(0.2 U/kg) (Humulin S, Lilly) being given intravenously. Blood glucose concentration fell to a nadir within 25-40 minutes (figure); this nadir coincided with the onset of the acute hypoglycaemic reaction, which was manifested by typical autonomic features, including sweating and tachycardia. Plasma adrenaline concentration, measured by a radioenzymatic assay, rose in all patients from a mean basal value of 0.34 (SEM 0.08) nmol/l to a peak of 5.2 (1.1) nmol/l 30 minutes after the nadir in plasma glucose concentration ($p < 0.01$). Plasma osmolality did not change in response to hypoglycaemia.

Mean (SEM) changes in intraocular pressure in right eye and blood glucose concentrations in response to insulin induced hypoglycaemia in 12 insulin dependent diabetics. All measurements were timed in relation to the acute hypoglycaemic reaction (R).

Intraocular pressures in both eyes were measured with a Perkins hand held aplanation tonometer; changes were similar in both eyes. In the left eye the mean basal pressure was 15.2 (1.3) mm Hg, which fell to 9.8 (0.8) mm Hg five minutes after the nadir in plasma glucose concentration; and in the right eye the mean basal pressure was 15.2 (1.5) mm Hg, which fell to 9.7 (1.3) mm Hg five minutes after the nadir in plasma glucose concentration (figure). The fall in intraocular pressures in both eyes was significant (basal *v* nadir, $p < 0.005$; Student's *t* test for paired data). In all patients intraocular pressures in both eyes returned to basal values within 30-40 minutes of the reaction.

Comment

In this group of patients with recently diagnosed diabetes the fall in intraocular pressure preceded the maximum rise in plasma adrenaline concentration; adrenaline is released in response to acute hypoglycaemia by activation of the sympathoadrenal system. Although adrenaline lowers intraocular pressure, the sudden fall coincided with the onset of the profound autonomic discharge provoked by acute hypoglycaemia. Both the sympathetic and parasympathetic components of the autonomic nervous system are activated,³ and the rapidity of the change in intraocular pressure suggests that it was mediated by the autonomic innervation to the eye and not primarily by circulating adrenaline. Autonomic innervation influences the rates of secretion and drainage of aqueous humour from the anterior chamber of the eye and so alters intraocular pressure. Conversely, raised intraocular pressure has been reported to be associated with autonomic dysfunction.⁴ Consistent changes in pupillary size in response to this degree of hypoglycaemia do not occur in normal subjects.³ Pupillary responses to light are often abnormal in patients with longstanding diabetes with autonomic neuropathy.⁵ Further evaluation of the effect of hypoglycaemia on intraocular pressure in diabetics with autonomic dysfunction may elucidate the neural mechanism underlying the changes in pressure.

Hypoglycaemia is a common side effect of insulin treatment in diabetic patients with good glycaemic control. Sudden changes in intraocular pressure may have potentially adverse effects on delicate and fragile capillaries produced during the neovascularisation of proliferative diabetic

retinopathy. This represents a further hazard of hypoglycaemia for diabetic patients treated with insulin.

We thank the medical staff of the ophthalmology department and the laboratory staff of the biochemistry department, Gartnavel General Hospital, for valuable practical help with this study; Mr Gordon Inglis for assaying plasma adrenaline concentrations; and Miss Alison Wood for secretarial help.

- 1 Wiechmann E, Koch F. Untersuchungen über den hypoglykämischen Zustand nach Insulininjektion. *Münchener Medizinische Wochenschrift* 1927;74:1536-7.
- 2 Larsen H-W, Poulsen JE. Intraocular tension and blood-sugar fluctuations in diabetics. *Acta Ophthalmol (Copenh)* 1962;40:580-9.
- 3 Corral RJM, Frier BM, Davidson NMCD, Hopkins WM, French EB. Cholinergic manifestations of the acute autonomic reaction to hypoglycaemia in man. *Clin Sci* 1983;64:49-53.
- 4 Clark CV, Mapstone R. Autonomic neuropathy in ocular hypertension. *Lancet* 1985;ii:185-7.
- 5 Smith SE, Smith SA. Reduced pupillary light reflexes in diabetic autonomic neuropathy. *Diabetologia* 1983;24:330-2.

(Accepted 12 November 1986)

Western Infirmary and Gartnavel General Hospital, Glasgow G12 0YN

B M FRIER, MD, FRCP, consultant physician, department of diabetes
D A HEPBURN, BMEDSCI, MB, senior house officer, department of diabetes
B M FISHER, MB, MRCP, medical registrar, department of diabetes
T BARRIE, MB, FRCS, consultant ophthalmologist, department of ophthalmology

Correspondence to: Dr B M Frier, Level 7, Gartnavel General Hospital, Glasgow G12 0YN.

Survival after burial in an avalanche

A young woman buried for 20 minutes in snow, during which breathing must have been impossible, was resuscitated and survived without brain damage.

Case report

A 32 year old woman skier was carried 20 m by a wet snow avalanche before being buried for 20 minutes. She was located by an advancing line of searchers with probes. The snow over her was not stood on at any time. She was found in a prone position with her body angled up at 45°, her head being buried at a depth of about 0.75 m and her feet at 1.5 m.

