Successful treatment of refractory schizophrenia with combined olanzapine and quetiapine in a patient with a prolactin secreting pituitary microadenoma

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Abstract

Treatment-resistant schizophrenia presents a particular problem in patients who, for whatever reason, cannot be treated with clozapine. Pharmacological strategies for the further management of such individuals usually involve the coadministration of two or more antipsychotic drugs, leading to an increased potential for adverse effects. Hyperprolactinaemia (elevation of serum prolactin levels) is a common side-effect of antipsychotics and one that it is especially important to minimize in patients with primary pituitary pathology. We present a patient with treatment resistant schizophrenia and a prolactin-secreting microadenoma of the pituitary who was intolerant of clozapine therapy. She was prescribed a combination of olanzapine and quetiapine and experienced almost complete resolution of her psychosis, with no elevation of serum prolactin levels. We suggest that this may be a strategy worthy of consideration in patients for whom conventional treatment methods have failed, particularly those who are sensitive to the prolactinogenic effects of many antipsychotic medications.

Keywords

olanzapine, pituitary microadenoma, prolactin, quetiapine, treatment resistant schizophrenia

Introduction

Treatment resistance in schizophrenia is a common problem in clinical practice, affecting approximately 30% of patients diagnosed with the illness (Wahlbeck et al., 2000). Clozapine has been shown to bring about significant improvements in symptomatology and functioning in between 30% and 60% of patients (Kane, 1992; Wahlbeck et al., 2000), although a recent re-examination by Moncrieff (2003) claims that its superiority to other antipsychotic agents may not be as great as previously thought.

Because of its particular side-effect profile, clozapine is unsuitable for some patients and poorly tolerated by others. In addition, some patients fail to respond to treatment with clozapine and evidence supporting augmentation strategies and drug combinations remains largely confined to anecdotal reports.

Hyperprolactinaemia is a common adverse effect of treatment with antipsychotic drugs. A study by Windgassen et al. (1996) found that 19% of patients taking antipsychotic medication had a raised serum prolactin level. Because prolactin levels are often not routinely measured in clinical practice and hyperprolactinaemia is often asymptomatic, it is likely that the condition frequently goes unnoticed. However, in some patients, hyperprolactinaemia can cause unpleasant physical effects, potentially interfering with treatment compliance.

In women, physical effects of hyperprolactinaemia include galactorrhoea, loss of libido, breast enlargement and tenderness, hirsutism, weight gain and disruption of menses. In men, it can result in loss of libido, impotence, reduced seminal fluid volume, gynaecomastia and galactorrhoea. In the long term, hyperprolactinaemia can result in loss of bone density, predisposing the individual to osteoporosis.

We present the case of a woman with refractory schizophrenia...
whose psychotic symptoms were almost entirely controlled with a combination of two atypical antipsychotic agents, olanzapine and quetiapine. The patient’s treatment was further complicated by the diagnosis of a prolactin-secreting microadenoma of the pituitary gland, but her serum prolactin levels remained within the normal range on this combination of medication. To our knowledge, this is the only published account of treatment with these particular drugs in combination and may be an option worthy of consideration, especially for patients who experience hyperprolactinaemia on other antipsychotic medication, as well as those with primary endocrine pathology.

Case report

The patient was a 35-year-old single woman who first presented to psychiatric services in 1992, at the age of 24 years. She was the elder of two sisters, her birth and milestones were normal and she had no illnesses or injuries in childhood. She enjoyed a good relationship with both parents. She left school at the age of 16 years with six GCSEs and trained in nursing, working as a nurse until she was forced to stop because of mental ill health. She had never married and had no children. The only family history of mental illness was bipolar disorder in an uncle.

Before her first presentation to mental health services, she reported that she had had periods of low mood, reduced volition, anhedonia and irritability since the age of 17 years. Her general practitioner (GP) had tried amitriptyline and dothiepin but she had not taken them due to their sedative effects. She experienced some benefit from oral flupenthixol (Fluanxol).

In April 1990, she was referred by her GP to a neurologist, complaining of visual disturbances, including coloured lights, wavy lines and flashing lights. There were no abnormalities on clinical examination, and no radiological investigations were performed. No firm diagnosis was reached, and the symptoms were thought to be due to stress. She was taking no psychotropic medication at this time.

