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CASE REPORT

Plasmapheresis Application in High-Dose Amitriptyline Intoxication

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ABSTRACT

Tricyclic antidepressant intoxication is one of the most frequently seen and life-threatening causes of drug poisoning-related emergency service applications. Especially in children, it is a major cause of mortality and morbidity. Intoxication symptoms are seen in the early phase because of the high distribution volume and protein binding rates. To prevent these effects, plasma exchange must be added to the treatment protocol, especially when the central nervous and cardiac systems are affected. In this report, we present the application and results of plasmapheresis in the emergency treatment of a case with high-dose amitriptyline intoxication.

Key words: *Intoxications, Tricyclic antidepressant, Plasmapheresis*

ÖZET

Yüksek Doz Amitriptillin Zehirlenmesinde Plazmaferez Uygulaması

İlaçla zehirlenme nedeniyle acil servislere başvuran olgular içerisinde trisiklik antidepresan ilaçlar sık görülen ve yaşamı tehdit eden zehirlenme nedenlerindendir. Özellikle çocuklarda önemli mortalite ve morbidite nedeni olmaktadır. Dağılım hacimlerinin yüksek olması ve proteinlere de yüksek oranda bağlanmaları nedeni ile zehirlenme bulguları erken ortaya çıkar. Yine bu nedenle özellikle kardiyak ve santral sinir sisteminin etkilendiği durumlarda acil tedavi protokolüne plazma değişimi de eklenmelidir. Bu olgu sunumunda; yüksek doz amitriptillin alan yirmi dört yaşındaki bir hastanın acil tedavisinde yer verdiğimiz plazmaferez uygulamasını ve sonuçlarını tartışmayı amaçladık.

Anahtar kelimeler: *Zehirlenmeler, Trisiklik antidepresan ilaçlar, Plazmaferez*

INTRODUCTION

Tricyclic antidepressant (TAD) intoxication is one of the most important causes of poisoning in both children and adults[1,2]. These drugs are used mostly for major depression and hyperactivity syndrome, enuresis nocturna, migraine, and neuropathic pain[2]. Cardiac toxicity signs like myocardial depression and ventricular dysrhythmia can be seen with the effect of sodium (Na^+) and potassium (K^+) channel blockage[1-3,4]. Central nervous system (CNS) signs can occur from the anticholinergic effects, alpha receptor inhibition and gamma amino butyric acid receptor-A (GABA-A) antagonism. Early diagnosis is important when these signs are encountered. The treatment includes gastric lavage and activated charcoal, fluid replacement and respiratory support when needed[5,6].

Recently, the benefits of plasmapheresis application in drug intoxications have been emphasized. Plasmapheresis is a type of therapeutic apheresis. In this procedure, plasma is cleared from toxins and replaced with appropriate fluids. The procedure is continued until a response is obtained. It is safer to excrete drugs with high plasma protein binding rates using this procedure. Because of these features, its use in TAD intoxications has been emphasized[7].

In this case report, we aimed to discuss the effect of plasmapheresis in addition to conventional methods in a patient who had ingested high doses of amitriptyline (50 mg/kg) with suicidal intent.

CASE REPORT

A 24-year-old male patient was brought to emergency service because of confusion, shallow breathing and agitation and was admitted to our clinic with the preliminary diagnosis of drug poisoning. According to information obtained from his relatives, he had ingested 50 tablets of amitriptyline 25 mg (Laroxyl®, Roche) approximately one hour previously and had vomited once before admission.

