

Stupor Due to Possible Interaction Between Lorazepam and Valproic Acid: Report of Two Cases



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SUMMARY

Valproate (VPA) and lorazepam are excreted mainly by glucuronide conjugation. VPA reduces the excretion of lorazepam as a result of the administration of these two medications together. As a result of these interactions, even if rarely, serious adverse effects such as coma may develop. Herein, we present two cases of stupor which developed after the addition of lorazepam to treatment administered with VPA. The first patient was being followed for five years with a diagnosis of schizoaffective disorder. She was subjected to a treatment of VPA at 1000 mg/day and an antipsychotic drug. On the twentieth day of the treatment, Lorazepam 2.5 mg was administered as an anxiolytic. The second patient was being followed with a diagnosis of schizophrenia for nine years. A VPA treatment of 750 mg/day was initiated together with an antipsychotic treatment. On the eighth day of the treatment, Lorazepam 2.5 mg was administered. A few hours later, a stupor manifestation developed in both of the patients. Administration of the entire medication to the patients was terminated and parenteral liquid administration was initiated. The clinical profile was back to normal approximately 24-36 hours following the termination of the medication.

Studies about the clinical reflections of the VPA and Lorazepam interaction are limited. However, it must be remembered that as a result of the interaction of these two medications, conditions that vary between stupor and coma may arise.

Keywords: valproate; lorazepam; stupor; drug interaction

INTRODUCTION

Besides being an antiepileptic drug, VPA is also utilized in psychiatry for the acute and prophylactic treatments of mood disorders. Lorazepam is preferred for the treatment of both mood and anxiety disorders, and the aggressive and anxious behaviors which are observed during the acute periods of schizophrenia and similar psychoses. Despite the differences with respect to their intended uses, mechanisms of action, pharmacodynamics and certain pharmacokinetic features, VPA and Lorazepam are excreted mainly by glucuronide conjugation. There are studies which demonstrate that VPA reduces the excretion of Lorazepam as a result of the administration of these two medications together (Samara et al.1997, Anderson et al.1994) Nevertheless, studies which reveal the clinical reflections of this interaction are limited (Lee et al.2002). In this article, two stupor cases which developed due to a possible VPA-Lorazepam interaction following the addition of Lorazepam

to the treatments by reason of behavioral disorders which were observed during the VPA treatments are presented.

Case I

A 25-year-old female patient was hospitalized due to aggressiveness and her refusal of drug administration. The patient was being followed for the last five years with the diagnosis of schizoaffective disorder. She was subjected to an outpatient treatment with haloperidol at 10 mg/day, and biperiden 2 mg/day. On admission, VPA 1000 mg/day was added. On the twentieth day of the treatment, Lorazepam 2.5 mg was administered orally as an anxiolytic. Approximately six hours later, a stupor manifestation developed in the patient. Overall routine biochemical analyses of the patient were requested. In addition, serum ammonium and VPA levels were also requested. The VPA level was 95 mg/l, and other biochemical analysis results were at the normal limits. The neurologic examination

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was normal except for the presence of stupor. Administration of all medications to the patient was terminated and parenteral liquid administration was initiated. After the termination of the medication, the patient started to recover consciousness and react to verbal and painful stimuli. The clinical profile was back to normal between approximately 18 and 24 hours following the termination of the medication.

Case II

A 26 year old female patient was being followed with a schizophrenia diagnosis for nine years. She was hospitalized in our clinic for the reason of excitation. She had not regularly received outpatient treatment (haloperidol 10 mg/day, biperiden 2 mg/day). She also had not used any depot antipsychotic medication. Upon observation of the hypomanic symptoms in the patient, a VPA treatment of 750 mg/day was initiated together with an antipsychotic treatment (haloperidol 10 mg/day, biperiden 2 mg/day) which was applied because of the psychotic symptoms. On the eighth day of the treatment, Lorazepam 2.5 mg was administered orally as an anxiolytic. In a few hours, a stupor developed in the patient. Overall routine biochemical analyses of the patients were requested. In addition, serum ammonium and VPA levels were also requested. The VPA level was 88 mg/l. Any metabolic anomalies or neuropathological findings responsible for the development of the stupor could not be demonstrated in the patient. Administration of all medications to the patient was terminated and parenteral liquid administration was initiated. The clinical profile was back to normal approximately 36 hours following the termination of the medication.

DISCUSSION

In the course of the administration of the VPA together with the antipsychotic treatment, consciousness disorders were not observed in either case. During the follow-up period, the VPA levels of both patients were identified as normal. A 2.5 mg dose of Lorazepam was administered orally to the first patient on the 20th day and to the second patient on the 8th day, and following these treatments a stupor developed in both patients. We could not demonstrate any cause to explain these conditions. Their routine biochemical analyses and serum ammonium and VPA levels were identified as normal. During their neurological examinations, any abnormal pathology was not observed. It was evaluated that the clinical manifestations in these two patients may have been related to a possible VPA and Lorazepam interaction. At their case presentation, Lee et al. have reported that a coma develops in the patients following a possible VPA and Lorazepam interaction manifestation (Lee et al. 2002). The studies demonstrated that VPA inhibits the metabolism of several

medications (lamotrigine, hydroxyphenobarbital, zidovudine, etc) which are eliminated by glucuronidation (Samara et al. 1997). Lorazepam is another drug which is eliminated by glucuronidation. For this reason, an interaction of the VPA with Lorazepam may be in question. There are several studies which demonstrate the interaction of these two medications (Chung et al. 2005, Chung et al. 2008). Anderson et al. have examined the VPA and Lorazepam interaction on rats (Anderson et al. 1994). Their study demonstrated that following the Lorazepam administration to the healthy rats that were subjected to a long VPA application, in the majority of the rats the Lorazepam clearance was reduced, whereas its blood levels were increased. In their study, Chung et al. revealed that the interaction between pharmacodynamic and pharmacokinetics of VPA and Lorazepam demonstrated certain differences among the patients. On the grounds of the gene analysis results, they argued that these differences which arose due to the interactions might be in question in the UGT2B7 gene, and especially in the homovariations of the UGT2B7 and UGT2B15 genes (Chung et al. 2005, Chung et al. 2008). Samara et al. examined the effect of the VPA on the pharmacodynamic properties and pharmacokinetics of Lorazepam in healthy volunteers. They demonstrated that the Lorazepam clearance was reduced 31% following the administration of Lorazepam together with VPA. They deduced that VPA affects the steady state pharmacokinetics of Lorazepam, resulting in modestly increased plasma levels and reduced apparent clearance from plasma (Samara et al. 1997). And they argued that, in connection with this, the sedative effects of Lorazepam may increase.

In conclusion, there are several laboratory and genetic studies which were performed on the interaction between VPA and Lorazepam (Samara et al. 1997, Anderson et al. 1994, Chung et al. 2005, Chung et al. 2008). Nevertheless, the references about the clinical reflections of the VPA and Lorazepam interaction is limited (Lee et al. 2002). It must be remembered that as a result of the interaction of these two medications, conditions which vary between stupor and coma may arise.

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