In this preliminary study we assessed the efficiency of glucagon given intranasally in raising blood glucose concentrations in normal subjects.

Subjects and methods

Seven normal adult subjects, all doctors or undergraduate medical students at this hospital, volunteered for the study. They were studied while in bed in the morning, after fasting overnight, and not smoking. After 30 minutes to ensure steady blood glucose and plasma glucagon concentrations drops of solutions containing glucagon (1 mg/subject) were inserted in both nostrils and the subjects were asked to take a deep breath. In four subjects control experiments were performed on a different occasion and distilled water was substituted for glucagon, the subjects being unaware of the contents of the drops. Finally, in two of the above subjects glucagon 1 mg was given intramuscularly.

Solutions to form nasal drops were obtained from porcine glucagon (Novo, Copenhagen, Denmark) diluted with sodium glycocholate 10 or 15 mg as a surfactant.⁶ Blood samples were obtained at the times indicated in the figure; placed in tubes containing heparin and aprotinin (10 000 KIU/ml), and centrifuged at 4°C. Blood glucose concentrations were estimated by an enzymatic method. Plasma was stored at -20°C until assayed for immunoreactive insulin and immunoreactive glucagon. Immunoreactive glucagon was assayed using the antibody R-78, C-terminus directed. Incubation lasted 48 h at 4°C and free immunoreactive glucagon was separated from bound immunoreactive glucagon by centrifugation at 2000 g for 20 minutes. Kits for immunoreactive insulin and immunoreactive glucagon were supplied by Serono Biodata (Rome, Italy).

Statistical analyses were performed by Student's *t* test for paired data and confirmed by the non-parametric Wilcoxon's test.

Effects of intranasally administered glucagon (1 mg, seven subjects, ○ - ○), of the diluent (four subjects, ● - ●) and of intramuscular glucagon (two subjects, □ - □) on plasma immunoreactive glucagon, blood glucose, and plasma insulin concentrations. Means (SEM) are indicated. Statistical differences: * *p* < 0.05; ** *p* < 0.01; *** *p* < 0.001 when comparing diluent and glucagon intranasally; ● *p* < 0.05; ●● *p* < 0.01; ●●● *p* < 0.001 when comparing glucagon by intranasal and intramuscular route.

Conversion: SI to traditional units—glucose: 1 mmol/l ≈ 18.02 mg/100 ml; immunoreactive insulin: 1 pmol/l ≈ 0.14 μU/ml.

Results

The figure shows that in all subjects the administration of nasal glucagon was accompanied by a sharp increase in plasma IRG concentrations and thereafter by an increase in blood glucose concentrations; immunoreactive insulin concentrations were also significantly increased. In control experiments immunoreactive glucagon, blood glucose, and immunoreactive insulin concentrations remained steady (figure). After intramuscular glucagon the peak immunoreactive glucagon concentrations were similar whereas

the fall in plasma immunoreactive glucagon concentrations was delayed and blood glucose concentrations were higher than after glucagon given intranasally.

Comment

Hypoglycaemic crises represent a common emergency in the daily management of patients with insulin dependent diabetes, especially those with unstable diabetes. Under these circumstances it would be desirable to have at hand drugs able to increase blood glucose concentrations which could be self administered or given by others if the patient was incapable. For this reason we evaluated the possible effect of glucagon given as nasal drops.

The results indicated that glucagon was well absorbed through the nasal mucosa and increased blood glucose concentrations. The concomitant release of insulin indicated that glucagon given intranasally exerted its traditional metabolic effect. On the other hand, the placebo was completely inactive.

At present the efficacy of glucagon given by the nasal route seems to be inferior to that of intramuscular glucagon; if evaluated from the blood glucose raising ability the potency ratio seems to be 1:2. We do not know whether this difference is linked to the different route of administration or is merely due to technical reasons. In general, spray solutions delivering droplets instead of drops ensure a better distribution on the nasal mucosa: with glucagon this might result in increased bioavailability and greater metabolic effects. Studies are in progress to characterise and improve the bioavailability of intranasally administered glucagon so as to make this route of administration safe, effective, and reproducible for routine use.

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Ethylenediamine and piperazine sensitivity

The problems of cross sensitisation between drugs used topically and related drugs used systemically is particularly well recognised with the antihistamine group.¹

We report a case in which an unexpected cross sensitivity produced considerable morbidity.

Case report

A 37 year old man had a 20 year history of a patchy red scaly rash affecting the forearms, calves, hands, and face and perineal irritation. He had been prescribed numerous steroid creams and ointments. In 1980, after his daughter was found to have threadworms, the whole family was treated with piperazine citrate. About 12 hours after taking the drug he developed an itchy morbilliform rash affecting his whole body, which scaled and cleared over three to four weeks. Although he attributed the rash to piperazine, he was reassured at the time that this could not be the case.

