Medical Memoranda

Adynamic Ileus and Nortriptyline

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Anti-depressants are now probably the most widely prescribed of any group of drugs (McQueen, 1963) and are divisible into two broad groups—the monoamine oxidase inhibitors and the iminodibenzyl derivatives. The iminodibenzyl derivatives (imipramine, desmethyl imipramine, amitriptyline, and nortriptyline) have atropine-like action (Benešová and Trinerová, 1963).

Ayd (1961) reported constipation as a side-effect in 60% of patients treated with amitriptyline and 40% of patients treated with imipramine.

A case of adynamic (paralytic) ileus occurring during the administration of amitriptyline was reported by Burkitt and Sutcliffe (1961), and a similar case by Gander and Devlin (1963). Three further cases of adynamic ileus complicating amitriptyline therapy were reported by Milner and Buckler (1964).

The following three case reports describe patients who developed adynamic ileus while receiving nortriptyline.

CASE 1

A spastic, severely subnormal girl, aged 14½ years and weighing 34.6 kg., was put on nortriptyline, 75 mg. each evening, for the control of enuresis. Her general physical health had been good, though she had poor abdominal muscular tone. The only recorded drug treatment this patient had received before the nortriptyline was a course of penicillin.

She was incontinent of urine several times every night. While on the drug she had two completely dry nights out of 14 and wet the bed less frequently than usual during the other 12 nights. After being on the nortriptyline for 12 days she developed constipation and abdominal distension. This was unrelieved by a Durolax suppository administered on the thirteenth and fourteenth days of receiving the drug. Her abdomen became tensely distended, tympanitic, and only a few tinkling bowel sounds could be heard. The nortriptyline was discontinued.

Radiographs showed that every part of the bowel contained gas. At laparotomy gross dilatation of the large bowel extending to the upper rectum was found. The cause of this was not discovered, but it was relieved by intragastric aspiration and the passage of a flatus tube.

Post-operatively she was maintained on intravenous fluids and gastro-duodenal suction for six days. During this time she passed no flatus or faeces. By the seventh day gastro-intestinal function had returned.

CASE 2

An 81-year-old lady was admitted to hospital following an overdose of barbiturates. Later she was given nortriptyline, 25 mg. three times a day. Previously she had received only meprobamate, 400 mg. at night, and vitamins. She complained of constipation and post-prandial epigastric discomfort. Eight days after starting nortriptyline she developed a distended tympanitic abdomen and bowel sounds were absent.

Radiographs of the abdomen showed plentiful gas shadows in the large and small bowel with fluid levels. The rectum was empty and ballooned.

Two days after stopping nortriptyline the patient improved. The abdomen was distended, but normal bowel sounds were audible. After several days regular bowel actions returned.

CASE 3

A 27-year-old woman was admitted to hospital because of abdominal pain—probably psychogenic. She had a history of recurrent abdominal pain and pelvic infection but no history of abdominal distension.

There was no evidence of pathological change either in the abdomen or in the pelvic region. Laboratory investigations disclosed nothing abnormal. She was given nortriptyline, 25 mg. three times a day, and chlorpromazine, 50 mg. three times a day, with paracetamol tablets.

After two days she developed abnormal distension with constipation. One day later the abdomen was tympanitic. Gynaecological opinion was sought and it was again asserted that there was no pelvic cause for her condition. The condition strongly suggested paralytic ileus and the nortriptyline was stopped. Thereafter the distension subsided.

COMMENT

Nortriptyline is 5-(3-methyl-aminopropylidene)10,11-dihydro-5H-dibenzo cycloheptene, given as the hydrochloride. It differs from amitriptyline in having one less methyl group (see Figure).

Animal studies have pointed to the following pharmacological effects of nortriptyline: (1) an atropine-like effect; (2) a central depressant effect; (3) an anti-reserpine action; (4) stimulant as well as depressant behavioural effects. Little has been reported about the human pharmacology of the drug (*B.M.J.*, 1964).

As pointed out by Hollister (1955), "Adverse reactions are the price of effective drugs. Published reports of adverse reactions represent only a small proportion of the more serious reactions. Unless the patient dies or his course is seriously complicated, the incident is likely to be forgotten. Data concerning adverse reactions in out-patients are even more fragmentary than reports of reactions in hospitalized patients."

It is difficult to decide whether such reactions are allergic, owing to interference with natural defences, or due to therapeutic or non-therapeutic effects of drugs (alone or in combination with dietary factors). It is especially difficult to elucidate the mechanism underlying a specific adverse reaction, since most cases are complicated by "polypharmaceutical prescribing."

The three cases described above, of adynamic ileus occurring in association with the administration of nortriptyline, may be regarded as evidence of a specific adverse drug reaction. The five similar cases previously reported occurring in association with amitriptyline therapy seem to support this hypothesis, as the two drugs are closely related.

