SHORT REPORTS

Severe headache and disturbed liver function during treatment with zimelidine

Zimelidine is effective in the treatment of depression.¹ Both zimelidine and its pharmacologically active metabolite norzimelidine act by inhibiting the re-uptake of 5-hydroxytryptamine by neurones.² In comparison with tricyclic antidepressant drugs zimelidine is fairly free of side effects.¹ We report two cases in which adverse effects developed during a clinical trial of the drug.

Case reports

Case 1—A 34-year-old woman was prescribed zimelidine 200 mg per day for depression of three months' duration. Two weeks later she was admitted to hospital complaining of severe frontal headache and photophobia. The headache had gradually increased over three days, was exacerbated by movement and coughing, and was associated with muscular aches, vomiting, and shivering. The patient was afebrile and full systematic examination showed no abnormality. Lumbar puncture yielded normal cerebrospinal fluid. Results of liver function tests (previously normal) were disturbed, with enzyme activities of: aspartate aminotransferase 56 IU/l; alanine aminotransferase 193 IU/l; and γ -glutamyltransferase 173 IU/l. Bilirubin concentration and alkaline phosphatase activity were normal. Zimelidine was withdrawn. The headaches and photophobia subsided over the next week and liver enzyme activities fell progressively to normal over 10 days. All other investigations gave normal results.

Case 2—A 44-year-old man presented with one month's history of anxiety and depression. Previous history included gastric surgery seven years earlier and outpatient investigation of headache after head injury (no organic cause found) five years earlier. Two weeks after being prescribed zimelidine 200 mg per day he was admitted to hospital complaining of headache, which had gradually increased in severity over the preceding week. It was worsened by coughing and head movement and was associated with photophobia and muscular aches. He was afebrile and full systematic examination gave normal results, except for a candida throat infection. Lumbar puncture produced normal cerebrospinal fluid at a pressure of 320 mm of cerebrospinal fluid. Liver function tests (previously normal) showed: aspartate aminotransferase 131 IU/l; alanine aminotransferase 333 IU/l; γ -glutamyltransferase 140 IU/l; and alkaline phosphatase 210 IU/l. Bilirubin concentration was normal. Zimelidine was withdrawn. The next day his temperature rose to 38.4°C, but thereafter he remained afebrile. He was treated with paracetamol and oral nystatin only. The headache and photophobia settled over 48 hours. Hepatic enzyme activities fell steadily and were completely normal one month later. Results of other investigations were normal.

Comment

Both patients were prone to functional illness and had previously complained of headache. In both cases, however, the headache now reported was dramatic in severity and distinctive in character. Though this type of headache and the abnormal liver function may not have been causally linked, the combination of features was so similar that a relation to zimelidine was suggested. Improvement began when the drug was withdrawn, and no other cause could be identified. In both cases results of serological tests for recent viral infection were normal, and hepatitis antibody titres showed only post infection with hepatitis A. Before admission, case 1 had taken Paramol-118 (dihydrocodeine tartrate and paracetamol; Duncan, Flockhart), and case 2 had been taking various analgesics for several months.

Though headache has been reported in connection with zimelidine treatment,³ there are no previous reports of this atypical headache syndrome caused by the drug. The mechanism that produces headaches may be related to a fall in the blood concentration of 5-hydroxytryptamine⁴ similar to that seen in migraine.⁵

There is one report of zimelidine causing fever and jaundice in a patient with a history of hepatic reactions to other antidepressant drugs¹ but no reports of the disturbance in liver function described here.

More than 100 patients have been treated with zimelidine in Glasgow. No others have shown these adverse effects.

¹ Copen A, Rama Rao VA, Swade C, Wood K. Zimelidine: a therapeutic and pharmacokinetic study in depression. *Psychopharmacology (Berlin)* 1979;**63**:199-202.

² Siwers B, Ringberger VA, Tuck JR, Sjoquist F. Initial clinical trial based on biochemical methodology of zimelidine (a serotonin uptake inhibitor) in depressed patients. *Clin Pharmacol Ther* 1977;**21**:194-200.

³ Syvalahti E, Kangasniemi P, Ross SB. Migraine headache and blood serotonin levels after administration of zimelidine: a selective inhibitor of serotonin uptake. *Current Therapeutic Research* 1979;**25**:299-310.

⁴ Ross SB, Jansa S, Wetterberg L, Fyro B, Hellner B. Decreased blood levels of 5-hydroxytryptamine by inhibitors of membranous 5-hydroxytryptamine uptake. *Life Sci* 1976;**19**:205-10.

⁵ Somerville BW. Platelet bound and free serotonin levels in jugular and forearm venous blood during migraine. *Neurology (NY)* 1976;**26**:41-5.

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Raised intraocular pressure—time for a rethink on referral procedure?

