Metabolic abnormality induced by streptomycin

Drs S FUCHS, N KAMINSKI, and M BREZIS (Department of Medicine, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel) write: Streptomycin sulphate is an effective aminoglycoside with limited nephrotoxicity. We report a case of renal electrolyte wasting that mimicked Bartter's syndrome and was induced by streptomycin.

A 40 year old woman presented with a four month history of fever, enlarged liver, and a macular rash. Results of physical examination, bone marrow and lymph node biopsies, computed tomography, and magnetic resonance imaging were normal. She was given intramuscular streptomycin (1 g daily) and tetracycline (2 g daily) by mouth for presumed brucellosis. Serological tests, however, showed that she had Q fever. Urine analysis gave normal results, making renal injury from Q fever unlikely.¹

After 14 days of treatment she developed hypokalaemia (serum potassium concentration 2.8 mmol/l) associated with a potassium urinary excretion of 41 mmol/day. These results suggested tubular wasting related to tubular injury induced by streptomycin. Her serum magnesium concentration was 0.46 mmol/l (normal reference range 0.8-1.0 mmol/l). Other serum electrolyte concentrations were creatinine 71 µmol/l, sodium 135 mmol/l, chloride 100 mmol/l, calcium 2.25 mmol/l, and bicarbonate 30 mmol/l (normal range 18-24). Blood pH was 7.43 and urinary chloride concentration was 145 mmol/l, typical of chloride resistant metabolic alkalosis.² Urinary osmolality was 222 mmol/l. Two weeks after the end of treatment all electrolyte and acid-base abnormalities had disappeared.

The tubular dysfunction induced by streptomycin in our patient presented as renal wasting of potassium and magnesium associated with chloride resistant metabolic alkalosis. This mimicked Bartter's syndrome, which is generally the result of a defect in the thick ascending limb of Henle's loop and may be caused by frusemide,³ poisoning with cisplatin,⁴ and prolonged administration of gentamicin and capreomycin.⁵ Streptomycin should be added to this list of drugs that can induce metabolic abnormalities mimicking Bartter's syndrome.

4 Lieber IH, Stoneburner SD, Floyed M, McGuffin WL. Potassium wasting-nephropathy secondary to chemotherapy simulating Bartter's syndrome. *Cancer* 1984; 54:808-10.

5 Steiner RW, Omachi AS. A Bartter's-like syndrome from capreomycin, and a similar gentamicin tubulopathy. *Am J Kidney Dis* 1986;7:245-9.

Rhabdomyolysis after treatment with interferon alfa

Drs S M GREENFIELD, R S HARVEY, and R P H THOMPSON (Gastro-intestinal Laboratory, Rayne Institute, St Thomas's Hospital, London SE1 7EH) write: A 46 year old man treated with interferon alfa for hepatitis C presented with acute rhabdomyolysis. Hepatitis C had been diagnosed two years previously (confirmed by results of polymerase chain reaction), and liver biopsy at that time had showed chronic active hepatitis.

Treatment with interferon alfa (Intron A) (5 MIU three times a week) had been started 10 weeks before presentation and the dose of drug gradually increased in an attempt to eradicate the virus.¹ The patient had been taking 15 MIU (8.2 MIU/m²) for two weeks when he presented with severe leg spasm and hyperventilation. On examination he was feverish and agitated, with a respiratory rate of 30/minute and periodic spasm of his legs. He was acidotic (blood pH 7.4 and bicarbonate concentration 10 mmol/l), with a serum creatinine kinase concentration of 28 180 IU/l, rising to over 100 000 IU/l. Acute rhabdomyolysis was diagnosed, interferon alfa was stopped, and the patient was treated with intravenous fluids, mannitol, dopamine, and bicarbonate to maintain an alkaline urine output. Serum creatinine concentration did not rise above 238 µmol/l and the patient made a complete recovery.

We decided not to restart treatment with interferon alfa. The patient had been taking lithium for manic depression for many years, and at the start of treatment with interferon alfa was mentally well and compliant with treatment. It is therefore extremely unlikely that the lithium was responsible for the rhabdomyolysis, although an interaction between lithium and interferon alfa cannot be ruled out.

To our knowledge, this is the first reported case of interferon alfa causing rhabdomyolysis and the first case reported to the Committee on Safety of Medicines. Schering-Plough, the manufacturers of Intron A, has received two reports worldwide about two patients who developed acute rhabdomyolysis after taking 3 MIU and 10 MIU Intron A (personal communication).

Our patient was treated with a higher dose than is usually recom-

mended,² although patients have been successfully treated with 10 MIU six times a week without a significant increase in side effects.¹ Creatinine kinase concentrations should be measured regularly in patients receiving interferon alfa to try to predict the onset of rhabdomyolysis.

1 Iino S. High dose interferon treatment in chronic hepatitis C. *Gut* 1993;34:S114-8.

2 Managing patients with hepatitis C. *Drug Ther Bull* 1993;31:61-2.

Ketoprofen gel and delayed hypersensitivity dermatitis

Professor V M S OH (National University Hospital, Singapore 0511) writes: Ketoprofen taken orally may cause urticaria in patients who are sensitive to aspirin.¹ I report a case of delayed skin hypersensitivity associated with ketoprofen gel.

