Tramadol hydrochloride is a synthetic analogue of codeine used for the treatment of moderate to severe pain. It has a dual mechanism of action. Tramadol and its active metabolite, O-desmethyltramadol, bind to μ-opioid receptors thus exerting their effect on GABAergic transmission. They also inhibit the reuptake of 5-hydroxy-tryptamine (serotonin) and noradrenaline (1). Studies have shown that tramadol-induced seizures can occur at therapeutic dosage (2). Seizure is rare (<1%) in therapeutic doses (3). Seizure can induce shoulder dislocation, mostly posterior type, in epileptic patients (4).

In a study by Rethnam et al, they found that about 50% of patients with a history of shoulder dislocation faced shoulder dislocation following the seizure (4). Since 2002 tramadol is used in Iran after the Food and Drug Administration’s approval (5). Concurrent with the introduction of the drug into the market, its abuse by different age groups, especially youths, has been reported (5,6). This study aimed to evaluate the shoulder dislocation following tramadol-induced seizure and its potential difference with other shoulder dislocations.

Case Report

**First case**
A 27-year-old male, who had taken 20 tablets containing 200 mg of tramadol (4 g) 3 hours before the admission, was transferred to the hospital by an ambulance due to loss of consciousness. He experienced an episode of tonic-colonic seizure before admission to the emergency department. He complained of pain and inability to move his right shoulder after regaining the consciousness. Anterior dislocation of the right shoulder was diagnosed by x-ray imaging (Figure 1). The tramadol positive was reported by urine drug screening.

**Second Case**
A 22-year-old male, with no history of seizure and dislocation was transferred to the hospital by an ambulance. He had taken 30 tablets of 100 mg tramadol (3 g). The seizure was reported before transferring to the hospital by his companions. He complained of severe pain in his left shoulder upon entering the hospital. The anterior dislocation of the right shoulder was reported in the x-ray imaging; positive phencyclidine and tramadol were also reported by urine drug screening.

**Third Case**
An 18-year-old male was transferred to the hospital,
following the use of 20 tablets of 200 mg (4 g) tramadol, by his companions with the history of tonic-colonic seizure and loss of consciousness. The patient had no history of dislocation and injury in his shoulder, but he complained of pain in his right shoulder after gaining the consciousness. The anterior dislocation was reported in the x-ray imaging. Positive tramadol was reported based on urine drug screening.

Fourth Case

A 20-year-old male was transferred to the hospital by Tehran emergency service following taking 20 tablets of 200 mg (4 g) tramadol 2 hours before the admission. In his medical history, the irregular use of tramadol was mentioned; he had no history of shoulder injury and/or dislocation. The diagnostic x-ray imaging was conducted following the pain and inability to move the right hand and consequently the greater tuberosity avulsion fracture and lateral movement with anterior dislocation of the right shoulder were diagnosed. The tramadol positive was reported by urine drug screening.

Fifth Case

A 35-year-old male was transferred to the emergency department of the hospital following the tonic-colonic seizure due to the consumption of 2 tablets containing 200 mg of tramadol. He was conscious at the admission and complained of severe pain in his right arm. He could not move his right shoulder, arm and neck. The comminuted neck and right arm fractures with the movement of broken bones and slightly posterior movement, and humeral epiphyseal fracture of the left arm with slight movement and lack of dislocation were diagnosed by x-ray imaging (Figure 2). The urine drug screening showed positive results for morphine and tramadol.

Sixth Case

A 20-year-old male with irregular use of tramadol (100 mg/d) was transferred to the hospital by an ambulance following the consumption of 10 tablets containing 200 mg of tramadol (2 g). There was no history of seizure and spontaneous dislocation in shoulder. The seizure happened one hour before admission and consequently the anterior shoulder dislocation, on radius and below the coronoid process, was reported (Figure 3). Tramadol positive was reported by urine drug screening.

Discussion

Seizure is one of the adverse effects of tramadol use, abuse or overdose (7-9). Evidence shows that tramadol-induced seizure is not dose-related and the seizure can be recurrent (10-12). However, seizure incidence is rare in its therapeutic dose and is reported to be less than 1% in described patients (3). This drug permeates the blood brain barrier completely. Ninety minutes after consumption, the drug’s plasma level reaches its peak and 5 to 6 hours after consumption, it is eliminated from plasma, mainly by kidneys. Therapeutic blood level is about 100 to 300 ng/mL (0.1-0.3 µg/mL) in adults (7,13).

