Olanzapine long-acting injection: insights from an early case series in the UK

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Abstract:

Objective: Olanzapine long-acting injection depot (OLAI) has been licensed in the UK since 2008. As a result of the recognition during clinical trials that in 0.07% of injections there may be inadvertent intravenous administration leading to post-injection delirium/sedation syndrome (PDSS), the licence mandates a 3 h observation after each injection and accompaniment of the patient to their final destination. The administration of OLAI may thus necessitate organization of local service provisions. We report on how a single healthcare facility in Northern Ireland has treated three initial patients and present a brief case series on these patients and their clinical outcomes.

Methods: In the first three patients with schizophrenia to receive OLAI, the clinical notes were retrospectively examined to provide clinical data.

Results: All three patients had acceptable clinical outcomes showing sustained clinical improvement and have continued on OLAI for over 1 year. Observation has been undertaken within an existing daycare unit staffed by nursing staff and occupational therapists for 3 h after each injection. No issues have emerged from the use of this service that has also provided educational and psycho-educational programmes for the patients. No cases of post-injection delirium/sedation syndrome were reported. There have been no additional cost implications.

Conclusions: In patients for whom OLAI may be clinically indicated, the utilization of an existing service to provide the 3 h of observation after each injection may represent a solution with a cost-neutral outcome.

Keywords: depot antipsychotic, healthcare facility, olanzapine, olanzapine long-acting injection, postinjection delirium sedation syndrome, schizophrenia

Introduction

Olanzapine is a well established antipsychotic in the treatment of schizophrenia that has been licensed in the UK since 1996. In 2008 olanzapine long-acting injection (OLAI) was licensed for the maintenance treatment of adult patients with schizophrenia sufficiently stabilized during acute treatment with oral olanzapine. During the clinical trial process it was recognized that in 0.07% of injections, a clinical syndrome presented as an adverse event that was consistent with the inadvertent intravenous administration of olanzapine [Zypadhera, 2011; Detke *et al.* 2010; McDonnell *et al.* 2010] and resulting in the symptoms and signs of olanzapine overdose. This has been given the term post-injection delirium/sedation syndrome (PDSS) [Zypadhera, 2011]. The symptoms

can be readily identified and have a median onset time of 25 min [Detke *et al.* 2010].

In an effort to minimize the incidence of PDSS, the Committee for Medicinal Products for Human Use mandated in the SPC for OLAI that the depot injection should only be administered in a healthcare facility; other requirements include a 3 h observation period after each injection that would allow any of the symptoms and signs of PDSS to be detected by appropriately qualified personnel [Zypadhera, 2011]. For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to postinjection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery. In

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addition, patients should not travel alone to their destination after the 3 h of observation. Currently, OLAI is the only antipsychotic treatment that contains such a mandate in its license and thus service providers have been challenged with providing a service whereby OLAI can be administered in accordance with the licence.

We present three clinical cases with details of how this has been managed in a clinical setting, which to our knowledge presents the first case series reported on OLAI usage in clinical practice.

Results

Case 1

A 24-year-old man who was a former university student with a 4-year history of schizophrenia initially responded well to 20 mg olanzapine but subsequently became nonadherent to medication with little insight into his illness and need for treatment. OLAI was commenced at 300 mg every 2 weeks in October 2010 and subsequently reduced to 405 mg every 4 weeks. The man began attending an existing acute day care service to receive his injection and undergo observation, staffed by nurses and occupational therapists taking part in their ongoing programme of activities. During the initial 12 months he has not missed an appointment. His clinical state has improved and he has gained some insight and so is able to do some voluntary work in a shop. He is accompanied to the clinic by a keyworker.

Case 2

A 48-year-old man diagnosed with his first episode of schizophrenia in 2008 following a long period of untreated psychosis presented with delusional beliefs about a neighbour. A diagnosis was made of paranoid schizophrenia. The patient also consumed excessive amounts of alcohol. He was initially treated with olanzapine 20 mg with some improvement, however adherence to medication was poor and his alcohol intake remained excessive. Following trials with long-acting risperidone injection which did not lead to significant clinical improvement and subsequently a 6-month trial of flupenthixol decanoate depot and procyclidine, he asked to be treated with olanzapine due to akathisia. After a second, short treatment course with oral olanzapine 20 mg, he was commenced on OLAI 300 mg every 2 weeks in June 2010 and attends an existing daycare service

for his injections. There have been no further relapses or hospitalization over an 18-month period. The 2-weekly injections have led to more social involvement that has gradually led to improvement in his interactions in the daycare unit. Due to the degree of clinical improvement and good tolerability, dosage has not been reduced. He is accompanied to the clinic by a keyworker.

Case 3

This case is a 61-year-old woman with a long history of chronic schizophrenia who has been hospitalized for the past 4.5 years. Management has proved difficult due to a variety of psychotic symptoms that have been diagnosed as De Clerambaults syndrome (erotomania) and Capgras syndrome. Over 20 years, delusions have included having a relationship with the local priest and the death of her family and hospital staff, including the consultant who has been replaced by an impostor. This has resulted in behaviours that have included significant paranoid and hostile interactions. Thus, management has been complicated, characterized by refusal to take any oral medication or to have blood tests. Treatments have included depot formulations of long-acting risperidone injection, flupenthixol decanoate, zuclopenthixol hydrochloride, haloperidol decanoate and pipothiazine palmitate.