During 1981 one person in seven visited an ophthalmic optician,¹ and one in eight of these was referred to a medical practitioner.² There is no information on whether the uptake of ophthalmic services is evenly spread within and between practices or on the evenness with which opticians recommend a further opinion. Again there is no detailed information on whether referral forms to general practitioners (OSC 1Z) regularly reach their intended destination or about how they are dealt with when they do. There are ample grounds for believing that the system of referral can irritate all affected by it, whether patients, opticians, general practitioners, or ophthalmologists. As preparation for a talk to opticians on "communication," we arranged a necessarily simple research project. We tested the hypothesis that, at least for patients found by opticians to have raised intraocular pressure, direct referral from optician to ophthalmologist might be better for the patient and would be acceptable to general practitioners—despite infringement of the principle of general-practitioner responsibility for all referral decisions on behalf of his patients.

Methods and results

The records of 100 consecutive new patients seen at an ophthalmology outpatient clinic after referral on form OSC 1Z were reviewed. Copies of five representative OSC 1Z forms (with all identifying details obscured) were then sent to 50 general practitioners selected at random. The doctors were asked for their views on several matters relating to referral in general and in relation to the enclosed selection.

Referrals—In the series of 100 patients attending the clinic, the final diagnosis was cataract in 28 patients, glaucoma or possible glaucoma in 18 (62% of the 29 patients in whom opticians suspected the diagnosis), and senile macular degeneration in 10. Other disorders (ranging from physiological cupping to retinal vein thrombosis) were noted in 28 patients and no abnormality reported in 16. Although the delay caused by referral from the optician to the general practitioner was normally less than two weeks, it was between two weeks and eight weeks in 12 cases and over two months in four cases: for one patient in six with suspected glaucoma, the delay exceeded two weeks. Due to hospital waiting lists the waiting time from general practitioner to ophthalmologist averaged a further six weeks but this was normally less for patients with raised intraocular pressure. In 43 cases the general practitioner passed on the OSC 1Z without adding further information.

General practitioner questionnaire—Forty-five of the 50 doctors replied to the questionnaire and one further had retired. Thirty-nine of the 45 respondents estimated they referred on to ophthalmologists 70% or more of patients about whom they received an OSC 1Z. Two of the specimen OSC 1Z forms related to patients with raised intraocular pressure. All 45 doctors would have referred a 48-year-old with pressures of 35 mm in each eye (who

did not have glaucoma) and 44 of 45 would have referred a 71-year-old with pressures of 25 and 27 mm (who did have glaucoma). Thirty-nine of 45 agreed that the optician should be able to refer direct to ophthalmologists for suspected glaucoma (with the general practitioner receiving a copy letter) and 31 of 45 expressed the view that direct referral for some further abnormalities would be acceptable.

Comment

The principle that referral to consultants should be through the general practitioner is good and should be breached only for good reason. Precedents are available: dentists refer directly to oral surgeons, and, of course, accident and emergency services often allow patients direct access to specialist services.

The modern ophthalmic optician sees his patients in excellent conditions and with increasingly sophisticated instrumentation available. When he feels anxious about a patient, and particularly when he finds raised intraocular pressure, few general practitioners will wish to delay referring the patient to an ophthalmologist. It seems logical to re-examine the present policy of referral. Opticians, general practitioners, and ophthalmologists will probably all want such discussions to reflect local traditions and services but probably a national agreement between representatives of the three groups will need to be a preliminary stage.

In the end the two issues that must take priority are that patients are seen by the most appropriate professionals with the least delay and that all clinical information relating to individual patients is efficiently co-ordinated. Our findings suggest the time may be right for some re-adjustment of the present policies relating to ophthalmic illnesses.

We thank Professor C I Phillips and the consultants at the Princess Alexandra Eye Pavilion for access to their records and the many general practitioners who replied to our questionnaire.

¹ Information Services Division, Common Services Agency for the Scottish Health Service. General ophthalmic services: work load and costs. In: *Scottish Health Statistics 1980*. Edinburgh: HMSO, 1982:128.

² House of Lords. *Official report (Hansard)* 1982 Feb 18;427:col 728.

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Osteoporosis and calcitonin deficiency

Generalised osteoporosis in young people is often secondary to an endocrine disorder such as thyroid or adrenal hypersecretion or a connective tissue disorder such as osteogenesis imperfecta. Juvenile osteoporosis is a distinct entity that develops in childhood and usually resolves spontaneously. We describe a patient who developed severe osteoporosis after puberty; he was found to have calcitonin deficiency, which may have been causally related to his bone disease.

Case report

A 19-year-old man presented with a three-year history of pain in his feet, knees, and spine together with progressive loss in height of 10 cm. For the previous 12 months he had been incapacitated by his pain. At the age of 16 he had fractured his right ankle and wrist in a motorcycle accident. A further motorcycle accident at the age of 18 had resulted in fractures of the right ankle and tibia. Normal puberty had been achieved from age 14 to 16 years. There was no history of drug or alcohol abuse and no relevant family history.

