hypotension, loss of consciousness, and times of onset varying between one minute and nine days. Investigations included history and general examination, prick skin tests with common allergens to determine atopic status, intradermal skin test with 0.2 ml 1/1000 lignocaine hydrochloride, and hospital admission for a direct challenge test.

PREPARATION FOR CHALLENGE TEST

Baseline observations of heart rate, blood pressure, and expiratory peak flow rate were recorded every 15 minutes for one hour and a blood sample taken.

Lignocaine injections were prepared from bottles of 1% and 2% plain lignocaine, free from preservative and vasoconstrictor. Dilutions of 1/10 (1 mg/ml), 1/100 (0.1 mg/ml), and 1/1000 (10 µg/ml) were made from 1% lignocaine, labelled, and kept.

Chlorpheniramine 10 mg intramuscularly was given to the patient.

Resuscitation agents were drawn up and placed by the patient's bed: adrenaline 1/1000 (1 ml for injection im), chlorpheniramine 10 mg (1 ml for injection iv), and hydrocortisone 100 mg (1 ml for injection iv).

CHALLENGE PROCEDURE

The patient was attended by a nurse throughout the test and the ward doctor was within one minute's call for 30 minutes.

Lignocaine injections were given as follows (intervals between doses were 60 minutes for immediate or 24 hours for late reactions): (a) intradermal injection of 0.02 ml at 1/1000 dilution; (b) subcutaneous injection of 0.05 ml at 1/100 dilution; (c) subcutaneous injection of 0.05 ml at 1/10 dilution; (d) subcutaneous injection of 0.05 ml undiluted 1% lignocaine; (e) subcutaneous injection of 0.25 ml undiluted 2% lignocaine; and (f) subcutaneous injection of 2.0 ml undiluted 2% lignocaine. If no reaction occurred the patient was allowed home with an escort one hour after the last injection unless the history indicated that a reaction could occur after several hours.

Emergency procedures were adopted if any reaction other than a local weal or flare developed: all further doses of lignocaine were stopped, further blood samples taken, and the patient attended constantly.

Results—Three patients were atopic and three had immune-related disorders (fibrosing alveolitis, recurrent urticaria, asthma with nasal polyps, and aspirin intolerance). Two of the atopic patients had positive reactions to skin tests with lignocaine (weal ≥ 4 mm, flare ≥ 11 mm). No patient showed any detectable reaction to the direct challenge.

Comment

In each of our eight cases it would be safe for the patient to receive plain lignocaine for further dental or aural or nasopharyngeal treatment. They have all now received such treatment without adverse reactions. Our regimen did not exclude the possibility that other components of the original formulation of the local anaesthetic could have provoked the presenting reaction. Multidose phials of lignocaine may contain methylparaben preservatives as well as a vasoconstrictor. These are known immunogens which may elicit both immediate and delayed hypersensitivity.^{3,4} The toxic effects of vasoconstrictors and of lignocaine itself⁵ are well known. Although these factors could have been ruled out in our patients, we had excluded hypersensitivity to lignocaine itself and therefore saw little justification for further investigation.

As far as the question of the test's safety is concerned, the starting dose was extremely low (0.2 µg); the presenting reactions had occurred with doses of 20–40 mg. This difference gives an adequate safety margin even if the patient is sensitised. Furthermore, our experience and published reports make us seriously doubt whether true anaphylaxis to lignocaine has ever been satisfactorily shown. Nevertheless, since this hypothesis can never be proved, every safety precaution must be taken during a direct challenge test with this drug. For practical purposes, the conclusion that our patients' presenting symptoms were not due to lignocaine hypersensitivity is adequate. As a precaution they have been advised not to receive any local anaesthetic preparation other than plain lignocaine, which is devoid of all preservatives and vasoconstrictors. We believe the benefits of the information gained from the direct challenge test far outweigh any potential risks.

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Endocrine pancreatic carcinoma and syndrome of inappropriate secretion of antidiuretic hormone

Inappropriate secretion of antidiuretic hormone is a well-known complication in malignancy, especially in oat-cell carcinoma of the lung. The syndrome has also been reported in pancreatic adenocarcinoma¹ but hitherto not in patients with an endocrine pancreatic tumour.

Case history

A 54-year-old man presented in 1979 with abdominal pain, weight loss, and an upper abdominal mass. At operation in October 1979 an inoperable tumour was found originating in the head of the pancreas and adherent to surrounding tissues. An excision biopsy specimen was taken.

Histological examination showed an undifferentiated monomorphic and highly vascular tumour with an organoid appearance. The densely packed tumour cells were of uniform size, and many mitotic figures were present (figure (a)). Aldehyde fuchsin staining yielded uniformly negative results, but Grimelius² staining showed some areas with endocrine activity in tumour cells (figure (b)). Electron microscopy showed α -like and δ -like granules (figure (c)). Malignant pancreatic islet-cell tumour was diagnosed. Immunohistochemical stainings for insulin, glucagon, somatostatin, and antidiuretic hormone were negative.

