Postinjection delirium/sedation syndrome with Haloperidol Decanoate Injection

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Abstract

Extrapyramidal side effects (EPSE) are frequently reported in the first few days after the administration of injection haloperidol decanoate. However, postinjection delirium/sedation syndrome (PDSS) has been reported after injection olanzapine pamoate but not after haloperidol decanoate. We present a case in which PDSS and EPSE occurred within two hours of administration of injection haloperidol decanoate 50mg because of its rarity.

Key words : *Haloperidol; post injection delirium/sedation syndrome; extrapyramidal symptoms; depot antipsychotics; schizophrenia*

Introduction

"Depot" or Long Acting Injectable (LAI) antipsychotics, were developed to help medication compliance especially during the maintenance phase of treatment of schizophrenia. [1] Benefits of LAIs include regular interactions between the patient and psychiatrist, supervised administration, stable plasma concentrations of the active drug, and possibly improved adherence rates. [2,3] Despite their availability for over 50 years, guidelines for their use and data on patients for whom LAI antipsychotics are most indicated are sparse and their acceptance by prescribers and patients remains variable. [4] Some patients dislike the feeling of being under control. [5] Difficulty in altering a dose if side effects develop always remains a challenge.[6] Local complications like pain, bleeding, hematoma, leakage, inflammatory nodules may discourage patient compliance.[7,8] LAI haloperidol decanoate contains 50 mg haloperidol as haloperidol decanoate 70.52 mg/ml in a sesame oil vehicle resulting in slow and sustained release of haloperidol. The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection and falling thereafter, with a half-life of about 3 weeks. Steady state plasma concentrations are achieved after the third or fourth dose. The relationship between dose of haloperidol decanoate and plasma haloperidol concentration is roughly linear for doses below 450 mg. However, the pharmacokinetics of haloperidol decanoate following intramuscular injections can be quite variable between subjects. Extrapyramidal side effects (EPSE) are frequently reported in the first few days after depot antipsychotics. Recently a postinjection delirium/sedation syndrome (PDSS), has been reported after LAI olanzapine pamoate but not after haloperidol decanoate.[9] A young patients who developed PDSS and EPSE two hours after LAI haloperidol decanoate is reported because of its rarity.

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Case Report

A 16 year-old Muslim male, educated up to 10th standard, was brought in OPD at RINPAS, by his father with the complaints of suspiciousness, muttering and smiling to self, abusive and aggressive behaviour and

decrease sleep for last 3 years. The onset was insidious with fluctuating course and deteriorating progress without any precipitating factor. His mood was irritable. Biological functions were disturbed. He had no past history of substance use disorder and medical illness and pre-morbid personality was well adjusted. There was no family history of mental illness. Mental status examination revealed irritable affect, delusion of persecution with third person auditory hallucination, impaired judgement and impaired insight. With a diagnosis of Paranoid schizophrenia he was treated with different antipsychotics but due to poor compliance, he remained symptomatic. He was drug free for last seven months before present consultation. He was prescribed Injection Haloperidol- depot 50mg im stat with tablet Olanzapine 10 mg/day and tablet Nitrazepam 10 mg in tapering dose. Depot injection was administered in Out Patient Department at 1:30 pm. Within two hours of administration of injection, he complained of difficulty in speaking and swallowing with profuse sweating, hypersalivation, restlessness, anxious and confused with altered gait. The initial moderate agitation subsided and later patient slipped into letharginess, drowsiness and stupor. On physical examination, there was stiffness of muscle of the limbs with difficulty in opening jaw and right twisting of the head with upward rolling of the eyeball. He was afebrile. Pulse was 96/minute, regular. Blood pressure was 100/70mm Hg. Systemic examination was within normal limit. He was treated with Injection Promethazine 50mg im and Injection Lorazepam 2mg im stat. I.V. line was secured for hydration. Vitals of the patients were monitored regularly. Injection Promethazine was repeated every 12 hours and injection lorazepam on S.O.S basis. Over 36 hours patients condition gradually improved and tablet trihexyphnidyl 2mg/day was prescribed. Further depot injections were stopped and patient was advised to continue oral antipsychotics.

