Respiratory Depression with Tramadol in a Patient with Renal Impairment and CYP2D6 Gene Duplication

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We observed opioid-related respiratory depression in a patient receiving tramadol via patient-controlled analgesia. Predisposing factors were the patient’s genetic background and renal impairment. Complete recovery occurred after naloxone administration, thus confirming opioid intoxication. Analysis of the patient’s genotype revealed a CYP2D6 gene duplication resulting in ultra-rapid metabolism of tramadol to its active metabolite (+)-O-desmethyltramadol. Concomitant renal impairment resulting in decreased metabolite clearance enhanced opioid toxicity. This genetic CYP2D6 variant is particularly common in specific ethnic populations and should be a future diagnostic target whenever administration of tramadol or codeine is anticipated, as both drugs are subject to a comparable CYP2D6-dependent metabolism.

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Tramadol, a racemic opioid, is widely used for acute and chronic pain management. Like codeine, it is classified as a World Health Organization II analgesic, as its potential for respiratory depression and development of tolerance, dependence and abuse is considered to be low.1,2 Hepatic cytochrome CYP2D6 metabolizes both analgesics, which are opioid prodrugs to their active metabolites, codeine to morphine and tramadol to O-desmethyltramadol (ODT), which both have analgesic properties.1 (+)ODT has been shown to have an affinity for μ-opioid receptors that is approximately 200 times more than that of the parent drug. Thus, (+)ODT is largely responsible for opioid receptor-mediated analgesia, whereas (+)- and (−)tramadol contribute to analgesia by inhibition of reuptake of serotonin and noradrenaline.3

Genetic variants of CYP2D6 significantly influence codeine and tramadol metabolism. Genetically determined poor metabolizers of CYP2D6 experience reduced analgesia owing to deficient enzyme activity and negligible formation of (+)ODT.3,4 The clinical implications for subjects carrying CYP2D6 duplications, so-called “ultra rapid metabolizers” (UM), displaying increased enzyme activity are sparse for tramadol. However, some data are available for codeine-induced side effects in UM genotypes.

A patient suffering from respiratory depression is presented, in whom an analysis of plasma concentrations of tramadol and ODT enantiomers and genetic profiling were performed.

CASE REPORT

A 66-yr-old man (70 kg, 172 cm, ASA II classification, regular medication of nifedipine, no further comorbidity) was scheduled for surgery due to a local recurring renal carcinoma. He reported two uneventful previous surgeries 4 yr ago. Anesthesia and postoperative pain management via IV patient-controlled analgesia (PCA) were administered without complications.

Anesthesia was performed according to the department’s standard protocol using fentanyl 150 μg, propofol 2 mg/kg, and cisatracurium 10 mg for induction and remifentanil, isoflurane, and cisatracurium for maintenance of anesthesia. Surgery was uneventful and the patient’s vital variables remained within the normal range. Crystalloid 1500 and 1000 mL colloid fluids were administered. Before the end of surgery, the patient was given tramadol 200 mg IV for postoperative analgesia (time point 0, Fig. 1).

In the recovery room, the patient complained of severe pain, described on a numeric rating scale (range, 0–100) as 80 at rest. Thus, two further boluses of tramadol 50 mg were administered within 35 min. A PCA-device was connected to the IV line and the patient self-administered bolus doses of tramadol 20 mg and dipyrone 200 mg (delivery time: 1.5 min, lockout time: 8 min). Because of continuing pain, the patient used the PCA-device frequently during the first hour (demanded/delivered bolus doses: 17/4). At discharge from the recovery room, his numeric rating scale had decreased to 40 at rest. He was conscious with heart rate, arterial blood pressure, and SaO2 within normal range.

At 5 h, the bedside visit from the pain service revealed the following results: Conscious patient, pain intensity of 10 at rest and 30 at deep inspiration or coughing. Forty-eight demanded and 11 delivered PCA doses were recorded. No side effects such as nausea, vomiting, or sedation had occurred.
At 7.5 h, the patient was tired, but responsive. No further tramadol doses had been demanded. Because the patient seemed increasingly drowsy, the anesthesiologist on duty reduced the PCA bolus dose to tramadol 10 mg. Additional O₂ via nasal tube was administered.

