An evaluation of the use of olanzapine pamoate depot injection in seriously violent men with schizophrenia in a UK high-security hospital

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Abstract

Background: Oral olanzapine is a well-established treatment for patients suffering from schizophrenia. Advantages of depot olanzapine may include improved compliance. However, it is expensive, causes metabolic side effects, and carries a risk of postinjection syndrome. Clinical trials have shown olanzapine pamoate to be effective, but further work is needed in this area. This study was a retrospective service evaluation, carried out in a high-security hospital, where the majority of patients have complex, treatment resistant schizophrenia spectrum disorder and a very high propensity for violence. Compliance is a significant problem, both in the high-security setting and on discharge. There has been no previous published work that the authors are aware of evaluating the effects of olanzapine pamoate in this subgroup of patients.

Methods: The aim of the study was to evaluate the clinical efficacy of olanzapine pamoate, its effect on violence as well as its side effects, in a high-security setting for the first time. Anonymized patient records were used to identify the main outcome measure and clinical global improvement, and to ascertain secondary outcome measures which included seclusion hours, risk of violence and side effects. Metabolic parameters and number of incidents were also recorded. Eight patients were treated with olanzapine pamoate.

Results: Six showed an improvement in symptoms, with an associated decrease in violence and number of incidents. Four showed an associated decrease in seclusion hours. Two showed an increase in body mass index and two showed an increase in glucose.

Conclusions: The findings of this study are important in showing that all patients who responded to olanzapine pamoate also showed a decrease in violent behaviour. The potential anti-aggression effects of olanzapine pamoate may represent a very promising area for further work. A depot antipsychotic medication that reduces violence could have significant implications for management of high-security patients.

Keywords: forensic, high-security hospital, olanzapine pamoate, schizophrenia, violence

Introduction

Oral olanzapine is well established as an effective treatment for schizophrenia [Taylor *et al.* 2012] and olanzapine is now available in depot form, as olanzapine pamoate. Depot antipsychotics may confer certain advantages relative to oral medication. If patients do not attend for their depot this will be immediately apparent to the clinical team and can be rapidly addressed. This may reduce noncompliance and thereby reduce rates of relapse. Evidence to support this argument is

mixed, but previous studies suggest that relapse rates may be lower in patients on long-term depot medication [Barnes and Curson, 1994]. Therefore, guidelines from the UK National Institute for Health and Care Excellence (NICE) recommend that depot medication is considered in patients for whom covert noncompliance is an issue [NICE, 2014].

The majority of depot preparations available are typical antipsychotics. A disadvantage of these is

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their association with extrapyramidal side effects. They are also less effective in addressing the negative symptoms of schizophrenia [Bishara and Taylor, 2008]. Olanzapine pamoate is one of a few atypical antipsychotics available as a depot preparation and is not associated with a high risk of extrapyramidal side effects [Lauriello *et al.* 2008; Bishara and Taylor, 2008].

However, olanzapine pamoate is among the most expensive of the available antipsychotic treatments [Taylor *et al.* 2012]. Like oral olanzapine, it is associated with metabolic syndrome, with adverse effects on lipid profile, blood sugar and body mass index (BMI) [Citrome, 2009]. Unlike oral olanzapine, the depot form is associated with postinjection syndrome (PIS). Absorption of olanzapine pamoate directly into the blood stream can result in sedation or delirium [Citrome, 2009]. Whilst no known cases have had fatal consequences, PIS has resulted in patients requiring intubation. PIS is rare, occurring in 0.07% of injections given [Detke *et al.* 2010]. Aspirating prior to injecting may reduce the risk, but does not rule out PIS [Detke *et al.* 2010]. Furthermore, the risk of PIS does not diminish with repeated injections and patients must therefore be monitored for 3 hours postinjection [Detke *et al.* 2010]. This may have significant implications. Outpatient settings may not have satisfactory facilities for patients to be observed for 3 hours. The patient group who may benefit from depot medication frequently have poor insight and compliance [Shi *et al.* 2007], and may be too chaotic or chronically unwell to tolerate 3 hours under observation. As pointed out by Devadason, 'olanzapine depot may be a very difficult treatment to administer to the patients who need it the most' [Devadason, 2010].