Discussion

The symptoms that were observed in the patient like sedation, dizziness, confusion, dysarthria or altered speech, letharginess , drowsiness and stupor are typical symptoms of PDSS reported with depot olanzapine pamoate. This syndrome first came to light when an unanticipated degree of sedation was observed in a small number of patients following an LAI of olanzapine pamoate. PDSS has occurred in 29 patients, an incidence of 1.4% of patients treated with olanzapine pamoate or 0.07% of injections given. PDSS usually occur within an hour of injection, but the median time ranged from 20 min to 3 h after injection. To date all patients have fully recovered from this adverse event, usually within 3–72 h, without permanent sequelae and the majority (67%) have continued to receive the LAI formulation.[9,10] Blood samples for olanzapine plasma concentrations taken during the events and were found to be substantially elevated. Solubility experiments have revealed that when olanzapine pamoate LAI is injected into the muscle as intended, the dissolution of the salt is gradual and results in a slow release of drug into the blood stream. However, if the salt comes into contact with a considerable amount of blood or plasma, as occurs if the needle punctures a vessel or enters a rich capillary bed during administration, the salt dissolves and therefore dissociates more quickly. Other factors thought to affect the dissolution rate of the pamoate salt are the volume and rate of blood flow and the degree of vascular injury. A haloperidol LAI antipsychotics possess a terminal alcohol (-OH) group, which allows them to be combined with carboxylic acids by a process of esterification. Long-chain esters show high oil solubility and low water solubility. Long-acting injectable formulations of these drugs contain long-chain drug esters (eg, decanoate) dissolved in a sesome oil. When injected intramuscularly, the oil forms a depot of drug: the drug ester slowly diffuses into the blood stream and is then rapidly hydrolyzed to release the parent drug. Olanzapine lack terminal -OH groups suitable for esterification and its long acting injectable drug release is brought by injecting a suspension (ie, water-insoluble particulate matter in water) of drug compound. [9] This mechanism is not present with LAI Haloperidol. Despite this, haloperidol decanoate salt can be dissolved much more rapidly when it is in contact with a larger amount of blood or plasma, releasing a large amount of Haloperidol by rapid hydrolysis of ester salt in blood over a short period of time. When utilizing an oily vehicle for injection, it is critical to ensure the correct placement of the injection as it forms an oily depot entering the tissue. [11] Both the injection site and the depth are key elements in the

efficacy of the delivered dose and chances of having side effects. Injections must be delivered deep into the muscle tissue, away from fat deposits and major nerve centers. Also important to note are the different blood flows that are observed in the two most common IM areas: the gluteus and the deltoid possess distinctively different rates (9.6 ml/100 g/min) and (11.6 ml/100 g/min), respectively. [12] With this rate of blood flow in mind, it appears obvious to administer the injection to the muscle that receives the less blood flow, ensuring a slower uptake into the bloodstream, allowing for an extended rate of release and is the ideology behind the administration of many extended-release depots in the gluteus tissue. If Haloperidol LAI is accidentally injected into vasculature or capillary rich tissue, this can result in very high plasma levels. Above all, individual variability can always be the explanation.

Ideally, it is recommended that patients being considered for haloperidol decanoate therapy should have been treated with and tolerated well short-acting haloperidol in order to reduce the possibility of an unexpected adverse sensitivity to haloperidol. In the present case due to lack of old documents this could not be done. The starting dose of haloperidol decanoate should be based on the patient's age, clinical history, physical condition and response to previous antipsychotic therapy. The preferred approach to determining the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed. For patients previously maintained on low doses of antipsychotics (e.g. up to the equivalent of 10 mg/day oral haloperidol), it is recommended that the initial dose of haloperidol decanoate be 10-15 times the previous daily dose in oral haloperidol equivalents. The initial dose of haloperidol decanoate should not exceed 100 mg regardless of previous antipsychotic dose requirements. In the present case the initial injection was of only 50 mg.

. EPSE categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis) are frequently reported after the administration of LAI haloperidol deconate, often during the first few days of treatment. While EPSE can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride. Symptoms of dystonia like abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms like tightness of the throat and swallowing difficulty was seen in our patient. An elevated risk of acute dystonia is observed in males and younger age groups like our patient. The Parkinsonian symptoms like stiffness of muscle of the limbs, restlessness, agitation were manifested by our patient.

A test dose has been proposed to avoid severe and prolonged adverse effects, if the patient has never been on a depot formulation earlier.[13] The use of test doses neither mitigate this complexity nor minimise tolerability difficulties, because EPSE may occur even after several doses have been given.[14,15] Some psychiatrists give simultaneous anticholinergic injections with LAI haloperidol or prescribe oral anti-parkinsonian drugs for four to five days after each injection. This is because patients are at increased risk of developing EPSE at the time the drug concentration reaches its peak.[5] There is no evidence for such a practice, and it is recommended that if EPSE appear oral anticholinergic must be given to the patient and there is no need for simultaneous anticholinergic injection when administering LAI haloperidol. Moreover, due to euphoric properties of anticholinergic medications, many patients abuse oral and particularly injectable anticholinergics.

Though first-generation antipsychotic LAIs are clearly linked to high rates of EPSE but possibility the present case raises the possibility of occurrence of PDSS after LAI haloperidol. Haloperidol LAI should therefore be administered by trained personnel in settings where a observation period for at least 3 hours by medical personnel is available. Individual variation should always be borne in mind and one must be vigilant in detecting the side effects early so that suffering on the part of patient can be minimized.

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