with comparisons following on a regional basis in England, where travelling expenses were usually funded either regionally or by districts. Indeed, some may claim that the whole intercomparison procedure would still be under consideration, rather than in progress, without this Scottish initiative.

Drug Points

Ceftriaxone and reversible cholelithiasis

Drs R H B MEYBOOM (Netherlands Centre for Monitoring of Adverse Reactions to Drugs, 2280 HK Rijswijk), H KUIPER (Academic Medical Centre, 1105 AZ Amsterdam), and A JANSEN (Sint Antonius Hospital, 3435 CM Nieuwegein, The Netherlands) write: Ceftriaxone is a new β lactamase resistant cephalosporin antibiotic for parenteral use. Its half life is 8 hours; 60% is excreted into the urine and 40% in bile. The recommended dose is 1 g once or twice daily. Animal experiments have shown that high doses of ceftriaxone may cause precipitations of the calcium salt of ceftriaxone in the gall bladder.¹ A recent case report described the development of ultrasonic signs of gall stones (diameter 15 mm) in an 18 year old man receiving ceftriaxone in a high dosage of 4 g (and 2.4 g clindamycin) daily. Previous ultrasonic examinations had been normal, and the echo free areas disappeared spontaneously within a month of ceftriaxone being stopped.²

We describe two patients with biliary colic developing in association with ceftriaxone, respectively 4 g and 2 g daily.³ One patient had ultrasonic evidence of small gall stones and was operated on four weeks after the attack and the stopping of ceftriaxone. No stones were found, however, and neither was there evidence of serious gall bladder disease. The other patient, a 34 year old woman, had three attacks of biliary colic after a 14 day course of ceftriaxone, the first three days after the course ended with further attacks five and 15 days after the first. Ultrasound and x ray investigations were performed only after the last attack and did not show biliary stones.

The manufacturer (Hoffmann-La Roche) informed us of several further patients with biliary "sludging" in association with ceftriaxone, with or without colic pain: three underwent surgery. Although some drugs, such as clofibrate, nicotinic acid, and oral contraceptives, have been associated with an increased risk of cholesterol gall stones,⁴ the precipitation of a drug in the bile has, to our knowledge, not been described previously. There is thus evidence that high doses of ceftriaxone may induce biliary precipitations and colic pain. Since these precipitations are probably transient and disappear after ceftriaxone has been discontinued some hesitation is advisable in treating such patients surgically.

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Hallucinations in association with ceftazidime

Drs M F AL-ZAHAWI, M S SPROTT (Department of Microbiology), and D J HENDRICK (Chest Clinic, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE) write: Several adverse effects on the central nervous system associated with ceftazidime have been reported to the manufacturer, including headaches, dizziness, convulsions, and visual hallucinations (Glaxo, personal communication). We report what we believe to be the first case of visual and auditory hallucinations.

A 62 year old woman with a 12 year history of low grade non-Hodgkin's lymphoma, bronchiectasis, recurrent chest infections, and chronic airways obstruction was admitted with signs and symptoms of chest infection. Initial investigations showed: oxygen ten-

sion 5.0 kPa, carbon dioxide tension 5.2 kPa (forced inspired oxygen 35%), creatinine 55 μ mol/l, and urea 4.2 mmol/l. Serum electrolyte concentrations, liver function tests, erythrocyte sedimentation rate, and full blood count were normal. The chest radiograph suggested bronchiectasis and collapse of the left lower lobe. Computed tomography showed diffusely abnormal lung parenchyma and some emphysema but no lymph node or parenchymal masses. She was treated with ampicillin 500 mg four times a day by mouth together with prednisolone, beclomethasone, and salbutamol and gradually improved. Ten days after admission she became more short of breath and developed worsening cough productive of purulent sputum. Bronchoscopy showed no evidence of tumour, and bronchial biopsy specimens showed inflammation without evidence of opportunistic infection or lymphoma. Coliform bacteria resistant to ampicillin were isolated from the sputum samples and bronchial secretions, and intravenous ceftazidime 2 g twice daily was started. Twenty four hours later the patient complained of auditory and visual hallucinations, although she remained well oriented in space, time, and person. Laboratory investigations showed normal liver and kidney function, but continuing anoxia (oxygen tension 6.5 kPa, carbon dioxide tension 5.3 kPa (forced inspired oxygen 35%)). Severe hallucinations persisted continuously and on the third day the dose of ceftazidime was reduced to 1 g twice daily. The symptoms resolved within 48 hours. A psychiatrist found no evidence of psychiatric disease.

Although hypoxia may have contributed to this patient's hallucinations, the degree of respiratory failure and systemic toxicity were no worse while she was experiencing these hallucinations. Their appearance 24 hours after ceftazidime was started and their cessation within 48 hours of the dose reduction suggest that ceftazidime was the probable cause. Central nervous system effects associated with ceftazidime have occurred mainly in the elderly (over 60 years) and in patients with renal impairment in whom the dose of ceftazidime had not been appropriately reduced. The occurrence of hallucinations in this elderly woman with a normal serum creatinine concentration may nevertheless have been the result of a prolonged half life attributable to impaired renal clearance.^{1,3}

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- 2 Molholm Hansen J, Kampmann J, Laursen H. Renal excretion of drugs in the elderly. *Lancet* 1970;ii:1170.
- 3 Naber K, Kees F, Grobecker H. Ceftazidime: pharmacokinetics in young volunteers versus elderly patients and therapeutic efficacy with complicated urinary tract infections. *J Antimicrob Chemother* 1983;12 (suppl A):41-5.

