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Authors: Ataman Kose, Seyran Bozkurt, Ahmet Celik, Ipek Agar, Huseyin Narci, Cuneyt Ayrik

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Primidon alımına bağlı şuur değişikliği ve atriyal fibrilasyon

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Giriş

Primidon esansiyel tremor tedavisinde kullanılan antikonvülzan bir ilaçtır. Yan etkileri yaygındır ve sıklıkla doza bağımlıdır. Ancak, literatürde ve ilacın prospektüsünde atriyal fibrilasyon yapıcı etkisi bildirilmemiştir. Bu çalışmada primidon kullanımı sonrası sedasyon, konfüzyon ve atriyal fibrilasyon görülen bir vakayı sunmak istiyoruz.
Olgu: 68 yaşında bayan hasta primidon (mysoline) 250 mg tablet aldıktan sonra bulantı, kusma, terleme ve uyku hali oluşması nedeni acil servisimize başvurdu. Hastaya esansiyel tremor neden ile nöroloj itarafından yaklaşık 2-3 hafta önce mysoline 250 mg tabletin dörtte birini kıllanılması için verilmiş. Hasta bilmeyerek tabletin tümünü (250 mg tablet) almış. Çekilen EKG'sinde hızlı ventrikül cevaplı atriyal fibilasyonu mevcuttu. Kardiyoloji ve şuur değişikliği için nörolojiye konsülte edildi. Nöroloji ve kardiyoloji primidon bağlı yan etki olarak düşünüldü.

Sonuç: Sonuç olarak primidon başladığında yan etkileri hakkında hastaların eğitilmesi ve dikkatli olmaları tavsiye edilmelidir. Acil servise başvuran yaşlı ve ritm bozukluğu olan hastalarda, yeni gelişen atriyal fibrilasyon, sedasyon ve konfüzyona primidon gibi ilaçların neden olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: primidon, atriyal fibrilasyon, sedasyon, acil servis

Altered consciousness and atrial fibrillation due to primidone intake

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Primidone is an anticonvulsant drug used for the treatment of essential tremor. Side effects may become more pronounced with increasing doses. However, atrial fibrillation as a side effect of the drug neither has been reported in the literature nor it is specifically indicated by the package insert. Here, we would like to report a patient who developed sedation, confusion, and atrial fibrillation after primidone use. A 68-year-old woman presented to our emergency department with nausea, vomiting, perspiration, and somnolence sometime after taking primidone (mysoline) 250 mg. It was learnt that mysoline 62.5 mg (a quarter of 250 mg tablet) had been begun by a neurologist for essential tremor 2-3 weeks before, although the patient had inadvertently taken a tablet per day. An admission ECG at the emergency department showed atrial fibrillation with a rapid ventricular response. Cardiology and neurology departments agreed that the atrial fibrillation episode was a side effect of primidone. It is recommended to instruct patients on and warn against the side effects when primidone is first used. It should be kept in mind that in elderly patients presenting to emergency department, drugs such as primidone which may cause sedation, confusion, and atrial fibrillation may be the culprit.

Key words: Primidone, atrial fibrillation, sedation, emergency department

Introduction

Drug use and associated complications are common in the elderly. Multi-drug use, comorbid diseases, and dosing errors are important factors for emergence of side effects. Inappropriate use of medications may be associated with increased rates of hospitalization, morbidity, and mortality and unexpected drug-related effects (1). Antiepileptic drugs are used for a variety of indications in the elderly. Primidone is an anticonvulsant drug primarily used in essential tremor. It is metabolized into phenobarbital and phenylethylmalonamide (PEMA). Its anticonvulsant actions are brought about by itself and its two active metabolites. However, its tremor suppressor action is superior than its metabolites and it is widely used for essential tremor therapy recently (2,3). Its side effects are common and generally dose-dependent. The number and rate of side effects may become more prominent as the dose of the medication is increased. (4,5).