Clozapine and olanzapine are similar in structure [EMA, 2004], and there is evidence showing that clozapine is effective in reducing levels of violence in patients with schizophrenia [Volkova *et al.* 2004; Topiwala and Fazel, 2011]. Clozapine's effect on violence is disproportionate to its antipsychotic effects and it may exert a specific anti-aggressive effect [Topiwala and Fazel, 2011]. Evidence that treatment with oral olanzapine may decrease levels of violence is mixed and there has been relatively little work done in this area. Some trials have shown no particular advantage for olanzapine in reducing violence relative to other typical and atypical antipsychotics [Swanson *et al.* 2008; Volkova *et al.* 2004]. However, other studies

have shown olanzapine to be superior to risperidone [Swanson *et al.* 2004b] and typical antipsychotics in reducing violence [Swanson *et al.* 2004a]. Further work is needed to clearly establish the effect of oral olanzapine on level of violence and, as far as the authors are aware, no published work has examined the effects of depot olanzapine on violence.

We report our experience of the use of olanzapine pamoate injections in patients at a high-security hospital in the UK. High secure hospitals treat mentally disordered offenders posing the highest level of risk and the predominant diagnosis within the population is schizophrenia. Patients have complex psychiatric presentations and are often treatment resistant. Compliance is a significant problem, both in the high-security setting and on discharge. There has been no previous published work that the authors are aware of evaluating the effects of olanzapine pamoate in this subgroup of patients. This study was carried out in retrospect and aimed to evaluate the efficacy of olanzapine pamoate, its effect on violent behaviour and its side effects in the high-security setting.

Method

Appropriate clinical governance approval was obtained in order to carry out the service evaluation. Electronic pharmacy records were used to identify all patients in the hospital currently prescribed olanzapine pamoate. Anonymised data were then collected from: the patients' clinical notes, care programme approach (CPA) or tribunal reports; Historical, Clinical, Risk Management 20 (HCR-20) forms [Webster *et al.* 1995]; the hospital incident reporting system; and the hospital medical centre records. In order to reduce bias, records and reports were anonymised by one of the data collectors and examined by another.

The patient records were examined, in retrospect, to gain an impression of the patients' clinical global improvement (CGI), which was the primary outcome measure. They were also used to ascertain secondary outcome measures which included hours in seclusion, side effects and whether the patient had been moved to a lower dependency ward. Patient records and HCR-20 forms [Webster *et al.* 1995] were used, in retrospect, to gain a clinical impression of the patients' risk of violence. This was divided into risk of aggression towards people, aggression towards property and verbal aggression. CPA and

tribunal reports were used to obtain background and demographic information about the patients. Patient records and reports were used to determine treatment resistance, according to International Psychopharmacology Algorithm Project (IPAP) criteria (IPAP, 2006). Health centre records were used to obtain information about patients' BMI, cholesterol and glucose before and after starting olanzapine pamoate.

The hospital's incident reporting system is an electronic intranet system where staff members log every clinical incident for each patient. It has been used for a number of years to generate information about incident trends in the hospital, and is reliable and comprehensive. Reports for each patient were generated. These were used to determine the number of incidents that had occurred during a time period before and after starting olanzapine pamoate. The length of the time period varied according to the duration of admission and of treatment with olanzapine pamoate. The end point of the 'before' time period was set at up to 1 month prior to starting olanzapine pamoate. This was because a high number of incidents can precipitate a change in medication. It was therefore decided that avoiding the period immediately preceding the medication change would provide a better reflection of the number of incidents that were occurring before starting olanzapine pamoate.

Results

Pharmacy records yielded eight patients on olanzapine pamoate. Two patients (number 2 and number 6) stopped the depot while the service evaluation was being carried out. It was decided that they should remain part of the service evaluation, as the decision to stop the depot may have reflected a lack of efficacy. The mean age of the patients was 38, with 7 aged between 35 and 44 and one outlier aged 19. Two patients were first presentations to mental health services. They had been known to suffer from a mental illness for less than a year. The remaining six had suffered from a chronic illness for many years. The range of duration of treatment with olanzapine pamoate was between 7 weeks and 2 years and 2 months.