After admission to the intensive care unit, monitoring of his heart rhythm through DII derivation, invasive systolic and diastolic blood pressures, central venous pressure through subclavian vein, and 24-hr urine output was started. On the physical examination, the patient was unconscious, agitated, and his breathing was shallow. His pupils were isochoric, light reflex was bilaterally positive and Glasgow Coma Score (GCS) was 7. Pulse rate was 140 beats per minute and blood pressure was 130/80 mmHg. Arterial blood gas (ABG) analysis values were pH: 7.47, pO_2: 48.3 mmHg, pCO_2: 30 mmHg, HCO_3: 22.1 mmol/L, and base excess (BE): -6.4 mmol/L. Nasal oxygen was given (2 L/min) but the patient was later intubated because of decrease in pO_2 levels in ABG samples and even shallower breathing; he was sedated with 0.1 mg/kg/h midazolam infusion. Nasogastric tube was inserted immediately for gastric lavage and activated charcoal was applied. Because of hypoactive bowel movements, repeated activated charcoal administration was not applied as it was considered not necessary. Intravenous metoclopramide was given to accelerate gastrointestinal passage.

Sinus tachycardia was present on the first electrocardiography (ECG). No pathologic wave form was present except for the missing R wave in accelerated ventricular rhythm (aVR) derivation. QRS (0.08 sec) and QTc (0.40 sec) periods were normal. Repeated ECG samples were also normal. First Na level was 135 mmol/L (N: 135-145 mmol/L) and K level was 2.9 mmol/L (N: 3.5-5.5 mmol/L) in biochemical analysis. Other parameters were normal. Fluid therapy and electrolyte replacement were planned. Daily electrolyte levels are shown in Table 1.

Chest X-ray showed infiltrative signs in the right lung considered secondary to aspiration and treatment was planned together with consultations to the infection and chest disease specialists. Cranial tomography was normal. In repeated ABG samples, pH and HCO_3 levels were similar, and no arrhythmias or hypotension was seen; alkalinization was not needed. ABG measurements before and during plasmapheresis are shown in Table 2.

On the same day, the patient, in a deep coma, was connected to a mechanical ventilator, and then plasmapheresis was undertaken and applied three times in total on the following days. The first plasma exchange was done with 1750 mL fresh frozen plasma (FFP).

Table 1. Serum electrolyte levels before and after plasmapheresis

	Na (135-145 mmol/L)	K (3.5-5.5 mmol/L)
Before plasmapheresis	136	2.9
After first plasmapheresis	129	3.2
After second plasmapheresis	135	3.9
After third plasmapheresis	137	4.3

Table 2. Arterial blood gas levels before and after plasmapheresis

	pH	pO_2 (mmHg)	pCO_2 (mmHg)	HCO_3 (mmol/L)	BE (mmol/L)
Before plasmapheresis	7.47	48.3	30	22.1	-6.4
After first plasmapheresis	7.42	82.1	32.3	24.2	-1.1
After second plasmapheresis	7.40	88.4	33.1	23.8	-1.8
After third plasmapheresis	7.38	76.1	35.2	22.4	-2.2

This exchange was done at a rate of 55-60 mL/min with Hemocare-COM-TEC equipment (Fresenius, Germany). Because the patient was sedated during the procedure, GCS could not be evaluated. In the second session 1950 mL and in third session 1850 mL plasma was exchanged. FFP was compatible with the patient's blood group. Sedation was stopped after the third session. As GCS was 10 on the 6th day, the patient was removed from the ventilator and then extubated. On the 10th day, laboratory findings and vital signs were stable and the patient was discharged.

DISCUSSION

TAD poisoning ranks first among drug intoxications worldwide. The most important effects are observed in the cardiovascular, autonomous and central nervous systems. The drug is quickly absorbed from the gastrointestinal tract after intake and reaches the maximum plasma concentration in 2-6 hours. Therefore, early diagnosis and treatment are very important in terms of mortality and morbidity[3].

Dose range of amitriptyline starts at 3 mg/kg and the threshold value for serious toxicity is 8 mg/kg in children. The dose varies between 10-30 mg/kg in adults[2]. Our patient received 3750 mg (50 mg/kg).

Gastric lavage and activated charcoal application to reduce the rate of absorption are applied in the early treatment period[3]. Activated charcoal was applied at a dose of 1 mg/kg. The bowel movements were hypoactive because of the antimuscarinic effect of the drug so doses were not repeated in view of perforation risk. Intravenous metoclopramide was also given to accelerate gastrointestinal passage.