Depending on the dosing of primidone, sedation, dizziness, and altered consciousness have been reported, although neither previous studies nor the package insert has indicated that atrial fibrillation is among its side effects. In this study we report a patient who experienced sedation, confusion, and atrial fibrillation after use of primidone.

Case report

A 68-year-old woman admitted to our emergency department with nausea, vomiting, perspiration, and somnolence after taking a primidone (mysoline) 250 mg tablet. Her past history was notable for hypertension and peripheral facial paralysis. She was begun a quarter of primidone 250 mg tablet per day by the neurology department for essential tremor 2-3 weeks before. However, she took one tablet a day (250 mg). She reported excessive sweating, nausea, palpitation, and vomiting, followed by altered consciousness and progressive somnolence after taking the drug. At initial examination her Glasgow coma score was 14 and her vital signs were stable. She had a body temperature of 36^{o}C, pulse rate of 145 bpm, blood pressure of 140/90 mmHg, respiratory rate of 20 per minute, and oxygen saturation of 94% in room air on pulse oximetry. The patient was monitorized, a peripheral IV access established, oxygen administered, and blood samples taken. Surface ECG showed atrial fibrillation with rapid ventricular response (Figure 1). As she had no history of heart or rhythm problems, she was considered to have new-onset atrial fibrillation and given anticoagulation as well as 25 mg diltiazem for ventricular rate control, although diltiazem could not control the ventricular rate adequately. She was thus consulted with the cardiology department for management of her atrial fibrillation and that department recommended amiodarone 150 mg infused in 100 cc isotonic saline in 20 minutes. Atrial fibrillation was converted to sinus rhythm after

amiodarone loading infusion (I.V. 150 mg Cordarone® in 100 ml 5 % dextrose in 15 minutes) [Figure 2]. An echocardiogram performed after restoration of her rhythm was normal. Her subsequent treatment regimen was adjusted by the cardiology department. Laboratory tests were all normal. The phenobarbital level was less than 0.5mg/dl and normal. On neurological examination the patient was somnolent and confused despite her speech and understanding were normal. Muscle strength, and sensory and reflex functions were also normal. She had no lateralizing muscle deficit. She was consulted with the neurology department for altered consciousness and somnolence. The neurology and cardiology departments jointly considered that the clinical condition of the patient was a primidone-associated side effect. The patient's mental status and cardiac rhythm were monitored at the emergency department. She was administered intravenous fluids and gastric protection. No further dysrhythmia occurred during a 36-hour emergency department stay. Her mental status also improved later and she was discharged upon recommendations of neurology and cardiology.

Discussion

Altered consciousness and rhythm problems may occur following intake of many medications or substances. The above complications may either indicate drug overdose or side effects. Antiepileptics (particularly phenytoin and phenobarbital) may also cause this type of adverse reactions (3,6). Primidone is a powerful central nervous system depressant. In the early stages of the treatment its side effects usually appear in the form of fatigue, somnolence, and confusion. Depending on the ingested dose, excessive dosing may cause varying levels of central nervous system depression, which includes ataxia, loss of consciousness, respiratory depression, and coma (3,5). Some patients, particularly the elderly, may complain of confusion, dizziness, sedation, ataxia, nausea, and fatigue even after doses of 50 mg/day or lower. The number and rate of side effects may become more prominent as the dose of the medication is increased. Thus, primidone should be started at very low doses (i.e. 25 mg or even 12.5 mg) and half of the tablet or a quarter of it, it should be taken at bedtime to avoid the side effects (dizziness and sedation) (3-5). Then, the dose can be increased to 250 mg every third day until symptoms are controlled or maximum tolerated dose is reached in adults. Our patient took one tablet at a time despite being advised to take a quarter of a 250 mg tablet. She later presented with nausea, vomiting, dizziness, and somnolence. This clinical picture was consistent with the primidone side effect that was reported by both literature data and primidone package insert.

