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Case Report

Effect of plasmapheresis on serum levels of clobazam, levetiracetam and topiramate

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ABSTRACT

A 27-year-old man with a diagnosis of new onset refractory status epilepticus (NORSE) was treated with five anti-seizure drugs (ASDs) including clobazam, levetiracetam and topiramate. He received plasma exchange (PE) for presumed autoimmune etiology. Serum ASD levels were serially monitored in two sessions. Levels of clobazam, levetiracetam and topiramate were significant reduced by PE. Serum clobazam level dropped down to at least 85% and 75% of the baseline during and after the procedure respectively; levetiracetam dropped down to 83% and 83%; and topiramate dropped to 86% and 79%. The results may imply a theoretical risk of breakthrough seizure during PE due to low ASD levels.

1. Introduction

Plasma exchange (PE) or plasmapheresis is a therapy involving removal of patient's plasma in exchange for exogenous fluid such as albumin. Its use in neurology is increasing as autoimmunity has been discovered to play an etiological role in many neurological diseases [1,2]. At the same time, seizures can occur in many neuroimmunological disorders such as autoimmune encephalitis, multiple sclerosis, paraneoplastic syndromes. There are concerns about whether PE would affect the serum concentration of anti-seizure drugs (ASD). Clinicians may query whether patients would have bare higher seizure risk around the time of PE and whether there is a need to adjust the ASD dosage for the procedure.

We present a patient with NORSE who was empirically treated with PE. His serum ASD levels before, during and after two of his PE sessions were recorded. To our knowledge, this is the first report of the effect of PE on serum levels of clobazam, levetiracetam and topiramate.

A 27-year-old man presented to us for a first generalized tonic-clonic seizure. He subsequently developed status epilepticus soon after hospital admission. There was no significant family history. He was afebrile upon presentation. Intubation and intensive care were required for his convulsive status epilepticus. He was put on five ASDs including clobazam, levetiracetam, topiramate, phenytoin and valproate for seizure control. Lumbar puncture showed lymphocytosis with normal glucose and protein levels in cerebrospinal fluid (CSF). Herpes simplex virus, varicella zoster virus and enterovirus PCR of the CSF were negative. Serum and CSF autoimmune markers were negative. Brain MRI showed T2-weighted hyperintensities over bilateral hippocampi and parahippocampal gyri. Autoimmune limbic encephalitis was suspected. The patient was started on PE as empirical treatment. A total of five sessions were carried out. He recovered slowly with seizure control. ASDs were gradually tailed down afterwards.

2. Methods

2.1. Plasmapheresis procedure

PE was performed with COBE machinery (manufactured by Terumo BCT, Tokyo, Japan). A total of 2000 mL plasma was removed in exchange for 2000 mL of 5% normal serum albumin in every session. The patient had a total of five sessions, with each lasting for about an hour. ASD levels were monitored in two of the five PE sessions, the third and the fifth, which were labeled as the first and second PE studies respectively.

Our patient was on five ASDs administrated at specified times around both PE studies (Table 1). All the ASDs had been started for at least two days before the first PE study. The majority of the ASDs were given by the intravenous route. The concomitant medication and intravenous infusion is listed (Table 2). His serum albumin levels were 29 g/L and 43 g/L before the first and second PE studies respectively.

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Table 1
ASDs given at the time of first and second PE studies, their routes of administration, dosage, frequency and timing of administration.

PE study	Medication	Route of administration	Dosage	Frequency	Timing
1st (started at 12 pm)	Clobazam	Nasogastric tube	20 mg	Every 12 h	8 am, 8 pm
	Levetiracetam	Intravenous	1500 mg	Every 12 h	8 am, 8 pm
	Phenytoin	Intravenous	100 mg	Every 8 h	12 am, 8 am, 4 pm
	Topiramate	Nasogastric tube	150 mg	Every 12 h	8 am, 8 pm
	Valproate	Intravenous	600 mg	Every 8 h	12 am, 8 am, 4 pm
2nd (started at 4 pm)	Clobazam	Nasogastric tube	20 mg	Every 8 h	12 am, 8 am, 4 pm
	Levetiracetam	Nasogastric tube	1500 mg	Every 12 h	8 am, 8 pm
	Phenytoin	Intravenous	100 mg	Every 6 h	2 am, 8 am, 2 pm, 8 pm
	Topiramate	Nasogastric tube	150 mg	Every 12 h	8 am, 8 pm
	Valproate	Intravenous	600 mg	Every 8 h	12 am, 8 am, 4 pm

Table 2
Other concomitant medications and intravenous infusion given around the time of the two PE studies.

