SHORT REPORTS

Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine

Skin eruptions may occur in up to 1.9% of patients receiving cimetidine, an incidence marginally higher than that found in patients receiving placebo.¹ The eruption most commonly described is mild, non-specific, erythematous, and maculopapular. Severe reactions, including bullous erythema multiforme have, however, been reported.² Erythema annulare centrifugum is a pruritic, erythematous eruption beginning as a papule and progressively enlarging at the margin while clearing at the centre. It has been reported occasionally to be associated with underlying malignancy, dermatophyte infection, or drug treatment, though usually no cause is found and the lesions eventually disappear spontaneously after months or years.^{3,4} We describe a patient in whom erythema annulare centrifugum complicated long-term cimetidine treatment.

Case report

A 69-year-old woman first presented in February 1980 with a three-year history of increasing diarrhoea, nausea, and vomiting and a weight loss of 7 kg over 12 months. Upper gastrointestinal endoscopy showed large gastric folds and severe erosive duodenitis in the first and second parts of the duodenum. A high basal gastric acid output did not increase with pentagastrin and persistently raised serum gastrin concentrations failed to suppress after secretin. Zollinger-Ellison syndrome was diagnosed. Complete control of her symptoms and a gain in weight occurred after treatment with cimetidine 200 mg thrice daily and 400 mg at night.

Six months after starting cimetidine a skin eruption developed, initially in the inguinal region and axillae, but soon becoming more widespread with moderate to severe pruritus. Individual lesions were fixed and lasted days to weeks. The eruptions consisted of slightly infiltrated circular erythematous lesions varying from 0.5 to 5.0 cm in diameter. The lesions tended to flatten and clear in the centre while activity remained at the edge. There was no scaling of the lesions at any stage. The inguinal and axillary regions were the most severely affected, but the lesions also occurred on the buttocks and upper trunk.

Comparative molecular structures of ranitidine and cimetidine.

Withdrawing cimetidine resulted in resolution of the eruption within three weeks, and treatment in that time consisted of simple emollients, including 1% menthol, 1% camphor in aqueous cream topically, and chlorpheniramine 4 mg thrice daily by mouth. These were stopped when the eruption settled. Gastrointestinal symptoms recurred, however, and could not be controlled by high-dose antacid treatment combined with anticholinergics. Reinstating cimetidine resulted in a return of the erythema annulare centrifugum within a week. Cimetidine was again discontinued and treatment with ranitidine 150 mg twice daily was begun, with continued control of her gastrointestinal symptoms. The eruption resolved over three weeks and had not recurred six months later.

Comment

A skin eruption clinically consistent with erythema annulare centrifugum developed during the first six months of treatment with cimetidine for Zollinger-Ellison syndrome. That the eruption was directly related to cimetidine was supported by its resolution after withdrawal of the drug and its reappearance on rechallenge. There was no cross-reaction with ranitidine, another H₂-receptor antagonist (figure), which probably reflected the differences in molecular structure between cimetidine and ranitidine.

¹ Kruss DM, Littman A. Safety of cimetidine. *Gastroenterology* 1978;**74**: 478-83.

² Ahmed AH, McLarty DG, Sharma SK, Masawe AEJ. Stevens-Johnson syndrome during treatment with cimetidine. *Lancet* 1978;ii:433.

³ Lazar P. Cancer, erythema annulare centrifugum, autoimmunity. *Arch Dermatol* 1963;**87**:246-51.

⁴ Shelley WB. Erythema annulare centrifugum due to *Candida albicans*. *Br J Dermatol* 1965;**77**:383-4.

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Herpes-zoster myelitis treated successfully with vidarabine

Myelitis is a rare complication of herpes-zoster infections that may progress to severe paralysis and death.¹ We report here a case of ascending myelitis after an attack of shingles in which there was a rapid improvement after treatment with vidarabine.

Case report

A 66-year-old man developed herpes zoster of the third and fourth thoracic (T3-4) dermatomes on the right. Two weeks later he noticed weakness of his right leg which caused him to drag the leg while walking. The weakness progressed so that his leg would give way while he was standing, and within a further two weeks he developed weakness of his right arm and hand. At this time he began to experience episodes of paraesthesia affecting his trunk and legs together with a more persistent numbness of his left leg.