In 1992, she was diagnosed by a consultant psychiatrist as suffering from depression and was treated with fluoxetine 20 mg daily. Her mood improved on this drug. In June 1993, she visited her GP complaining of galactorrhoea. Her prolactin level was elevated at 722 mU/l (normally < 450 mU/l). This problem occurred intermittently over the next 12 months and resulted in referral to an endocrinologist in June 1994. At that time, she had galactorrhoea, which was confirmed on examination. Her prolactin level was 628 mU/l. Again stress was felt to be the cause. She was taking Prozac (fluoxetine) at the time that both the elevated prolactin levels were noted.

In December 1994, she was admitted to hospital suffering from an episode of acute psychotic illness. Although a final diagnosis of mania was made, a large degree of diagnostic uncertainty was noted, largely due to the nature and severity of her psychotic symptoms. As well as mood elevation, over-activity, garrulousness and over-spending, there was evidence of auditory hallucinations, delusions of reference, delusional misinterpretation and passivity. The antidepressant was discontinued and she was discharged on lithium. She was also treated with risperidone and thioridazine.

Over the next year, she was intermittently troubled by depressive symptoms. However, she also suffered continuously from psychotic symptoms, particularly third-person auditory hallucinations and passivity phenomena. When she was readmitted in 1995, she was exhibiting these symptoms plus thought insertion and withdrawal, persecutory delusions, formal thought disorder and second-person command hallucinations. Her diagnosis was changed to schizoaffective disorder.

During the following 9 months, she was rarely well, being admitted to hospital on four occasions. On three of these occasions, the prominent symptoms were of psychosis and, on one, of depression. During this period, she was treated with antipsychotic medication (droperidol, sulpiride, haloperidol, risperidone and flupenthixol), antidepressants (fluoxetine, paroxetine) and lithium. None of the antipsychotic drugs controlled her symptoms effectively, despite being used in combination at times.

In 1996, she was admitted for initiation of clozapine. This had been offered previously, but she had refused to take it. Clozapine was increased gradually up to a dose of 200 mg b.d. but caused side-effects of profound hypotension, hypersalivation, sweating and urinary incontinence, and she was not willing to continue with it. Sertindole (up to 16 mg per day) was tried, but was ineffective. Olanzapine (20 mg) was partially effective. Depot zuclopenthixol (200 mg every 2 weeks) was added to the olanzapine and she was discharged on this combination of medication in early 1997. During this admission, her lithium had been stopped with the result that she became hypomanic. Lithium was restarted.

Over the next 5 years, she was looked after in a different area and managed to remain out of hospital, although she remained significantly disturbed by psychosis throughout and attended a day hospital for almost 4 years. During this period, she was managed on varying amounts of olanzapine, oral zuclopenthixol and chlorpromazine, as well as mood stabilizers and intermittent courses of antidepressants.

In March 1998, she was re-referred to endocrinology by her GP. By this time, she was established on a combination of antipsychotic medications, including both typical and atypical agents. Her prolactin was 1940 mU/l. A repeat test soon afterwards showed a rise to 2500 mU/l. She was experiencing daily galactorrhoea and had had no menstrual periods for 3 years. At the appointment, she complained that she experienced headache and blurred vision. Visual field testing and a magnetic resonance imaging (MRI) scan were ordered. Cabergoline 0.5 mg twice weekly was started in an attempt to reduce the prolactin level. Unfortunately, this precipitated a worsening of her psychotic illness and had to be stopped.

In June 1998, visual field testing showed a marked bitemporal defect. However, MRI scanning 2 weeks later revealed no abnormality. Contrast was not administered, at the patient’s request. In July 1998, she was restarted on cabergoline at a dose of 0.5 mg twice weekly and, on this occasion, she tolerated the dose. By November 1998, her prolactin was down to 778 mU/l. During this period, she was managed on varying doses of olanzapine and quetiapine, as well as mood stabilizers.

In February 1999, she was referred for a second opinion to a professor of endocrinology, who felt that the history was very suspicious of pituitary pathology and that the most likely diagnosis was a pituitary microadenoma.