In March 2010, the patient was commenced on OLAI 300 mg every 2 weeks and remains on that dosage at the time of writing. Administration of OLAI and the 3 h observation period are undertaken at the daycare unit. The patient continues to be delusional and to refuse blood tests but the delusions are less intense with a reduction in the number of auditory hallucinations. She has become more socially interactive and has started to go to mass again. The clinical improvement is considered to be significant by the patient and staff.

Daycare unit

The unit is sited in an inpatient facility of a psychiatric hospital, Gransha Hospital, and has a mental health nursing and occupational therapy staff of five. All professionals have generic mental health skills, including mental health and risk assessment, and are appropriately qualified to observe patients for signs and symptoms of PDSS for at least 3 h post injection. The unit provides a

broad treatment programme to adults with mental health issues as an alternative to home treatment or hospital admission and has 25 places. It is open to patients from 9 a.m. till 5 p.m. Patients include outpatients and current inpatients that might benefit from earlier discharge. There are a number of individual and group interventions, including cognitive behavioural therapy, anxiety management and confidence building. Sessions include medication awareness, dietary choices, physical fitness, gardening and teaching life skills, in addition to monitoring for adverse events from medication. Users are encouraged to be involved in the planning of their individual programme. Inpatients may attend for the duration of their admission and outpatients are expected to attend for a minimum of 2–3 days per week for 3 weeks, when progress is reviewed. Full-time attendance would be up to 5 days or nine sessions. Should any event suggest a possible diagnosis of PDSS there is an on-call physician.

Discussion

This small case series demonstrates that patients with schizophrenia for whom OLAI is appropriate can be treated within an existing healthcare facility with minimal restructuring of processes. Although each case has had an acceptable outcome and the clinical status of each patient has improved, this case series cannot provide definitive clinical outcome data.

Adherence to medications is a challenge in all therapeutic areas. For specific patients who respond to olanzapine but who are nonadherent to oral medications depot medication may provide a solution. Adherence to medication is often overestimated by clinicians and extensive data support the view that using clinical research tools to measure adherence rates results in significantly lower adherence than previously thought [Velligan *et al.* 2009]. Data from the olanzapine therapeutic monitoring service, which assesses plasma olanzapine levels guiding dosage and estimates adherence, have recently been audited [Patel *et al.* 2011]. A key finding from this audit of 5856 samples obtained in the period 1999–2009 was that there was no detectable olanzapine in 6% of samples. Dose, smoking, gender, age and body weight explained only 24% of the variance in plasma olanzapine levels, suggesting that adherence may have a significant role in explaining the remaining variance. Usage of effective depot medications may also reduce hospitalization rates, as recently

shown in a nationwide study from Finland in a first-hospitalization cohort of 2588 patients. In this study the risk of hospitalization in patients receiving depot antipsychotics was about one-third of that for patients receiving oral medications (adjusted hazard ratio 0.36, 95% confidence interval 0.17–0.75) [Tiihonen *et al.* 2011]. Mortality was also significantly reduced in medication-adherent cohorts, which was consistent with previous findings on mortality in schizophrenia [Bushe *et al.* 2010]. In our case series it is not possible to be specific about reasons for good clinical outcome, however improved adherence is a likely factor in addition to the ongoing psychosocial support within the daycare unit. OLAI is administered after the initial 2 months at same dosage as an expected oral dose and has been shown to have similar clinical efficacy over 24 weeks as oral olanzapine [Kane *et al.* 2010].

In premarketing clinical trials on OLAI, PDSS was reported for less than 0.1% of injections (<1 in 1000 injections) and approximately 2% of patients [Zypadhera, 2011] presenting with predominantly varying degrees of sedation (mild to coma) and delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairments). Symptom onset was predominantly in the first hour after injection with a median onset of 25 min [Detke *et al.* 2010]. In a long-term, open-label safety study on OLAI, interim data at 190 weeks on 931 patients reported 26 cases of PDSS in 25 patients, and 19 of these 26 patients chose to continue treatment with OLAI after resolution of PDSS [McDonnell *et al.* 2011]. In a summary of data from all completed OLAI trials based on 45,000 OLAI injections given to 2054 patients, 30 cases of PDSS were reported occurring in approximately 0.07% of injections. All patients recovered in 1.5–72 h without sequelae [Detke *et al.* 2010]. Delirium-related adverse events were reported in 97% of cases and sedation-related adverse events in 87%, with 83% of cases having both [Detke *et al.* 2010]. However, in terms of early recognition, in 40% of PDSS cases initial symptoms were also those of general malaise, anxiety, agitation or irritability [Detke *et al.* 2010]. Detection of PDSS will hence be dependent upon observation and conversation with the patient. Specific measurements of blood pressure, pulse and temperature are not required according to the SPC and in the 30 cases of PDSS detected there were no clinically significant decreases in vital signs relating to blood pressure, heart rate and respiration. Due to the mechanism

