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OLGU SUNUMU / CASE REPORT

Propofol addiction after treatment of refractory migraine

Dirençli migren tedavisi sonrası gelişen propofol bağımlılığı

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Abstract
Propofol is a potent intravenous anesthetic agent that rapidly induces sedation. Recently it has been considered as a treatment option for refractory headaches.We report a case of 38 years of female who has received propofol treatment for her refractory headaches and severe dependence on propofol has occured. She had excessive withdrawal symptoms after discontinuing propofol and was succesfully treated. The abuse and dependency potential of propofol has recently been recognized and several cases of suicide have emerged. Although intravenous propofol is an efficacious treatment for patients with refractory headaches, the severe dependency and abuse potential must be taken into consideration.

Key words: Intractable headache, propofol, drug abuse

Öz
Propofol hızlı sedatif etki gösteren oldukça potent intravenöz uygulanan anestetik bir ajandır. Son zamanlarda refrakter başağrılarında bir tedavi seçeneği olarak kullanılmaya başlanmıştır. Bu vakada 38 yaşında bayan hastada refrakter başağrıları nedeniyle propofol tedavisi uyganmış ve propofole karşı bağımlılık gelişmiştir. Propofol tedavisinin kesilmesi ile hastada çok şiddetli çekilme belirtileri gözlenmiş ve tedavi başlanmıştır.Son yıllarda propofolün bağımlılık yapıcı etkisi, kötüye kullanım potansiyeli ve sonuç olarak intihar girişimi olan vakalarla sık karşılaşılmaktadır. Refrakter başağrılarında intravenöz propofol tedavisi oldukça etkili olmakla beraber bağımlılık yapıcı etkisi ve kötüye kullanımı mutlaka göz önünde bulundurulmalıdır.

Anahtar kelimeler: Dirençli başağrısı, propofol, ilaç kötüye kullanım

INTRODUCTION

Propofol is widely used as an intravenous (IV) sedative in gastrointestinal endoscopy, spinal anesthesia and in intensive care units with minimum side effects. In addition it is used to treat refractory migraine and tension headaches, severe alcohol withdrawal and delirium tremens[1]. Propofol depresses the central nervous system by facilitating the inhibitory transmission through post-synaptic activation of the GABA -A (gama–aminobutyric acid) receptor-chloride complex. It also inhibits excitatory transmission by modulating the NMDA (N-methyl-D-aspartic acid) subtype of glutamate receptor and slow calcium channels and inhibits voltage –gated sodium channels[1]. It has been found that there is a mulfunctioning of the GABA system in migraine causing cortical hyperexcitability therefore propofol's remarkable stimulating effect on GABA receptors plays an important role in treating migraine headache attacks[2,3,4].

The abuse potential of propofol is well known[5,6]. All drugs of abuse increase dopaminergic activity of the main component of the mesocorticolimbic reward circuit within the brain and such effect may contribute to the development of propofol abuse[7]. The prevalence of addiction and abuse of any substance (except nicotine) is as follows: 10.9 % for alcohol, 59% for anxiolytics and hypnotics, 41 % for cannabis, 69 % for opiates 5.5 % for cocaine and amphetamines, 1.9 %, for ketamine and propofol[8]. The abuse of propofol has a high risk of death. There have been case reports of death due to propofol abuse which are related with apnea, a sudden decrease of blood pressure and hemorrhagic pancreatitis[6]. The case presented here highlights the

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importance of abuse potential of propofol even in applying in treatment of refractory migraine.

CASE

We report a case of 38 years old female patient. She is married, college graduated not working, mother of two children. She has been complaining from the increase of the frequency of her headache attacks, insomnia and mood changes for the last two years. Initially her headaches were localized unilaterally, lasted approximately 8-10 hours. Nausea, photophobia, phonophobia and seldomly vomitting accompanied her attacks. Her headache attacks met migraine criteria and had the attacks since she was 18. Initially her migraine attacks were occuring 3 times in a week and was responsive to analgesic treatments. Yet for the last 2 years she suffered from chronic daily headache attacks. Her daily headache attacks were localized bilaterally without photophobia, phonophobia and nause accompanied seldomly. She was taking daily simple analgesics and non steroid antiinflammatory drugs yet there was no response to treatment. During this period Corticosteroids, dihydroergotamines or neuroleptics was not prescribed to the patient as far as learned from the history.

She was diagnosed with chronic migraine as headache attacks were more than 15 days per month. In addition medication overuse headache was diagnosed due to excessive use of analgesics more than 3 months , and also her headache attacks were more than 15 days per month and worsened during medication overuse. The patient was also diagnosed by her neurologist with moderate depression by interview and was prescribed paroxetine 20 mg/day. She was also prescribed intravenous (ıv) petidine by her doctor propably due to her intractable headaches which was unresponsive to simple analgesics and non steroid antiinflammatory drugs. She stopped taking paroxetine after one month due to unresponsiveness. On follow up different antidepressant treatments were recommended yet she didn't use them regularly.