The sample was a good reflection of the complexity of diagnoses seen in a high-security setting and suffered from schizophrenia spectrum disorders (see Table 1). Three patients also suffered from comorbid personality disorder, most commonly

antisocial and paranoid personality disorders. Four of the six patients were treatment resistant according to IPAP criteria [IPAP, 2006].

Primary and secondary outcome measures are displayed in Table 2. Six of the eight patients showed a clinical improvement after starting the olanzapine pamoate. Two were very much improved, two were much improved and two were minimally improved. Two of the eight did not improve and no change was identifiable in these patients. In all of the patients showing a clinical improvement, there was an associated decrease in violent behaviour. In three of these patients the decrease in violence was very marked. The majority (five of the six) showed a decrease in the level of violence they directed towards other people. Four of the six 'improvers' also spent less time in seclusion. All of these four were patients who required long-term segregation. After starting the depot they spent greater periods of time in association. One of the six did not show a change in time spent in seclusion, because he had not required seclusion at all either before or after starting olanzapine pamoate.

Seven patients showed a decrease in the number of incidents occurring before and after the depot as shown in Figure 1. All the six patients who showed an improvement in CGI also showed a reduction in the number of incidents as recorded in the hospital's incident recording system.

Metabolic monitoring in these patients was limited due to patient refusal. Two patients' BMI increased. One patients' total cholesterol increased, but remained within the normal range. Two patients' glucose levels increased, although one of these patients (patient 7) was known to suffer from Type 2 diabetes, and this had been diagnosed prior to starting olanzapine pamoate. One patient was documented as complaining of side effects. In two patients, treatment with olanzapine pamoate was stopped. In one case this was due to the development of an abscess at the injection site. The other patient stated a preference to return to clozapine treatment, rather than receive regular injections. This was due to his dislike of receiving regular injections. None of the patients suffered from PIS.

Discussion

We report on our experience of the use of olanzapine depot antipsychotic injection in a high-security

Table 1. Patient demographics and clinical details.

Patient	Age	Diagnosis	Index offence	Duration of illness	Previous treatment with depot medication	Duration of olanzapine pamoate treatment (months)	Concurrent medication	Treatment resistant according to IPAP criteria?
1	40–44	Schizo-affective disorder Antisocial personality disorder	Actual bodily harm	14 years	Yes	1.75	Simvastatin	Yes
2	40–44	Delusional disorder Mixed antisocial and paranoid personality disorder	Manslaughter, grievous bodily harm	27 years	Yes	3.5	Procyclidine	Yes
3	40–44	Schizophrenia	Rape, sexual assault, false imprisonment	9 months	No	2	None	No
4	35–39	Schizophrenia	Wounding with intent	16 years	Yes	26	None	Yes
5	35–39	Schizo-affective disorder	Possession of an imitation firearm Threats to kill	17 years	Yes	10	Diazepam, oral olanzapine	Yes
6	40–44	Schizophrenia	Convicted of threats to kill; affray; committing arson recklessly; assault occasioning actual bodily harm	16 years	Yes	2	Sodium valproate, clonazepam, venlafaxine, diazepam	Yes
7	40–44	Schizophrenia	Grievous bodily harm with intent	16 years	Yes	19	Metformin	Yes
8	15–19	Schizophrenia Dissocial personality disorder	Arson Actual bodily harm Wounding with intent to cause bodily harm	7 months	No	1.25	Promethazine, lorazepam	No
IPAP, International Psychopharmacology Algorithm Project.								

Table 2. Primary and secondary outcome measures.

Patient	CGI	Seclusion hours	Risk of violence	Risk of violence towards people	Risk of violence towards property	Risk of verbal aggression	Move to lower dependency	Treatment continued?
1	4	N/A	=	=	=	=	No	No
2	4	=	=	=	=	=	No	Yes
3	2	→	→	→	→	→	No	Yes
4	1	→	→	→	→	→	No	Yes
5	3	→	→	=	→	→	No	Yes
6	2	=	→	→	→	=	No	No
7	3	N/A	→	→	=	=	No	Yes
8	1	↓	↓	↓	↓	=	No	Yes

CGI: 1 – very much improved; 2 – much improved; 3 – minimally improved; 4 – no change; 5 – minimally worse; 6 – much worse; 7 – very much worse; 0 – not assessed. **Seclusion hours/violent behaviour:** ↓ – reduction; ↑ – increase; = – no change; N/A – no seclusion before or after starting olanzapine. As assessed by HCR-20 and hospital's risk assessment. CGI, clinical global improvement; HCR-20, Historical, Clinical, Risk Management 20.

