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Myotoxicity Induced By Clonazepam: A Case Report

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A 15 year old boy developed an apparent marked adverse drug reaction after three, 1 mg doses of oral clonazepam manifest by confusion, agitation, myotoxicity and elevated levels of creatine phosphokinase (CPK); all symptoms resolved on stopping the drug.

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Introduction

A number of drugs may have adverse effects on the musculoskeletal system, with manifestations including myalgia, weakness and fatiguability[1]. Myotoxicity has been reported to occur in patients with chronic psychotic disorders treated with clozapine[2]. Acute rhabdomyolysis has been reported only rarely in association with benzodiazepines[3-5]. We describe a boy who developed a marked adverse drug reaction (ADR), including myotoxicity, following three doses of oral clonazepam.

Case report

A 15 year old boy had experienced a non-progressive and mild essential tremor of his hands from one year of age. The patient had never complained previously of any muscle symptoms or fatiguability and there was no evidence of cognitive impairment. There was no family history of neuromuscular disease. Neurological examination had been consistently normal, in particular showing no evidence of muscle wasting, weakness or myotonia. Sensation and muscle stretch reflexes were normal. The following investigations were all normal: computerised tomography of the brain, plasma copper and caeruloplasmin, creatine phosphokinase (CPK), liver function tests, full blood count, plasma and urinary amino acids. The patient remained under review until 10 years of age, with no progression or deterioration in the tremor.

The patient re-presented at 15 years of age, concerned that the tremor was more obvious, particularly when working in design and art. On direct questioning, the patient reported infrequent jerks that occurred at any time during the day and occasional startles to loud noises that had developed over the previous two years. The patient had never experienced absence or generalised tonic-clonic seizures.

On examination, the patient had a subtle tremor of his outstretched hands that became more obvious the longer his hands were outstretched and also on performing actions. Although the patient showed a slightly exaggerated startle response to touch, there was no habituation on repeating nose or glabella tapping. Neurological examination was otherwise normal and specifically showed no muscle weakness, hyperreflexia or myotonia. The patient's sleep-deprived electroencephalogram was normal. Neurological examination of the patient's parents was normal.

The patient was considered to have a benign essential tremor or, less likely, hyperekplexia (startle disease). The patient was commenced on clonazepam 1mg, three times a day. Following the third 1mg dose of clonazepam, the patient became somewhat confused, agitated, aggressive, ataxic, vomited and developed an ataxic dysarthria. Within the following few hours he developed a headache and facial swelling. There was no muscle swelling, tenderness or weakness but the patient stated that some of his joints felt "looser" and that the tremor was, "not as bad". On examination the patient appeared slightly agitated but not confused. There was no muscle swelling or tenderness and muscle strength and stretch reflexes were normal; the patient's tremor was unchanged. There was no fever, rash or hepatosplenomegaly. The patient had not experienced any trauma prior to the onset of these symptoms and denied any substance abuse including alcohol and recreational drugs. The clonazepam was discontinued and the symptoms gradually resolved over the next 10 days. There was no clinical evidence of myoglobinuria.

Investigations undertaken six days after the patient had discontinued clonazepam revealed the following: aspartate transaminase (AST) and alanine aminotransferase (ALT) concentrations were raised at 109 iu/L and 51 iu/L respectively (reference range for our laboratory, <41 iu/L and <36 iu/L respectively). The plasma CPK was markedly raised at 5969 iu/L (reference range for our laboratory, <195 iu/L). Total plasma bilirubin, alkaline phosphatase, copper, caeruloplasmin, troponin T and creatine kinase cardiac isoenzyme (CK-MB) were all within the reference ranges for our laboratory. The creatine kinase skeletal muscle isoenzyme (CK-MM) was markedly elevated suggesting that the high CPK was almost certainly derived from skeletal muscle. Urine analysis revealed no myoglobinuria or evidence of substance abuse. Twelve days later the plasma ALT had returned to within the reference range, but the plasma AST and CPK remained elevated at 66 iu/L and 2940 iu/L respectively. All enzyme activities were within the reference ranges one month later.

Discussion

This patient's musculoskeletal and other symptoms (apparent myotoxicity) appeared to be temporally related to the use of clonazepam. There had been no preceding illness, infection or trauma (to head or limbs). The patient denied taking any other medications or substances and there was no family history of any neuromuscular disorder. Although the patient had a long-standing history of tremor, this had been non-progressive and had never been associated with any neurological (including neuromuscular) features. The patient's infrequent jerks were not considered to represent myoclonus or myoclonic seizures.

ADRs on the musculoskeletal system are well-recognised[1] and have been reported with a variety of drugs including clofibrate[6], epsilon-aminocaproic acid[7], vincristine[8], amphotericin B[9], chloroquine[10], anaesthetic agents (usually in patients with malignant hyperpyrexia)[11], neuroleptics [as part of neuroleptic malignant syndrome (NMS)][12-16], phenytoin[17], sodium valproate[18] and, rarely, benzodiazepines[2,3]. Most reports on benzodiazepine-induced myotoxicity and rhabdomyolysis have been following either intravenous use or oral overdose[4]. As far as we are aware there has been only one previous report to the Committee on Safety of Medicines of myotoxicity and this was a case of rhabdomyolysis following an accidental overdose[5].

Numerous drugs are potentially myotoxic. They may produce inflammatory, necrotising, lysosomal-related, mitochondrial, electrolyte disturbance-related or protein synthesis-related muscle damage[1, 19].

The mechanism of muscle injury associated with clonazepam in our patient is unknown. The patient described developed non-specific symptoms, including facial swelling and it may be that the myotoxicity was part of a hypersensitivity reaction caused by the clonazepam. In cases of muscle dysfunction associated with treatment with clozapine, a dibenzodiazepine derivative, it was hypothesised that clozapine may have myotoxic effects in susceptible individuals through interactions with cytochrome P450 proteins or calmodulin, which are involved in muscle metabolism[2]. Similar mechanisms may or may not have been responsible for our patient's apparent ADR to clonazepam.

Another possible explanation for this patient's symptoms and elevated plasma CPK is NMS. The pathogenesis of NMS remains unclear but is thought to be a disorder of central dopaminergic neuro-transmission[12, 13], and may arise as a potentially fatal adverse effect of neuroleptic drugs[12-16], including haloperidol and the phenothiazines. There is still no consensus on diagnostic requirements for NMS, but fever and rigidity are generally considered to be essential features[12-16]. Other features typically include an elevated plasma CPK that usually exceeds 20,000 iu/L (reflecting rhabdomyolysis), tachycardia, abnormal blood pressure, tachypnoea, altered level of consciousness, diaphoresis and leucocytosis. However, there may be a broad

spectrum of severity in NMS, particularly in children and adolescents[12-16], and rarely, without pyrexia[14, 16]. Finally, there is a single case report of NMS being associated with a benzodiazepine (diazepam)[15]. Although it is possible that the apparent ADR to clonazepam in our patient, which included agitation, myotoxicity and an elevated plasma CPK, may have represented a 'forme frusté' of NMS, we consider this is unlikely in view of the absence of rigidity and pyrexia.

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