Tramadol-induced seizures have been reported to be generalized by tonic-colonic in nature, without auras or focal symptoms (14,15). A recent cross-sectional study examined 106 patients who had experienced seizures after ingesting tramadol. All the patients had witnessed generalized tonic-colonic seizures within 12 hours of taking tramadol orally not only in supra therapeutic doses (363.2 ± 303.1 mg) but also in recommended doses even as low as 50 mg. More than 80% of patients had seizure(s) after ingesting recommended doses of tramadol. 13.2% of patients had a history of epilepsy, but their seizures were well controlled and they did not have any seizures during 1 year before their evaluation. This is in line with our study. Tramadol ingestion was considered as a precipitating factor in this group. Talaie et al performed electroencephalography (EEG) and computed tomography (CT) scan of the brain in 132 patients who were considered as tramadol-induced seizure. Of 35 patients with documented seizure, all showed generalized tonic-colonic seizure and 12 patients had abnormal EEG (35.3%). They concluded that the incidence of seizure with tramadol is not dose dependent. Talaie et al reported that the most common dose of tramadol intake in patients with seizure is 500 to 1000 mg and concluded that the incidence of seizure with tramadol is not dose dependent (16). Nakhaei Amroodi et al studied the prevalence of
anterior shoulder dislocation following tramadol-induced seizure in 15 patients. They stated that 20.83% of patients suffer from recurrent shoulder dislocation followed by tramadol-induced seizures (17). They reported that shoulder dislocation following tramadol-induced seizures in 100% of patients was anterior type (17). Farajijadana et al studied trauma-induced seizures followed by tramadol use and reported that 4.3% of 232 patients had shoulder dislocation. They stated that shoulder dislocation was the most common trauma followed by tramadol-induced seizures after head injury. Farajijadana et al studied all traumas caused by tramadol-induced seizure and reported 10 patients with shoulder dislocation. All patients had anterior dislocation (11). Nakhaei Amroodi et al reported 15 patients with shoulder dislocation who had used tramadol. Their shoulder dislocations were after seizure, and all of them were male with mean age of 29 ± 2.0 years. In contrast to the above-mentioned studies, we did not find any women in our cases, but patients were mainly in young ages (17). In the current study, 6 cases, 5 cases and 1 case were reported due to the consumption of tramadol, anterior dislocation, and arm bone fracture respectively. The mean age of the cases was 23 ± 67 years which is inconsistent with those of Nakhaei Amroodi et al (17) and Shadnia et al (1). In addition, all cases evaluated in our study were male and no female was reported which was similar to the study of Nakhaei Amroodi et al (17). Since most of the tramadol consumers are juveniles, the most probable injuries can also be predicted in this age range. In the current study, the anterior dislocation of the shoulder was reported in all 5 cases with shoulder dislocation following the seizure induced by the use of tramadol. This finding is in line with the study of Farajijadana et al (11). However, in the study by Gardner et al (3), the number of reported anterior and posterior dislocations was similar. It is noteworthy that, the diagnosis and suspicion for the anterior dislocation of shoulder is much easier than posterior dislocation, considering the symptoms and signs; generally, failure to diagnose the posterior dislocation is possible as tramadol consumers usually experience to some extent the loss of consciousness (18). In the fourth case of the current study, the anterior dislocation was reported with the greater tuberosity fracture, which was similar to the findings of Cottias et al (19), and Hovelius et al (20). In our study, the mean dose of tramadol was 2.9 g; however, the seizure happened in the authorized normal range. According to the history of 6 cases, seizures were tonic-clonic, which was inconsistent with those of Petramfar (14) and Labate et al (15). Seizures happened 1-3 hours after the use of tramadol. It is acceptable since the tramadol reaches its maximum level 90 minutes after the consumption (7,13). All fracture and dislocation cases in the current study were diagnosed following the conduction of x-ray imaging and the report of a radiologist. Also, to determine the amount of consumed tramadol, the urine drug screening was used along with the reliable medical history of the patients.

Conclusion
According to the findings of the present study, tramadol use and tramadol-induced seizure may increase the risk of shoulder dislocation. Our study and some other similar studies show that anterior shoulder dislocation following tramadol-induced seizure is the most common type; thus, the association between seizure and direction of shoulder dislocation should be investigated in broader and more specific studies.

Ethical issues
The study was according to ethical principles of the Declaration of Helsinki and all patients were aware of the study and signed a written consent form.

Authors’ contributions
BB: Study design; RK: Collecting the cases; ND: collecting the cases; MA: writing the article.

References