Her head was uncovered first; the mouth was not blocked with snow, but mouth to mouth resuscitation was not possible owing to the weight of snow surrounding her chest. When the chest was uncovered, ventilation was easy. On examination she was deeply unconscious and not breathing; she had a scarcely perceptible irregular carotid pulse of around 40 beats/minute. The mucous membranes were translucent grey white. She was wearing normal ski clothing but no hat; the clothing was dry. She was warmed with extra clothing and the sunshine. Mouth to mouth resuscitation was continued until spontaneous respiration returned after two minutes. Her pulse and colour gradually returned to normal. She regained consciousness slowly and was fully conscious after 20 minutes, shivering violently and complaining of extreme cold. She had no injuries and recovered fully, leaving hospital after two days.

Comment

Complete burial in a snow avalanche has only a 19% survival rate.¹ Snow can weigh as much as 800 kg/m³ (water weighs 1000 kg/m³) and may freeze solid around a victim when the avalanche stops; as a result death is usually due to asphyxia.^{1,2} It is sometimes possible to breathe during burial, depending on factors such as air pockets between blocks of snow and lack of chest compression. This has been experienced by the few survivors who have remained conscious, enduring cold and extreme difficulty breathing.^{1,2}

Anecdotal reports of survival after short periods of burial—for example five minutes—are numerous, but longer burial times—for example, 20 hours—are exceptional.^{1,2} The unique feature of this case is the demonstration that respiration could not have occurred, to any degree for the entire 20 minutes of burial, because of the weight of densely packed snow. I, being a registrar anaesthetist, was probably better able to judge this than other rescuers, who are usually laymen. As apnoea for 20 minutes normally results in death, important protective mechanisms must operate during burial in an avalanche.

Comparisons of surviving burial in an avalanche and immersion in cold water, when respiratory arrest and cooling also occur, can be made. Survival after as long as 40 minutes' immersion³ has been attributed to the protective effect of generalised hypothermia and the diving reflex, whereby facial

immersion in cold water causes bradycardia.⁴ These effects may occur during burial in an avalanche of snow. Hypothermia often occurs in burial in an avalanche.^{1,2} The face is often the only area unprotected by clothing and in direct contact with the snow, which may be important as it is the face that triggers the diving reflex. This is unlike immersion in cold water, when cooling is more uniform. During immersion water may enter the nasopharynx, causing cooling of the brain, or may be inhaled, causing rapid cooling of the heart and brain before circulation stops. Although this would not occur during burial in snow, snow has been found packed in the mouth and nose and may be inhaled, possibly with similar effects (N J MacDonald, personal observations).

I thank Dr M Harris of Northwick Park Hospital for his help in preparing this report.

- 1 MacInnes H. *International mountain rescue handbook*. 2nd ed. London: Constable, 1984.
- 2 Fraser C. *The avalanche enigma*. London: John Murray, 1966.
- 3 Siebke H, Breivik H, Rod T, Lind B. Survival after 40 minutes' submersion without cerebral sequelae. *Lancet* 1975;ii:1275-7.
- 4 Harries M. Drowning and near drowning. *Br Med J* 1986;293:122-4.

(Accepted 5 February 1987)

Health Centre, Aviemore PH22 1SY
DUNCAN GRAY, MB, CHB, trainee general practitioner

Gynaecomastia induced by phenytoin in men with epilepsy

Long term anticonvulsant treatment may be associated with loss of libido and gonadal dysfunction.^{1,2} Changes in sex hormone binding globulin and free testosterone concentrations may explain these phenomena.^{1,3,4} We recently observed gynaecomastia in five men receiving long term anticonvulsant treatment, phenytoin being common treatment in all five cases.

Case reports

Case 1—A 42 year old man with chronic temporal lobe epilepsy of several years' duration who had taken phenytoin 100 mg thrice daily for five years and carbamazepine 200 mg thrice daily developed a tender lump in the right breast and enlargement of the left breast. There was no loss of libido, and the genitalia were clinically normal. Plasma prolactin concentration was normal. The breast lump was excised, and histological examination showed benign hyperplasia. When phenytoin was stopped his gynaecomastia resolved.

Case 2—A 20 year old man with a two year history of infrequent major seizures had been treated with phenytoin 300 mg daily since the diagnosis of epilepsy and valproate 200 mg daily. He developed tender enlargement of both breasts; libido was undisturbed, and the genitalia were normal. Carbamazepine was substituted for phenytoin, and the gynaecomastia resolved.

Case 3—A 36 year old man with a 16 year history of infrequent generalised convulsions had received phenytoin 300 mg daily since the diagnosis of epilepsy with clobazam 20 mg at night. During the past four years he had been noted to have moderate gynaecomastia. Genitalia and secondary sexual characteristics were normal, and there were no other abnormalities. His libido was normal.

Case 4—A 42 year old man with a 36 year history of epilepsy associated with a right temporal focus on electroencephalography complained of impotence and breast enlargement. He had received phenytoin 300 mg daily for over 20 years. His libido was normal. Clinical examination confirmed moderate gynaecomastia; there were no other abnormalities.

