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Case Report: Guillain-Barre Syndrome Due to Tramadol

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ABSTRACT

Tramadol is a powerful prescription medication used for pain relief of varying intensities. Tramadol was initially produced in Germany to alleviate postsurgical and chronic pains. We describe a case of a 22-year-old male with no past medical history who took tramadol for the second time and then had a tonic-clonic seizure episode that worsened the weakness of his inferior limbs and followed by loss of consciousness. According to physical examination, clinical and paraclinical tests, he was diagnosed with Guillain-Barre syndrome. After treatment with intravenous immunoglobulin, he was improved and discharged 9 days after treatment. He was recommended to continue physiotherapy. The relation between tramadol using and Guillain-Barre syndrome development is unknown but it can be due to reactive oxygen species generation.

1. Case Presentation

We were presented with a case of a 22-year-old male with no past medical history. His only positive history was taking one 200 mg tramadol tablet 20 days earlier which was followed by seizure and then quadriplegia. He did not refer to any medical center or receive any medical care. He took another tablet of tramadol on the day of admission. He had a tonic-clonic seizure episode that worsened the weakness of his inferior limbs and he then lost his consciousness. He was taken to a local hospital and intubated before he was referred to our Toxicology Center due to loss of consciousness and respiratory distress. He was admitted to the intensive care unit with a tramadol toxicity diagnosis in our center.

Early after hospitalization, his vital signs were taken (HR=83 beats/minute, BP=100/74 mm Hg, T= 37.2° C). He did not respond to pain, light, and sound. His Glasgow coma scale was 6 out of 15, so precise evaluation of cen-

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tral and peripheral nervous systems and muscle forces was not possible in advance. Brain CT scan, brain, and cervical MRI were normal in imaging studies. The cerebrospinal fluid analysis was normal too. His consciousness level was raised and he was extubated on the second day of hospitalization without respiratory distress or swallowing problems.

In the examination, his deep tendon reflexes of four limbs had been decreased, muscle forces were two out of five.

Four limbs EMG-NCV study was done and reported acute severe peripheral sensorimotor neuropathy with mixed demyelinating and axonal loss nature.

Other abnormal paraclinical findings were Aspartate transaminase (AST)= 296(1^{st}) >48(7^{th}), alanine transaminase (ALT)=657(1^{st}) >178(7^{th}), Creatinine kinase= 134(1^{st}) >32(5^{th}), Lactic Dehydrogenase (LDH)=654(1^{st}) >420(5^{th}).

Liver sonography and viral markers were normal.

Neurology consultation was requested and he was diagnosed with Guillain-Barre syndrome based on physical examination and electrodiagnostic findings. Immunoglobulin was indicated 25 g/d for four days and 30 g on the fifth day. Simultaneously physiotherapy of limbs was done. Besides, he received gabapentin, vitamin B1 orally.

IgA serum level in second day was 143 mg/dL (normal range: 70-400 mg/dL).

Muscle forces increased four days after Immunoglobulin administration (upper limbs 4/5, lower limbs 3/5). He improved and was discharged 9 days after treatment and was recommended to continue physiotherapy.

2. Discussion

Tramadol with its opioid and non-opioid properties is vastly used in the relief of mild to moderate pain and is a centrally acting analgesic [1]. It is known that tramadol has a low affinity for μ- and κ-opioid receptors and also suspends the reuptake of both norepinephrine and serotonin (5-hydroxytryptamine) neurotransmitters [2]. It invigorates the dopamine (D2) receptors and also inhibits the gamma-aminobutyric acid release in the central nervous system [3, 4]. Moreover, it has some N-methyl-D-aspartate antagonistic properties [5, 6]. Tramadol has been listed in Iran's national drug list since 2003 [7]. There has been a rise in tramadol overdose, misuse, and abuse in Iran [8-10]. The prominent effects of tramadol misuse include nausea, dizziness, somnolence, drowsiness, increased sweating, vomiting, and dry mouth [11, 12]. The two main drug reactions which are considered to be life-threatening are seizure and apnea, and these alarming symptoms can be seen in therapeutic and toxic doses [8, 10, 13].

