the small bowel particularly ileum, consisting of alternating segments of constriction and dilatation, coarsening of the mucosal folds, and circumscribed 'polypoid' areas. Ileal loops were flexible, but painful on palpation and compression.

On stopping clofazimine, the patient's abdominal symptoms and diarrhoea subsided rapidly. The skin ulceration soon healed completely. Fourteen months after stopping the drug, a repeat barium meal examination of the small bowel was normal.

Although not confirmed by laparotomy or intestinal biopsy, no infective, parasitic or neoplastic cause was found for the intestinal symptoms and radiological abnormalities, and it is considered that they were closely associated with the ingestion of clofazimine. Other cases in the literature are reviewed in which it has been well established that clofazimine may crystallize out in human tissues, including the sub-mucosa of the bowel and intra-abdominal lymph nodes. This drug, which is of great value in the treatment of leprosy, should be used in other conditions with caution, especially if alternative treatment is available. In leprosy, a dose of 100 mg three times weekly has been found effective and acceptable. Doses higher than this should only be used under exceptional circumstances and for short periods of time.

Introduction

Since Browne and Hogerzeil[1] first reported the good effect of clofazimine (Lamprene: B663) in the treatment of leprosy in 1962, extensive experience has fully confirmed their preliminary findings. The main drawback of

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clofazimine is a cosmetic one; even a low dosage imparts a reddish discolouration of the skin, especially in light skins, and the leprosy lesions acquire a blue-black hue. These pigmentary changes usually disappear within months after stopping teatment. In some cases the skin of forearms and legs becomes dry, even ichthyotic. Gastro-intestinal side effects, however, have sometimes been serious when high dosage has been prolonged. They have been fully reviewed by Jopling[2] and since that publication Plock and Leiker[3] have reported severe gastro-intestinal disturbance in 7 out of 17 leprosy patients given 100–600 mg daily for periods up to 5 years, and Mason *et al*[4] have reported eosinophilic enteritis in a Samoan woman who received up to 600 mg/day for 3 years.

Following the original description of a new mycobacterial infection in man by MacCallum and associates in Australia,[5] and the reports of Janssens and other Belgium scientists from the Congo,[6] infections due to *Mycobacterium ulcerans* were recognized in several different parts of the world. Lunn and Rees[7] drew attention to the activity of clofazimine in this infection both *in vitro* and *in vivo*. We report in this article the case of an adult female patient who developed severe abdominal symptoms and radiological abnormalities of the ileum, while under treatment for this condition with clofazimine.

Case report

A religious sister of Italian origin, aged 38, working and living for several years in the vicinity of Kinshasa (Zaire) was admitted on 26 December 1974 to the Leopold II Clinic of the Institute of Tropical Medicine, Antwerp, for a chronic ulceration on the outer side of the left ankle. This lesion began in September 1974 in Zaire and increased regularly in spite of local and general treatment, including various antibiotics. The superficial ulceration was circumscribed by a red, oedematous border with granulomatous tissue in the centre. The patient was afebrile, in good general condition and had no enlargement of the inguinal lymph nodes. An X-ray of the left ankle on admission, revealed only a mild degree of osteoporosis. Biopsy specimens taken from the border of the ulceration were sent to the departments of bacteriology (Professor Pattyn) and histopathology (Professor Gigase) of the Institute on 30 December 1974. Multiple acid-fast bacilli were found in the necrotic tissue but a massive surinfection with *Pseudomonas aeruginosa* hindered a culture on Löwenstein–Jensen medium. Eventually, however, the organism was identified as *Mycobacterium ulcerans* in May 1975. The first biopsies taken from the necrotic tissue were also inconclusive but repeat biopsy in March 1975 revealed histopathological changes typical for this infection.[8]

Clofazimine was started in a dose of 100 mg three times daily after meals. Improvement in the ulcer was slow, but became more evident after a few

weeks. By September, nearly three months after starting the drug, her tolerance decreased, with frequent complaints of nausea, occasional vomiting, diarrhoea and colicky abdominal pain. Stool examination was repeatedly negative for ova, parasites and cysts of pathogenic bacteria. By early 1976, and particularly in April, diarrhoea was persistent and severe; at this stage the patient had taken clofazimine 300 mg daily, to a total of 81 g.