Before and after operation the patient had hyponatraemia with a serum sodium concentration of 115 mmol (mEq)/l, serum osmolality of 243 mmol (mosmol)/kg, and urine osmolality of 546 mmol/kg. There were no clinical or laboratory signs of cardiac, pulmonary, neurological, renal, hepatic, or endocrine disease, and he received no medication.

After operation fasting concentrations of gastrin, glucagon, vasoactive intestinal peptide, insulin, somatostatin, and calcitonin were all within the normal range; the pancreatic polypeptide concentration was slightly raised (150 pmol/l; normal limit 100 pmol/l). β -Human chorionic gonadotrophin was not found. Serum sodium concentration and osmolality returned to normal after intake of water was restricted to 1000 ml daily.

Three months after operation, before starting treatment with streptozotocin, the patient was in fairly good clinical condition. With a water intake of 1000 ml daily serum sodium concentration was 133 mmol/l, serum osmolality 276 mmol/kg, and urine osmolality 970 mmol/kg. Plasma concentration of antidiuretic hormone, determined by radioimmunoassay,³ was 18 pg/ml (normally not exceeding 2 pg/ml if serum osmolality is less than 285 mmol/kg^{3,4}). After an oral water intake of 1400 ml in 15 minutes serum sodium concentration fell to 126 mmol/l and serum osmolality to 260 mmol/kg; urine osmolality remained unchanged at around 900 mmol/kg.

After four courses of streptozotocin (500 mg/m² daily for five days every five weeks) a similar water intake caused adequate diuresis and no fall in serum osmolality. With a free water intake plasma concentration of antidiuretic hormone was within the normal range. During the treatment the size of the tumour decreased somewhat, as shown by echography.

Comment

Corrin *et al*⁵ described a patient with an oat-cell carcinoma of the pancreas of islet-cell origin and the syndrome of inappropriate secretion of antidiuretic hormone. Because of several interfering factors, however, they could not conclude that the syndrome was due to elaboration of vasopressin by the tumour. In our patient known

causes of the syndrome, other than ectopic production of vasopressin, were excluded and the islet-cell origin of the tumour was clearly shown by Grimelius staining and electron microscopy, which showed the typical granules. The syndrome disappeared when the tumour decreased in size after treatment with streptozotocin; this is compatible with the tumoral origin of the syndrome.

The negative results of immunohistochemical staining of the tumour cells for antidiuretic hormone does not contradict production

of antidiuretic hormone in the tumour, since different parts of islet-cell tumours can produce different (or no) hormones. Even if the vasopressin-containing cells had been present in the biopsy specimen the false-negative results might easily be explained by a low concentration of antidiuretic hormone in the cells or a diminution of its antigenicity due to the fixation procedures.

We conclude that endocrine pancreatic tumours may be the cause of the syndrome of inappropriate secretion of antidiuretic hormone.

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Electrocardiographic abnormalities and autonomic dysfunction in Guillain-Barré syndrome

The Guillain-Barré syndrome is an acute polyneuropathy. Paralysis may be severe and widespread and assisted ventilation needed. Preceding events are common but not essential to the diagnosis. Of these, viral infections are most frequently incriminated, but other associated disorders include surgery, trauma, lymphomas, and systemic lupus erythematosus.

Autonomic neuropathy has been recognised for at least 30 years and may be the cause of sudden death which occasionally occurs in even well-ventilated patients. Osler¹ might have been alluding to autonomic dysfunction when he described patients with "acute febrile polyneuritis" who succumbed to "paralysis of the heart." Other manifestations include bladder paralysis, pupillary abnormalities, cardiac arrhythmias, labile blood pressure, and pulse and electrocardiographic changes.^{2,3}

We describe a patient with Guillain-Barré syndrome and autonomic neuropathy who developed exceptional acute electrocardiographic abnormalities.

Case report

A 62-year-old woman presented with three days of interscapular pain, rapidly progressive weakness of legs, and numb, cold feet. One week before she had had headache, nausea, vomiting, and diarrhoea for three days.

On admission (day 1) she had severe flaccid, areflexic tetraparesis with loss of vibration and joint position sense below the knees. White cell count was $15.0 \times 10^9/l$ (normal differential), and cerebrospinal fluid and an electrocardiogram were normal. Over the next 48 hours she deteriorated with the appearance of bilateral facial weakness and bilateral ophthalmoplegia, which affected the pupils. Vital capacity measured eight-hourly fell from 1.3 to 0.4 l on day 3, and tracheostomy and intermittent positive-pressure ventilation were instituted. Despite a forced inspired oxygen concentration of 50% she could not maintain satisfactory oxygen pressure, and positive end-expiratory pressure of 2 cm water was used for the first 18 hours of ventilation with good effect.

On day 4 wide fluctuations in pulse rate (70-150/min) and blood pressure (75/35-180/120 mm Hg) were recorded. On day 8 she developed tachycardia

(a) 1-μm thick Epon section, toluidine blue stain, showing densely packed tumour cells with mitotic figures (arrows). (b) 4-μm thick paraffin section, Grimelius stain, showing positively staining tumour cells (right side). (c) Electron micrograph showing small dark-staining granules in tumour cells (arrows).