

Consalvo Mattia
Sandro Mazzaferro
Flaminia Coluzzi
Marta Luzi

Respiratory depression following iatrogenic tramadol overuse in a patient with chronic renal failure

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C. Mattia (✉) • F. Coluzzi • M. Luzi
Department of Anaesthesiology,
Intensive Care Medicine and Pain Therapy,
La Sapienza University,
Viale del Policlinico 155, I-00161 Rome, Italy
e-mail: consalvo.mattia@uniroma1.it

S. Mazzaferro
Department of Clinical Science,
La Sapienza University, Rome, Italy

Abstract We describe a case of tramadol-related respiratory depression in a 69-year-old man, admitted to our hospital because of severe anemia and melena in the context of chronic renal failure and dialysis treatment. He complained of back pain due to spondylodiscitis, and analgesic therapy was established with tramadol (200 mg/day intravenously). The patient received a total daily dose of 400 mg tramadol because of a therapeutic mistake. The patient tolerated this dosage for about two days before experiencing symptoms of opioid overdose that disappeared after naloxone treatment. In contrast with other opioids, few cases of tramadol-related

respiratory depression have been described, in patients with impaired renal function, as tramadol is mainly excreted by kidneys. This case report emphasizes the need to avoid tramadol overuse in patients with renal failure, who could experience side effects such as respiratory depression.

Key words Chronic renal failure • Tramadol • Respiratory depression

Introduction

Tramadol hydrochloride is a centrally acting analgesic drug that is widely used in the treatment of pain. It exhibits good analgesic efficacy and a potency comparable to codeine [1]. Besides its proven clinical efficacy, tramadol is a safe drug with few cardiovascular side effects; respiratory depression and drug abuse and dependency are of minor clinical relevance, unlike for some other opioids [2].

We describe a case of respiratory depression that ensued in a 69-year-old man with renal failure who was accidentally given a high dosage of tramadol during hospitalization.

Case report

A 69-year-old man (72 kg) was admitted to our hospital because of severe anemia (Hb, 5.7 g/dl) and melena. The patient had an 8-year history of hypertension. He suffered from chronic renal failure and had been undergoing dialysis treatment every other day, for 4 months. Fifteen days before admission, he received the last of four transfusions, because of severe anemia, likely due to kidney dysfunction. Three months before admission, he was evaluated at our hospital, in the Infectious Disease Department, for back spondylodiscitis.

On admission, blood pressure was 100/60, pulse was arrhythmic, heart rate was 75 beats/min and respiration rate was 12 per min. On physical examination, the lungs were clear and the abdomen was normal. A grade 4 systolic ejection murmur was present at the mitralic area. The results of laboratory tests are shown in Table 1.

On admission, he was treated with antibiotics, proton pump inhibitors, diuretics, erythropoietin, iron and calcium carbonate.

Esophagogastroduodenoscopy revealed two active ulcers, in the pyloric area and in the first duodenal portion, and gastritis of the antrum. Biopsies were negative for *Helicobacter pylori*.

Since the patient complained of back pain, a magnetic resonance imaging examination of the vertebral column was performed. Gadolinium-enhanced images, showed spondylodiscitis of T1-T2, T7-T8 and T10-T11 segments.

Table 1 Clinical parameter of a 69-year-old man with chronic renal failure, severe anemia and melena

	Value	Normal range
Hematologic values		
Hematocrit, %	19.5	35–50.5
Hemoglobin, g/dl	6.4	12–16.3
Red blood cells, $10^3/\text{mm}^3$	2280	4000–5700
White blood cells, mm^3	7080	4000–10000
Platelets, mm^3	312 000	140000–400000
Blood chemistry values		
Urea nitrogen, mg/dl	37	11–23
Creatinine, mg/dl	4.7	0.7–1.5
Glucose, mg/dl	65	50–100
Sodium, mmol/l	136	135–145
Potassium, mmol/l	6.4	3.9–5.2
Fibrinogen mg/dl	526	200–400
Partial thromboplastin time	1.32	0.8–1.2
Prothrombin time	13.6	10–14
INR	1.10	0.8–1.2

Table 2 Arterial blood gas analysis 2 days after the erratic administration of tramadol at 400 mg/day to a patient with chronic renal failure, in relation to subsequent therapy with naloxone and dialysis

Time	Clinical notes	pH	PaO ₂ , mmHg	PaCO ₂ , mmHg
8:30 a.m.	Respiratory depression	7.2	28	85
8:50 a.m.	Naloxone 0.4 mg i.v.; O ₂ therapy, 40%	7.2	37	50
9:40 a.m.	Naloxone 0.4 mg i.v.; O ₂ therapy, 40%	7.3	33	44
10:00 a.m.	Naloxone 0.4 mg in 250 ml saline infusion			
	Dialysis started for 2.5 h			
12:00 p.m.	Naloxone 0.4 mg i.v.; O ₂ therapy, 40%	7.2	37	50
12:40 p.m.	O ₂ therapy, 40%	7.3	38	52
4:30 p.m.	O ₂ therapy, 35%	7.3	86	42
8:30 a.m.	Air	7.3	53	44

Therefore, he was prescribed tramadol (Contramal) X gtt (25 mg three times per day; 75 mg/day) and bromazepam (Lexotan) XV gtt (2.5 mg) at bedtime. Pain relief was obtained only for a few days; thus, the oral dose of tramadol was increased to 150 mg/day.

