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(Accepted 18 August 1982)

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Bromocriptine-induced psychosis in acromegaly

Dopaminergic mechanisms have been implicated in the pathogenesis of schizophrenia.¹ Psychosis induced by the dopamine-receptor agonist bromocriptine has been described mainly with high-dose regimens in Parkinsonism and less frequently with the lower doses used in hormonal disorders.²⁻⁴ The following case is of interest because of the insidious onset of psychosis and the family history of paranoid schizophrenia.

Mean growth hormone and prolactin concentrations before, during, and after treatment

	Basal	After glucose	While taking bromocriptine			Weeks after having stopped bromocriptine	
			10 mg/day	20 mg/day	30 mg/day	1 week	6 weeks
Growth hormone (mU/l) (normal range <10)	587	400	128	147	114	696	556
Prolactin (µg/l) (normal range <20)	107	—	4.5	5.5	—	54	125

Case report

A 32-year-old married composer of popular music, previously a successful artist, presented in November 1981 with a breast lump, one month before the birth of his first child. For three years he had become increasingly immersed in his music and more irritable, and he and his wife had become socially isolated. He had no history of psychiatric disorder or drug abuse, but his mother had been successfully treated for a well-documented paranoid schizophrenic episode in 1973, when aged 60.

Acromegaly was diagnosed on the basis of a five-year history of enlargement of the face, hands, and feet and grossly raised growth hormone concentrations (table). Skull radiography showed an enlarged pituitary fossa with destruction of the posterior wall and floor. Computed tomography showed asymmetry of the sella floor and right-sided destruction but no appreciable suprasellar or extrasellar tumour extension. Visual fields were normal. An excision biopsy specimen of the breast lump showed duct ectasia with some "lactational" change.

Bromocriptine 2.5 mg daily was started on 28 January 1982, increasing to 10 mg over the next two weeks and to 30 mg over the following month; this was continued until his admission in a psychotic state on 30 April. In retrospect, two weeks after starting bromocriptine he had become totally absorbed in his music, believing that it had a unique, inexpressible "three-dimensional" quality. His musical ideas became more bizarre and complex over the next 10 weeks and he spent long periods in bed engrossed in their interrelated meanings. Ten days before admission he had a vivid dream of a mother with a child with Down's syndrome, which he took to be a direct experience of God. He became preoccupied with ideas of good and evil and increasingly frightened. This led to a delusional misinterpretation that the devil was outside their home, and he and his wife fled to relatives. They began to suspect that his disturbance was due to the bromocriptine, which he discontinued, and they came to the casualty department. Up to this point his wife had shared his ideas, but this changed when he stated that she was evil and absconded with their child from casualty. He returned within hours, was admitted to a medical ward, and was later transferred to the psychiatric unit.

On admission he was in a fearful, paranoid, agitated state, showing partial insight in the presence of clear consciousness and absence of overt mood disorder, hallucinations, passivity phenomena, or formal thought disorder. On treatment with thioridazine 250 mg daily his paranoid ideas disappeared within a week. He was discharged taking trifluoperazine, which he failed to continue, and was readmitted two weeks later, for 10 days, with a mild recurrence of paranoid ideation that responded to trifluoperazine 10 mg daily. This was tailed off over a month with no recurrence of psychotic symptoms. Subsequent pituitary surgery was planned.

Comment

This psychotic episode appears to have been precipitated by bromocriptine. There is evidence of a liability to levodopa-induced affective disorder in those with a family history of affective illness.⁵ This case suggests an analogous genetic vulnerability to bromocriptine-induced psychosis. A family history of schizophrenia in addition to a personal history may be relevant in considering the use of bromocriptine.

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(Accepted 18 August 1982)

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Treatment of digoxin overdose with antigen-binding fragments of digoxin-specific antibodies

Severe digoxin toxicity due to accidental or deliberate overdose is rare, but is often life-threatening, especially if there is pre-existing cardiac disease. Treatment with gastric lavage, adjustment of electrolyte balance, antiarrhythmic drugs, pacing, and, when necessary, low-voltage DC shock is not always effective and the ultimate aim must be to lower circulating free digoxin concentrations. Dialysis and haemoperfusion clear digoxin but blood concentrations are rapidly restored from the large extravascular pool.¹ We treated a patient with severe digoxin toxicity using digoxin-specific antibodies and we report the efficacy of this treatment in a potentially lethal condition.

Case report

A 60-year-old man with a history of left ventricular failure, mitral regurgitation, and intermittent atrial fibrillation treated with digoxin, diuretics, and warfarin, was admitted after a suicide attempt with 12.5 mg digoxin, 150 mg warfarin, and 40 mg diazepam. On examination he was alert, in sinus rhythm at 60 beats/min, and blood pressure was 110/60 mm Hg. He was not in overt heart failure and cardiac signs were unchanged. Electrolyte balance and cardiac enzyme activities were normal. Chest x-ray film showed an enlarged heart. There was complete left bundle-branch block and left axis deviation on the electrocardiogram as previously, but the P-R interval was now prolonged to 0.28 seconds and there were frequent ventricular ectopics, some of which were multiple and multifocal. The initial serum digoxin concentration was 13 g/l (therapeutic range up to 2.2 g/l) and prothrombin index 7.9.