Many adverse effects and complications in acute and chronic tramadol use were reported.

According to Le Berre et al. research, tramadol induced hyponatremia as a consequence of inappropriate antidiuretic hormone secretion [14]. Liver and kidney function tests disorders such as AST, ALT, and LDH level rising was seen in some studies [15-17].

Tramadol can trigger seizure episodes, especially with high doses, or if it is accompanied by the use of medicines that lower the seizure threshold. A high risk of developing serotonin syndrome has been seen in people who use tramadol with serotonergic medicines. To minimize the risk of developing such cases, the lowest possible dose should be prescribed and in cases, with a history of seizure prescribing, tramadol must be avoided. It is advisable to use other analgesics instead of tramadol in patients with a history of seizures or serotonin syndrome [18]. in our case, he had no additional, seizure, or medical history. He was diagnosed with GBS after taking tramadol. There has not been any report of Guillain-Barre's development after tramadol taking or after seizure yet.

Once the immune system damages the peripheral nervous system, one may develop Guillain-Barre syndrome. Early symptoms normally include changes in sensation or pain accompanied by muscle weakness, starting in the feet and hands. It usually spreads to the arms and upper body, engaging both sides. The symptoms progress over hours to a few weeks [19]. This disorder can be life-threatening during the acute phase since statistically, 15% of patients are at risk of developing weakness of the breathing muscles requiring mechanical ventilation [20].

Some patients suffer changes in the function of the autonomic nervous system leading to dangerous abnormalities in heart rate and blood pressure [19]. It is yet unknown as to why this occurs [19]. This reaction involves an autoimmune disorder such that the body's immune system mistakenly attacks the peripheral nerves damaging their myelin insulation [19]. In some cases, the cause of this immune dysfunction includes an infection or less commonly due to surgery and rarely by vaccination [19, 20]. In this case, the cause of Guillain-Barre's development after tramadol taking and then seizure is unknown too.

Using the exclusion method, with the support of tests such as nerve conduction studies and examination of the cerebro-

spinal fluid, the diagnosis is usually made along with examining signs and symptoms [19]. A frequent expression of posterior reversible encephalopathy syndrome in the background of Guillain-Barre syndrome is epileptic seizures.

Hinchery et al. were first to describe this clinicoradiological entity with the exact wording of reversible posterior leukoencephalopathy syndrome [21].

There is likely a connection between the initiation and progression of epilepsy and oxidative stress resulting from excessive free-radical release [22, 23].

Various neurological disorders have been linked to oxidative stress through the shifts in the levels of reactive oxygen species and antioxidative parameters.

Mojdeh Ghabaee was able to demonstrate Antioxidant Activity (AOA) and malondialdehyde levels in people affected with Guillain-Barre syndrome. They concluded that in Guillain-Barre patients an imbalance between the levels of AOA and MDA in both CSF and serum can be detected [24]. Free radical toxicity may also be a factor in GBS patients [25].

Tramadol is metabolized by the cytochrome P450 system and as a result oxidative stress is induced in different organs [26]. Tramadol is metabolized by CYP3A4 and CYP2D6 into a more potent opioid analgesic metabolite M1 [27, 28]. Moreover, hepatotoxicity was increased by CYP2D6 gene polymorphisms by the accumulation of tramadol bioactive metabolite (M1) followed by oxidative stress induction [28, 29].

An individual's CYP genetics influences the opioid analgesic potency because people with poor metabolism have faced little conversion to the more active M1 opioid metabolite, whereas people with higher metabolic rates experience the greatest analgesic effects [27, 30].

3. Conclusion

According to the mentioned information, reactive oxygen species generation due to tramadol using and also seizure could have been the cause of developing Guillain-Barre in our case. Also based on the CYP450s level of activity in individuals that metabolize tramadol, reactive oxygen species generation rates can be different from person to person. This hypothesis needs more investigation.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Author's contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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