Case of acute akathisia from intravenous metoclopramide
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ABSTRACT
Intravenous (IV) metoclopramide is a frequently prescribed medication in the emergency department (ED). Extrapyramidal side effects like tardive dyskinesia are known to develop with chronic use of metoclopramide, while acute akathisia is a lesser known side effect following IV administration. Akathisia is characterised by a sensation of restlessness and distress, as well as constant, non-purposeful limb movement. It can present as a diagnostic challenge, cause distress and hinder the management of the primary condition of the patient in the ED. However, akathisia can be readily reversible, with a successful patient outcome if promptly diagnosed. We report a case of acute akathisia in a young female patient after IV bolus metoclopramide was administered to treat her gastroenteritis in our ED. We highlight the diagnostic process, the difficulties in the management of the primary condition resulting from her akathisia and its successful management using IV diphenhydramine and midazolam.

Keywords: akathisia, diagnosis, intravenous, management, metoclopramide

INTRODUCTION
Akathisia is a movement disorder characterised by a feeling of restlessness and distress, as well as constant non-purposeful movement of the limbs.\(^1\) It is commonly seen as a side effect of various medications, including neuroleptic agents, serotonin reuptake inhibitors, L-dopa, calcium channel blockers and phenothiazide antiemetics.\(^2\)

Metoclopramide, a dopamine-2 receptor antagonist commonly used in the emergency department (ED) for the management of nausea, vomiting and vascular headaches, has been implicated in the causation of akathisia. However, an overwhelming majority of the literature outside the ED setting have only reported the development of tardive akathisia in the chronic use of metoclopramide.\(^3,4\) In all of these cases, the patients were either uncooperative or rejected treatment. Few case reports associate tardive akathisia with acute metoclopramide administration.\(^5\) Lagorio et al reported a case series where the patients refused surgery after the preoperative administration of metoclopramide.\(^6\)

It is important to recognise acute akathisia as a potential side effect of metoclopramide, especially in a busy setting like the ED, as it is readily reversible if promptly treated. Failure to do so may cause patients to become agitated or refuse adequate treatment for their primary conditions, or even develop suicidal ideation.\(^7\) We highlight a case of acute akathisia secondary to the administration of a single bolus of intravenous (IV) metoclopramide in the ED, which was subsequently identified and treated successfully.

CASE REPORT
A 26-year-old Malay woman presented to an acute, urban, tertiary ED with a five-day history of colicky abdominal pain, vomiting and diarrhoea. There was no travel or contact history, and she reported having eaten fast food prior to the development of these symptoms. The patient did not have any significant medical condition or drug allergies. On examination, she was calm and oriented. Her vital signs were stable and she was afebrile. Her tongue appeared dry, but no sclera icterus or pallor was observed. Abdominal examination revealed a soft abdomen with mild epigastric tenderness. Examination of the cardiorespiratory and neurological systems was otherwise unremarkable.

With a working diagnosis of gastroenteritis, the patient was administered with an IV bolus of metoclopramide 10 mg and tramadol 50 mg to relieve her symptoms. After five minutes, she complained of an uneasy sensation and chest tightness. She appeared anxious, and became agitated and restless. The attending doctor and consultant suspected acute akathisia secondary to IV metoclopramide based on the temporal sequence of drug administration and onset of the symptoms. The patient was treated with a bolus dose of IV diphenhydramine 25 mg and investigated for other possible causes. All blood and urine investigations, including capillary blood glucose, urea and electrolytes, full blood count, liver function test, urinalysis and urine pregnancy test, were normal.
The patient’s symptoms did not improve and a second bolus of IV diphenhydramine 25 mg was administered. Her symptoms temporarily subsided and she was noted to be sleeping comfortably. After half an hour, the patient awoke with the uneasy sensation again. She threatened to remove her IV plug and leave the hospital. The patient was then treated with an IV bolus of midazolam 2 mg, which partially improved her anxiety. After an IV infusion of diphenhydramine 50 mg over two hours, her akathisia improved markedly, with a complete resolution of symptoms. There was no recurrence after eight hours of monitoring, and the patient was subsequently discharged.

DISCUSSION

We have demonstrated the diagnostic process, adverse consequences and successful treatment of a case of acute akathisia secondary to an IV bolus of metoclopramide. Acute akathisia is a subjective feeling of inner restlessness and the urge to move about, as well as an objective observation of stereotypical movements, especially of the lower limbs. The diagnosis of drug-induced akathisia is largely clinical, as our case has demonstrated. There are no relevant laboratory tests to support it. As a result, doctors may experience difficulty in making the diagnosis, as these patients may not only present in various ways, but that the condition may also mimic other clinical syndromes. This is especially so in a busy setting like the ED, where time constraints and frequent distractions are imposed on the attending doctor.