At 10.5 h, the patient was unresponsive, presenting with bradypnea (respiratory rate of 2–3/min with 4 L O₂/min via nasal tube), narrow pupils, and not reacting to painful stimuli (Fig. 1). There were no demands from the PCA device during the last 6.5 h. Assisted mask ventilation was established, and 0.4 mg naloxone was injected IV. The patient regained consciousness and his respiration normalized. He was transferred to the intensive care unit for further monitoring. His recovery was uneventful.

Laboratory analysis revealed a preoperative creatinine 195.4 μmol/L, urea 61 mmol/L, with a reduced creatinine clearance (method of Cockcroft and Gault) of 30 mL/min. His postoperative creatinine values were between 214.7 and 191.8 μmol/L.

**DRUG CONCENTRATIONS AND GENOTYPING**

Blood samples were drawn 30, 90, and 180 min after the initial tramadol administration. After the administration of naloxone, further blood drawings, samples of the PCA syringe contents, the crystalloid infusion, and the infusion line were retained for toxicological investigation.

Toxicology revealed no additional sedating drug or opioid in the last blood sample or in the fluid samples taken from the infusion, the infusion line, or the PCA syringe. Filling of the PCA device was as expected, with a tramadol concentration of 20 mg/mL. Plasma concentrations of tramadol and ODT enantiomers measured by liquid chromatography-tandem mass spectrometry are displayed in Figure 1.

Genotyping by polymerase chain reaction and real-time polymerase chain reaction for the poor-metabolizer-associated CYP2D6*3, *4, *5, *6, *7, *8, polymorphisms, and the intermediate-metabolizer-related CYP2D6*10 and *41 polymorphisms resulted in wild-type sequences, whereas the duplication/multiduplication assay confirmed an UM genotype.

**DISCUSSION**

Although tramadol-related respiratory depression has been considered of minor clinical relevance, there are some reports of tramadol abuse, dependence, and
poisoning. Most cases were fatalities due to a combination of drugs.7–9

In a clinical setting, respiratory depression is extremely rare. Compared with oxycodone 0.04 mg/kg and meperidine (pethidine) 0.6 mg/kg, an approximately equipotent dose of tramadol 0.6 mg/kg has not been associated with impaired respiratory effects in spontaneously breathing anesthetized patients.10,11 Hullett et al.12 highlighted the advantage of tramadol compared with morphine in children undergoing adenotonsillectomy for obstructive sleep apnea. There were fewer episodes of desaturation up to 3 h postoperatively, with 26% fewer episodes in the second hour. Pain and sedation scores were comparable. However, animal trials demonstrated that tramadol increased the apneic threshold and decreased the total CO2 sensitivity.13 Naloxone completely reversed these effects, whereas pretreatment with naloxone preserved more than half of the expected ventilatory depression in these animals. Human experimental studies confirmed that tramadol 100 mg p.o. reduced the ventilatory CO2 response by 30%, acting at the respiratory integrating centers within the brainstem.14 However, subjects were healthy volunteers without pain and surgical stress, and therefore some caution is suggested in extrapolating the findings to perioperative patients.14

In none of the few clinical cases of respiratory depression reported in patients under tramadol analgesia was the genetic background analyzed as a possible contributing variable. Barnung et al.15 described a 75-yr-old man with chronic renal failure (creatinine 183–317 μmol/L). Respiratory depression requiring naloxone reversal occurred after dose escalation from 3 × 100 mg to 4 × 100 mg/d; renal failure was considered the cause of the severe side effect. Two further cases were observed in children.16

Genetic analysis was, however, performed in three cases of codeine overdose: Comparable to tramadol, O-demethylation of the prodrug codeine into its metabolite morphine is essential for its opioid activity and, thus, the CYP2D6 genotype specifically influences the efficacy and side effects of both weak opioids, codeine and tramadol.