Case 1 seems especially significant, since the girl, though spastic and weighing only 34.6 kg., received a relatively small dose of nortriptyline (75 mg./24 hr.)—the usual adult dose being 150–200 mg./day. She was on no other drugs and her bed-wetting was reduced, probably owing to the action of the nortriptyline.

The iminodibenzyl anti-depressants seem generally safe, except in association with a monoamine oxidase inhibitor or alcohol (Lockett and Milner, 1965). Amitriptyline and nortriptyline appear more likely to cause potentially dangerous atropine-like side-effects than imipramine or desipramine. It may be that the atropine-like effects of amitriptyline and nortriptyline commonly cause constipation and may precipitate adynamic ileus.

Accordingly the prudent physician might initially prescribe imipramine or desipramine for the treatment of mild and early depressive states, later changing to another anti-depressant only if this were indicated. E.C.T. is probably the treatment of choice for moderate to severe depressions (Robin and Harris, 1962; Greenblatt *et al.*, 1964; Lockett and Milner, 1965; Medical Research Council Psychiatric Committee Report, 1965).

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Rheumatoid Arthritis Presenting with Laryngeal Obstruction

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In recent years there has been an appreciation of the clinical manifestations of cricoarytenoid arthritis and the frequency of its occurrence in rheumatoid disease (Montgomery, 1963; Wolman, Darke, and Young, 1965). The gamut of symptoms includes sensations of fullness and tightness in the throat, dysphagia, pain with speech, dyspnoea, and stridor. In a small proportion of cases there occurs airway obstruction of sufficient degree to warrant an emergency tracheostomy. On visualization of the larynx, redness and swelling over the arytenoids are noted in the acute stage, and roughness and thickening of the mucosa and fixation of the arytenoids with various degrees of narrowing of the glottic chink in the chronic stage. The incidence of cricoarytenoid involvement among patients attending an arthritis clinic was 26% as determined by indirect laryngoscopy (Lofgren and Montgomery, 1962). Seven out of eight patients with rheumatoid arthritis on whom necropsies had been performed showed pathological evidence of cricoarytenoid arthritis (Bienenstock, Ehrlich, and Freyberg, 1963). Most cases have been found among patients with long-standing affection of other joints (Wolman *et al.*, 1965). The appearance of laryngeal disease as the first manifestation of rheumatoid arthritis has not, to our knowledge, been reported. Such a case is described below.

CASE REPORT

In October 1962 a 54-year-old man, previously healthy, developed dyspnoea and stridor. This progressed rapidly, leading to emergency hospitalization after several days. On laryngoscopy the vocal cords appeared thickened and moved poorly. The glottic chink was markedly narrowed. Tracheostomy was performed immediately. On subsequent examinations over the next 10 days there was little change.

Multiple biopsies from the cords and surrounding tissues showed "chronic inflammation." With the tracheostomy tube still in place, the patient returned to work and was well until March 1963, when he developed a cough and sore throat. After two weeks of antibiotic treatment his upper respiratory symptoms had improved, but he had a rather sudden onset of severe joint pain and swelling. He

was admitted to hospital and improved after treatment with cortisone, but the joint symptoms recurred when attempts were made to discontinue the medication. In August 1963, on admission to the Lemuel Shattuck Hospital, a diagnosis of rheumatoid arthritis was made on the basis of swelling and limitation of motion in multiple joints, rheumatoid nodules, positive latex-fixation test, and characteristic radiographic changes. On laryngoscopy under general anaesthesia there was no active or passive motion at either cricoarytenoid joint; the glottic chink was narrow but adequate. There was a nodular swelling at the posterior aspect of the right cord. Biopsy from this area showed a chronic inflammatory reaction with infiltration of lymphocytes, histiocytes, and plasma cells. His tracheostomy tube was removed without recurrence of respiratory distress, but the stoma has not closed completely after two years. Progressive deformity during this period has confirmed the diagnosis of rheumatoid arthritis.

COMMENT

The patient had no joint symptoms until five months after the appearance of laryngeal obstruction severe enough to require a tracheostomy. In view of later laryngoscopic findings typical of chronic cricoarytenoid arthritis it is reasonable to suppose that his earlier obstruction was due to acute cricoarytenoid involvement, though the diagnosis was not made at the time.

Chronic laryngeal symptoms and acute obstruction may have many causes. The physician should consider cricoarytenoid arthritis even in patients without urgent or obvious joint signs and symptoms; careful inquiry and examination may reveal evidence of mild arthritis. The diagnosis can usually be made without difficulty by indirect laryngoscopy. The present case points out that the cricoarytenoid joint may be, as is true for virtually every other joint in the body, the site of the initial appearance of rheumatoid arthritis.

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