PAPERS AND SHORT REPORTS

Psychotic reactions during treatment of pituitary tumours with dopamine agonists

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Abstract

Of 600 patients treated with the dopamine agonist drugs bromocriptine and lisuride for functioning pituitary tumours, eight developed drug related psychoses. Symptoms included auditory hallucinations, delusional ideas, and appreciable changes in mood. These reactions occurred with lower doses of the drugs than previously reported and remitted when treatment was stopped.

The possibility of psychiatric side effects with dopamine agonist treatment should be recognised in view of the strain that may be placed on patients and their families.

Introduction

Psychotic reactions to high doses (50-100 mg/day) of bromocriptine are well known in the treatment of parkinsonism.[1 2] Recently there have been isolated reports of similar reactions associated with the lower doses (7·5-30 mg/day) used in acromegaly and hyperprolactinaemia.[3-5] In all these cases either there was a history of psychotic illness or considerable changes in behaviour or mood, or both, had occurred before treatment. We now report the occurrence of such reactions in patients who were not so predisposed; of a series of 600 patients with hyperprolactinaemia or acromegaly treated with the dopamine agonists bromocriptine or lisuride, eight developed a clear cut psychiatric illness that appeared to be related to treatment. These reactions are of particular interest as they occurred, in four cases, with relatively low doses of dopamine agonists.

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Patients and methods

Six hundred patients received either bromocriptine or lisuride for acromegaly or hyperprolactinaemia. Acromegaly was diagnosed on the basis of the typical clinical features of the disease together with the finding of non-suppression of circulating growth hormone during an oral glucose tolerance test. Hyperprolactinaemia was confirmed when prolactin concentrations were persistently greater than 800 mU/l (normal <360 mU/l). Eight patients developed a psychotic illness. Mental state was assessed by an experienced psychiatrist (TT or JC) in seven. The remaining case was evaluated retrospectively from the notes. As minor changes in mood and behaviour are common in endocrine illness a clear relation between drug use and altered mental state had to be established definitely before the psychopathology was considered to be drug induced. The table shows the essential features of the eight patients affected, and three cases are described in detail below.

CASE REPORTS

Case 1—A 38 year old woman had hyperprolactinaemia due to a prolactinoma. She was treated with bromocriptine 7·5 mg daily for seven months. During that time she became increasingly depressed, anxious, and tearful with initial and late insomnia. She became convinced that she was being followed by a couple for whom she worked, was afraid for her life, and described people talking about her in the street and attempting to try their keys in the lock of her front door. She stopped taking bromocriptine because of her mood state and lost her schizophreniform symptoms within a month. She subsequently had minor depressive symptoms but no recurrence of hallucinations or delusional beliefs.

Case 3—A 58 year old woman with hyperprolactinaemia, visual field defects, and right sided third and fourth cranial nerve palsies due to a macroadenoma was treated with bromocriptine 30 mg daily for six months, then 45 mg daily for 12 months. Her tumour shrank back into the pituitary fossa, which became partially empty. The field defects disappeared and the diplopia improved. She was left with mild third nerve palsy. Psychiatrically she remained well apart from being "easily nervous" until the final two months of the above treatment, when she developed a widespread dermatitis on her face, arms, and legs. She described itching and "worms" crawling out of her eyebrows to lay eggs and sent a lump of clotted blood by post to her physician to be checked for worms. The result was negative. Examination showed widespread excoriations on her face, arms, legs, and abdomen. A consultant dermatologist assessed these as self induced and typical of "delusional parasitosis." Bromocriptine was stopped, and her skin condition improved appreciably within four weeks. Because of rising prolactin concentrations the drug was then

Characteristics of patients treated with dopamine agonists who developed psychiatric side effects

