CASE REPORT

Immediate resolution of acute, choreatic hyperkinesias following intravenous fentanyl

J Finsterer, J Rettensteiner

Krankenanstalt Rudolfstiftung, Vienna, Austria

Abstract

Acute hyperkinesia after discontinuation of tramadol in a patient with chronic pain using citalopram and pramipexole for restless legs syndrome (RLS) has not been reported. An 81-year-old female was admitted for increasing hyperkinesias of the whole body after she had discontinued tramadol 300 mg (taken during 3 months) without tapering 4 days earlier. In addition, she was on treatment with pramipexole (0.18 mg) for RLS for years, citalopram 10 mg/day for ~4 years, and fentanyl 75 μg/day for 1 year. Hyperkinesias did not respond to benzodiazepines, quetiapine, biperiden, or valproic acid. Surprisingly, hyperkinetic bursts resolved immediately upon 15 mg fentanyl intravenously. Obviously, tramadol withdrawal had enhanced the preexisting RLS. Overdosing of pramipexole or serotonin syndrome was excluded. Sudden discontinuation of tramadol in a patient under pramipexole for RLS may cause severe, choreatic hyperkinesias for hours, which immediately resolve upon intravenous fentanyl. In patients under pramipexole for RLS and tramadol and fentanyl for chronic pain, sudden discontinuation of tramadol should be avoided to prevent induction of restless body syndrome.

Key words: Choroid hyperkinesias, DOPA-agonists, extrapyramidal syndrome, opiates, opioids, side effects, withdrawal

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Introduction

Acute drug-associated hyperkinesias are rare[1] and have not been reported in association with opiate treatment and restless leg syndrome (RLS). Here, we present a patient under citalopram, fentanyl, and pramipexole for RLS who developed severe hyperkinesias after immediate discontinuation of tramadol.

Case Report

The patient is an 81-year-old nonsmoking, HIV-negative, Caucasian female, height 165 cm, weight 66 kg, who was admitted in June 2015 because of acute-onset recurrent bursts of hyperkinesias affecting the lower and upper limbs, trunk, and head since 8.00 pm. On admission at 10.00 pm, she was alert, adequately reacting, and was able to walk unaided. She denied headache, vertigo, exsiccosis, intake of illicit drugs, previous journey to the tropics, coughing, close contact with animals, tuberculosis, fever, or diarrhea. Her previous history is listed in Table 1. She was on a permanent medication with acetyl-salicylic acid (100 mg/d), L-thyroxin (100 mg/d), pantoprazole (40 mg/d), bisoprolol (1.25 mg/d), valsartan (20 mg/d), furosemide (30 mg/d) since 2 years, citalopram (10 mg/d), pramipexole (0.18 mg/d) since years with interruptions but regularly again since 1.5 years, transdermal fentanyl (75 mg/d) since 1 year, budesonide plus formoterol (540 mg/d), and tiotropium-bromide (18 mg/d). Four days before

Address for correspondence:
Dr. J Finsterer,
Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria.
E-mail: fifigs1@yahoo.de

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admission, she herself had discontinued tramadol (300 mg/day) because of hyperhidrosis, which replaced diclofenac she had been taken during years until 3/2015. On demand, she also took paracetamol (500–1000 mg/day).

To stop progressing hyperkinesias, she initially received diazepam (10 mg), and because of ineffectivity, consecutively, she received quetiapine (25 mg), lorazepam (4 mg), and diazepam (20 mg), all without a beneficial effect. At 3.00 am on hospital day (hd) 2, she was first referred to the neurologist who found a somnolent patient inconsistently following his requests and presenting with severe choroid hyperkinetic movements, which followed a recurrent pattern of involuntary leg and arm movements followed by pushing up to a sitting posture and rotatory motions involving the head. Hyperkinetic bursts were interrupted by episodes of

Table 1: Previous history of the described patient

Time	Diagnosis	Management
2/2015	Leucaraiosis	None
2/2015	Hearing impairment	None
7/2014	Polyneuropathy	Physiotherapy
4/2014	Coronary heart disease	Stenting of LAD, acetyl-salicylic acid
2013	Diffuse large B-cell lymphoma	Chemotherapy with 6x CHOP 9-12/2013 (regarded as cured)
Since7/2012	Cervicalgia, vertebrostenosis without myelopathy at C5/6	Analgesics
Since at least 2009	Renal insufficiency with recurrent Na↓, Ca↓, Mg↓	Furosemide, liquids
Since>5y	Misuse of non-steroidal analgesics	None
Since>5y	Left-sided double kidney	None
Since>5y	Anemia	None
Since>5y	Lumbalgia due to OCH, SPA, vertebrostenosis L4/5	Analgesics
Since>5y	Hyperlipidemia	Low fat diet
Since>5y	Arterial hypertension	Bisoprolol, valsartan
Since>5y	Gastritis, reflux, hiatus hernia	Pantoprazol
Since>5y	Right gonarthrosis	Analgesics, prosthesis scheduled
Since>5y	Varicositas	None
Since>5y	Diverticulosis	None
Since>5y	Hyperuricemia	Diet
2006	Cataract	Bilateral surgery
Since~2005	Restless leg syndrome	Pramipexole
Since~2005	Muscle cramps (thighs, calves, foot) intensified after chemotherapy	Magnesium
Since 2000	Chronic obstructive lung disease	Budesonide, tiotropium-bromide
1984	Thyroid adenoma, hypothyroidism	Thyroid resection, L-thyroxin
1973	Endometriosis	Hysterectomy and partial adnexectomy
~1955	Peritonitis after delivery	Antibiotics