Katano et al. (7) reported a case of hyperammonemic encephalopathy with impaired consciousness after primidone intake. The patient had elevated ammonia and phenobarbital

levels despite normal routine laboratory tests. Unlike our patient, that patient also had an intracranial tumor. Our patient developed the clinical picture without concurrent primidone intoxication. The clinical picture improved upon cessation of primidone. Koch et al. (8) observed that primidone-induced sedation may augment altered consciousness in the elderly, particularly in those with dementia. Thus, they recommended that repeat examination be performed at regular intervals and non-sedative antiepileptic agents prescribed in such conditions.

Some antiepileptic drugs (phenobarbiturates, phenytoin) have been shown to induce cardiac arrhythmias in a dose-dependent fashion (6). Potassium, sodium, and calcium ion channels are central to cardiac rhythm generation (9). Although upregulation of the GABA-A receptors has a vital role for the emergence of the effects of phenobarbital and primidone, these agents may also act through inhibition of sodium, potassium, and calcium ion channels. The latter have been implicated in primidone's anticonvulsant and antitremor activities (6,10,11). Hence, it has been suggested that taking these drugs in inappropriate doses may pose an arrhythmia risk associated with the suppression of the ion channels. Some studies have reported that primidone is not an arrhythmogenic agent (12), but rather it is an anticonvulsant agent with cardiac arrhythmia correction and QT interval shortening effects (13). Nevertheless, it caused atrial fibrillation in our patient and this rhythm disorder may be related to suppression of the conduction system.

The actions of primidone are mediated by itself and its two active metabolites (phenobarbital and PEMA). Thus, phenobarbital level is usually checked in primidone toxicity. Since the phenobarbital level was normal and the intake did not occur at very high dose, toxicity was not the case in our patient. Depending on the dose taken, the side effects may have appeared owing to advanced patient age and high serum drug concentrations. Compared to primidone, the serum levels of phenobarbitone and PEMA tend to be higher. Renal clearance of all compounds (primidone, PEMA, and phenobarbitone) is moderately impaired in the elderly, which is possibly related to reduced renal function with aging (2).

Conclusion

In conclusion, this case report suggests that primidone has sedative and arrhythmogenic potential. Patients who are prescribed primidone should be instructed on the drug’s usage and warned about its side effects. Primidone should be remembered in the differential diagnosis of new-onset atrial fibrillation, especially in the elderly.

Conflict of Interest: Authors decelerated no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

The patient consent: The patient consent was obtained as verbal from patients' relatives.. In addition, it was not taken as the picture of patient does not include, and blood tests was taken for routine use.