From February 1999, until the start of her most recent admission, she remained under the care of the endocrinologists,
continued to take antipsychotic medication (both typical and atypical throughout) and cabergoline 1 mg twice weekly. She remained psychotic throughout this period, but managed to avoid admission. For most of 1999, her prolactin level remained between 1800–2000 mU/L, but, in December 1999, it reduced to 595 mU/L, although there were no significant changes in psychotropic medication to account for this reduction.

Prolactin levels then remained relatively stable until her most recent admission in July 2002, due to a deterioration in her mental state over the preceding few weeks. She presented as distressed and agitated with multiple psychotic symptoms. Auditory hallucinations were present, in both the second and third person, in the form of two male and one female voice. The voices were derogatory at times, calling her names and insulting her. At other times, they appeared to be providing a running commentary on her actions. Most distressing were the command hallucinations, which were increasing in intensity and urging her to kill family members and herself. She felt that the voices came from members of a ‘clan’, who were working for the devil. She believed that the messages she received were from the devil and stated that she was also able to pick up messages from the devil from other people’s minds via a process of telepathy. She also complained of a number of visual hallucinations, including malignant ‘bugs’, flowers and ultraviolet rays. She also appeared to experience somatic hallucinations, in the form of hands touching her, olfactory hallucinations of unpleasant smells and passivity phenomena, believing that the devil took control of her actions. Although she described her mood as ‘up and down’, at the time of admission, there were no obvious signs of depression or hypomania.

On admission, she was taking a combination of medication: olanzapine 15 mg at night; zuclopenthixol 30 mg daily; chlorpromazine 50 mg tablets in varying amounts; procyclidine 5 mg twice daily; thyroxine 50 mcg daily; cabergoline 1 mg twice weekly, as well as various nutritional supplements and the oral contraceptive pill. She was taking no antidepressants or mood stabilizers on admission. She refused a re-trial of clozapine, because of the unpleasant side-effects she had experienced previously. She was initially weaned off the zuclopenthixol tablets gradually and her olanzapine increased to the maximum dose of 20 mg per day. Although her mental state did improve, she still remained significantly symptomatic and, because of the history of elevated prolactin levels, it did not appear to be appropriate to add a conventional antipsychotic agent. Olanzapine was therefore increased beyond BNF (British National Formulary, 2003) limits, to a total daily dose of 30 mg. Although her mental state was much improved for a number of weeks, to the point at which weekend home leave was possible, this benefit was not sustained and her mental state deteriorated once more, to the extent that she required several doses of intramuscular clopoxil clophacse. In addition, she was complaining of extra pyramidal side-effects on the higher dose of olanzapine.

After discussions with the patient, it was decided to add quetiapine to the olanzapine to see if additional therapeutic benefit could be gained. Quetiapine was gradually increased to the maximum dose of 750 mg per day, with concomitant improvement in mental health. It was possible to decrease the olanzapine back to the maximum BNF dose of 20 mg per day. On this combination of treatment, she reported that she felt better than she had for many years. Her psychotic symptoms were completely controlled, with the exception of a quiet, ‘background’ running commentary which she said had been present continually from the start of her illness.

She complained of no side-effects from the treatment. The extrapyramidal side-effects that she had experienced on the higher dose of olanzapine resolved, she was not troubled by sedation, hypotension or any other adverse effect and her prolactin level remained within normal range. The prolactin level on discharge was 369 mU/L. During periods in which she had been using high doses of p.r.n. typical antipsychotics (including acuphase), her prolactin had been elevated, with the highest reading being 2199 mU/L. During her prolonged admission, she was subject to significant mood fluctuations and was started on sodium valproate to control these. She was also treated with small doses of the antidepressant drug venlafaxine, and together these medications controlled her affective symptoms well. During the first half of her admission, cabergoline was also stopped on the advice of the endocrinologists, who felt it may be worsening her psychosis and would not be producing much therapeutic benefit because dopamine blocking drugs were being used simultaneously. Although it is difficult to be certain, because cabergoline has such a long half-life, the cessation of this medication did not appear to dramatically influence her mental state.

Discussion

This is a complex case and one in which there is some diagnostic uncertainty surrounding the question of whether she does in fact have a prolactin-secreting microadenoma of the pituitary or whether all her hyperprolactinaemia has been due to medication. Clearly, in a patient taking antipsychotic drugs, these would be the most obvious cause of hyperprolactinaemia. It is well known that typical antipsychotic agents such as haloperidol, zuclopenthizol and chlorpromazine can cause markedly increased levels of serum prolactin (Meltzer and Fang, 1976; Korbonits and Grossman, 2000), although it is still advisable to rule out other possible causes for this if the level exceeds 2500 mU/L.