She continued to use petidine for two months and was switched to ıv propofol by another physician probably due to refractory headache attacks. On follow up the severity of her depression symptoms increased measured by Beck Depression Scale and after 5 months she attempted suicide. The initial dose of propofol was 30-40 mg/day but this was increased to 70 mg/day in 3 weeks. During that period her complaints were anhedonia, difficulty to concentrate, hypersomnia, lack of appetite, unhappiness and suicidal tendencies. During this period she only used propofol and seldomly she also took analgesics for the headache attacks but was not on medication for depression or for suicidal tendency. The patient applied to our psychiatry department and was hospitalized. After 16 hours from the last propofol dose she started to suffer anger and panic attacks, distress, anxiety, sweating, palpitations, nausea, weakness, irritability, stomach spasms and severe sleeplessness. In addition she also had headache attacks during this period. The complete blood count, blood chemistry (including electrolytes, renal and hepatic indexes, and glucose), thyroid function tests, brain computed tomography, electrocardiogram, electroencephalogram were all normal. She had excessive cravings for propofol. The diagnosis of propofol use disorder has been made according DSM 5 criteria. The patient met the following of DSM 5 substance use disorder criteria: 1.Reccurent propofol use resulting in failure major obligations at home and work; 2. Craving or strong desire to use propofol; 3. The propofol had been taken in larger amounts and over a longer period than intended;. 4. There was a persistent desire and unsuccessful effort to cut down the substance; 5. The patient supported at least the 2 diagnostic criteria of Hypnotic withdrawal (1-Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm). 2- Hand tremor. 3- Insomnia. 4. Nausea or vomiting).

Venlafaxine, mirtazapine, quetiapine, and alprazolam were used during the hospitalization period.Venlafaxine was started with a dosage of 75 mg/day and increased to 150mg/day. Mirtazapin was started with a dosage of 15 mg/day, quetiapine 300 mg/day and alprazolam was started with a dosage of 4 mg/day. After the fifth day, her sleep was better but stomach spasms, panic attacks and irritability continued with the same severity. On the 10th day of admission her symptoms regressed and she didn't have any withdrawal symptoms. Alprazolam and quetiapine were reduced gradually and her depressive symptoms and headache attacks remitted at the end of 5th week .

DISCUSSION

Since migraine is a common disease many studies

have been conducted to find the efficacious treatment. During migraine attacks especially intravenous route is preferred because of absorption disorders[9]. Propofol has been a treatment option in refractory headaches in clinical practice yet there are few studies conducting the effect of propofol in migraine. It has been found that propofol causes a significant and fast relief in headache attacks[3,10,11,12,13]. The main reason of propofol's remarkable effect is reported as the high tendencyto GABA receptors that are in low functional status in refractory migraine so that propofol overcomes in this physiological process through stimulating GABA receptors[11].

Propofol is structurally distinct from other anesthetic agents. It acts by depressing the central nervous system with the mechanism involving facilitation of inhibitory transmission through post synaptic activation of the GABA-A (gama–aminobutyric acid) receptor-chloride complex. Propofol also reduces respiratory drive, causes airway obstruction and reduction in blood pressure. These potent pharmacodynamic effects on the cardiovascular and respiratory systems make propofol potentially dangerous and lethal[1]. Propofol has several desirable properties superior to other sedatives. These are easy access, rapid onset and short duration of action, and minimal or no residual side effects[5]. These properties make propofol predispose to addiction. There are signs that propofol addiction has both psychological (euphoria, stress relief, sexual fantasies and dreams, sexual disinhibition) and physical (tolerance, tachycardia, anxiety, insomnia) components. The psychological dependence are more common and these effects lead to drug-craving and loss of control over the amount and frequency of drug injections. The possible mechanism of psychological abuse can be the fast activation of central Gamma-Aminobutyric acid (GABA –A) receptors. Even with the ultra short pharmacological effect of propofol the recurrent stimulation of central GABA-A receptors might be the cause of addiction symptoms like tolerance and withdrawal[8].

The reported symptoms of propofol withdrawal are seizures, tachycardia, hyperhydrosis, concentration problems, anxiety, insomnia and irritability. In our case the patient had cravings and physical symptoms such as panic attacks, sweating, insomnia, irritability and stomach spasms. The patient had several untreated depression episodes and had never used antidepressants in sufficient time and dosage. She had also migraine attacks and anxiety symptoms, and tried to cope by using propofol.

Even though propofol is an effective treatment in refractory headaches there is an high abusive potential and this condition is mostly precipitated by uncontrolled prescription of the drug by the physician as in our case. In another case propofol was prescribed to a patient with tension headaches, and the patient experienced relaxation and euphoria, and the tension was reduced - but soon tolerance and abuse of propofol occurred [2]. Studies regarding subjective effects of propofol reported that drug evokes positive feelings like euphoria[4,14]. In our patient euphoria was the most important cause for her craving.