Case 5—A 32 year old man with a 10 year history of focal temporal lobe fits and generalised convulsions had moderate gynaecomastia. He described normal libido, and secondary sexual characteristics were normal. Treatment had consisted of phenytoin 300-400 mg daily for 10 years and phenobarbitone.

Results of liver function tests were normal in all patients. The table shows hormonal data for three patients (cases 3, 4, and 5). The phenytoin concentrations in all five patients were in or below the usual therapeutic range; in only one patient (case 4) were toxic values recorded occasionally. Apart from transient ataxia in this patient and minor gum hyperplasia in case 3 there were no other signs of drug toxicity.

Comment

The resolution of gynaecomastia when phenytoin was stopped in cases 1 and 2 suggested a causal relation with this drug and raised the possibility that phenytoin was responsible for the gynaecomastia in the remaining three patients, who underwent more detailed endocrine assessment.

A possible mechanism is provided by reports of a reduction in circulating free testosterone concentration in patients receiving long term treatment

Sex steroid and gonadotrophin concentrations in three patients

	Normal range	Case 3	Case 4	Case 5
Total testosterone* (nmol/l)	10.4-34.7	22.0	22.0	14.0
Total 17 β oestradiol* (pmol/l)	14-180	159	168	200
Sex hormone binding globulin† (nmol/l)	10-50	69	43	15
Luteinising hormone‡ (IU/l)	2-10	8.1	22.1	5.0
Follicle stimulating hormone‡ (IU/l)	2-5	13.7	9.7	0.9
Free androgen index§	median 75.2	31.9	51.2	93.3
Free oestrogen index	median 0.37	0.23	0.39	1.33
Prolactin (mU/l)	<360	465	137	55

*St Thomas's Hospital SAS assay.

†Method in ref 3.

‡Chelsea kit.

§Testosterone $\times$ 100/sex hormone binding globulin.

|| Oestradiol $\times$ 0.1/sex hormone binding globulin.

with various anticonvulsants.^{1,4} The free androgen index was low, gonadotrophin concentration raised, and free oestrogen index normal in cases 3 and 4, whereas in case 5 the free androgen index was normal but the free oestrogen index raised. The data are consistent with the hypothesis that phenytoin treatment decreases free testosterone concentration as a result of increasing the concentration of sex hormone binding globulin and induces increased conversion of testosterone to 17 β oestradiol. Gynaecomastia may result from either one or a combination of these effects⁵ and, with loss of libido and subfertility, should be borne in mind as a possible side effect of long term treatment with phenytoin. One patient (case 3) had a slightly raised plasma prolactin concentration; two others (cases 4 and 5) had normal concentrations. Although certain anticonvulsants have been associated with increased plasma prolactin concentrations,² this does not seem to have been relevant to the gynaecomastia observed in our patients.

We are grateful to Dr J Wright for referring two of the patients (cases 1 and 2). We also thank Dr H L J Makin and the staff of the steroid laboratory, department of chemical pathology, for the hormone assays.

- 1 Toone BK, Wheeler M, Nanjee M, Fenwick P, Grant RHE. Sex hormones, sexual drive and plasma anticonvulsant levels in male epileptics. In: Parsonage M, Grant RHE, Craig AG, Ward AA, eds. *Advances in epileptology. XIVth epilepsy international symposium*. New York: Raven Press, 1983:313-7.
- 2 Rodin E, Subramanian MG, Gilroy J. Investigation of sex hormones in male epileptic patients. *Epilepsia* 1984;25:690-4.
- 3 Barragry JM, Makin HLJ, Trafford DJH, Scott DF. Effects of anticonvulsants on plasma testosterone and sex hormone binding globulin levels. *J Neurol Neurosurg Psychiatry* 1978;41:913-4.
- 4 Dana-Haeri J, Oxley J, Richens A. Reduction of free testosterone by antiepileptic drugs. *Br Med J* 1982;284:85-6.
- 5 Turkington RW, Topper YJ. Androgen inhibition of mammary gland differentiation in vitro. *Endocrinology* 1967;80:329-36.

(Accepted 28 November 1986)

The London Hospital, London E1 1BB

J P MONSON, MD, MRCP, senior lecturer in endocrinology, medical unit
D F SCOTT, FRCP, DPM, consultant in charge, department of clinical neurophysiology

Correspondence to: Dr Scott.

Severe cholestasis associated with stanozolol

Although stanozolol has been in clinical use for over 20 years, the Committee on the Safety of Medicines knows of only four cases of jaundice associated with it and only one case has been reported.¹ We report on three patients with severe cholestatic jaundice, two with associated renal failure, in whom stanozolol was the only agent that could be implicated.

Case reports

All three patients presented with jaundice and pruritus. Their history and examination did not show any evidence of liver disease, and none had previously experienced any adverse drug reactions. In all cases hepatitis A and B were excluded by specific serological tests. Autoantibodies, including anti-mitochondrial antibody, were also absent in cases 1 and 2. Extrahepatic obstruction was excluded by operative cholangiography in case 1, ultrasonography and endoscopic cholangiography in case 2, and ultrasonography alone in case 3.