In 1981 threadworms were again diagnosed in the family and again he was

treated with piperazine. On this occasion he developed a severe exfoliative erythroderma within three hours and was admitted to hospital. The rash cleared over several weeks with the use of topical steroid ointments. Some weeks later with his agreement he was readmitted and challenged with 50 µg piperazine hydrate by mouth. This provoked a generalised maculopapular erythema within hours with shivering, anxiety, and a tachycardia of 140 beats/min. Subsequent patch testing showed him to have a contact allergy to 1% ethylenediamine (+ + reaction at 48 and 96 hours) but not to 1% promethazine, 1% mepyramine, 1% diphenhydramine, 0.5% antazoline, and the standard European battery of contact allergens. On further inquiry he identified Tri-Adcortyl cream (Squibb) as a medicament that he had used previously. The constituents of Tri-Adcortyl cream include triamcinolone acetonide, neomycin, gramicidin, nystatin, parabens, and ethylenediamine.

Comment

Initial inquiry to the manufacturers produced the reply that they were unaware of any dermatological adverse effects associated with the use of piperazine. In 1978 Burry reported a case from Australia of a patient sensitised to ethylenediamine by topical use of Kenacomb cream (the Australian equivalent of Tri-Adcortyl) who developed a systemic reaction to piperazine,² and Calnan had previously drawn attention to cross sensitivity between the two.³

The potential danger of administering aminophylline to a patient who has a contact allergy to ethylenediamine is well known.¹ Topical use of Tri-Adcortyl cream is probably the commonest cause of contact allergy to ethylenediamine,^{1,4} and the potential importance of these cross reactions is such that prescribing physicians should be aware of the hazards that may accompany sensitisation to ethylenediamine.

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Primary hepatic cryptococcosis

Cryptococcosis, a widespread disease caused by the fungus *Cryptococcus neoformans*, is uncommon in the United Kingdom.¹ The disseminated form of the infection usually occurs in immunocompromised patients and may affect the central nervous system, lungs, skin, bones, and other organs. Primary cryptococcosis of the liver in an otherwise normal patient has not previously been reported; we report one such case.

Case report

A 33 year old housewife presented with an upper respiratory tract infection. One week later she developed abdominal pain and nausea and was referred to hospital. On admission she was feverish and had severe upper abdominal tenderness. Cholecystitis was diagnosed provisionally, and she was treated with intravenous antibiotics, fluids, and analgesics.

Investigations showed a haemoglobin concentration of 11.1 g/dl and a white cell count of $30.5 \times 10^9/l$ with 85% neutrophils. Electrolyte concentrations were normal, and a raised alkaline phosphatase activity of 776 IU/l (normal 350 IU/l) was the only abnormal result of liver function tests. A chest x ray film was normal, and routine bacteriology of blood, urine, and sputum did not yield any significant pathogen. An ultrasonic scan of the upper abdomen showed gall stones; the liver and pancreas were normal.

Her clinical condition deteriorated, and laparotomy was performed within 48 hours of admission. At operation the gall bladder was tense and contained stones. The liver was studded with multiple white lesions; a frozen section of one lesion was reported as non-malignant. A cholecystostomy was carried out. Subsequent paraffin sections of the liver nodules showed florid granu-

lomatous changes, and staining by Grocott's technique showed the presence of yeastlike organisms. Cryptococcosis was diagnosed by the finding of an encapsulated yeastlike fungus in a specimen of bile, isolation of the organism on Sabaraud's medium, and identification of *C. neoformans* by biochemical tests. A cryptococcal agglutinin titre of 1/8 in serum taken on the sixth day of illness was consistent with the diagnosis.

She was treated with intravenous amphotericin and flucytosine for six weeks. She recovered completely and remained well.

Biopsy specimen of liver nodule showing yeastlike fungi.

Comment

Sabesin *et al* reported on a patient with hepatic cryptococcosis who apparently had no primary illness and presented with features of liver failure.² Necropsy showed disseminated cryptococcosis affecting various organs including the liver. In our patient there was no clinical or radiological evidence to suggest that other systems were affected.

The respiratory tract is recognised as the most common portal of entry for cryptococci, although the evidence for this is mostly circumstantial.³ The disease has been produced in experimental monkeys by the oral route.⁴ As only the hepatobiliary system was affected in our patient, we consider that ingestion was probably the method of infection.

Successful treatment with amphotericin and flucytosine has been reported by others.¹ Our patient, however, suffered from an acute toxic delusional state, which is a recognised side effect of amphotericin. This and other serious side effects may accompany this regimen and indicate the need for an assessment of alternative antipneumococcal regimens.⁵

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