Addiction and seizure ability of tramadol in high-risk patients

Sir,

I read with interest a recently published article by Raiger et al. entitled, ‘Seizures after intravenous tramadol given as premedication’.\[1\] As tramadol poisoning is common in Iran and we have published articles on the topic of tramadol poisoning,\[2-8\] I read the article carefully and have several concerns.

The authors have reported a case of seizure after administration of 100 mg tramadol in a female patient with a history of epilepsy. The authors state that it is the first case of seizure due to tramadol administration in India. Although the rate of seizure due to tramadol seems quite low in India, it is higher in some countries such as Iran, and can reach up to 30% in cases of tramadol overdose.\[2,3\] In our previous study, the smallest reported dose associated with seizure was 200 mg.\[2\] Other studies have reported the smallest dose of tramadol-associated seizure to be as low as 300 mg.\[4\]

Tramadol is a racemic mixture of enantiomers of tramadol: (+) and (−) tramadol. Each of these enantiomers has a different affinity for the mu and delta receptors and also has different effects on the re-uptake of serotonin and norepinephrine.\[5\] Depending on their ratio, they affect seizure threshold differently. Tramadol is metabolised to its active metabolite, o-desmethyltramadol and multiple non-active metabolites. O-Desmethyltramadol has a different affinity for the receptors and biogenic amine re-uptake, and may affect the seizure threshold. In addition, because liver metabolism of tramadol is prone to genetic polymorphisms, any co-ingested drug with the potential to affect Cytochrome P450 (CYP) enzymes will affect the tramadol peak blood levels and their seizure thresholds. As the reported case has received anti-epileptic drugs for treatment of epilepsy, it may affect the CYP enzymes and decrease the seizure threshold. Our previous study has shown that there is no significant correlation between a higher tramadol concentration and the presence of seizure, in cases of poisoning, which may indicate that even a low dose of tramadol can induce seizure in high-risk patients.\[2\]

The authors also state that tramadol has a lower ability for abuse or addiction. I believe this is true, but I would like to draw attention to the increasing abuse of tramadol in our society. Moreover, it seems that people from Iran and other Middle East countries are more likely to be ultra-rapid CYP2D6 metabolisers. In Iran, the frequency of the CYP2D6 ultra-rapid metabolisers is up to 12% of the population, so we expect that people in this region are more susceptible to opioid effects, such as dependency and sedation.\[6\] In addition, in our previous study, it was revealed that 44% of the tramadol-poisoned cases were chronic tramadol abusers and 24% of them were addicted to other illegal drugs.\[3\] In another study, 7.4% of the cases had used tramadol for replacement of other opioid drugs and 29.6% of the cases abused tramadol for euphoria.\[2\] These data show us that in Iran tramadol is increasingly abused by opioid-addicted subjects and it is an interesting material or drug for abuse similar to other illegal agents.\[5-7\] We encourage examination of the addiction ability of tramadol by further studies as well as providing programs, to teach doctors to prescribe tramadol with more caution in patients having a high-risk of seizure.

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Sir,

A 16-year-old American Society of Anesthesiologists class I male patient weighing 50 kg with dorsolumbar scoliosis, with Marfan's syndrome and mitral valve regurgitation, was scheduled for posterior instrumentation and fixation. His pre-operative investigations were within normal limits. In the operating room, all routine monitors were attached to the patient and general anaesthesia was induced with fentanyl 100 mcg, propofol 100 mg and vecuronium 5 mg. The patient's trachea was intubated with a cuffed orotracheal tube no. 7 mm and he was positioned prone for surgery with necessary precautions. As an intraoperative motor-evoked potentials monitoring was planned, anaesthesia was maintained with total intravenous anaesthesia (TIVA) with propofol infusion (100 mcg/kg/min). Two hours after starting TIVA, milky pink urine was observed. Surgeons were asked to stop the surgery and look for any pressure to the kidneys. As we had internet access in the operating area, a net search revealed that TIVA could be the suspected cause of the milky pink urine. TIVA was immediately withheld and the urine sample was sent for analysis. As the quantity of urine was adequate, and vital parameters of the patient were within normal limits, the surgeons were asked to re-commence the surgery. One hour after stopping propofol infusion, the urine started to become clear and, 2 h later, the urine was completely clear [Figure 1]. The urine sample was sent for analysis again on the first post-operative day. Post-operative recovery was uneventful. Intraoperative urine analysis revealed uric acid and, in the post-operative urine sample, there was no presence of uric acid. There were no pus cells or casts in the intraoperative as well as in the post-operative samples. Rest of the renal functions were within normal limits in both the samples. The patient was discharged home after 1 week.

Three types of colored urine have been described in the literature: Green, [1-3] white [4] and milky pink. [5,6] The true incidence of this urine discoloration is not known. Green urine is attributed to phenol metabolites, [3] which are excreted renally. White urine was reported by Nates et al. [4] in four patients, and they attributed it to the vehicle of propofol emulsion. Milky pink urine was observed initially by Masuda et al. [5] in 9 patients, and they attributed it to intraoperative hypotension and oliguria that cause accumulation of propofol and its metabolite in urine. They inferred that all patients with milky urine were those patients who were posted in the late afternoon and were relatively dehydrated. However, in our patient, there was no episode of intraoperative hypotension or oligouria, and the surgery was scheduled first in the day. Masuda et al., [6] in their study of 23 patients, performed a urine analysis of all patients undergoing surgeries with TIVA (n = 11) and sevoflurane (n = 12) anaesthesia. They inferred that all patients on TIVA had increased urine uric acid. However, only two of 11 patients had milky urine. Milky color urine is observed more frequently in operation theatres with ambient temperature less than 24°C. [6] The reason attributed to this is that decreased temperature causes decreased solubility to uric acid crystals.

In our patient, the most probable cause seems crystallization of uric acid in the cold ambient temperature of the operating room, which was 18°C. Urine discoloration is self-limiting and transient and is not associated with any long-term renal damage.