proposed for PDSS it is unsurprising that 80% occurred within 1 h post injection [Detke *et al.* 2010]. In 22 of 30 cases, the patient was deemed incapacitated, with a median time of incapacitation of 60 min. However, what is clear is that special precautions must include use of a proper injection technique and the postinjection observation period. If PDSS is suspected, close medical supervision and monitoring should continue until examination indicates that the signs and symptoms have resolved. Hospitalization was reported in 77% of cases, with 63% receiving either no specific treatment or only fluids [Detke *et al.* 2010]. Clear risk factors and concomitant medications were not identified as predictors for PDSS and hence observation needs to be undertaken in all patients after every injection [Zypadhera, 2011; McDonnell *et al.* 2010; Detke *et al.* 2010].

Accidental intravascular injection is a known risk for all intramuscular injections. For example, similar rates of a postinjection type syndrome have been reported for penicillin procaine G which, when injected intravascularly, dissociates leaving the procaine component to cause a toxic reaction known as Hoigne's syndrome [Detke *et al.* 2010; Downham *et al.* 1978]. OLAI is a salt-based depot combining olanzapine and pamoic acid, the properties of which make the compound practically insoluble in aqueous solution but with substantially greater solubility and dissolution rates in plasma than in environments similar to muscle tissue [McDonnell *et al.* 2010]. The clinical implications are that solubility and dissolution become far more rapid should the compound be inadvertently injected intravascularly [McDonnell *et al.* 2010]. These pharmacokinetic and pharmacodynamic properties suggest inadvertent vascular injection is the most likely explanation for the temporal and clinical symptoms of PDSS [McDonnell *et al.* 2010; Detke *et al.* 2010]. In a laboratory study of this issue no other explanation relating to product quality or administration could coherently explain PDSS [McDonnell *et al.* 2010]. No predictors of PDSS, such as dose administered, could be defined [McDonnell *et al.* 2010; Detke *et al.* 2010]. Supportive of this hypothesis are the plasma olanzapine levels measured during the PDSS event in 12 of the 30 initial cases reported, with levels being higher than the expected range of 5–73 ng/ml [McDonnell *et al.* 2010]. Concentrations exceeded 100 ng/ml in all cases and measured more than 600 ng/ml in some

cases, but returned to the expected range within 72 h [McDonnell *et al.* 2010]. The expected therapeutic range was derived from clinical studies of OLAI in which the range 5–73 ng/ml equated to the 10th percentile for 150 mg/2 weeks and the 90th percentile for 300 mg/2 weeks at steady state [Kane *et al.* 2010].

Intravascular injection with long-acting risperidone has been reported with different symptomatology due to the microsphere formulation leading to retinal artery occlusion in a patient with patent foramen ovale [Tang and Weiter, 2007]. However, the clinical symptoms and signs of PDSS have not been observed with risperidone long-acting injection or paliperidone palmitate [Alphs *et al.* 2011]. In 15 completed trials, using approximately 115,000 injections with risperidone long-acting injection, there were no cases of PDSS and only a single case in the placebo cohort in 10 completed trials, using 33,906 injections in paliperidone palmitate studies [Alphs *et al.* 2011].

The clinical issue often relates to the practicality of providing 3 h of observation for each patient, which can be undertaken by any appropriately qualified healthcare professional, and accompanied home, which does not need to be done by a healthcare professional. Currently OLAI is the only depot antipsychotic for which such observation is mandated, and to achieve it, incorporating patients into an existing unit may be an option. In this case an existing daycare unit staffed by healthcare professionals has proven a reasonable option that has also allowed patients to take advantage of ongoing psycho-educational programmes. The unit has a capacity for 25 places, therefore the addition of three additional patients for 3–4 h every 2–4 weeks is unlikely to be onerous.

Implications for clinical care

Throughout the UK there may be many other clinics set up to provide specific services that include clozapine monitoring, lithium monitoring, weight and lifestyle management and other day clinics, which feasibly could host a small number of patients requiring 3 h of observation. PDSS cannot be prevented by any of the current measures [Detke *et al.* 2010] and the likelihood is that an incidence rate per injection of 0.07% (approximately 1 in 1400 injections) will remain constant. Any clinic must thus be managed by an appropriate healthcare professional who

can detect PDSS and initiate management. Management in most cases should be symptomatic [Zypadhera, 2011] with transfer to a short-term accident and emergency facility if appropriate. Most patients have required only further observation and in some cases administration of intravenous fluids [Detke *et al.* 2010]. There are patients who may benefit from OLAI and clinicians are learning adaptive strategies to ensure treatment can be accessed. The use of pre-existing facilities and services may provide a pragmatic solution at least in the short term until the degree of usage of OLAI can be further assessed.

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Conflict of interest statement

CB is a full time employee of Eli Lilly and Company who manufacture olanzapine long-acting injection.

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