Cardiovascular toxicity results in myocardial depression, conduction anomaly and ventricular arrhythmia. These effects are seen because of the Na^+ channel blockage in Purkinje's fibers and ventricular muscle. QRS interval prolongation causes slow cardiac depolarization. QT interval extends with K^+ channel blockage. Anticholinergic and alpha adrenergic blockages make clinical status more severe. Seizures occur over QRS period 0.10 second and ventricular arrhythmia occurs over 0.16 second. The QRS period is a more specific indicator than blood drug level in TAD poisoning[2,3,4,6,8-10]. Furthermore, right-axis (130-170°) deviation and R amplitude varieties in aVR are toxicity signs. When R amplitude is 3 mm or over, conduction is affected. QRS and QT interval and right-axis derivation degrees are used in recognition[11]. In this case, sinus tachycardia was present in the first ECG. QRS (0.08 sec) and QTc (0.40 sec) periods were normal, R wave was missing in aVR, axis was normal, no pathologic wave form was present, and repeated ECG samples were normal.

Alkalinization with sodium bicarbonate is an important step in the treatment. It is known to be useful for patients with serious arrhythmia and hypotensive shock, so the pH levels must be maintained between 7 and 8. Sodium bicarbonate improves ventricular arrhythmia, refractory hypotension and QRS duration. Otherwise, hyperventilation is effected in poisoning[2,3,12]. As there was no cardiac toxicity or acidosis, sodium bicarbonate infusion was not applied in our patient.

TAD drugs cause hypotension with alpha blockage. To prevent this effect, hypertonic NaCl is used. When that is not sufficient, vasopressor agents like dopamine, epinephrine, norepinephrine, and dobutamine can be added to the therapy. Epinephrine is the most effective drug for this effect[3]. In our case, vasopressor agents were not needed.

Convulsions can be seen in TAD poisoning, especially in children. This effect results from GABA receptor antagonism, neuronal Na channel blockage and central cholinergic activity, with the result being an increase in cholinergic enzyme activity[6]. In this case, agitation and confusion reflected involvement of

the central neuronal system. However, no seizure occurred. After a short period of calm in the hospital, the patient was intubated because his breathing grew shallower, and he was sedated with 0.1 mg/kg/h midazolam infusion.

Antidepressant risk assessment criteria are recommended for clinical evaluation. These criteria include QRS prolongation, arrhythmia, altered mental status, seizures, respiratory depression, and hypotension. Absence of these criteria is classified as low risk, and presence of one or more criteria as high risk[13]. Our patient was classified as high risk because of his altered mental status and respiratory depression following the overdose. Since he was in deep coma and diagnosed early, plasma exchange was added to the therapy.

Plasmapheresis application is the second category for drug poisoning according to the 2007 American Apheresis Association Guide. First, primary treatment is done. Plasmapheresis is accepted as additional and supportive treatment[7]. Like hemofiltration and hemoperfusion, plasma exchange may also have a beneficial role in serious drug poisoning because of the high plasma protein binding rates of drugs. This procedure facilitates rapid poison excretion in elective patients with serious poisoning. Moreover, plasmapheresis can be applied in risky and fatal cases or in cases when the ingested drug is unknown. It is very effective in amitriptyline, theophylline, diltiazem, carbamazepine, L-thyroxin, verapamil, heavy metals like mercury, and vanadate poisoning[14,15,16,17]. For these reasons, plasmapheresis was applied immediately in this case.

Drug and toxic substance excretion using granular charcoal hemoperfusion has become available for poisoning, especially in children. This procedure uses the highly absorbent feature of activated charcoal, but it is not prevalent and requires more controlled studies[5,18,19].

In conclusion, plasmapheresis can be applied as an excretion method for medical and supportive treatment because of the high plasma protein binding rates and lipid solubility of the drug in TAD overdose. We believe routine plasmapheresis application especially in high-risk patients according to the ADORA criteria requires more studies before firm conclusions can be drawn.

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