RADIOLOGICAL EXAMINATION OF THE GASTRO-INTESTINAL TRACT

A barium meal examination in April 1976 revealed normal stomach and duodenum, with a moderately increased transit time of barium to the ileo-caecal junction. The jejunum was normal, but ileum showed coarse, oedematous mucosal folds (Fig. 1) with the presence of several polypoid filling defects. These were striking in some of the distal loops (Fig. 2), which though flexible, were painful on palpation.

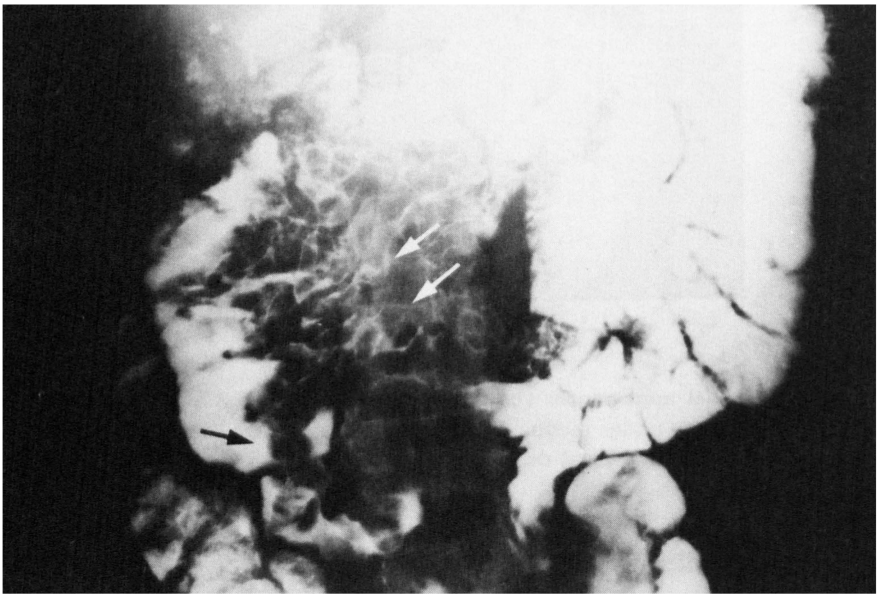


Figure 1. Radiographic appearance of the small bowel after 9 months therapy with clofazimine in a dose of 100 mg three times daily. (8.4.76). Thirty min after intake of barium meal: slight acceleration of the intestinal transit time; normal jejunal findings; coarse, oedematous mucosal folds in ileum (↙) with presence of polypoid filling defects (↘).

Clofazimine was stopped in mid-April 1976 because of the combined patient's continuing symptoms and the radiological findings described above. Her complaints rapidly subsided, although it is of interest that a further barium meal examination in June 1976 (Figs. 3 and 4) revealed slight improvement in