CHOP=Cyclophosphamide, hydroxy-daunorubicin, vincristine, prednisone; OCH=Osteochondrosis; SPA=Spondylarthrosis

Table 2: Results of blood tests in the described patient

Parameter	RL	261009	140412	250115	110615*	120615	150615	160615
Creatine-kinase	<170 U/l	118	167	77	100	**248**	nd	121
Pro-BNP	<194 ng/	nd	nd	nd	nd	nd	**1348**	**1276**
Cholesterol	30-200mg/dl	nd	nd	nd	nd	**236**	**255**	**246**
C-reactive protein	0.0-5.0 mg/l	2.8	**100.0**	5.0	**6.9**	**6.8**	4.7	3.6
Leukocytes	4.0-9.0 G/l	6.9	**9.5**	5.2	6.5	**9.1**	nd	4.1
Erythrocytes	4.0-5.2 T/l	4.31	4.25	**3.40**	4.05	**3.69**	nd	4.0
Hemoglobin	12.0-16.0 g/dl	12.6	**11.0**	**9.6**	**10.6**	**9.7**	nd	**10.8**
Hematocrit	38-48%	**37**	**34.1**	**29.0**	**33.4**	**30.3**	nd	**32.9**
Thrombocytes	150-400 G/l	331	343	257	315	297	nd	296
D-dimer	0.00-0.5 µg/ml	**0.7**	**0.9**	nd	nd	nd	nd	nd
Creatinine	0.5-0.9 mg/dl	0.84	0.88	**1.25**	0.96	0.59	0.6	0.58
GFR	>90mL/min/1.73BS	**70**	**62**	**41**	**56**	98	96	100
Sodium	136-145 mmol/L	136	138	135	**134**	138	**128**	**131**
Potassium	3.4-4.5 mmol/L	4.3	4.3	**4.7**	**4.8**	4.1	nd	**4.7**
Calcium	2.2-2.55 mmol/L	2.5	nd	2.29	2.34	2.3	nd	nd

RL=Reference limits; *=Day of admission; ProNP=Pro-brain natriuretic peptide; GFR=Glomerular filtration rate; BS=Body surface; nd=Not determined

Table 3: Possible causes of hyperkinesias excluded in the described patient

Possible cause	Arguments in favor	Arguments against
Side effect of		
Pramipexole	Induces hyperkinesias	Low dose, fentanyl was effective
Citalopram	None	No hyperkinesias reported
Fentanyl	Induces myoclonus	No chorea reported
Tramadol	None	Not reported
Withdrawal of		
Pramipexole	None	Regular intake, steady dosage
Citalopram	None	Regular intake, steady dosage
Fentanyl	None	Regular intake, steady dosage
Tramadol	Dose reduced 4 days prior	None
Paraneoplastic syndrome	None	Not reported, fentanyl effective
Malignoma		
Lymphoma	None	No indication for relapse
Occult neoplasm	None	No indication for malignancy
Meningitis/encephalitis	None	Normal CSF investigation
Stroke, bleeding, thrombosis	None	No acute lesion on cerebral CT or MRI
Seizures	None	Normal EEG, BD and VPA ineffective, CK ⊥
Metabolic defect		
Tetanic seizures	None	Normal serum calcium, normal CK
Hepatic encephalopathy	None	Normal liver function
Thyroid encephalopathy	None	Normal thyroid function tests
Limbic encephalitis	None	Normal MRI, almost normal CSF
Genetic disorder		
MIMODS	Several [table 1]	Fentanyl was effective
Basal ganglia disorder	None	Negative family history, acute manifestation

CNS=Central nervous system; EEG=Electroencephalography; BD=Benzodiazepines; VPA=Valproic acid; CK=Creatine-kinase; CSF=Cerebro-spinal fluid, IMODS=Mitochondrial multi-organ disorder syndrome

relative rest for a few seconds. Biperiden (10 mg) resulted in slight reduction of the intensity of hyperkinesias and induced sleep with snoring. Urine bladder catheterization and release of 500 ml urine were ineffective. Valproic acid (400 mg) intravenously did not reduce hyperkinesias either. Except for somnolence and impaired hearing, neurologic examination was normal.