Atypical antipsychotics are said to produce less effect on prolactin levels, although there is good evidence that serum prolactin levels are frequently raised by risperidone (Kleinberg et al., 1999) and amisulpride (Grunder et al., 1999; Colonna et al., 2000). A recent study by Turron et al. (2002) suggested that there may be an increase of shorter duration with clozapine and olanzapine, which have not previously been thought to cause this problem. There appears to be no evidence of raised prolactin levels associated with the use of quetiapine.

The patient reported galactorrhoea and had tests confirming a raised level of serum prolactin in 1993 and 1994, before commencing antipsychotic medication. However, at that time, she was taking fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI). Serotonin is known to be a releasing factor for prolactin, although there are published reports of galactorrhoea and hyperprolactinaemia related to the use of fluoxetine (Meltzer et al., 1997;
Peterson, 2001) and galactorrhoea is listed as an adverse effect of SSRIs in the BNF. It would be possible therefore to explain all of her hyperprolactinaemia as the effects of various types of psychotropic medication.

Although she has a diagnosis of pituitary microadenoma, this has not been demonstrated on MRI scan. However, a benign microadenoma cannot be ruled out solely on the basis of a negative scan. The picture is complicated by the presence of a bitemporal hemianopia, which may indicate that there has been pressure on the optic chiasm at some point. Also, she was seen by a neurologist in 1990 (before commencement of psychotropic medication) complaining of visual symptoms and, although no cause was found on physical examination, no radiological investigations were carried out at this time. It is possible that she had a pituitary microadenoma that was worsened by antipsychotics with a strong dopamine blockade but receded, along with a drop in the prolactin level, when these drugs were withdrawn and she was commenced on olanzapine, and later quetiapine. Malhotra et al. (2001) described the case of a 64-year-old woman with a pituitary adenoma which completely resolved following a switch from risperidone to olanzapine, with concomitant reduction in serum prolactin levels. Whether or not a pituitary microadenoma had a role in this patient’s hyperprolactinaemia, the fact remains that, for whatever reason, she was extremely sensitive to the prolactinogenic effects of medication and, on several occasions, developed symptomatic elevations in serum prolactin.

During the course of her long illness, she has been variously diagnosed as suffering from bipolar affective disorder, schizoaffective disorder and schizophrenia. In cases as complex as this, it is often necessary to take a longitudinal view and to review the diagnosis periodically. Clearly, the nature and extent of her positive psychotic symptoms would not support a diagnosis of bipolar affective disorder alone. The distinction between schizoaffective disorder and schizophrenia is more problematic. Clearly, she has described symptoms of both major affective disorder and schizophrenia that would meet diagnostic criteria and which have occurred within the same episode of illness. However, the distinction is also based upon what is referred to in the ICD-10 Diagnostic Criteria for Research (WHO, 1993) as ‘an approximate “balance” between the number, severity and duration of the schizophrenic and affective symptoms’. Furthermore, DSM-IV (APA, 1994) states that, for a diagnosis of schizoaffective disorder, ‘the mood symptoms are present for a substantial proportion of the total duration of the illness’, and further qualifies that clinical judgement is required to determine what constitutes a substantial proportion. In our judgement, the balance of symptoms in her case was in favour of a primary diagnosis of schizophrenia with a comorbid affective disorder, due to the duration of her affective symptoms being relatively short compared to the lengthy periods during which only the positive psychotic symptoms were present.

Our patient had very severe schizophrenic symptoms, which had failed to respond to several antipsychotics given in large doses and often in combination with each other. The combination of quetiapine and olanzapine produced improvement far in excess of that experienced with previous drugs and combinations of drugs and, in addition, produced no side-effects.