He was admitted six weeks after his first symptom, and at this time he had a global weakness of his right arm (MRC grade 4) and right leg (grade 4 proximally, grade 2 distally). He had impaired light touch sensation below T4 on the right and impaired pain and temperature sensation below T6 on the left. Joint-position sense was impaired bilaterally at the toes, and vibration sense was impaired bilaterally below the sternum. Both knee and ankle jerks were brisk, and plantar responses were extensor. Haemoglobin concentration and white cell and platelet counts were normal and remained so throughout the illness. Radiography of the cervical and thoracic spine showed spondylitic changes. Findings on myelography were normal. Complement-fixing antibodies to varicella zoster in the serum were 1/32 (19 December 1980), 1/512 (5 January 1981), 1/1024 (20 January), 1/256 (2 February); in the cerebrospinal fluid they were 1/4 (13 January), less than 1/2 (20 January); cerebrospinal fluid protein concentration was 0.3 g/l, two lymphocytes/ μ l (19 December 1980); cerebrospinal fluid protein concentration was 0.8 g/l, acellular (13 January 1981).

Deterioration continued after admission so that in the eighth week of his illness grip in the right hand became very weak (grade 2) and there was increased weakness in the right leg (grade 2 proximally, grade 0 distally). All modalities of sensation were now impaired bilaterally with a sensory level at T4 on the trunk, but in addition light-touch sensibility was impaired to the C6 dermatome on the right arm. Within a further week he had difficulty passing urine and was experiencing paraesthesia and numbness on the right side of his face. He was treated with vidarabine (5 mg/kg/day) for 10 days 10 weeks after the onset of his shingles. The treatment caused no side effects or haematological disturbances. Within three days of the start of the

treatment the facial paraesthesia had ceased. After a further two days sensation was normal in the right arm and the sensory level on the trunk had descended to T6 on the right and T8 on the left. Grip in the right hand had improved (grade 3-4) and he was again able to move his right leg at the hip and knee (grade 3) and ankle (grade 2). After 10 days' treatment he was able to walk with a single stick. Five weeks after the start of the treatment he was able to walk unaided, having only slight proximal weakness in the right leg. Power was normal in his right hand, though dexterity was impaired. Sensation was normal, with the exception of vibration sensation, which was impaired below the sternum. The plantar response was extensor on the right, and reflexes were brisk in the right leg.

Comment

Herpes-zoster myelitis is rare, and in their review of the published reports Rose *et al*¹ found only seven reported cases and added a case of their own. At necropsy their case showed extensive haemorrhagic necrosis of the spinal cord. The neurological symptoms and signs developed four days to six weeks after the herpetic rash, and the myelitis progressed over hours, days, or weeks. Four of the patients had died while the others recovered with variable neurological deficits. Although an autoimmune response had been proposed as the process causing central nervous system damage after herpes-zoster infections,^{1,2} Hogan and Krigman³ subsequently showed direct invasion of the spinal cord by herpes-varicella virus in a case of ascending myelitis.

In our patient symptoms and signs of myelitis progressed inexorably for four weeks until treatment with vidarabine was begun. Vidarabine is an antiviral agent which has proved valuable in the treatment of herpes-simplex encephalitis and in herpes-zoster infections in immunocompromised patients.⁴ Its use has not been reported in herpes-zoster myelitis. Within days of starting the treatment our patient began to improve, and within five weeks he could walk unaided. Although herpes-zoster myelitis may improve spontaneously,¹ we think that the improvement was so dramatic after the start of treatment that it was not a mere coincidence. We therefore suggest that a parenteral antiviral agent should be given as soon as zoster myelitis is diagnosed.

¹ Rose FC, Brett EM, Burston J. Zoster encephalomyelitis. *Arch Neurol* 1964;**11**:155-72.

² Appelbaum E, Kreps SI, Sunshine A. Herpes zoster encephalitis. *Am J Med* 1962;**32**:25-31.

³ Hogan EL, Krigman MR. Herpes zoster myelitis: evidence for viral invasion of spinal cord. *Arch Neurol* 1973;**29**:309-13.

⁴ Whitley R, Alford C, Hess F, Buchanan R. Vidarabine: a preliminary review of its pharmacological properties and therapeutic use. *Drugs* 1980;**20**:267-82.

