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Case Report

Status Epilepticus Caused by Nefopam

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Nefopam, a centrally acting analgesic, has been used to control postoperative pain. Reported adverse effects are anticholinergic, cardiovascular or neuropsychiatric. Neurologic adverse reactions to nefopam are confusion, hallucinations, delirium and convulsions. There are several reports about fatal convulsive seizures, presumably related to nefopam. A 71-year-old man was admitted for surgery for a lumbar spinal stenosis. He was administered intravenous analgesics : ketorolac, tramadol, orphenadrine citrate and nefopam HCl. His back pain was so severe that he hardly slept for several days; he even needed morphine and pethidine. At 4 days of administration of intravenous analgesics, the patient suddenly started generalized tonic-clonic seizures for 15 seconds, and subsequently, status epilepticus; these were not responsive to phenytoin and midazolam. After 3 days of barbiturate coma therapy the seizures were controlled. Convulsive seizures related to nefopam appear as focal, generalized, myoclonic types, or status epilepticus, and are not dose-related manifestations. In our case, the possibility of convulsions caused by other drugs or the misuse of drugs was considered. However, we first identified the introduced drugs and excluded the possibility of an accidental misuse of other drugs. Physicians should be aware of the possible occurrence of unpredictable and serious convulsions when using nefopam.

Key Words : Adverse drug reaction · Barbiturate · Nefopam · Status epilepticus.

INTRODUCTION

Nefopam (Acupan®, Pharmbio Korea, Chungju, Korea), a centrally acting analgesic and cyclic analogue of orphenadrine, has been used to control postoperative pain[1,8]. The precise mechanisms underlying the pharmacological actions of nefopam remain unclear. Its analgesic properties may be related to the inhibition of serotonin, epinephrine, and dopamine synaptosomal uptake[2,3]. Recent evidence also suggests a possible action of nefopam on central neurotransmission mediated by glutamate[9] or by means of a blockade of voltage-sensitive sodium channel receptors[14].

Usual doses of nefopam are 30 to 90 mg per oral three times daily, or 20 mg by intramuscular or slow intravenous injection repeated every 4 to 6 hours, if necessary; maximum recommended doses orally and parenterally are 200 and 120 mg/24 h, respectively[5]. Reported adverse effects are mostly minor, and include drowsiness, nausea, vomiting, and sweating[2]. Potentially more serious adverse effects are confusion, convulsive seizure and tachycardia. There are 5 cases in which patients experienced convulsive seizures[2,11]. Life-threatening adverse effects have been reported in relation to nefopam overdose. These comprise acute neurological impairment with disorientation, generalized seizure, confusion, and cardiac and anticholinergic effects such as mydriasis, tachyarrhythmia, and respiratory depression[2,6,10,12,13]. Fatal acute intoxication was reported for 5 cases in whom generalized seizures were noticed before cardiac arrhythmia[6,10,12,13] and cerebral edema was identified on postmortem brain histology[6].

Neurological adverse effects related to nefopam are usually serious and can occur without overdose[2]. Recently nefopam has been used more commonly for controlling postoperative pain and neuropathic pain[7]. There needs to focus on the rare, but serious neurologic side effects of this drug. The following case presented with status epilepticus that required intensive seizure control.

CASE REPORT

A 71-year-old man was admitted for surgery to correct back and left leg radiating pain. He was diagnosed as having a lumbar spinal stenosis. His pain began 5 days before and was getting so severe that he could barely lie down on his back. His visual analogue scale score was 7 to 8 for back and leg pain. He had diabetes mellitus (DM), which was controlled with an oral hypoglycemic agent (metformin HCl 500 mg qd). Blood glucose was 114 mg/dL at admission. He did not have hypertension or a seizure disorder. During preoperative assessments, the function of