Clinical examination showed dorsal kyphosis with tenderness over the lower dorsal and lumbar spines. Height was 172 cm, span 181 cm, and weight 56.7 kg. There were no other clinical abnormalities. Investigations (table) showed normal renal, hepatic, pituitary, thyroid, adrenal, and gonadal function. Haematological variables were normal, and sex chromosome karyotype was normal XY. Radiological studies showed generalised osteoporosis with multiple biconcave wedged vertebral bodies. Biopsy of the iliac crest after tetracycline double labelling showed severe osteoporosis with low trabecular bone volume, thin and abnormally porous cortices, and a high

remodelling rate. The ratio of type III to type I skin collagens was normal. The only abnormal laboratory findings were a slightly increased urine hydroxyproline excretion and an undetectable circulating calcitonin concentration, which did not rise in response to stimulation with oral alcohol (50 ml 40% w/v ethanol), intravenous pentagastrin (0.5 µg/kg body weight as bolus), or intravenous calcium (50 µmol (2 mg)/kg body weight over one minute). Other members of his family had normal calcitonin secretion.

Biochemical values in patient, and normal values

	Patient	Normal values
Serum calcium (mmol/l)	2.50	2.15-2.65
Serum phosphate (mmol/l)	1.26	0.80-1.40
Serum alkaline phosphatase (total) (IU/l)	110	30-130
Serum alkaline phosphatase (bone) (IU/l)	78	< 95
Plasma calcitonin (ng/l)	< 2	20-100
Plasma parathyroid hormone (ng/l)	460	< 730
Plasma 25-hydroxy vitamin D (nmol/l)	61	20-108
Plasma 1,25-dihydroxy vitamin D (pmol/l)	65	50-100
24-hour urine hydroxyproline (µmol/l)	390	< 310
24-hour urine calcium (mmol)	4.0	< 7.5

Conversion: SI to traditional units—Serum and urinary calcium: 1 mmol/l ≈ 4 mg/100 ml. Serum phosphate: 1 mmol/l ≈ 3.1 mg/100 ml. Plasma 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D: 1 nmol/l = 0.4 ng/ml. Hydroxyproline: 1 mmol ≈ 131 mg.

Synthetic human calcitonin (Cibacalcin) 0.5 mg daily by subcutaneous injection was started. His backache began to resolve after nine months of treatment, and he was asymptomatic by 12 months, when reassessment was undertaken: urine hydroxyproline excretion was normal (mean 150 µmol (19.5 mg)/24 hours), but radiographs showed further compression of L3 and L4 vertebral bodies, although it was not known when, during the 12 months, this had occurred. Biopsy of the iliac crest showed an appreciable reduction in osteoid surfaces, osteoid seam thickness, and cortical hyperremodelling and porosity compared with the pretreatment biopsy. Trabecular bone volume was not greatly increased.

Comment

Calcitonin acts direct on bone to inhibit bone resorption by reducing the activity and number of osteoclasts. The physiological function of the hormone in man is thought to be that of long-term skeletal maintenance, especially when concentrations of bone-resorbing hormones are raised.¹ In women calcitonin secretion is to some extent oestrogen dependent, and postmenopausal calcitonin deficiency may sensitise the skeleton to the actions of bone-resorbing hormones.² Furthermore, there is evidence of decreased calcitonin secretion in postmenopausal women with osteoporosis.³ In this patient a deficiency of calcitonin might have allowed the bone-resorbing hormones 1,25-dihydroxy vitamin D and parathyroid hormone to act on bone unopposed. A dramatic effect on the skeleton would not be expected unless concentrations of bone-resorbing hormones became increased. 1,25-Dihydroxy vitamin D concentrations, however, may be raised during the peripubertal growth spurt⁴; increased bone resorption could thus take place at this time and the skeletal consequences would become apparent in ensuing years.

Total thyroidectomy is apparently not associated with skeletal problems, although no prospective studies directly assessing bone mass have been carried out. Animal studies have shown extrathyroidal sites of calcitonin production,⁵ and thus patients who have undergone thyroidectomy do not necessarily lack calcitonin.

We consider that the calcitonin deficiency in this patient may have been causally related to his osteoporosis. Some symptomatic and histological improvement subsequently occurred with calcitonin treatment, although any major benefit is likely to be seen only in the long term. Calcitonin deficiency should be considered in young patients with osteoporosis in whom other causes have been excluded.

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³ Taggart HM, Chesnut CH, Ivey J, *et al.* Deficient calcitonin response to calcium stimulation in postmenopausal osteoporosis? *Lancet* 1982;ii:475-8.