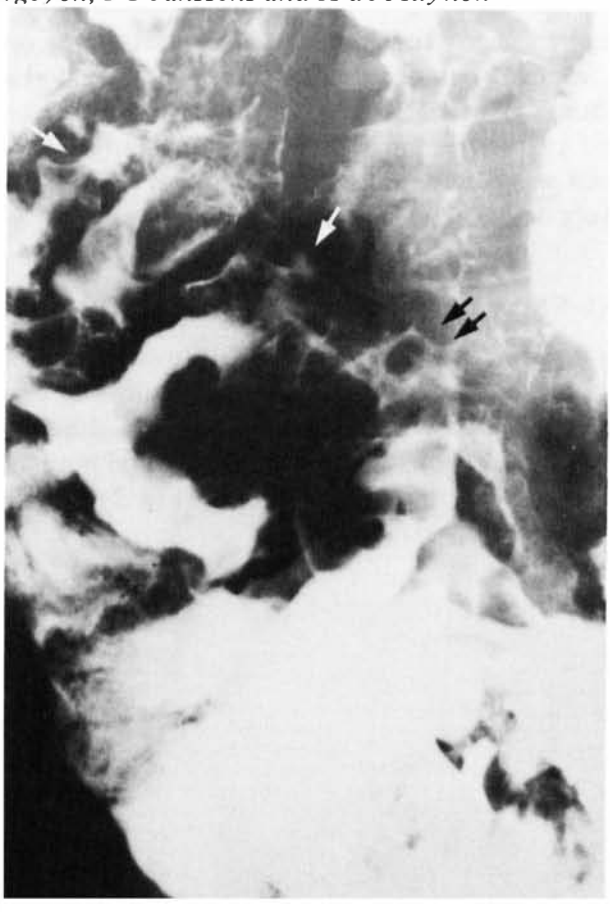


Figure. 2. Small bowel appearances (8.4.76) 60 min after intake of the barium meal. Spot film of distal ileal loops under manual compression shows large, oedematous mucosal folds (↙) with presence of round filling defects (↙↙).

the abnormal findings on first examination; numerous polypoid filling defects remained. Meanwhile, the ulcer healed slowly but surely, and the patient was discharged with the ulcerated area covered by apparently normal skin in July 1976. In June 1977, 14 months after stopping the drug, a third barium meal examination of the small bowel was completely normal in all respects.

Discussion

Although not confirmed by laparotomy or intestinal biopsy, we record the findings in this case, since the clinical and radiological evidence, including improvement on stopping drug therapy, make it very likely, in our opinion,

that intestinal upset was closely associated with the use of clofazimine. Symptoms of the type experienced by this patient have already been recorded in the leprosy literature, and in Table 1 we summarize some of those which have included radiological findings. Enlarged mesenteric and other lymph nodes have been noted in several cases, and it is just possible that some of the polypoid filling defects noted in our barium studies were in part due to hypertrophic nodes containing large amounts of the drug; this, however, is difficult to establish with certainty on radiological examination.

The therapeutic outcome as far as the infection with *Mycobacterium ulcerans* was concerned was excellent in this case, but in retrospect one may question the high doses of clofazimine used. It is possible that an equally good result would have been obtained with considerably lower doses and over a shorter period of time. Clofazimine has found its greater application in the treatment of leprosy, but it is of interest to note that it has recently been reported as effective – in some cases highly so – in the treatment of pyoderma gangrenosum[9, 10, 11] and in discoid lupus erythematosus.[12] Those who use it in conditions other than leprosy and who are less familiar with its side effects in high and prolonged dosage, would do well to note that in leprosy it has generally been found effective and well tolerated in doses in the order of 100 mg three times weekly. The present case emphasizes that doses in excess of this should be used only under exceptional circumstances, and for limited periods of time.

