

## 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'.<sup>[1]</sup> As tramadol poisoning is common in Iran and we have published articles on the topic of tramadol poisoning,<sup>[2-8]</sup> 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.<sup>[2,3]</sup> In our previous study, the smallest reported dose associated with seizure was 200 mg.<sup>[2]</sup> Other studies have reported the smallest dose of tramadol-associated seizure to be as low as 300 mg.<sup>[4]</sup>

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.<sup>[3]</sup> 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.<sup>[2]</sup>

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.<sup>[8]</sup> 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.<sup>[3]</sup> 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.<sup>[2]</sup> 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.<sup>[5-7]</sup> 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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