Case No	Sex	Age (years)	Endocrine disorder	Mean serum concentration				Drug	Duration of treatment before psychiatric diagnosis (months)	Highest daily dosage* (mg)	Principal symptoms	Psychiatric diagnosis
				Before treatment		During treatment						
				Prolactin (mU/l)	Growth hormone (mU/l)	Prolactin (mU/l)	Growth hormone (mU/l)					
1	F	38	Prolactinoma	887		120		Bromocriptine	7	7·5	Anxiety and depression; hallucinations; delusions of persecution	Schizophreniform psychosis (paranoid type)
2	F	36	Prolactinoma	>1260		60		Bromocriptine	52	7·5	Auditory hallucinations; delusions of infidelity	Schizophreniform psychosis (paranoid type)
3	F	58	Prolactinoma	>4000	3	119	2	Bromocriptine	18	45	"Delusional parasitosis"	Paranoid state (MHP)†
4	F	32	Prolactinoma	3840		1576		Lisuride	4	1·2	Auditory hallucinations; delusions of persecution	Schizophreniform psychosis (paranoid type)
5	F	35	Acromegaly	233	19	<60‡	13	Bromocriptine	4	40	Auditory hallucinations; delusions of persecution	Schizophreniform psychosis (paranoid type)
6	M	29	Acromegaly	175	52	<60	18	Bromocriptine	6	100	Hyperactivity; disinhibition; euphoria	Hypomania
7	M	63	Acromegaly	1200	480	<60	45	Lisuride	6	1·8	Disinhibition; euphoria; insomnia	Hypomania
8	F	20	Prolactinoma	>4000	2·7	516	2	Bromocriptine	11	60	Delusional mood; ideas of reference; auditory hallucinations	Schizophreniform psychosis (paranoid type)

*Lisuride 0·2 mg is roughly equivalent to bromocriptine 2·5 mg.
†MHP (monosymptomatic hypochondriacal psychosis) has been regarded as a variant of paranoid illness.[19]
‡Undetectable.

restarted at a dose of 30 mg daily, and over the next year her skin lesions persisted and grew worse. She became sensitive to noise, stopped watching television, and insisted on washing her clothes separately from those of her daughter to prevent contamination by the parasites. Subsequent reduction of the bromocriptine to 7·5 mg daily again led to a distinct improvement in her lesions within six weeks, noted by both herself and her physician. A relapse did not occur subsequently, and she stopped thinking that she had, or ever had had, worms.

Case 7—A 63 year old man with acromegaly was treated with lisuride up to 1·8 mg daily. Over the course of six months he became disinhibited, distractible, and irritable. His mood varied from the abrupt to the overcheerful, his concentration was impaired, and his sleep pattern appreciably changed with nocturnal insomnia and sudden naps during the day. His wife wrote to the unit, concerned about his "character change," especially his instability and erratic behaviour. On clinical assessment he was noted to be disinhibited and euphoric with behaviour characteristic of hypomania. Lisuride was stopped and within three weeks he had returned to being the quiet reliable man he had been, a fact reported spontaneously, and with relief, by his wife.

Discussion

Clearly, psychotic reactions may develop in patients with no previous psychiatric history as a rare side effect of the use of the dopamine agonists bromocriptine and lisuride in the treatment of functioning pituitary tumours. Four of our patients were taking doses of dopamine agonist that have only previously been associated with psychosis in susceptible patients with a personal or family history of schizophrenia.[3–5] In those predisposed patients psychosis may have been a coincident reaction to physical illness (hyperprolactinaemia), and the exact role of bromocriptine was therefore uncertain. One clear case of psychosis in acromegaly without predisposing factors has been reported, occurring after 20 months' treatment with bromocriptine 60 mg/day.[6]

Mania in the puerperium associated with treatment with bromocriptine has been reported,[7 8] which may reflect an undue susceptibility to dopamine agonists in the postpartum period.[9] Puerperal psychoses are, however, notoriously unpredictable in form and severity; thus the aetiological role of bromocriptine in these cases was admitted by the authors to be uncertain. Another dopamine agonist, piribedil, has also been reported to trigger mania in a depressed bipolar patient,[10] the authors inferring an inherited susceptibility to such reactions, a suggestion also made by Le Feuvre *et al.*[3] None of our affected patients admitted to a family history of paranoid or affective disorder. Nevertheless, dopamine agonists may merely have precipitated a psychosis in those likely, perhaps via an inherited factor, to have developed such an illness anyway. Long term follow up will be needed to resolve this question.

Our findings, however, are important as the first substantial evidence, in patients with pituitary diseases, of de novo psychotic reactions associated with dopamine agonist treatment. In all cases remission occurred after the stopping or reduction in dosage of these agents. In three patients (cases 4, 5, and 7) the relation between illness and treatment was highlighted by their further relapses when the dopamine agonist was restarted before the possible connection was noticed. Management of one patient (case 8) was affected by this earlier experience; prompt reduction in dosage twice led to early remission and minimal morbidity. As a rule the reactions were dose dependent, with a wide interpersonal variation and susceptibility in some patients at much lower doses than had previously been reported. There was no evidence that other treatment or the rate of increase in dosage were significant factors. Although several patients were regarded as being especially anxious before treatment, no consistent personality profile was noted.