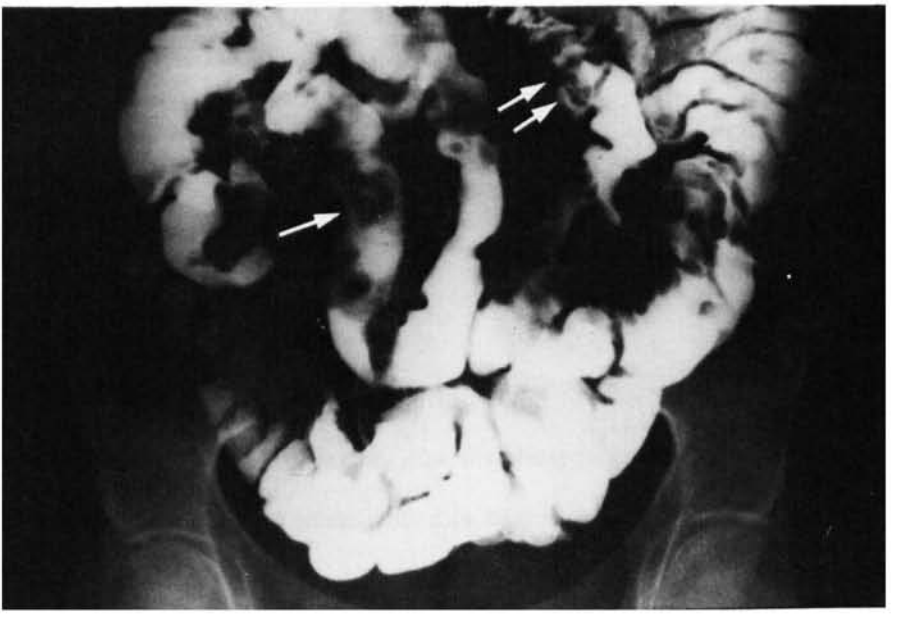
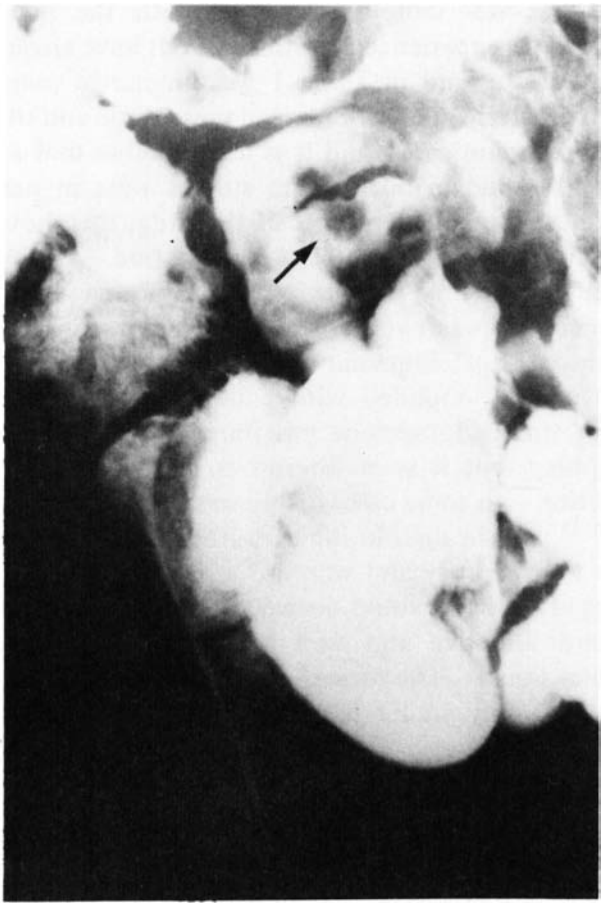


Figure 3



Figures 3 and 4. Small bowel barium meal study (24.6.76). Transverse oedematous mucosal folds (↗↗) are still evident in some ileal segments. Polypoid filling defects remain visible on distal ileal loops (↗).

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Table 1. Effect of lamprene (B663) on gastro-intestinal tract

Authors & Date	No of patients	Treatment dosage	Side effects on GI tract	Laparotomy	Histopathology	Radiology
[13] Williams *et al.*, 1965	2/3	4–20 months up to 600 mg/day	Diarrhoea Pain	–	–	No lesions
[14] Atkinson *et al.*, 1967	1	Several months	Pain Vomiting Loss of weight	–	Normal mucosa Crystals in lamina propria	Coarse mucosa Segmentation
[15] Schultz, 1971	3/123	3–4 months 300 mg/day	1 patient with pain Nausea		–	No lesions
[16] Karat, 1975	2/120	6–13 months	Colicky pain	18 cm of ileum thickened Large lymph nodes	Granuloma on crystals in lamina propria	Narrow ileum Dilatation of proximal loops
[2] Jopling 1976	1	5 years up to 200 mg/day: stopped in 1971	Diarrhoea Epigastric pain	Enlarged lymph nodes 4 years after stopping Lamprene	Crystals in mesenteric lymph nodes, after 4 years	No lesions
[4] Mason *et al.*, 1977	1	3 years, up to 600 mg/day	Pain No diarrhoea Colicky pain Subobstruction?	20 'nodules' in ileal wall Large mesenteric lymph nodes	Granulomas Crystals in lymph nodes	Coarse mucosa Cobblestone aspect of ileal mucosa
de Bergeyck *et al.*, 1980	1	9 months 300 mg/day	Pain Diarrhoea Colicky pains	–	–	Coarse mucosa and polypoid changes in ileum

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