PE study	Medication or infusion	Route of administration	Dose	Frequency	Timing
1st (started at 12 pm)	Acyclovir	Intravenous	500 mg	Every 8 h	12 am, 8 pm, 4 pm
	Amoxicillin and clavulanate	Intravenous	1200 mg	Every 8 h	12 am, 8 pm, 4 pm
	Pantoprazole	Intravenous	100 mg	Every 8 h	12 am, 8 am, 4 pm
	Thiamine	Intravenous	100 mg	Every 24 h	12 pm
	Dextrose 5%	Intravenous	60 mL per hour	Continuous	
2nd (started at 4 pm)	Acyclovir	Intravenous	500 mg	Every 8 h	12 am, 8 pm, 4 pm
	Lansoprazole	Nasogastric tube	15 mg	Every 24 h	12 pm
	Piperacillin and tazobactam	Intravenous	4500 mg	Every 8 h	12 am, 8 pm, 4 pm
	Thiamine	Intravenous	100 mg	Every 24 h	12 pm
	Vancomycin	Intravenous	1000 mg	Every 12 h	8 am, 8 pm

2.2. Specimen collection

Serum samples for clobazam, levetiracetam, topiramate, phenytoin and valproate assays were collected before, around the middle and half an hour after each PE study.

2.3. Drug level assay

The serum levels of clobazam, levetiracetam and topiramate were measured by National Medical Services Labs (Willow Grove PA, USA) using liquid chromatography tandem-mass spectrometry. The serum level assays of phenytoin and valproate were done by the biochemistry laboratory of our institution. Serum phenytoin level was measured by competitive immunoassay with VITROS PHYT Slide, manufactured by Ortho-Clinical Diagnostics (Rochester, NY, USA). Serum valproate was measured by competitive immunoassay with VITROS 5600 Integrated System, manufactured by Ortho-Clinical Diagnostics (Rochester, NY, USA). The total, instead of free drug fractionated levels were measured.

Table 3
Changes of serum ASD levels around the two PE studies.

PE study	Medication	Pre-PE (mg/L)	During PE (mg/L)	Post-PE (mg/L)	Amount of ASD eliminated (mg)
1st	Clobazam	1.40	0.84 (60%)[a]	1.00 (71%)	3
	Levetiracetam	26	22 (85%)	19 (73%)	315
	Phenytoin	<3.02	<3.02	<3.02	NA[b]
	Topiramate	3.4	2.7 (79%)	2.5 (74%)	47.25
	Valproate	67.56	50.80 (75%)	46.31 (69%)	NA
2nd	Clobazam	2.00	1.70 (85%)	1.50 (75%)	3.75
	Levetiracetam	12	10 (83%)	10 (83%)	90
	Phenytoin	<3.02	<3.02	<3.02	NA
	Topiramate	4.3	3.7 (86%)	3.4 (79%)	47.25
	Valproate	59.76	81.74 (136%)	85.49 (143%)	398.40

[a] Percentage of plasma level when compared with the pre-PE value is shown in the brackets.
[b] Not assessed due to the reasons stated in the text.

3. Results

Changes in the plasma level of the five ASDs around the two PE studies are shown (Table 3). The patient did have a convulsion during and immediately after these two PE sessions. The serum levels of clobazam, levetiracetam and topiramate dropped appreciably during the course of PE. The drops in ASD level during and after PE varied between 60% to 86% compared with the pre-PE levels as baseline (Fig. 1).

The changes in serum phenytoin could not be assessed as the serum levels of the drug remained low so that they were unable to be reliably quantified by our laboratory. This was probably because our patient was a fast metabolizer of phenytoin. A case of a persistent low serum phenytoin level due to hypermetabolism has been described [3].

The serum valproate levels showed a reduction in the first PE study. However, in the second PE study, there was a rise in serum valproate level. We considered the results unreliable in reflecting the effect of PE as there was an intravenous bolus dose of 600 mg valproate at the start of the PE process (Table 2). The valproate levels during and after PE may be affected by the injection directly.