The Barnes rating scale was developed in 1989 to assess the severity of akathisia secondary to drug use. In the mild forms, patients may complain of a vague feeling of apprehension and unease, or an unusual feeling of restlessness. If not promptly treated, patients may become visibly distressed, anxious or angry, displaying non-purposeful voluntary movements of the limbs and a compulsive need to move around. The failure to identify this condition may lead to decreased compliance to treatment, with distressed or violent patients leaving the hospital without reason; they may even develop suicidal intentions. Our case demonstrated the more severe form of akathisia secondary to drug use as well as the difficulties encountered in the treatment of the patient’s primary condition.

Differential diagnoses of acute akathisia include psychotic agitation, anxiety, restless legs syndrome and drug withdrawal states. The temporal association with a drug known to cause acute akathisia is an important component of establishing the correct diagnosis. Acute akathisia usually develops during the introduction or escalation of the dose of relevant medications. It is important to distinguish acute akathisia from other conditions, as the former is readily reversible whereas a diagnosis of psychiatric conditions may involve the addition of other psychoactive drugs that may exacerbate akathisia.

Several hypotheses have been proposed for the development of acute akathisia, including antagonism of the dopaminergic receptors in the mesocortical and mesolimbic pathways. The involvement of the noradrenergic and serotoninergic pathways has also been suggested. However, no single hypothesis has been satisfactory in explaining the symptoms of acute akathisia. Metoclopramide is a dopamine-2 receptor antagonist that is frequently prescribed in the hospital for its antiemetic and prokinetic actions.

The incidence of akathisia following metoclopramide use has not been well studied. Braude et al compared three common antiemetics used in the ED and reported the incidence of akathisia in metoclopramide use to be 25% as compared to 71.4% for droperidol and 35.3% for prochlorperazine. Other studies reported the incidence of acute akathisia in neuroleptic use to be around 8%–76%. The risk of developing akathisia has also been found to be weakly associated with the dose and rate of increment of neuroleptics. As akathisia secondary to metoclopramide use is common, physicians need to be aware of this adverse effect and maintain a high degree of suspicion whenever mental changes occur in their patients following its administration.

A review of the literature suggests that drug-induced akathisia may be preventable. Prevention of the development of acute akathisia includes using the minimum therapeutic dose of metoclopramide and controlling the rate of administration or escalation of the dose. Two randomised, prospective, double-blind trials have shown that slow IV infusion of metoclopramide 10 mg over 15 minutes significantly reduces the incidence and severity of akathisia in patients, as compared to an IV bolus administration over two minutes. As such, the slow infusion method as compared to a bolus administration may be more ideal in preventing acute akathisia. However, issues involving the differences in efficacy between the two administration modes need to be explored in order to decide on the risk-benefit balance of each mode.

Once the diagnosis is made, the offending drug (in our case, metoclopramide) should be promptly withdrawn. Treatment of akathisia includes the use of anticholinergic agents, antiadrenergic agents, benzodiazepines and other drugs such as ritalinserine, amantadine and tricyclic...
antidepressants.\textsuperscript{(1)} Diphenhydramine, an antihistamine with central anticholinergic activity, has also been shown to be effective. These medications are thought to work by restoring the balance between cholinergic and dopaminergic actions. Sachdev recommended the use of anticholinergic or beta-antagonists as first-line agents.\textsuperscript{(14)} If clinical improvement of the symptoms is unsatisfactory, benzodiazepines may be employed as second-line agents, as demonstrated in our case. Parlak et al in their randomised, double-blind trial compared the efficacy of midazolam and diphenhydramine in the treatment of drug-induced akathisia. Their results showed that benzodiazepines are more effective in easing the symptoms of akathisia, but they are associated with higher sedation rates.\textsuperscript{(15)} In our case, IV diphenhydramine was used both as a bolus and a slow infusion in the management of akathisia. However, as the patient reported only partial response, IV midazolam had to be administered as a rescue therapy.

In addition, our case demonstrated the need for a prolonged period of monitoring (eight hours) for recurrence and the sedative effects of IV diphenhydramine and midazolam. Patients should also be informed and educated about the symptoms of drug-induced side effects in order to prevent future occurrences. In conclusion, our case report highlights the importance of prompt recognition of metoclopramide-induced akathisia, which can be successfully treated.

REFERENCES