Case Report

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Intramuscular clozapine in the acute medical hospital: Experiences from a liaison psychiatry team

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Abstract

We present two cases demonstrating safe and effective use of intramuscular clozapine for patients who are physically unwell in acute medical care settings. Both patients described were admitted to inpatient medical care units and required treatment with clozapine to control their psychotic symptoms, but were unable or unwilling to take oral clozapine. We describe the use of intramuscular clozapine in these patients, including dosing decisions, administration routes and frequency of dosing. Outcome was measured by a reduction in psychotic symptoms, sufficient to allow treatment for physical illness. Both patients successfully received intramuscular clozapine, allowing timely treatment of their physical health conditions. There were no adverse events, and significant improvement in their mental health presentations was achieved. We have shown that intramuscular clozapine is a safe and effective treatment for patients with serious mental health illness in the acute medical hospital.

Keywords

Clozapine, intramuscular, schizophrenia, liaison psychiatry, antipsychotic

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Strengths and limitations

- We describe real-world cases of complex pharmacology and clinical comorbidities.
- Use of intramuscular clozapine outside mental health settings and in medically unwell patients has not been previously reported.
- The limitations of extrapolating outcomes from individual case reports and applying experience to other patients should be considered.

Introduction

Clozapine is an antipsychotic used where all else has failed. Therefore, it cannot be replaced by another antipsychotic. "Can't you just switch it to something else?" is the sometimes exasperated plea from general medical colleagues trying to treat acute physical illness in someone receiving clozapine. The answer is frequently "no," but the challenges in continuing a drug with multiple pharmacodynamic actions and interactions in patients with rapidly changing physical health states are many and complex. Furthermore, until recently, the availability of clozapine solely as an oral treatment limited continued use to patients who were able or willing to comply with oral therapy. The availability of intramuscular clozapine in Western Europe has changed this. Here, we discuss with illustrative cases some of the benefits and some of the practical and ethical difficulties pertaining to the use of intramuscular clozapine in the acute hospital setting.

Clozapine is available in the United Kingdom in three licensed forms: tablets, orodispersible tablets and solution. For decades, the only treatment option for patients who refused or were unable to comply with oral therapy was to abandon clozapine entirely. Forced administration of

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clozapine suspension via nasogastric (NG) tubes has been described[1,2] but is seldom used outside highly secured forensic settings and has considerable practical drawbacks (not least the need to restrain patients in order to site an NG tube, potentially daily). In the last 3 years, intramuscular clozapine has been available in the United Kingdom as an unlicensed product, imported from the Netherlands. While experience is increasing,[3,4] its use is (to the best of our knowledge) entirely restricted to inpatient mental health settings.

Non-adherence to treatment is common in all medical specialties, but patients with psychotic disorders pose particular challenges.[5] Psychotic symptoms may prevent patients from complying with treatment and monitoring of physical health conditions. Treating the psychotic symptoms may allow the patient to regain capacity to be able to make a decision concerning their physical health treatment. In the United Kingdom, decisions regarding the treatment of physical illness can be made by the treating team in the patient's best interests if the patient is deemed to lack the capacity to make such decisions, allowing treatment against their will if necessary. However, the practicalities of performing investigations (including blood tests or diagnostic scans) or administering treatments to patients who are able to actively resist mean that doing so may only be a theoretical option, as overall the risks mean that it would not be viewed as being in their best interests. For patients with illnesses that respond to non-clozapine antipsychotics, drug treatment can usually be administered without the patient's consent via intramuscular routes (as short-acting intramuscular or long-acting injection where response has been demonstrated to oral or short-acting intramuscular formulations).

For patients with treatment-resistant psychosis, the possibility of a parenteral non-clozapine antipsychotic gaining sufficient control of their psychosis to allow treatment of their physical health is vanishingly small: patients with "treatment-resistant" schizophrenia, defined as non-response to two different antipsychotics, have perhaps a maximal 7% chance of their psychotic symptoms responding to a non-clozapine antipsychotic.[6,7] The seminal study of clozapine in treatment-resistant schizophrenia[8] suggested only 4% of patients responded to a non-clozapine antipsychotic. The superiority of clozapine over other antipsychotics in treatment-resistant schizophrenia has been repeatedly demonstrated in multiple meta-analyses since these trials.[9,10] Violence and agitation that can accompany untreated psychosis are difficult to manage in acute hospital settings, putting patients and staff at risk, as well as precluding medical treatment. Sedation of patients may be the only option available to maintain safety and allow any form of treatment, but this is not sustainable or desirable. With the arrival of intramuscular clozapine, treatment options for these patients are widened.