4. Discussion

Therapeutic PE is a process involving extracorporeal separation of plasma from the cellular component of blood, removing the plasma in exchange for replacement fluid which in our case was albumin. Drugs within the plasma component of the patient's blood were inevitably removed. Among the ASDs we monitored, except the discarded results of phenytoin and valproate in the second PE study due to the aforementioned reasons, there was a trend of significant ASD level reduction after PE. Serum valproate levels showed a drop of 31% after the first PE study and is comparable with other published reports [4,5]. Given that our patient's weight was 75 kg, and the volume of distribution of clobazam, levetiracetam, topiramate and valproate are 1.31 L/kg, 0.6 L/kg, 0.7 L/kg and 0.25 L/kg respectively, the amounts of drugs eliminated by PE are as charted (Table 3).

The extent of serum drug level reduction should depend on both the pharmacokinetics of a drug and patient's physiology. There are few systematic trials analyzing ASD pharmacokinetics during PE. Most of

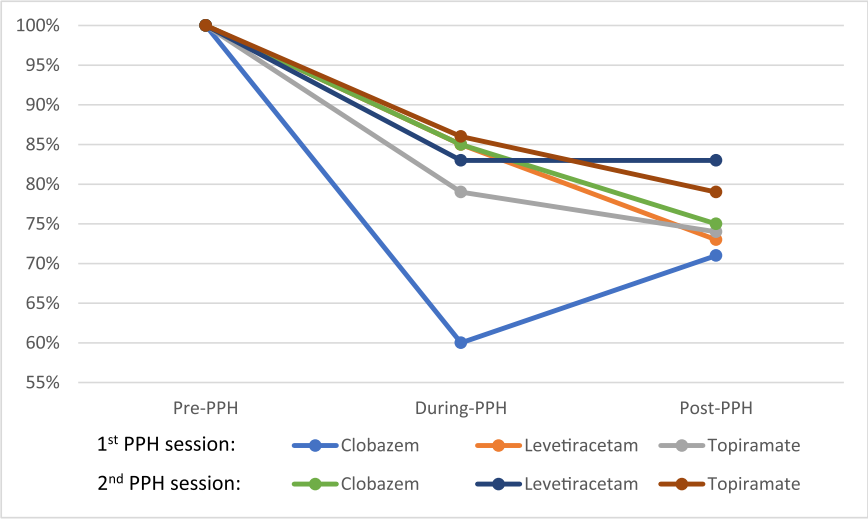

Fig. 1. Relative changes in plasma levels of clobazam, levetiracetam and topiramate during and after PE when using the pre-PE levels as a baseline reference.

the available information are from case reports. However, there are several factors we can take into consideration to estimate the effect of PE on ASD level.

Considering drug factors, the higher protein binding tendency of the drug, the greater portion of drug remains in blood and thus can be removed by PE [6]. This is in contrast to other extracorpereal treatments such as hemofiltration and hemodialysis in which drugs that are more protein bound are theoretically less likely to pass through the semipermeable membrane and get removed [7]. Also, the lower the volume of distribution of a drug means a larger proportion of it is within the intravascular compartment [6]. As a result, larger amount of the drug is removed by PE. For example, theophylline, a drug with high plasm protein binding and low volume of distribution, has been reported to be effectively removed by PE [8].

Timing of dosing also plays a role. Intravenous medication dosed shortly before the beginning of PE means that the plasma concentration of drug is highest because the drug has yet to distribute to other body compartments. Thus, the higher the concentration of the drug at the start of the PE means a larger portion of it ended up being removed. Practically, it may be advisable to suggest a longer time gap between drug administration and PE in order to minimize medication removal by PE.

The drops in ASD plasma levels during and after PE may lead to the concern of the patient's vulnerability to seizures and hence the necessity to increase the dosage of the anticonvulsant before PE. In clinical practice, it may be challenging to do so. First, the amount of dosage increment is difficult to predict as the impact of PE on ASD serum level depends on multiple factors including; the pharmacokinetics, patient factors which may vary temporally and individually, and drug interactions. In our case, we did not give an extra ASD dose after PE. On the other hand, PE has been proposed as a therapy for drug intoxication [9,10]. Rebound of the plasma drug level is possible though it was not explored in our case.

5. Conclusion

To the best of our knowledge, this is the first report to describe the changes in serum levels of clobazam, levetiracetam and topiramate by PE. There is a consistent decrease in serum levels of all the three ASDs after PE. Larger cohort studies are needed to verify our findings. Though there are probable drops in serum ASD levels after PE and theoretical risk of a breakthrough seizure, we do not recommend routine replacement doses of ASD before PE at this stage until further clinical research is available.

Disclosure of conflicts of interest

All authors have nothing to disclose.

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