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Movement Disorders Induced by Gastrointestinal Drugs: Two Paediatric Cases

Abstract

A number of frequently prescribed gastrointestinal drugs can cause movement disorders in children, as well as in adults. In our centre for paediatric neurology, we saw a 3-year-old girl with abnormal movements mostly of the legs with an inner restlessness (akathisia) while using cisapride. Another patient, a 17-year-old male, developed a hemiballism (a fierce movement of one arm and shoulder with a hurling appearance) while using ranitidine for gastric distress. In both children, the movement disorder disappeared after discontinuing the drug. The pathophysiological mechanisms of these drug-induced movement disorders might be related to the central function of histamine in the developing brain. These cases illustrate the importance of being alert for possible drug-induced events early in the process of diagnosing abnormal movement disorders.

Key words
Movement disorder · drug · gastrointestinal · H2 receptor antagonists · cisapride · adverse drug reactions

Introduction

Drug-induced movement disorders are rare and therefore difficult to recognise as adverse drug reactions (ADR), in children as well as in adults. Neuroleptics, in particular, but also psychostimulants and antidepressants, are known for their extrapyramidal effects. The increasing use of these drugs in children has led to an increase in drug-induced movement disorders.

Drug-induced movement disorders can be divided into three main categories [24]: (1) Acute disorders appear shortly after drug exposure and rapidly build up to a maximum. They include acute dystonia [19], the neuroleptic malignant syndrome (NMS), and the serotonin syndrome [17], (2) continuous disorders occur after variable exposure to the offending drug and persist as long as the causative agent is administered. Examples are drug-induced Parkinsonism, akathisia [10], chorea [21], (hemi)ballism [27], and tremor [17,24], and (3) tardive disorders appear after long-term drug use and persist beyond discontinuation. Tardive dyskinesia [4], myoclonus [24], dystonia and drug-induced tourettism■ [17] have been described [7,24].

The extrapyramidal ADRs of neuroleptics are well known [7]. However, a broad scale of other drugs, often prescribed to children or even bought over-the-counter, may also induce movement disorders. Dopaminergic anti-emetics (e.g., metoclopramide and domperidone) [8,16], dopamine agonists (especially levodopa) [24], anticonvulsants [17], antidepressants such as TCA's and SSRI's [9,17], stimulants such as amphetamine and methylphenidate [19], calcium channel blockers [2], oral contraceptives [18], histamine-2 antagonists [14], theophylline [23] and codeine-containing cough suppressants [22] have all been associated with movement disorders in paediatric case reports.

This article presents two childhood cases of movement disorders induced by gastrointestinal drugs: a case of akathisia in a 3-year-

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old girl induced by cisapride, and a case of hemiballism in a 17-year-old boy induced by ranitidine.

It is important to draw attention to these ADRs. Awareness of the possible relationship between drugs and movement disorders, early in the diagnostic path, prevents unnecessary treatment delay and distressing diagnostic investigations. Generally, in the case of acute and continuous disorders, the abnormal movements disappear as soon as the offending drug is discontinued.

Furthermore, the occurrence of drug-induced movement disorders can increase our insights into the pathophysiological mechanisms of these disorders. Structural damage to the basal ganglia, e.g., asphyxia, and genetic factors create individual vulnerability to these disorders [7,18]. Genetically determined polymorphisms of the different transmitter receptors may partially explain why one individual does, and others do not, develop movement disorders when exposed to the same drug [20].

Dopaminergic transmission in the basal ganglia plays an essential role in the pathophysiology of movement disorders. Dopamine supersensitivity due to an up-regulation of D2 and D3 receptors in patients with extrapyramidal ADRs has been known to cause drug-induced movement disorders for a long time [20]. The observation that anticholinergics increase tardive dyskinesia and that acetylcholine agonists can be used to treat many drug-induced movement disorders led to an expansion of the dopaminergic hypothesis. It has been proposed that drug-induced movement disorders result from an imbalance between dopaminergic and cholinergic transmission in the basal ganglia [17]. Destruction of dopamine neurones and other neurotransmitter systems by free radicals is gaining acceptance as one of the mechanisms underlying pathophysiology of drug-induced movement disorders. Neuroleptics are lipophilic and thus incorporate into cell membranes where they might produce free radicals that evoke structural changes. The observation that higher concentrations of lipid peroxidation products are found in cerebrospinal fluid of patients using dopaminergic anti-emetics than in controls supports this theory [17].

This paper will emphasise that, besides dopamine, histaminergic transmission also plays an important role in movement disorders.

Case Reports

Patient 1

A 2-year-and-10-month-old girl was born after an uneventful pregnancy in breech delivery at a conceptual age of 34 weeks. Respiratory failure, requiring artificial ventilation, developed immediately after birth, due to pulmonary hypoplasia and congenital diaphragmatic herniation. The girl was treated with extracorporeal membrane oxygenation (ECMO) for 104 hours. The diaphragmatic herniation was surgically corrected.