Inappropriate secretion of antidiuretic hormone associated with lorazepam

Drs W RICART ENGEL and A GRAU (Endocrinology Service, Hospital de Girona General Alvarez de Castro, 17007 Girona, Spain) write: The syndrome of inappropriate secretion of antidiuretic hormone has been recognised in association with many diseases, and many drugs can cause it, though benzodiazepines have so far not been implicated. Recently we observed a case of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone related to the ingestion of lorazepam.

An 81 year old white woman who took lorazepam 1 mg/day for insomnia was admitted because of confusion and visual hallucinations. She had suffered headache, nausea, and vomiting for 12 hours two days before her admission and had drunk more than 3 litres of water a day. Her history was negative for any factors known to be associated with hyponatraemia. She denied the intake of any other drugs. Physical examination showed obtundation and confusion but neither dehydration nor oedema. She had hyponatraemia (120 mmol/l), hypernatruria (152 mmol/l), and low serum osmolality (259 mmol/kg H₂O) and was suspected of having the syndrome of inappropriate secretion of antidiuretic hormone. Lorazepam was withdrawn and she was treated with hypertonic saline infusions and subsequent water restriction. Three days later she had recovered, with serum sodium concentration 140 mmol/l, urinary sodium 66 mmol/l, and serum osmolality 292 mmol/kg H₂O. Hyperglycaemia, hyperlipidaemia, hyperproteinaemia, and renal, adrenal, thyroid, cardiac, and hepatic diseases were excluded as causes of the hyponatraemia. Other organic disorders causing the syndrome of inappropri-

ate secretion of antidiuretic hormone—central nervous system disorders, pulmonary disease, and neoplastic diseases—were excluded. One week later a water load test was performed. She excreted 96% of the load in five hours, showing minimal changes in serum sodium concentration, serum osmolality, and progressive urine dilution (table). Plasma renin activity and aldosterone increased normally after intravenous frusemide stimulation. The patient agreed to take lorazepam 1 mg every 12 hours for three days and to repeat the water load test. Hyponatraemia and low serum osmolality were observed, although the urinary osmolality remained disproportionately high. At the end of the test the antidiuretic hormone concentration was 1.5 ng/l (table).

Water load test before and after lorazepam

	Before treatment		After treatment	
	Basal	After 5 hours	Basal	After 5 hours
Serum osmolality (mmol/kg)	288	282	287	261
Urinary osmolality (mmol/kg)	450	120	551	403
Serum sodium (mmol/l)	139	145	137	124
Urinary sodium (mmol/l)	66	41	113	64
Antidiuretic hormone (ng/l)				1.5
Total diuresis (ml)		1250		320
Load excreted (%)		96		25

The intake of water was 1300 ml-20 ml/kg body weight.

This case fulfils the criteria for the syndrome of inappropriate secretion of antidiuretic hormone: hypotonicity of plasma, inappropriately concentrated urine, natriuresis in the presence of hyponatraemia, plasma antidiuretic hormone not suppressed, absence of other causes of decreased diluting capacity, and reversal of renal sodium wasting after water restriction.¹ In our patient antidiuretic hormone was at the lower limit of normal, but when serum osmolality is below 270 mmol/kg and serum sodium below 130 mmol/l antidiuretic hormone should not be detected.²

Hyponatraemic hypoaldosteronism may cause hyponatraemia in the elderly, but it can be excluded in this case because serum and urinary potassium values as well as plasma renin activity and serum aldosterone concentrations measured under basal conditions were normal.³ Age may be important in hyponatraemia because elderly people do not have enough compensatory ability to conserve sodium in body fluid⁴ and antidiuretic hormone release is greater than it is in the young.⁵ Elderly patients show a delay in reaching peak urine flow after water load,⁶ but our patient showed a normal maximum diluting capacity. Our patient increased her water intake a few days before admittance. Clinical manifestations of the syndrome of inappropriate secretion of antidiuretic hormone occur only when water intake exceeds minimal urinary output and insensible loss. Nausea is a potent stimulus for antidiuretic hormone secretion,⁷ but this mechanism produced a short lived rise in antidiuretic hormone values.

None of these explanations account for the hyponatraemia in our patient, in whom the water load test showed the characteristic features of the syndrome of inappropriate secretion of antidiuretic hormone only when lorazepam was administered. These results would support the hypothesis that hyponatraemia induced by lorazepam may be related to inappropriate secretion of antidiuretic hormone.

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- 4 Epstein M, Hollenberg NK. Age as a determinant of renal sodium conservation in normal man. *J Lab Clin Med* 1976;87: 411-7.
- 5 Goldstein CS, Braunstein S, Goldfarb B. Idiopathic syndrome of inappropriate antidiuretic hormone secretion possibly related to age. *Ann Intern Med* 1983;99:185-8.
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