Pharmacologically, it is difficult to understand why this particular combination of agents should have been so successful. Most case reports concerning the coadministration of two atypical antipsychotic agents or an atypical and typical agent together involve one of the two being added to enhance D2 receptor blockade; for example, clozapine administered with sulpiride (Shiloh et al., 1997), amisulpride (Mathiasson et al., 2001) or risperidone (Henderson and Goff, 1996; Raskin et al., 2000b); olanzapine administered with risperidone (Lerner et al., 2000), sulpiride (Raskin et al., 2000a) or pimozide (Takah, 1999). In this case, the two agents used are similar pharmacologically, with both having a wide range of activity at receptor sites of several neurotransmitters, including dopamine, histamine, serotonin and noradrenaline.

It has been suggested that quetiapine may differ from olanzapine in that it has greater affinity for D₂ receptors in the limbic system compared to those in the striatal system (Stephenson et al., 2000). Our patient was unable to tolerate doses of olanzapine in excess of BNF limits due to extrapyramidal symptoms. It may be that the addition of quetiapine was able to provide a higher level of limbic D₂ receptor occupancy without causing this particular side-effect, due to greater specificity for receptors in this area.

Obviously, the question remains as to whether her psychosis could have been managed with quetiapine alone. There is no evidence that quetiapine is generally of particular value in treatment-resistant schizophrenia, although this would not rules out a good response in an individual patient. However, in view of her level of treatment resistance, the fact that she had been an inpatient continuously for 9 months and the level of behavioural disturbance, risk and personal distress that her symptoms caused, she was very reluctant to consider changes to her medication. It was therefore decided that we would not attempt to reduce or stop the olanzapine at this stage. Although, obviously, it would be ideal to know whether both drugs were essential, it was felt that this was something that could be considered at a later date, with the priority at present being the patient’s stability and quality of life.

Although the combination of olanzapine and quetiapine would evidently need further evaluation before it could be recommended as a treatment strategy, it may be an option worth considering in patients with resistant illness in whom avoidance of hyperprolactinaemia is of paramount concern and in those patients who are unwilling to take, or unable to tolerate, clozapine.

Implications for clinical care

Prevention

Prolactin sparing antipsychotics would be an appropriate choice of first-line therapy for patient groups particularly vulnerable to hyperprolactinaemia or its effects. Such groups would include patients with pituitary pathology, patients with a history of somatic hyperprolactinaemia and postmenopausal women.

In general, using the lowest effective dose of any antipsychotic is likely to reduce the risk of the patient experiencing adverse effects, including hyperprolactinaemia.
Recognition

Serum prolactin can be easily measured, either routinely or in patients with suggestive symptoms such as amenorrhea, gynae-comastia and galactorrhea. If levels are particularly high [Korbonits and Grossman (2000) suggest > 2500 mU/L] patients should be investigated for pituitary pathology. This would normally involve referral to an endocrinologist, MRI scanning, visual field testing and pituitary hormone assays (growth hormone and thyroid stimulating hormone in addition to prolactin).

Pituitary microadenomas, as demonstrated by our patient, are difficult to detect and to diagnose with certainty.

Management

In patients with pituitary pathology and those vulnerable to hyperprolactinaemia, we would suggest quetiapine as the most appropriate first line antipsychotic. Olanzapine, having little effect on prolactin levels, would also be a reasonable choice. In patients with treatment resistant schizophrenia, clozapine would be the obvious choice, as a prolactin sparing agent and the only anti-psychotic with evidence to support its use in treatment resistance.

The combination of olanzapine and quetiapine, as used in our patient, would not be a routine choice but was used in this case because of the exceptional circumstances.

The Royal College of Psychiatrists Consensus Statement (Thompson, 1994) on the use of high dose antipsychotic medication, whilst formulated at a time when atypical antipsychotics (except clozapine) had not been introduced, nonetheless established the principles of prescribing antipsychotics in doses beyond BNF limits. In particular, the use of high dose antipsychotics is considered acceptable in treatment resistant patients who have been carefully reviewed to ensure the accuracy of diagnosis and for whom the careful use of individual antipsychotics has been shown not to be effective. In such cases the polypharmacy or combination of two antipsychotics is acceptable provided consent is obtained from the patient, there are no co-existing medical conditions which might prove a contraindication to the medications and an ECG has ruled out cardiac contraindications, in particular prolonged QT syndrome. In such cases during high dose treatment the dosage of medication should be increased slowly and routine checks of vital signs and relevant laboratory tests should be carried out. Our patient was hospitalized and under close monitoring.

References


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