Case 1

A 72-yr-old man developed life-threatening respiratory depression after a 3-day treatment with codeine 3 × 25 mg/d for cough relief. The adverse event was mediated by (a) high concentrations of codeine’s active metabolite morphine owing to an UM genotype, (b) transient reduction in renal function with reduced clearance of the metabolites, and (c) comedication blocking CYP3A4 (clarithromycin and voriconazole), an alternative metabolic pathway of codeine.17

Case 2

A breast-fed neonate whose mother received codeine 30 mg/d died on day 13 because of morphine poisoning. The mother had an UM genotype and, thus, high amounts of morphine were formed from codeine which then were transferred to the baby.18

Case 3

A 29-mo-old previously healthy child experienced apnea resulting in brain injury after a dose of acetaminophen and codeine 2 days after an uneventful anesthesia for tonsillectomy.19 Genotyping revealed the UM status. The child was of North African descent, which increased the risk of CYP2D6 gene duplication compared with Caucasian subjects nearly threefold.20 The prevalence of UM status varies widely among different geographical regions of the world (Table 1).

An experimental trial in volunteers confirmed that a single dose of codeine 30 mg resulted in 50% higher plasma concentrations of morphine and its glucuronides in UMs compared with extensive metabolizers (individuals with normal CYP2D6 activity).21 Comparable results were obtained from patients receiving tramadol for postoperative pain control. Area under the concentration–time-curve of (+)ODT was about 2–4 times higher in UMs compared with extensive metabolizers.5 In contrast to these UMs, the present patient with impaired renal function displayed double the (+)ODT concentrations 30 min after the initial loading dose. At 3 h, (+)ODT increased nearly threefold compared with mean concentrations of other UMs.5

Elimination of tramadol as well as ODT is slow, and characterized by an elimination half-life of 5–6 h.22 In patients suffering from renal impairment, tramadol’s elimination half-life is prolonged 1.5–2 times.16 The question arises why respiratory failure did not occur earlier during the postoperative period. (+)ODT plasma concentrations already peaked after 3 h and remained stable for up to 10.5 h. This lag period needed for the transfer of the hydrophilic active opioid compound across the blood–brain barrier seems to be the key variable responsible for this delayed onset of central nervous system (CNS) toxicity. The slow equilibration between peaking plasma concentrations of (+)ODT and the brain as effect compartment has been reported for morphine and its metabolite, morphine-6-glucuronide (M6G). Because of its water-soluble properties, transfer between blood and CNS is slow. In cases of normal renal function,
M6G is eliminated before accumulating sufficiently in the brain to cause intoxication. Multiple dosing and renal failure were specific risk factors for morphine toxicity.\textsuperscript{23} However, a fatal respiratory depression after multiple IV morphine injections was also observed in a patient without any renal problems and was attributed solely to clinically relevant, delayed CNS effects compared with plasma concentrations of M6G.\textsuperscript{24} Further variables influencing sensitivity to opioids and opioid-induced respiratory effects, such as the genetic background (e.g., deriving from sex steroids) and sex differences in morphine analgesia, have been described.\textsuperscript{25,26} In women, a greater morphine potency has been observed; however, with a slower onset and offset than in men.\textsuperscript{26}

Whether tramadol, as well as codeine-induced respiratory depression in adults, is also possible without any renal impairment cannot be concluded from the available data. In contrast, small children seem to be specifically prone to the excessive metabolite concentrations induced by the UM genotype.\textsuperscript{18,19}

Furthermore, clinical practice shows that activity in the patient’s surrounding, e.g., in the recovery room, during transfer to the peripheral ward and during frequent rounds in the early postoperative period, are stimuli, which can keep the patient awake. On the ward, with significantly less disturbance, opioid-induced sedation becomes more prevalent. However, an experienced anesthesiologist might have recognized impending respiratory depression earlier. From a retrospective view, knowledge of the patient’s renal impairment, regional analgesic technique or the use of a different opioid (e.g., piritramide, and hydromorphone) would have been more advisable.

Overall, this case confirms that CYP2D6 duplication resulting in highly increased transformation to the active metabolite (+)ODT and concomitant renal impairment slowing (+)ODT clearance predispose patients to life-threatening opioid intoxication by tramadol’s active metabolite. CNS effects might be significantly delayed because of slow plasma–brain equilibration of the hydrophilic metabolite. Repeated tramadol administration should be discouraged in patients of the UM genotype and with concomitant renal impairment, until more safety data are available. Of course, it has to be acknowledged that in daily clinical practice, information about the metabolizer status is not readily available. Hopefully, in the future, a more individualized analgesic therapy will become available with the help of genotyping.

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REFERENCES