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(*Accepted 4 March 1981*)

SHORT REPORTS

Intramuscular cimetidine is safe and acceptable

Cimetidine is available as tablets, a syrup, or a preparation for intravenous injection, but in some patients administration by the intramuscular route is desirable. We therefore studied the safety and acceptability of intramuscular injection of cimetidine.

Patients, methods, and results

We studied 27 men and 11 women aged 22-79 (median 65·5) years. Twenty-five had duodenal or gastric ulceration, five oesophagitis, two duodenitis, two dyspepsia, and one each gastric erosions, bleeding oesophageal varices, a deformed duodenal bulb, and pruritus. All were inpatients already receiving oral cimetidine 200 mg thrice daily plus 400 mg at night.

Nineteen patients were studied in a double-blind cross-over trial. On the first day the midday dose of cimetidine was replaced by either intramuscular cimetidine 200 mg and a placebo tablet, or a placebo injection and cimetidine 200 mg by mouth. The next day the alternative treatment was given, the order being randomised. The two injections were given into opposite buttocks. Blood samples for creatine kinase activity were taken immediately before, and 24 hours after, each injection. Pain at the injection site was assessed as none, mild, moderate, or severe 10 minutes and six hours after each injection, and at the same time the site was inspected for any local reaction. The remaining 19 patients received intramuscular cimetidine 200 mg six hourly for 24 hours, oral cimetidine being omitted. Each injection site was numbered serially, and two to four hours after the last injection the appearance of each site was noted.

The cimetidine injection (200 mg in 2 ml) for intramuscular use was the same formulation as the standard intravenous preparation. The placebo injection was 2 ml 0·9 % sodium chloride. All injections were given by trained nursing staff. Written informed consent was obtained from each patient, and the study had the approval of the hospital ethical committee.

After a single intramuscular injection of cimetidine one patient reported mild pain at 10 minutes that had resolved by six hours and another had moderate pain at six hours that had disappeared by the next day. After placebo injection two other patients reported mild pain at six hours but none had pain at 10 minutes. The injection sites appeared normal except after a placebo injection in one patient, who had erythema at 10 minutes that had resolved by six hours. Serum creatine kinase activity remained normal after all injections. One patient felt light-headed transiently after injection of cimetidine, while another complained of aching in the buttock for a few hours after both injections.

Of the 19 patients receiving intramuscular cimetidine six hourly, 14 had no reaction at any of the injection sites. One patient had erythema with some swelling at one site and erythema alone at another site. The remaining four patients had erythema at one injection site. No adverse events occurred and no patient had to be withdrawn from either part of the study.

Comment

Our study showed that reactions at the injection site were uncommon and as likely with placebo as with intramuscular cimetidine. Though parenteral cimetidine may be overused by hospital doctors,[1] oral medication cannot be given to patients with an ileus or persistent vomiting. Because of occasional reports of hypotension[2] and cardiac arrhythmias[3] after intravenous cimetidine many hospitals do not allow nurses to give the drug by this route.

Peak plasma concentrations after intramuscular cimetidine are 30-50% of those achieved after similar intravenous doses, and there is no significant difference in bioavailability (D Rowley-Jones, personal communication). Intramuscular administration of cimetidine is therefore a convenient and safe alternative to intravenous administration when the parenteral route is indicated.

This paper was based on work presented to the first World Conference on Clinical Pharmacology and Therapeutics, London, August 1980.

We thank the special trustees of St Thomas's Hospital, and Smith, Kline and French Laboratories for supplying the cimetidine and placebo tablets and injections.

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(*Accepted 18 February 1981*)

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Familial colorectal cancer and hereditary brachydactyly

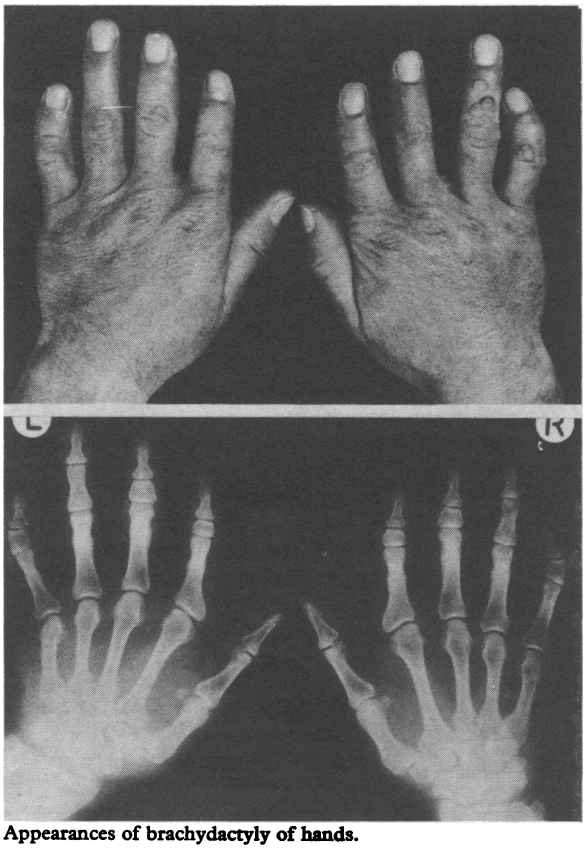
Soft-tissue and skeletal abnormalities are associated with colorectal cancer in Gardner's, Turcot's, and Peutz-Jeghers's syndromes. Detailed radiological studies have shown osteomas in most patients with familial polyposis coli.[1] Osteomas and fibromas may also be associated with colorectal cancer in the absence of multiple polyposis.[2] To our knowledge the only other reported skeletal abnormality associated with colorectal cancer is the nail-patella syndrome.[3] We describe a family with hereditary brachydactyly associated with colorectal cancer.