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Figure legends

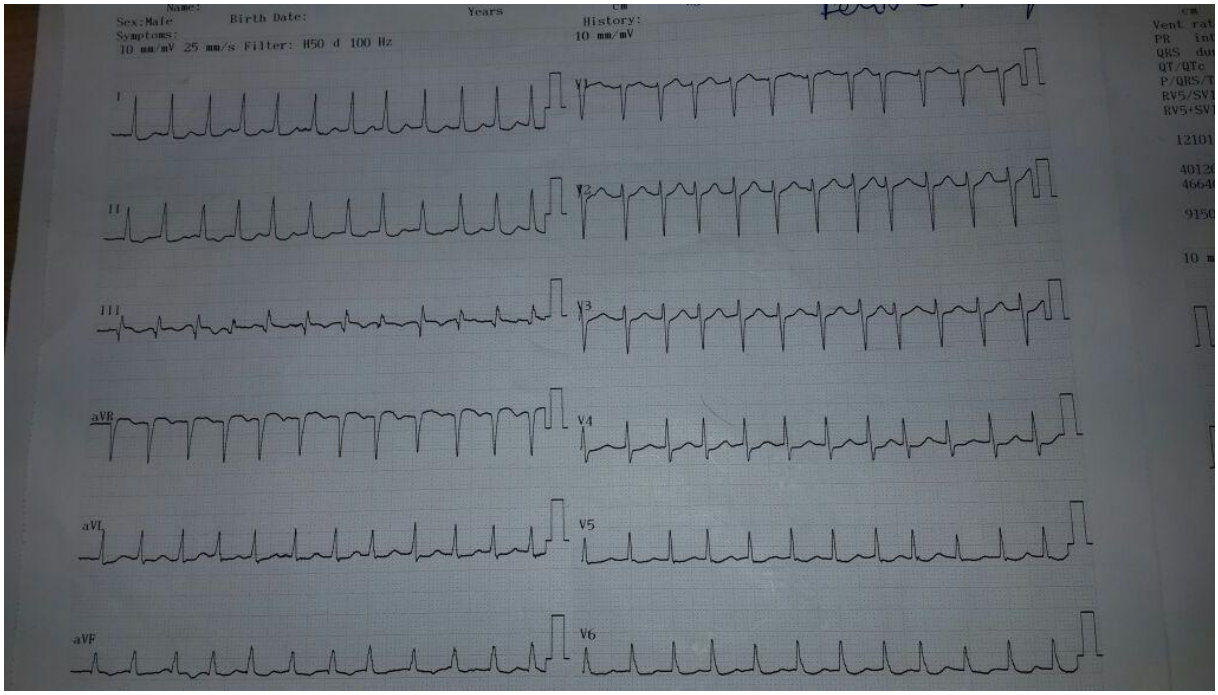

Figure 1. Atrial fibrillation in the initial ECG

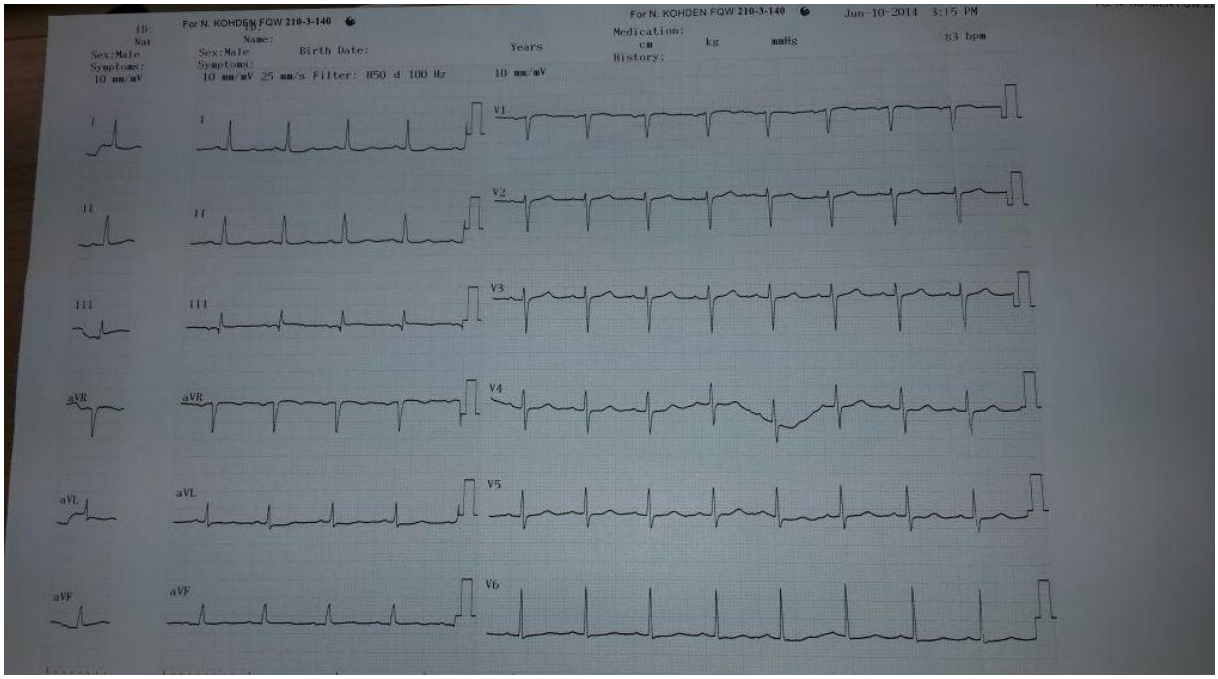

Figure 2. The rhythm converted to normal sinus rhythm after amiodarone infusion