Intramuscular clozapine has no UK license. It is made by Broacef (Netherlands) and imported to the United Kingdom by Durbin PLC. The strength of the injection is 25 mg/mL, and each ampoule contains 5 mL (125 mg). It is administered by deep intramuscular injection, usually into the gluteal muscle, and may be painful. The maximum volume that can be injected into any site is 4 mL (100 mg); doses greater than this must be split over different injection sites.[3] Oral bioavailability of clozapine is fairly low, with the lowest estimate being 27%[11] and the highest being 47%.[12] Usual practice is to halve the oral dose and give the intramuscular injection once daily.[3,4] All mandated blood monitoring and precautions taken with oral clozapine also apply to the intramuscular preparation. Patients must be registered with a clozapine monitoring company for this purpose.

Our first case describes a patient for whom the cessation of clozapine resulted in florid psychosis, precluding investigations or treatment of her serious physical illness. Refusal to comply with oral clozapine meant that her physical condition would have gone undiagnosed were it not for rapid control of her psychosis using the intramuscular preparation. Our second case describes a patient for whom access to intramuscular clozapine meant effective control of his treatment-resistant illness during a period of lack of oral access, where untreated psychosis risked significant harm to himself and others.

Case study 1

Ms A was a 50-year-old Black British woman with a long history of schizoaffective disorder, managed in the community on clozapine. She had a significant forensic history, but had been relatively well controlled on clozapine (although chronic delusions that she was married to Jehovah persisted).

Ms A presented to the emergency department with abdominal pain and nausea. She was found to have liver abscesses and was treated for a resultant sepsis, but intermittently refused intravenous antibiotics as she had delusional beliefs that the abdominal pain and nausea were signs that she was pregnant with Jehovah's child. Further radiological investigations raised the possibility that the lesions on her liver represented metastases from a distant site instead of abscesses. The definitive investigation was a liver biopsy, but Ms A refused, stating that it would harm her unborn child. Notably, she refused to take clozapine on admission (having also been non-compliant for 48 h prior to this), resulting in deterioration in mental state.

Ms A became verbally aggressive, paranoid and disinhibited on the ward. She was detained under mental health legislation, but continued to refuse oral clozapine, and her floridly psychotic mental state worsened. No further investigations could be performed without physical restraint and chemical sedation. She refused all oral medication, including those for her physical health. Her inflammatory markers and liver function tests worsened, reflecting an overall deterioration in her physical health.

Review of her medication history showed a clear lack of response to any other antipsychotic, so Ms A was re-titrated

on clozapine via the intramuscular route. Titration was completed over a week, to a dose of 150 mg intramuscularly (split in two doses of 75 mg into each injection site). Neutrophil and white cell counts remained within normal ranges (or high, due to infection) throughout the admission. Due to morbid obesity, the clozapine was given in her deltoid muscle under restraint. Ms A's usual dose of oral clozapine was 300 mg; she was administered 150 mg intramuscularly once daily. Consideration was made to split the dose into twice-daily administration due to the relatively large (3 mL) injection volume required per site, but the risk to the patient and staff of multiple restraint episodes was felt to be high. She tolerated the relatively large (3 mL) injection volume with no reported problems, and no other clozapine-induced side effects (including blood dyscrasias) were noted.

After a few days of receiving her usual dose of clozapine, there was a marked improvement in her mental state; her paranoia, hostility and aggression gradually resolved, and she became more amenable to taking clozapine orally. Crucially, she also started complying with medical investigations which regrettably revealed an untreatable liver carcinoma.

The use of intramuscular clozapine, via a novel route (deltoid), on an inpatient ward in an acute hospital allowed investigation and treatment of a serious physical illness, as well as control of severe psychotic symptoms. The urgency of proceeding with medical investigations when malignancy was raised as a differential, coupled with the significant risks Ms A posed to herself and others while psychotic, made it a priority to stabilize her mental state rapidly. The use of intramuscular clozapine in this case enabled Ms A to recover quickly from her psychotic relapse. Although her cancer was ultimately sadly untreatable, her final weeks were spent in a calm, dignified and unrestricted way with her family.

Case study 2

Mr B was a 47-year-old White British gentleman with a long-standing history of schizophrenia. He was initially brought to the emergency department by the police, having been found unresponsive in the street. He had stopped treatment with clozapine a number of months prior, and re-titration was commenced on the acute hospital ward. At this time, Mr B was compliant with oral therapy, but before therapeutic plasma levels could be reached, and despite antipsychotic "cover" with olanzapine during clozapine dose titration, he had assaulted several members of staff and was urgently transferred to psychiatric intensive care.

When on the mental health ward, he refused oral antipsychotic treatment and was given intramuscular short-acting and then long-acting zuclopenthixol instead. He remained psychotic and 3 months later jumped from a third floor window in an attempt to abscond, sustaining significant injuries. He was transferred back to the medical hospital and titration on oral clozapine via NG tube was initiated while he was intubated in the intensive care unit. A dose of 300 mg daily with a plasma concentration of 0.21 mg/L was achieved. Mr B was stepped down to management on a surgical ward and clozapine treatment continued via NG tube. After a few days of stability on 300 mg of oral clozapine, Mr B removed his NG tube. He refused to allow the tube to be replaced, resisting any attempts to do so and attempting to assault staff members. Owing to extensive spinal fractures, Mr B's swallowing was dangerously impaired with a high risk of aspiration. Oral drug treatment was therefore unsafe and repeated NG tube insertion also risky.