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the lungs, heart, and kidneys were checked, which revealed no remarkable abnormalities. At the time of admission he was taking an oral analgesic and a muscle relaxant (talniflumate 370 mg tid, afloqualone 20 mg tid), which were prescribed 3 days before, when he visited the emergency room in our hospital due to his back and leg pain. After admission, he was administered intravenous (IV) analgesics in addition to oral analgesics : ketorolac (30 mg) and tramadol HCl (50 mg) injected bid; orphenadrine citrate (120 mg) and nefopam HCl (80 mg) mixed with 1 L of plasma solution infused at 42 mL/hour; morphine (2.5 mg) and pethidine HCl (50 mg), injected once on the 2nd and the 3rd day of admission, respectively. Fasting blood glucose was 174 mg/dL on the 2nd day and 109 mg/dL on the 3rd day of admission. At 4 days after admission, a nurse performing rounds checked the IV line when the patient had been infusing IV orphenadrine citrate and nefopam HCl solution; she injected 2 mL of saline into the line to flush it. Thirty seconds after the nurse's round, the patient started generalized tonic-clonic seizures, which lasted for 15 seconds. The seizures ceased with the administration of 4 mg IV lorazepam. Blood pressure was 150/90 mm Hg and pulse rate was 78/min with a regular sinus rhythm; there was no fever. After the 1st seizure attack, blood glucose was 159 mg/dL and cardiac enzymes were unremarkable : troponin I 0.424 ng/mL and CK-MB 1.88 ng/mL; serum sodium was 135 mEq/L. Thirty minutes after the 1st attack of seizures, he again developed seizures, primarily of the myoclonic type. Diffusion weighted and FLAIR brain MRI were performed, which showed no cerebral infarctions or other structural lesions. Serum calcium was 9.4 mg/dL and phosphorus was 4.1 mg/dL, which were within normal ranges. Repeated injections of lorazepam and phenytoin loading failed to control the seizures. He was intubated and transferred to the intensive care unit. Anticonvulsant loading with phenytoin (500 mg) followed by continuous midazolam infusion at a rate of 0.1 mg/kg/hour was performed with mechanical ventilation, but the dyskinetic contraction of the perioral muscles and both arms was not resolved. Barbiturate coma therapy commenced with the loading of pentobarbital (2.5 mg/kg) every 15 minutes for one hour, 10 mg/kg/hour for the next 3 hours, and a maintenance dose of 3 mg/kg/hour after that. We confirmed burst suppression on electroencephalography (EEG), and slowly tapered the pentobarbital out for 72 hours. He recovered completely, without additional seizures, and did not complain of back or leg pain thereafter.

DISCUSSION

A report based on the French Pharmacovigilance database from 1995 to 2004 described adverse drug reactions (ADR) to nefopam[2]. This report divided the ADRs as 'expected' and 'unexpected'. The 'expected' ADRs were sweating, nausea, tachycardia, malaise and vomiting; the 'unexpected' ADRs were hallucinations, confusion, cutaneous, and anaphylactic ADRs. They reported the 'serious unexpected neuropsychiatric ADRs' as confusion, hallucinations, convulsions, delirium and included a case of a 72-year-old with fatal convulsions[2]. Nefopam has been reported to have a prominent anticholinergic effect[15]. An increase in cholinergic activity can be expected and it is related with acute intoxication[4]. Serious side effects related with nefopam are neuropsychiatric and cardiovascular. Neuro-cardiovascular ADRs have been reported from acute intoxication and overdose due to abuse. Both acute intoxication and overdose can be potentially fatal. The fatal cases presented with confusion, convulsions, hallucinations, tachycardia, bundle branch blocks, or cardiac arrest[6,12,13]. However, the issue is that the serious neurological ADRs can occur whilst remaining within the therapeutic dosage[2]. Status epilepticus was not likely related to acute intoxication with nefopam in our case. Previous reports of nefopam-related convulsions or seizures are as follows : a 65-year-old female presented with petit mal seizures, which developed only when she took nefopam at 60 mg per day for 5 days. She had also been taking carbamazepine because of an underlying seizure disorder. There was no recurrence of seizures after withdrawal of nefopam[11]. A 17-year-old male developed convulsions after taking 60 mg of nefopam; he had no underlying disease[11]. A 25-year-old female presented with repeated and prolonged grand mal seizures while taking 120 mg of nefopam daily for back pain[11]. Additionally, a 40-year-old female was taking nefopam (120 mg per day) for 9 months. She presented with grand mal convulsions three times. She had been taking amitriptyline (75 mg) daily. A 72-year-old man suffering from nephritic colic experienced convulsions 30 minutes following nefopam administration. Nefopam was the only drug administered to this patient without relevant medical history[2]. Considering the reported cases, convulsive seizures can develop within the recommended dose of nefopam, present as focal, generalized, or myoclonic types or status epilepticus, and are not dose-related manifestations.