In September 1992 a healthy Chinese physician developed pain in the elbow. Wrist extension against resistance with the arm straight and fingers flexed caused maximum pain, suggesting damage to the extensor carpi radialis brevis tendon.² Pumping up a sphygmomanometer cuff repeatedly was thought to be to blame, an occupational form of extensor tendinitis.² After consulting a rheumatologist the patient applied topical diclofenac 1% (three times daily for one week) and ketoprofen gel 2.5% (twice daily for three weeks). The treatment was stopped when a papular rash appeared on the elbow in February 1993. A vesicular dermatitis developed, which was cleared in five days by topical beclomethasone. In a skin patch test ketoprofen caused a papular rash after 48 hours; neither diclofenac nor propylene glycol (1% and 5% solutions) caused a reaction. A rechallenge with ketoprofen gel reproduced the original rash on the left forearm after 68 hours. The original tendinitis finally resolved spontaneously after nine months.

The Committee on Safety of Medicines has received 15 reports of skin reactions to ketoprofen gel, including two each of dermatitis and urticaria.

1 Frith P, Dolovich J, Hargrave FE. Life-threatening asthma, urticaria, and angio-oedema after ketoprofen. *Lancet* 1978; ii:847-8.

2 Cyriax J. *Textbook of orthopaedic medicine*. Vol 1. 5th ed. London: Cassell, 1969:307-16.

Convulsions after clomiphene citrate

Dr M R RIMMINGTON, S J VINE, and D K C CHUI and Mrs S M WALKER (University of Wales College of Medicine, Cardiff CF4 4XN) write: A 29 year old woman with a four year

history of secondary infertility had premenstrual convulsions in two consecutive cycles after induction of ovulation with clomiphene citrate. She had previously had a normal delivery and a first trimester abortion. She had hypothyroidism, which was well controlled by 100 µg thyroxine daily. She had an irregular menstrual cycle, and pelvic ultrasonography showed the ovaries to be polycystic. Her mid-luteal serum progesterone concentration was low, consistent with anovulation. She had no history of epilepsy or drug allergy.

We treated the anovulation with clomiphene citrate (50 mg on the second to sixth days of the menstrual cycle). In two consecutive treatment cycles she had nocturnal grand mal convulsions, preceded by general malaise. Her husband described typical tonic-clonic convulsions with urinary incontinence, convulsions lasting two to three minutes and being followed by drowsiness. All investigations, including electroencephalography and computed tomography of the brain, gave normal results. We stopped the clomiphene citrate, after which no further convulsions occurred.

Clomiphene citrate is an anti-oestrogen of proved therapeutic benefit; it is commonly used in gynaecological and general practice to induce ovulation,¹ often empirically in women who seem to be ovulating but are infertile. Its widespread use is consistent with its being a safe drug. Since 1963, five cases of convulsions in patients prescribed clomiphene citrate (two grand mal and three non-specific seizures) have been reported to either the Committee on Safety of Medicines or the manufacturers (Merrell Dow Pharmaceuticals).

Many women are prescribed clomiphene citrate, so these convulsions may be coincidental. In our case the convulsions do not seem to be coincidental because all investigations gave normal results and the convulsions ceased when treatment was stopped. Complications after clomiphene citrate treatment include ovarian hyperstimulation,² adnexal torsion,³ heterotopic pregnancy,⁴ and swings of mood. Epileptic women treated with clomiphene citrate experienced an 87% reduction in convulsions.⁵

1 McKenna KM, Pepperell RJ. Anti-oestrogens: their clinical physiology and use in reproductive medicine. *Baillieres Clin Obstet Gynaecol* 1988;2:545-65.

2 Chow KK, Choo HT. Ovarian hyperstimulation syndrome with clomiphene citrate. Case report. *Br J Obstet Gynaecol* 1984;91:1051-2.

3 Bider D, Goldenberg M, Ben-Rafael Z, Oelsner G. Bilateral adnexal torsion after clomiphene citrate therapy. *Hum Reprod* 1991;6:1441-4.

4 Sotrel G, Rao R, Scommegna A. Heterotopic pregnancy following clomid treatment. *J Reprod Med* 1976;16:78-80.

5 Herzog AG. Clomiphene therapy in epileptic women with menstrual disorders. *Neurology* 1988;38:432-4.

1 Perez-Fontan M, Huarte E, Tellez A, Rodriguez-Carmona A, Picazo ML, Martinez-Ara J. Glomerular nephropathy associated with chronic Q fever. *Am J Kidney Dis* 1988;11:298-306.

2 Harrington JT, Kassirer JP. Metabolic alkalosis. In: Cohen JJ, Kassirer JP, eds. *Acid-base*. Boston: Little Brown, 1982:287.

3 Ben-Ishay D, Levy M, Birnbaum D. Self-induced secondary hyperaldosteronism simulating Bartter's syndrome. *Isr J Med Sci* 1972;8:1835-9.