To exclude the central nervous system (CNS) disorder, cerebral computed tomography (CT) with contrast medium under general anesthesia was carried out. After she had received fentanyl intravenously (15 mg) as a premedication, surprisingly, hyperkinesias immediately and permanently stopped. Nonetheless, she received propofol (80 mg) followed by rocuronium (50 mg) and was intubated. Cerebral CT showed leukoaraiosis and precluded ischemia, bleeding, tumor, or edema. Large cerebral arteries and veins were patent. Lumbar puncture only showed positive oligoclonal bands. Blood tests showed mild anemia, mild renal insufficiency, and mild hyponatremia [Table 2]. Creatine kinase, thyroid function, and procalcitonin were normal. β-microglobulin was 2.3 mg/L (*n*, 0.8–2.2 mg/L). Screening for intoxication with ethanol, barbiturates, benzodiazepines, and tricyclic antidepressants was negative. Flumazenil was not administered as seizures could not definitively be excluded. After extubation at 9.00 am on hd-2, hyperkinesias did not recur. Electroencephalography at 11.00 am on hd-2 did not show paroxysmal activity. Cerebral magnetic resonance imaging on hd-5 showed periventricular leukoaraiosis, pontine gliosis, and lipomatosis of the cerebellar vermis. The patient consented with publication of his case.

Discussion

The presented patient is interesting for immediate resolution of severe, generalized, periodic choroid hyperkinesias by intravenous fentanyl, which had started 9 h earlier and increased over time. Several speculations can be raised to explain hyperkinesias: Overdosing, side effect, or withdrawal of a drug, intoxication, paraneoplastic syndrome, relapse of lymphoma, vascular impairment, meningitis/encephalitis, immune-mediated condition, metabolic impairment, polypharmacy, or genetic disease [Table 3]. Most of these differentials were excluded by history, clinical examination, instrumental investigations, and the effect of fentanyl [Table 3].

Remaining explanations for hyperkinesias were overdosing of pramipexole, serotonin syndrome (SS), opiate withdrawal, or genetic defect. Overdosing of pramipexole is unlikely since the dosage was low and constant, since metabolization

of pramipexole was not impaired, and since fentanyl was effective. Furthermore, pramipexole has been reported to reduce but not to increase L-DOPA-induced dyskinesia.[2] SS was excluded upon the absence of tremor, seizures, dizziness, insomnia, headache, hyperreflexia, arterial hypertension, ocular clonus, or whole body pain.[3] Further, arguments against SS are that hyperkinesias are not a manifestation of SS[3] and that citalopram was taken since years at a constant dosage. Since Hunter's criteria (Hunter serotonin toxicity criteria) or Sternbach's criteria for diagnosing SS were not accomplished, cyproheptadine, the treatment of choice for SS, was not administered.[3] Whether there was an underlying genetic defect which manifested as multi-organ disorder syndrome (MODS) remains speculative. Arguments in favor of an underlying mitochondrial MODS (MIMODS) are the short stature, impaired hearing, cataract, hypothyroidism, diverticulosis, renal insufficiency, arterial hypertension, hyperlipidemia, double kidney, muscle cramps, and polyneuropathy. Lymphoma may be part of MIMODS as well since the prevalence of malignancies is increased in MIMODS.[4] Further, diagnostic work-up into this direction was refused by the patient.

The impressive beneficial effect of fentanyl suggested that opiate deficiency or insensitivity of opiate receptors was responsible for hyperkinesias. The cause of opiate deficiency, however, remains speculative. One explanation could be reduced provision of the drug, but the patient denied having forgotten to fix the transdermal patch. It is also conceivable that resorption of fentanyl via the skin had decreased due to the co-medication or metabolic factors. Nonetheless, discontinuation of tramadol 4 days before onset of hyperkinesias was the most likely cause. Possibly, tramadol withdrawal enhanced the preexisting RLS. From animal studies, it is known that opiates sensitize dopamine receptors.[5] In addition, it is known that dopamine receptor antagonists decrease opiate tolerance.[6] In addition, pramipexole has a beneficial effect on restlessness caused by opiate withdrawal.[7] It is also conceivable that one of the drugs or its combination displaced fentanyl from opiate receptors. Arguments against drug interaction, however, are that they were taken since years and that except for tramadol, the dosage of those affecting the CNS, was low and constant. Another explanation for opiate deficiency could be increased demand of the drug due to upregulation of the number of opiate receptors or tachyphylaxia. However, there was no evidence for increased excretion (diuretic, renal insufficiency) or increased liver metabolism of opiates. She had not received naloxone before admission.

Conclusion

This case shows that discontinuation of tramadol in a patient under pramipexole for RLS may cause severe choroid hyperkinesias over hours, which immediately resolve upon intravenous fentanyl. In patients with RLS treated with pramipexole and chronic pain treated with tramadol and fentanyl, sudden discontinuation of tramadol should be avoided to prevent triggering of restless body syndrome.

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Conflicts of interest
There are no conflicts of interest.

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