She was referred to our outpatient clinic because of fluctuating paroxysmal restless movements, which had been present for over 2 years since the neonatal period. They consisted of pouting of the lips while making a monotone noise and thrashing about with an extension of the legs, after which she appeared relieved (Fig. **1**). She gave the impression of enjoying this. During the episodes, she remained fully conscious, and distracting her attention made it possible to suppress the movements. Apart from these symptoms, motor and mental development after the neonatal period was normal. The family history was unremarkable. Since the neonatal period, she was given appropriate dosages of ipratropium, budesonide and cisapride. Physical examination revealed no abnormalities except for the restless movements, best described as akathisia: an irresistible urge to move.

Because cisapride is known to sporadically cause extrapyramidal side effects, it was stopped. In the 2 months following, the abnormal stereotypic movements gradually disappeared. As such, the classification of the movement disorder met the criteria for a continuous drug-induced movement disorder. At the age of 5 years, her development has been thoroughly assessed as part of the follow-up of ECMO treatment. Motor and mental development was rated as satisfactory to good. No movement disorders were noticed. A recent examination revealed that our patient was doing very well. The abnormal movements never reappeared.

Patient 2

The second patient is a 17-year-old male. Pregnancy and delivery were uneventful, but his motor milestones were slow. In his primary school years, he received physical therapy for his clumsiness. Intellectual development was above average. Family history revealed that his father had had epileptic seizures as a child. He was referred for progressive involuntary hemiballistic movements, which had persisted for over a year. The movements began with involuntary squeezing of the hands, especially during saxophone playing. Later the squeezing worsened to a paroxysmal hemiballistic movement of the left arm. Occasionally, the head and left leg were also involved. Initially the movements occurred sporadically, later almost daily. The patient was not able to suppress the movements. The amplitude was variable, ranging from small muscle contractions to "sweeping a dish from the ta-

Fig. **1** Video derived graphs for case 1: cisapride-induced akathisia.

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Table **1** Summary of the literature on movement disorders induced by gastrointestinal drugs

Offending drug	*Described movement disorders*	*Number of patients described (sex, age)*	*Ref*
Metoclopramide	tardive dyskinesia, dystonia, myoclonus, akathisia, tics, Parkinsonism, neuroleptic malignant syndrome	1047	[17]
Domperidone	extrapyramidal movement disorder	1 (female, 27 years)	[8]
	chorea, dystonia	7 (< 3 years)	[16]
	dystonia	1 (male, 4 months)	[28]
Cisapride	dystonia, orofacial dyskinesia	1 (female, 43 years)	[6]
	aggravation Parkinson tremor	2 (not specified)	[25]
	dystonia	1 (infant)	[1]
	myoclonus	1 (male, 8 months)	[15]
Ranitidine	Meige's syndrome (blepharospasm and buccolingual dyskinesia)	1 (female, 72 years)	[13]
	dystonia: reappearing after rechallenge	1 (male, 72 years)	[17]
	chorea	1 (female, 76 years)	[14]
Nizatidine	akathisia, Parkinsonism	1 (female, 16 years)	[3]

ble". Apart from ranitidine for gastric distress, he used no drugs. Street drug use was denied.

Physical examination was normal. Earlier multiple EEGs, an MRI of the brain and an EMG revealed no abnormalities. A complete metabolic work-up including urine, serum and CSF examination was normal. There was no evidence for borreliosis. In view of the diagnostic work-up already performed, it was decided to discontinue the ranitidine, his sole medication. The involuntary movements gradually disappeared. Two months later, the patient reported cessation of the involuntary movements. The gastric distress disappeared after *Helicobacter pylori* eradication.

Discussion

In both patients, discontinuation of the suspected drug resulted in a gradual disappearance of the movement disorder. In both cases, no evidence for another diagnosis was found, and the abnormal movements never reappeared after cessation of the drug. Understandably, no rechallenge took place.

Cisapride-induced akathisia is still the most plausible diagnosis in our first patient.

Akathisia literally means: "not able to sit". The central symptom is an inner restlessness, which causes abnormal movements, mostly of the legs. Akathisia is reported to be a symptom of Parkinsonism or iron deficiency anaemia, but is often drug-induced [10].

Acute akathisia usually appears days to weeks after introduction of a drug and disappears on discontinuation. Tardive akathisia also exists, which does not always disappear [12]. Patients experience akathisia as very disturbing. It may be accompanied by strong feelings of anxiety or anger, and even aggressive and suicidal behaviour [12].

Within the group of anti-emetic drugs, movement disorders are most often associated with the use of metoclopramide, a dopamine-2-receptor antagonist. Domperidone has been found to be a better alternative, as it crosses the blood-brain barrier less easily. Table **1** shows that dystonic side effects also occur with this drug. Debontridder, in 1980 [8], described the case of a 27-year-old woman with extrapyramidal ADRs on metoclopramide. About a year later, she used domperidone for severe vomiting, and again an impressive movement disorder emerged [8].