Gastric lavage was carried out one and a quarter hours after the overdose. A lignocaine infusion was started and a prophylactic temporary transvenous pacemaker inserted. Potassium concentrations were closely controlled. Despite these measures bradycardia worsened and the electrocardiographic changes persisted. We decided to lower the digoxin concentrations with antigen-binding fragments of sheep digoxin antibody. After preliminary test

doses intradermally and then 2 mg antigen-binding fragments in saline intravenously an infusion of 200 mg in 5% dextrose was set up and given over one hour with close monitoring of vital signs. The infusion started 24 hours after ingestion. The free serum digoxin concentration fell dramatically to undetectable concentrations (<1 ng/ml) while the total blood concentration, comprised almost solely of digoxin bound inactively to antigen-binding fragments, correspondingly rose (figure). The reduction in free

Time course of total serum digoxin concentration, free serum digoxin concentration, and serum potassium concentration immediately before and after injection of antigen-binding fragments of digoxin. Values are expressed as units on a logarithmic scale. Arrows indicate timing of infused potassium supplements.

digoxin was accompanied by a fall in serum potassium, which was corrected by infused supplements, using a total of 120 mmol. The electrocardiogram showed resolution of ectopic activity and sinus bradycardia. The coagulation disturbance was corrected using fresh frozen plasma and vitamin K.

Comment

Receptor-digoxin interaction is reversible and digoxin-specific antibodies have been shown to prevent or reverse digitalis-induced toxic arrhythmias, inotropy in isolated cardiac muscle, and inhibition of sodium, potassium, and adenosine triphosphatase in animals.³ These antibodies, produced by immunising animals with protein-bound digoxin, have the potential to cause anaphylaxis. Antigen-binding fragments were developed that lacked the antigenicity of the intact immunoglobulin while still retaining high affinity and specificity.³ In contrast to the parent molecule the antibody had a larger volume of distribution, equilibrated more rapidly with digoxin, and was excreted by the kidneys, taking most of the drug with it.^{1,3,4} Furthermore, reversal of digoxin-induced arrhythmias in dogs was more rapid and predictable for antigen-binding fragments than for the equivalent dose of parent digoxin-specific IgG.⁵

The use of antigen-binding fragments for the successful treatment of digoxin overdose has been reported⁴ but only recently has the potential importance of this mode of treatment been widely recognised. Antibody inhibition of several important drugs has been shown, but clinical use will probably be restricted to those drugs such as digoxin that are dangerous when taken in excess, in common use, and not always controlled by conventional measures.

We thank The Wellcome Research Laboratories, Beckenham, Kent, for supply of the digoxin antibody, and Dr Thomas W Smith, Peter Bent Brigham Hospital, Boston, Mass, for expert advice in management of this case and for analyses performed in his laboratory.

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(Accepted 24 August 1982)

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Short-term control of brittle diabetes using a Biostator

The Biostator (Miles Laboratories Ltd) is a machine which continuously samples venous blood, measures the blood glucose concentration, and then infuses either insulin or glucose intravenously. The rate of infusion is determined by an algorithm stored in the machine's computer.¹ We report the first use of this machine to control brittle diabetes (as defined by Pickup *et al*²) in the medical ward of a district general hospital.

Case report

A 13-year-old girl (weight 55 kg) usually achieved satisfactory control using subcutaneous Actrapid insulin delivered by a Mill Hill infuser² (average daily dose 60 units). Three or four times each year she used to become resistant to doses of more than 500 units of subcutaneous and intramuscular insulin and rapidly became ketoacidotic. Control was usually re-established without difficulty using intravenous insulin (60-120 units daily), which was continued for 1-2 weeks until the resistance to subcutaneous insulin settled spontaneously.

On 27 December 1981 she was admitted to hospital because of resistance to subcutaneous insulin, and for the first time it was impossible to achieve stable control with intravenous insulin although blood samples were taken every 1-2 hours by day and at night. Blood glucose concentrations were measured using BM-Test-Glycemic 20-800 strips (Boehringer-Mannheim Corporation) and fluctuated rapidly between 1 and 44 mmol/l (18 and 792 mg/100 ml). Between 26 and 30 January 1982 her diabetes was controlled using a Biostator. The constants used to determine the infusion rates of insulin or glucose were those preprogrammed into the computer,¹ except that the variance, which determines the response rate to a change in blood glucose concentration, was increased from 100% to 200% during the first 24 hours. Blood glucose concentrations during the second and third days of this treatment are shown in the figure. Lack of suitable veins for the sampling cannula, which had to be replaced three times, resulted in the treatment being stopped after four days, during which time the blood glucose

Blood glucose concentrations during the second and third days' treatment with the Biostator. The record begins after a two-hour interruption due to a blocked cannula. Arrows marked S indicate gaps for standardisation; unmarked gaps are due to cannula blockages.

Conversion: SI to traditional units—Blood glucose concentration: 1 mmol/l $\approx$ 18 mg/100 ml.