In addition propofol as a GABA agonists, affects norepinefrin transporter function and alter neurotransmission. It was demonstrated in a study that norepinefrin transporters (NET) and serotonin transporters (SERT) were selectively inhibited by propofol and ketamine. Chronic treatment with inhibitors of NET and SERT modulate the inhibitory effects of IV anesthetics on the uptake function of both NET and SERT. Chronic antidepressant treatment may modify the effects of IV anesthetics on monoamine transporters in patients receiving antidepressant therapy[15].

Case reports of recurrent use of propofol in endoscopy and afterwards occuring of abuse and addiction show us that propofol abuse can start very soon after using it - as in our case[16] . The use of propofol has a very fast, euphoric effect which causes a relaxation in people. In sub anesthetic doses it has a mood altering effect. This mechanism might be related to a fast addiction process. The treatment of propofol withdrawal is not well described in literature. Since propofol has its effects due to central GABA-A receptors and have similar pharmacological properties with sedatives[1] we have used benzodiazepines during the withdrawal period. Other possible medications which could be used are gabapentine and valproate and especially in seizures diazepam can be used[17].

Propofol is an effective treatment option for refractory headaches but only as an alternative treatment to opiods in emergency. The speed and rate of response to migraine headache treatment is considerably high. Yet abuse and dependency potential is an important side effect therefore it

should be used cautiously and not for long term headache treatment.

REFERENCES

1. Marik PE. Propofol:therapeutic indications and side-effects. Curr Pharm Des. 2004;10:3639-49
2. Schneider U, Rada D, Rollnik JD, Passie T, Emrich HM. Propofol dependency after treatment of tension headache. Addict Biol. 2001;6:263-5.
3. Krusz JC, Scott V, Belanger J. Intravenous propofol: unique effectiveness in treating intractable migraine. Headache. 2000;40:224-30.
4. Plummer PN, Colson NJ, Lewohl JM, MacKay RK, Fernandez F, Haupt LM et al. Significant differences in gene expression of GABA receptors in peripheral blood leukocytes of migraineurs. Gene. 2011;490:32-6.
5. Cha HJ, Cha JH, Cho HY, Chung EY, Kwon KJ, Lee JY et al. Dependence potential of propofol: behavioral pharmacology in rodents. Biomol Ther (Seoul). 2012;20:234-8.
6. Tezcan AH, Ornek DH, Ozlu O, Baydar M, Yavuz N, Ozaslan NG et al. Abuse potential assessment of propofol by its subjective effects after sedation. Pak J Med Sci. 2014;30:1247-52.
7. Roussin A, Montastruc JL, Lapeyre-Mestre M. Pharmacological and clinical evidences on the potential for abuse and dependence of propofol: a review of the literature. Fundam Clin Pharmacol. 2007;21:459-66.
8. Luck S, Hedrick J. The alarming trend of substance abuse in anaesthesia providers. J. Perianesth. Nurs. 2004;19:308-11.
9. Snow V, Weiss K, Wall EM, Mottur-Pilson C. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002;137:840-9.
10. Drummond-Lewis J, Scher C.Propofol: a new treatment strategy for refractory migraine headache. Pain Med. 2002;3:366-9.
11. Soleimanpour H, Taheraghdam A, Ghafouri RR, Taghizadieh A, Marjany K, Soleimanpour M. Improvement of refractory migraine headache by propofol: case series. Int J of Emerg Med. 2012;5:19.
12. Bloomstone JA. Propofol: a novel treatment for breaking migraine headache. Anesthesiology. 2007 ;106:405-6.
13. Mendes PM, Silberstein SD, Young WB, Rozen TD, Paolone MF. Intravenous propofol in the treatment of refractory headache. Headache. 2002;42:638-41.
14. Zacny JP, Lichtor JL, Coalson DW, Finn RS, Uitvlugt AM, Glosten B et al. Subjective and psychomotor effects of subanesthetic doses of propofol in healthy volunteers. Anesthesiology. 1992;76:696-702.
15. Zhao Y, Sun L. Antidepressants modulate the in vitro inhibitory effects of propofol and ketamine on norepinephrine and serotonin transporter function. J Clin Neurosci. 2008;15:1264-9
16. Roh S, Park JM, Kim DJ. A case of propofol dependence after repeated use for endoscopy. Endoscopy. 2011;43 Suppl 2 UCTN:E362.
17. Bonnet U, Banger M, Leweke FM, Specka M, Muller BW, Hashemi T et al. Treatment of acute alcohol withdrawal with gabapentin results from a controlled two center trial. J Clin Psychopharmacol. 2003;23;514-9.