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Gastric mucus secretion in ranitidine-treated patients

Ranitidine is a new H₂-receptor antagonist which at a dosage of 200 mg daily is reportedly as effective as cimetidine in the short-term treatment of duodenal ulcer.¹ Despite the remarkable antiulcer properties of cimetidine, this drug alters the composition of gastric mucus,²⁻³ which apparently influences the rate of ulcer recurrence when treatment is stopped. The quality of gastric-soluble mucus appears to affect duodenal as well as gastric mucosal defences. Maintenance treatment with carbenoxolone after healing of duodenal ulcers by cimetidine is associated both with return to normal of the gastric mucus and with a comparatively low relapse rate once treatment is stopped. In contrast patients healed and maintained with cimetidine whose gastric mucus is of persistently poor quality show a significantly higher rate of ulcer recurrences.³

Acute intravenous infusion of ranitidine failed to affect pentagastrin-stimulated output of N-acetyl-neuraminic acid, suggesting a lack of effect on mucus secretion.⁴ Nevertheless, the influence of prolonged ranitidine administration on gastric mucus has not been investigated.

Indeed, the effect of a single dose of the drug cannot be taken to predict the behaviour of mucus in ranitidine-treated patients. While gastric mucus secretion is unaffected by a single intravenous dose of cimetidine,⁴ appreciable alterations in the mucus properties are detectable after prolonged oral administration.²⁻³ We have studied the behaviour of gastric mucus in patients given ranitidine for one month.

Patients, methods, and results

Twelve outpatients aged 26-73 years with endoscopically proved duodenal ulcer were given ranitidine 150 mg twice daily for four weeks. Treatment was then stopped and all patients subjected to endoscopy. Neutral and acid mucoproteins in fasting gastric juice were measured before and after treatment and a "mucoprotective index" calculated as: $(B/(A+B)) \times 100$, where A=acid mucoprotein complex (g/l) and B=neutral glycoprotein complex (g/l), the latter containing the bulk (75.2%) of carbohydrates.^{2,3}

After the four weeks of ranitidine endoscopy showed complete healing of the ulcers in 11 of the 12 patients. No significant changes in mucoprotective indices were found after ranitidine (mean values before and after treatment 69.9 ± SEM 1.23 and 69.8 ± 0.9 respectively; $p > 0.05$ (Student's *t* test for paired data)).

Comment

Our results show that, unlike cimetidine, ranitidine does not influence gastric mucus secretion. This suggests that the cimetidine-induced alterations in gastric mucus are not related to the H₂-receptor blockage but are due to the drug itself. Differences between the two drugs have been reported. Aminopyrine metabolism, for example, is altered by cimetidine but is unaffected by ranitidine.⁵ Indeed, ranitidine appears to be structurally different from cimetidine, being a substituted furan derivative with no imidazole ring; and this may account for different behaviour of the two drugs in many respects. Whether the lack of damaging effects on gastric mucus by ranitidine will result in a lower rate of ulcer recurrence in healed patients remains to be determined.

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¹ Langman MJS, Henry DA, Bell GD, Burnham WR, Ogilvy A. Cimetidine and ranitidine in duodenal ulcer. *Br Med J* 1980;**281**:473-4.

² Guslandi M, Testoni PA, Fesce E, Ballarin E, Tittobello A. Behaviour of gastric mucin during pirenzepine treatment: a double-blind controlled study versus cimetidine. *Current Therapeutic Research* 1980;**27**:714-8.

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⁴ Domschke W, Lux G, Domschke S. Furan H₂-antagonist ranitidine inhibits pentagastrin-stimulated gastric secretion stronger than cimetidine. *Gastroenterology* 1980;**79**:1267-71.

⁵ Henry DA, MacDonald IA, Kitchingman G, Bell GD, Langman MJS. Cimetidine and ranitidine: comparison of effects on hepatic drug metabolism. *Br Med J* 1980;**281**:775-7.

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Primary systemic amyloidosis presenting as extreme hyperlipidaemia with tendon xanthomas

Hyperlipidaemia is not a recognised complication of amyloidosis in the absence of nephrotic syndrome. We describe a patient with primary systemic amyloidosis in whom tendon xanthomas associated with extreme rise in plasma remnant and low-density lipoproteins were presenting features and preceded detectable renal disease.