Cisapride increases gastric motility by stimulating cholinergic transmission in the mesenteric plexus. The drug is chemically related to domperidone and metoclopramide [25], but is not supposed to produce dopaminergic inhibition [6]. Cisapride is not believed to penetrate the blood-brain barrier, and is thus considered to have fewer neurological adverse effects than metoclopramide. The cases mentioned in Table **1**, as well as our case, show that adverse extrapyramidal drug reactions can occur with cisapride. Awareness of this side effect remains relevant, although cisapride in Europe and the USA, nowadays, is only prescribed in special cases.

There are some reasons why our first patient might have been more vulnerable to drug-induced movement disorders. At the start of treatment with cisapride, she was only a few weeks old. It is known that, at least until the age of one year, the blood-brain barrier has not fully developed. Furthermore, optimal central oxygenation had not been fully reached at the time the drug was started. Pranzatelli et al., in 1991, suggested a role for hypoxia in the occurrence of drug-induced movement disorders [23].

In addition, this child had a history of ECMO treatment for four days, which made interruption of the internal carotid artery and jugular vein necessary. Possible brain dysfunction cannot be fully excluded, even though daily cerebral ultrasound imaging during ECMO showed no structural cerebral abnormalities. Further-

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more, mental and motor developmental assessment at age 2 and 5 years were age appropriate.

Movement disorders are seen more often after a period of asphyxia [7]. But our patient had Apgar scores of 6, 7 and 8 at 1, 5 and 10 minutes postnatal.

Finally, cisapride is metabolised by CYP450 3A4, which is underdeveloped in neonates. Interaction with budenoside and ipratropium by this enzyme is unlikely.

The course of the movement disorder in the second patient suggests ranitidine-induced hemiballism. His motor clumsiness might have predisposed this patient to such a side effect.

(Hemi)ballism can be considered as the proximal variant of chorea. The literal meaning of chorea is "dance". It is an excessive, abrupt, irregular, spontaneous, not repeating movement. (Hemi)ballism consists of movements with relatively high amplitude. Often a unilateral, fierce movement of a limb with a hurling appearance is seen. Differential diagnosis of chorea and hemiballism is very extensive. Neither history nor additional diagnostics gave any indication for an underlying disease in our case.

Cimetidine and ranitidine are competitive antagonists of histamine that block gastric histamine-2 receptors and are typically prescribed for dyspeptic complaints. Though the use of histamine-2 antagonists has decreased after the introduction of the potent and not drug related proton pump inhibitors, ranitidine is still prescribed in some cases, and is freely available over the counter in several countries.

H2 receptors are found in the brain and H2 antagonists cross the blood-brain-barrier.

In the brain, histamine is produced by mast cells, particularly in the thalamus, and also by specific neurons. In the rat, histaminergic neurons project to almost all areas of the brain and spinal cord. Thus, histamine might play a modulating role in the central nervous system, as dopamine, noradrenalin, and serotonin do. The release of histamine is enhanced during extreme circumstances, such as dehydration or hypoglycaemia. The highest concentrations of H2 and H3 receptors in the brain can be found in the basal ganglia. Their function is not fully clear, but they obviously play a role in movement disorders. For example, in Huntington's disease, a dramatic decrease of H2 and H3 receptors in the striatum is seen. The decrease is directly linked to the severity of symptoms [11]. In contrast, the concentration of histamine receptors in Parkinson's disease remains stable [5].

In humans, extrapyramidal side effects induced by ranitidine and cimetidine have been mentioned (Table **1**). Lehman (1988) described an interesting case of a 76-year-old woman who developed choreatic movements of mouth, face, neck and arm while using ranitidine. The ranitidine was replaced and the abnormal movements disappeared. A month later, she received cimetidine during an emergency admission. Within 5 days, the chorea reappeared but disappeared after cessation of the drug [14]. This case suggests a class-effect.

Domperidone and metoclopramide (Table **1**) are not approved for younger children in Germany.

Recently Bhanji et al. (2004) described extrapyramidal symptoms in a 16-year-old patient that were likely related to nizatidine use as an add-on therapy while the patient also received quetiapine and paroxetine [3].

Nizatidine was started for the indication of obesity. Because of initial positive benefits, in the absence of adverse effects, the nizatidine dosage was increased to 300 mg twice a day. Within 4 days after this dosage increase, the patient started pacing and could not sit still. Mild Parkinsonism was also present. Concern for these extrapyramidal symptoms led to a decrease in the nizatidine dosage to the original 150 mg twice a day. The patient's abnormal movements disappeared over the next 5 days. At a 3-month follow-up visit, no further adverse effects had been observed [3].

We have searched the databases of the Uppsala Monitoring Centre of the WHO on Adverse Drug Reactions to assess these adverse drug events. No association with akathisia could be found for cisapride. However, extrapyramidal disorder is reported with a Reporting Odds Ratio (ROR) of 3.14 (95% CI 2.53 – 3.90), which is disproportional, indicating an association between this drug and extrapyramidal disorders. For ranitidine, extrapyramidal disorders are reported but the ROR is 0.53 (95% CI 0.38 – 0.76), which means the association is not significant.

In this article, we have presented two cases of extrapyramidal symptoms due to gastrointestinal drugs and supported our findings with information from the literature and a pharmacovigilance database.

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