Because ineffective pain management, analgesic therapy had to be changed to 200 mg/day tramadol intravenously (4 50-mg phials in 500 ml saline, 21 ml/h continuous intravenous infusion with Baxter elastomeric pump). This therapy was started after dialysis treatment.

Forty-eight hours after the start of analgesic infusion, the patient was found stuporous, arrhythmic and bradypnoic. Neurological examination showed pin-point pupils, purposeful movements to painful stimuli and no response to verbal stimuli. Arterial blood gas analysis showed severe abnormalities (Table 2).

A therapeutic mistake was revealed: 100-mg, instead of 50-mg phials had been administered. Thus, the patient received a tramadol dose of 400 mg/day instead of 200 mg/day. Tramadol was suddenly stopped and 4 mg naloxone (Narcan) was injected intravenously. Oxygen therapy was started using Ventimask 40% (O₂, 8 l/min). The patient regained consciousness, pupils normalized and respiratory rate became 15/min.

About one hour later, blood gas abnormalities persisted and a new dose of naloxone (0.4 mg) was given. An infusion with naloxone (0.4 mg in 250 ml saline over 2 h) was recommended.

After 2.5 h of dialysis, the patient appeared soporose, with respiratory depression, myotic pupils and flexion motor response to painful stimuli. Clinical conditions and blood gas values improved after another 0.4-mg dose of naloxone. At 1.00 p.m., a new evaluation showed the patient awake and in oxygen therapy. At 4.30 p.m., the oxygen rate was decreased (Ventimask 35%) and blood gases were analyzed again. The day after, blood gases had normalized, though an oxygen deficit remained (Table 2).

Discussion

In contrast to other opioids, tramadol is unlikely to produce clinically relevant respiratory depression [3]: two cases have been reported in small children, and one case has been described in a patient with impaired renal function [4]. Tramadol is a centrally acting analgesic, structurally related to codeine. Its effects are mediated via two different mechanisms that act synergistically to produce analgesia. Specifically, it is produced as a racemic mixture and the two enantiomers have different opioid-receptor affinities and differently inhibit monoaminergic reuptake and metabolic pathways. The (+) enantiomer has a slightly higher affinity for μ -receptors, and a greater inhibition of serotonin reuptake than does the (-) enantiomer. Conversely, the (-) enantiomer better inhibits noradrenaline reuptake than the (+) enantiomer [5].

After oral administration, tramadol is excreted by the kidneys (90%) and in the feces (10%). The cumulative renal excretion of unchanged tramadol was 16% (i.v.) and 13% (p.o.), suggesting that approximately 85% of a dose is metabolized [3]. In patients with moderately impaired renal function (creatinine clearance, 10–30 ml/min), the elimination half-life of tramadol increases 1.5- or 2-fold, therefore the dosing interval should be increased to 12 hours with a maximum daily dose of 200 mg [6].

Our patient received a total daily dose of 400 mg tramadol, because of a therapeutic mistake. Despite severe renal failure requiring dialysis, the patient did not complain of any side effects during the first two days of administration; then he experienced symptoms of opioid overdose, which disappeared after naloxone treatment.

Although the combination of the two tramadol enantiomers produces better analgesia, as they act synergistically, their interaction does not result in similar additional side effects [5]. On the contrary, synergistic effects of the two enantiomers produce less intense side effects for the same

level of analgesia. For respiratory depression, in particular, the two enantiomers seem to block each other's effects [6].

In this patient with renal failure, respiratory depression occurred as a consequence of accidental tramadol overuse. In fact, dialysis was programmed every other day, but during the 48 hours of tramadol infusion, he did not undergo dialysis, resulting in plasmatic accumulation of the drug. However, when performed, dialysis was ineffective to eliminate the drug, as the clearance is only 7% of adsorbed dose. A dosage of 400 mg/day i.v. or higher (up to 600 mg/day) could be well tolerated in patients with normal hepatic and renal functions.

Most experimental studies, using naloxone as a measure of opioid involvement in tramadol analgesic effect, showed only a partial antagonism [7]. Conversely, yohimbine, an α -adrenergic antagonist, reduced the analgesic effect of tramadol in rats. Similar results were obtained in healthy volunteers, confirming the role of mechanisms other than opioid receptor binding in the antinociceptive effect of tramadol.

Recent evidence of effectiveness of naloxone (0.1 mg/kg) in reversing tramadol-related respiratory depression in cats [8] is consistent with the finding of the effectiveness of naloxone in antagonizing respiratory side effects complained of by our patients, strongly supporting that they are mediated by μ -opioid-receptor agonism. More specifically, respiratory depression due to tramadol overuse could be consistent with the excessive build up of its major opioid component, i.e. the (+) enantiomer of the O-desmethyl (M1) metabolite, and not a build up of tramadol itself [9].

Recommendations to use tramadol (-) enantiomer alone in the treatment of patients with impaired renal or hepatic functions are based on the idea that this tramadol component lacking μ -opioid-receptor agonism would decrease the extent of respiratory depression. However, this would also lead to a significantly lower analgesic effect, mostly related to the tramadol affinity for the μ -opioid receptors and could also cause other side effects [10].

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