Given the significant risks posed to himself and others by Mr B when treated with non-clozapine antipsychotics, urgent arrangements were made to switch his oral clozapine prescription to the intramuscular preparation. Swift communication between medical and psychiatric teams allowed conversion of his 300 mg oral clozapine to 150 mg intramuscular clozapine within 24 h, avoiding any need for re-titration of the dose. There followed a rapid improvement in mental state, and Mr B started to comply with medical treatments and physiotherapy. He later regained his swallowing reflex and agreed to comply with oral clozapine, and was discharged back to the care of mental health services a month later. Neutrophil and white cell counts remained within normal ranges throughout treatment and no other clozapine-related side effects were reported.

The rapid availability of intramuscular clozapine allowed effective treatment of Mr B, averting likely mental health crisis in someone known to be violent and aggressive when unwell, and inevitable medical sequelae.

Discussion

The cases presented here demonstrate the safe and effective use of intramuscular clozapine in patients who are medically unwell, being treated in non-mental health settings. Little is published describing the use of intramuscular clozapine, and where data exist, they exclusively refer to patients in psychiatric settings.[3,4]

There are clearly legal considerations when administering any antipsychotic intramuscularly. If the patient has capacity to agree to intramuscular administration and is agreeable to this route, then it can be given with the patient's consent. However, if a patient either lacks capacity to agree to its administration or refuses to agree, in the United Kingdom detention under the mental health legislation is required to give this treatment.

There are also ethical considerations when giving clozapine to medically unwell patients. First, it is a drug with multiple side effects which, although rare, are potentially fatal (e.g. neutropenia, myocarditis and constipation).[13] Second, it interacts with many other drugs.[13] Both of these factors may worsen an acute or chronic physical health problem. For example, in the case of a patient with chest pain where acute coronary syndrome is suspected, it is often felt safer to stop clozapine. However, if this results in relapse of psychotic

illness, and associated non-compliance with medical investigations and treatment, it may be the least worst option to continue, with close monitoring of cardiac function.

The importance of the multi-disciplinary team and the involvement of the patient, and their family members or carers, are critical here. Making the decision to treat with clozapine, especially intramuscularly in medically unwell patients who lack capacity to consent, is not one to undertake lightly. It should be taken as part of a structured "best interests" process, where the advantages and disadvantages of various options are discussed, and with the patient if possible, or with their family or advocate.[14] Patients' families and advocates need to be informed of the risks if this option is pursued, especially as intramuscular clozapine is an unlicensed product (see below).[14] There will need to be close working between the medical and liaison psychiatry teams to ensure that the patient's physical health is monitored closely during the titration, and that clozapine plasma concentrations are checked appropriately. If the patient deteriorates physically, it may be necessary to stop or pause the clozapine titration.

Intramuscular clozapine is an unlicensed product. Administration of clozapine to patients in the United Kingdom requires registration of the patient, prescriber and pharmacy with one of three clozapine monitoring companies, ensuring regular monitoring of the full blood count (this is not mandated in many other countries).[15] An agreement must be reached with the relevant company (usually the company with an existing relationship with the hospital or the one with which the patient is already registered) to accept the patient on to their treatment register, despite not receiving treatment with their licensed clozapine preparation. As with all unlicensed medicines, every effort should be made to outline the reasons for the use of the unlicensed preparation to patients and/or their next of kin. Reasoning around the choice of treatment should be clearly documented.[14]

Given the unlicensed status of intramuscular clozapine and the paucity of experience and published data regarding its use (especially in acute medical settings), we suggest that responsibility for prescribing, monitoring and follow-up should lie with the liaison psychiatry team. It will be a local decision whether the drug should be supplied by the acute medical hospital or the affiliated mental health hospital; in either case, close relationships with prescribers and pharmacists with expertise in clozapine use are strongly encouraged.

Conclusion

Intramuscular clozapine remains a novel and unusual treatment in mental health settings; to our knowledge, it is unheard of in acute medical hospitals. It is, however, a uniquely valuable formulation. It offers an alternative to partial or complete sedation in intensive care settings in order to provide essential medical treatment where treatment-resistant psychosis cannot be controlled with other parenteral antipsychotics. It allows therapeutically effective "bridging" for periods when oral access is temporarily lost, where the alternative is treatment with antipsychotics known to be ineffective. The cases we present here show the potential for it to allow safe and timely treatment of medical conditions for patients where the alternative would be anesthesia, delayed access to treatment or investigations, or denial of treatment entirely. Instead, use of intramuscular clozapine allowed dignified, effective treatment for patients with serious mental illness in the acute hospital.

Authors' contributions

S.G. conceived and designed the article and drafted the manuscript. I.McM., C.W. and S.Y. wrote the case reports and legal and ethical discussion. D.T. revised and drafted the manuscript.

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