In our case orphenadrine and nefopam were being infused when the patient suffered seizures. Nefopam may cause seizures. Orphenadrine has not yet been reported to cause convulsive seizures. We ruled out general medical conditions to developing this serious phenomenon. Previously ingested drugs, other than nefopam, that may have caused seizures were considered. The possibility of convulsions caused by pethidine is low because it was administered only once a day before the attack. Ketorolac and tramadol are not reported to induce convulsions. However, an investigation at the manufacturing company resulted in the recommendation to avoid using ketorolac and nefopam simultaneously (personal communication). This is not yet represented in reports regarding their clinical use. The misuse of drugs, other than saline for IV line flushing, is unlikely; when the patient developed seizures, we first identified the introduced drugs and excluded the possibility of an accidental misuse of other drugs.

Recently nefopam has been used more commonly, even for cases with neuropathic pain[7]. However this unexpected and serious side effect seems to be overlooked by physicians.

CONCLUSION

Physicians should be aware of the possible occurrence of unpredictable and serious convulsions when using nefopam, especially because these can occur at normal therapeutic dosages.

References

1. Beaver WT, Feise GA : A comparison of the analgesic effect of intramuscular nefopam and morphine in patients with postoperative pain. **J Clin Pharmacol 17 (10 Pt 1)** : 579-591, 1977
2. Durrieu G, Olivier P, Bagheri H, Montastruc JL : French Network of Pharmacovigilance Centers : overview of adverse reactions to nefopam : an analysis of the French Pharmacovigilance database. **Fundam Clin Pharmacol 21** : 555-558, 2007
3. Fuller RW, Snoddy HD : Evaluation of nefopam as a monoamine uptake inhibitor in vivo in mice. **Neuropharmacology 32** : 995-999, 1993
4. Godier A, Babinet A, el Metaoua S, Fulgencio JP, Bonnet F : [A new cause of postoperative confusion syndrome : nefopam]. **Ann Fr Anesth Reanim 21** : 538-539, 2002
5. Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS : Nefopam : a review of its pharmacological properties and therapeutic efficacy. **Drugs 19** : 249-267, 1980
6. Kerr DE, Fletcher AK : Fatal nefopam overdose. **Emerg Med J 27** : 407-408, 2010
7. Kim KH, Abdi S : Rediscovery of nefopam for the treatment of neuropathic pain. **Korean J Pain 27** : 103-111, 2014
8. Mimoz O, Incagnoli P, Josse C, Gillon MC, Kuhlman L, Mirand A, et al. : Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. **Anaesthesia 56** : 520-525, 2001
9. Novelli A, Díaz-Trelles R, Groppetti A, Fernández-Sánchez MT : Nefopam inhibits calcium influx, cGMP formation, and NMDA receptor-dependent neurotoxicity following activation of voltage sensitive calcium channels. **Amino Acids 28** : 183-191, 2005
10. Piercy DM, Cumming JA, Dawling S, Henry JA : Death due to overdose of nefopam. **Br Med J (Clin Res Ed) 283** : 1508-1509, 1981
11. Pillans PI, Woods DJ : Adverse reactions associated with nefopam. **N Z Med J 108** : 382-384, 1995
12. Tracqui A, Berthelon L, Ludes B : Fatal overdosage with nefopam (Acupan). **J Anal Toxicol 26** : 239-243, 2002
13. Urwin SC, Smith HS : Fatal nefopam overdose. **Br J Anaesth 83** : 501-502, 1999
14. Verleye M, André N, Heulard I, Gillardin JM : Nefopam blocks voltage-sensitive sodium channels and modulates glutamatergic transmission in rodents. **Brain Res 1013** : 249-255, 2004
15. Villier C, Mallaret MP : Nefopam abuse. **Ann Pharmacother 36** : 1564-1566, 2002