The incidence of such reactions has been said to be 1-2% in parkinsonism,[11] which accords roughly with our experience in pituitary diseases. A more formal survey would be required to assess this. Because, unlike patients with Parkinson's disease, our patients had no known prior disorder of dopamine metabolism, they provide clearer evidence of the role of dopamine in the pathogenesis of some psychotic illnesses. Although lisuride has an additional serotonin antagonist activity, bromocriptine does not; this reinforces our inference that it is the dopamine agonism with which these reactions are associated. The use of a specific dopamine antagonist such as pimozide while maintaining dopamine agonist treatment might have proved this point, but given the distressing condition of the patients this would clearly not have been ethical. In this respect one patient (case 3) is of particular importance as pimozide has been used successfully to treat delusional parasitosis.[12]

Of further interest is the form of the psychoses; the present cases combined with those reported previously have been restricted to 11 paranoid and four manic illnesses. Functional psychoses are, by tradition, broadly divided into schizophrenic and affective groups. Among patients with schizophrenia, however, a subgroup has been postulated with "positive" symptoms associated with acute illness and a good response to dopamine blocking neuroleptics.[13] Similar drugs are also known to be effective in mania,[14] and bromocriptine has been reported to exacerbate manic symptoms.[15] Dopamine receptors may possibly take part in the pathogenesis of both paranoid and manic illnesses despite the traditional diagnostic distinction, and this common pathogenetic mechanism may be the cause of a superficial likeness in aspects of their clinical symptomatology. Although in our group all the women developed paranoid illnesses and the two men became manic, a much larger series would be required to establish any significant sex difference.

Although the reactions reported above were almost certainly due to the dopamine agonists per se, it must be noted that little is known of the incidence of psychotic symptoms in untreated acromegaly or hyperprolactinaemia. Apart from isolated case reports,[16-18] only generalised anecdotal comment is available. In our series neither endocrine state nor the pattern of response to treatment was predictive of a psychiatric relapse. We believe, in view of the time course of relapse and remission and the relation to drug treatment, that these illnesses were not simply a reflection of the underlying endocrine disorder.

Clearly, these side effects must be recognised in view of the particular strain that may be placed on the patients and their families. Alterations in day to day behaviour, non-compliance with treatment, unusual changes in work or social life, unaccountable moodiness or misery are all suggestive and should alert the physician. The stigma of such illness remains strong, and we cannot absolutely exclude the possibility that some cases have gone unrecognised. Nevertheless, it must be emphasised that only eight out of 600 patients treated with dopamine agonists definitely developed this type of reaction.

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Calcium supplementation and postmenopausal bone loss

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Abstract

A series of 103 early postmenopausal women completed a questionnaire about their dietary calcium intake and were then divided into three groups: those with an intake below 550 mg/day, those with an intake between 550 and 1150 mg/day, and those with an intake above 1150 mg/day. Thereafter they were given a daily supplement of 500 mg calcium for two years and had their bone mineral content measured every three months. Any changes found were taken as an estimate of bone calcium balance.

All three groups showed a similar fall in bone mineral content over the two years, indicating that a calcium intake of 1000-2000 g daily is ineffective in preventing bone loss in the early menopause.

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Introduction

The amount of bone lost yearly in the period immediately after the menopause approaches 2%. Although this rate then declines, bone loss will reach such a magnitude that by the age of 70 some 40% of women will have had at least one spontaneous postmenopausal fracture.[1] Hip fracture, the most severe, is associated with a six month mortality of 20%, and the incidence of these fractures seems to be increasing.[2] Since there is no treatment for osteoporosis, some means of prevention is urgently required. Oestrogen may delay or prevent postmenopausal bone loss[3-5] and reduce the risk of fractures.[6] This effect is probably dose related,[7] and there is evidence that a combination of calcium and oestrogen may increase bone mass.[3] Calcium balance is almost invariably negative in early postmenopausal women. Oestrogen probably impedes bone resorption, resulting in a decreased loss of calcium. Although it might be possible to identify potential fast bone mass losers, such women may not readily accept hormone treatment, and we cannot exclude the risk of unwanted side effects of long term administration.

The search for an agent that will increase bone mass has been intensive. Dihydroxycholecalciferol ($1,25(OH)_2D$) stimulates calcium absorption, but its effect on bone mass, and that of its analogue 1α-OHD, has proved disappointing.[3 8] Heaney *et al* found a positive correlation between calcium intake and