Family study

The brachydactyly consisted of hypoplasia of the second, third, and fifth middle phalanges of both hands (figure), the severity of the condition varying among family members. In some cases the hypoplasia was restricted to the fifth finger, whereas in others the fourth and fifth metacarpals were also affected. One subject had changes in the segmental ratios of phalanges and metatarsals in both feet.

Brachydactyly had been present in five out of seven siblings. Three of the five had died of colorectal cancer, and the other two had died of unrelated disorders at 29 and 68 years of age. One of the two siblings without hand

deformity was well (aged 69), and the other had died at 70 years from coronary artery disease. Out of 16 members of the next generation (including two with brachydactyly), 11 aged 45-54 years were screened for occult blood and by flexible sigmoidoscopy. One was found to have adenomatous polyps, and two metaplastic polyps; only one of these, however, had brachydactyly.



Appearances of brachydactyly of hands.

Comment

Features of the brachydactyly in this family were similar to those described by Vidal,[4] and the variation in severity among family members has been reported.[5] The association of the condition with colorectal cancer may have been due to chance or may be a true syndrome, permitting identification of patients at risk for colorectal neoplasia. We should be interested to hear from others who may have observed the association.

In view of the high incidence of colorectal cancer in this family we propose to keep the family under periodic surveillance.

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(*Accepted 9 February 1981*)

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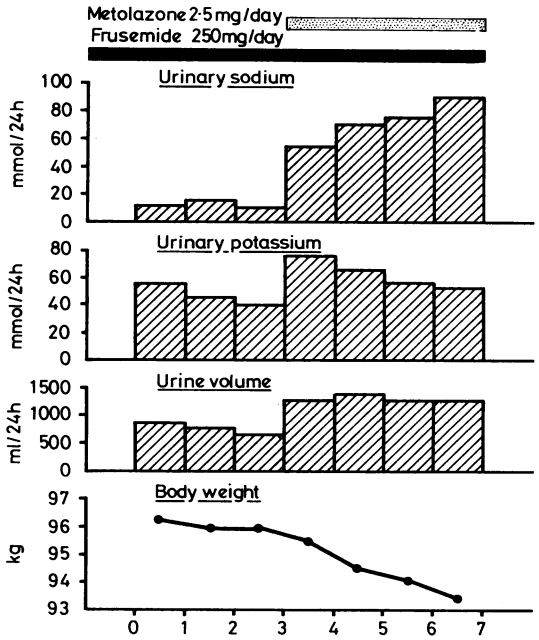
Synergistic action of metolazone with "loop" diuretics

Metolazone (Metenix) and frusemide are synergistic diuretics. Six out of seven patients with resistant oedema responded with appreciable diuresis after using this combination.[1] In other clinical studies, adding metolazone to frusemide 320 mg[2] or 500 mg[3] daily given for cardiac, hepatic, or renal oedema promoted a prompt and substantial diuresis in all patients. Before 1978 we gave metolazone 5 mg daily to nine patients with oedema resistant to frusemide 80-750 mg daily and noted an immediate increase in urinary volume and solute excretion with associated weight loss in every case. Further experience confirmed the high proportion of patients with frusemide-resistant oedema who develop a satisfactory diuresis after frusemide-metolazone combination. Moreover, it became evident that synergism with metolazone occurs with several "loop" diuretics, including frusemide, ethacrynic acid, bumetanide, and piretanide.

Case reports

Case 1—A 50-year-old man with gross oedema from the nephrotic syndrome was found to have impaired renal function (serum albumin concentration 15 g/l, creatinine concentration 475 mmol/l (5·4 mg/100 ml), glomerular filtration rate 33·4 ml/min/1·7 m²). Renal biopsy showed membranoproliferative glomerulonephritis. Frusemide was increased to 250 mg daily, and oedema persisted. Metolazone 2·5 mg daily was therefore added, and the oedema disappeared over two weeks. The figure shows the changes in urinary volume, electrolyte excretion, and body weight.



Case 1. Changes in urinary volume, electrolyte excretion, and body weight after adding metolazone to frusemide.
Conversion: SI to traditional units—Urinary sodium and potassium: 1 mmol/24 h = 1 mEq/24 h.

Case 2—A 65-year-old man with ischaemic heart disease and congestive cardiac failure of five years' duration was admitted with gross oedema after stopping frusemide on account of deafness. Ethacrynic acid was substituted and the dosage increased to 100 mg daily. Oedema persisted. Mean urinary excretion was 1·96 l/24 h, with sodium 100 mmol(mEq)/24 h, chloride 172 mmol(mEq)/24 h, and potassium 102 mmol(mEq)/24 h. Metolazone 2·5 mg was added. Mean urinary excretion rose to 2·78 l/24 h, with sodium 174 mmol/24 h, chloride 239 mmol/24 h, and potassium 144 mmol/24 h. The mean fall in body weight when using ethacrynic acid alone was 0·1 kg/day; after adding metolazone this increased to 0·3 kg/day. Potassium supplements were needed for hypokalaemia.

Case 3—A 71-year-old man with ischaemic heart disease of eight years' duration developed congestive cardiac failure with gross oedema. Blood pressure was 140/80 mm Hg. He was treated with bumetanide 4 mg daily, and mean body weight fell by 0·16 kg/day. Mean urinary excretion was 1·02 l/24 h, with sodium 86 mmol/24 h, chloride 135 mmol/24 h, and potassium 68 mmol/24 h. Metolazone 5 mg a day was added, and mean