Figure 1. Number of incidents before and after starting olanzapine pamoate.

hospital in patients with schizophrenia spectrum disorder and a significant history of violence. Six out of eight patients treated with olanzapine pamoate showed a clinical improvement in symptoms, with an associated decrease in violent behaviour and a decrease in the number of reported incidents. Four of these patients were treatment resistant prior to starting olanzapine pamoate.

Worsening metabolic parameters (BMI and random glucose) were seen in four patients. These findings are in keeping with what is known about the effects of both oral and depot olanzapine on metabolic parameters [Citrome, 2009]. It reiterates the importance of balancing risks with benefits when considering olanzapine and of metabolic monitoring.

Six of the eight patients treated with olanzapine depot showed a clinical improvement. Four of the six responders had suffered from schizophrenia for over a decade and had been treated with a number of antipsychotic medications. It should be reiterated that this is a small sample of patients, and that this is an exploratory and descriptive study. However, these findings do show olanzapine pamoate to have been an effective treatment in this sample of patients. Evidence for the efficacy of olanzapine pamoate in the literature is mixed. Trials have shown olanzapine pamoate to be as effective as oral olanzapine in controlling symptoms in acutely unwell patients with schizophrenia [Lauriello *et al.* 2008] and in maintaining long term recovery [Kane *et al.* 2010]. However,

one study has shown olanzapine pamoate to be no more effective than typical antipsychotic depots [Fricchione *et al.* 2011]. There is also evidence to suggest olanzapine pamoate may be less cost effective than other atypical depot preparations [Einarson *et al.* 2013]. There is no literature on the use of olanzapine depot in forensic psychiatric population and the authors believe this to be a first report.

It is of particular interest that all patients who responded to olanzapine pamoate also showed a decrease in violent behaviour. It may be that treatment with olanzapine pamoate resulted in an improvement in symptoms and therefore a decrease in violence. For example, in four of the patients in this study, the index offence was clearly driven by delusional beliefs. Effective treatment with olanzapine may have decreased the strength of their delusions and reduced the ongoing violent behaviour and risk that they posed. On the other hand, it may be that olanzapine pamoate has a direct 'anti-aggression' effect. In four of the six patients showing an improved CGI score, there was a very marked decrease in violence, in particular towards other people. While it is important to note that only very limited conclusions can be drawn from this study, it did not appear that the reduction in violence was mediated by an improvement in symptoms.

This report is retrospective and descriptive, and examines a small sample of patients. Because this is a service evaluation, carried out without a control group, it is not possible to know whether the improvements observed are due to treatment with olanzapine pamoate, or to other factors such as nursing care, psychological therapies or other medications. The findings must therefore be interpreted with caution. However, research exploring pharmacotherapy in forensic patients is difficult to conduct and as a result, the subjects that are enrolled in randomised control trials are not representative of the most difficult-to-manage patients in secure units [Volkova and Citrome, 1999]. This study examines real world outcomes which are clinically relevant. It is also the first work that the authors are aware of which explores the use of olanzapine pamoate in the high-security setting.

The potential anti-aggression effects of olanzapine pamoate may represent an important area for further work. Many forensic patients have such poor compliance, and present such a high level of

risk, that clozapine or other oral medications are not a viable treatment option. Furthermore, treatment adherence in itself has been found to independently predict a decrease in violence risk [Swanson *et al.* 2004b]. This study has been carried out in the high-security setting, where the majority of patients are treatment resistant. The need to address violent behaviour in the subgroup of patients involved in this service evaluation is paramount.

This study is a service evaluation and the findings are exploratory only. However, there is some suggestion that olanzapine pamoate could address risk of violence. Furthermore, its availability as a depot may also solve the compliance problems to which clozapine is subject. This could have significant implications for management of high-security patients. A depot antipsychotic medication that reduces violent behaviour might help facilitate discharge from high-security services to medium secure, or even ultimately to general adult services.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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