Serican Journal of Medicine
2025, VOL. 2, NO. 1, 23229
https://doi.org/10.17161/sjm.v2i1.23229

A possible drug interaction between sodium valproate and clonazepam resulting in severe drowsiness and limb weakness: A case report and literature review

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ABSTRACT

The treatment process of an 11-year-old girl diagnosed with Angelman syndrome, who experienced severe drowsiness and limb weakness following the combination of sodium valproate and clonazepam, is analyzed herein. Initially, the patient was prescribed levetiracetam, clobazam, clonazepam, and sodium valproate. However, she subsequently developed significant lethargy and weakness in her limbs. Upon her admission, the clinical pharmacist take medication reconciliation the following day, identifying clonazepam as a highly relevant factor in her condition. The medical team collaboratively adjusted the inappropriate medications. Ultimately, the patient's symptoms improved, leading to her discharge.

ARTICLE HISTORY
Received: Dec. 19, 2024
Accepted: Jan. 19, 2025

KEYWORDS
valproate, clonazepam, limb weakness

EDITED BY
Jun Pang

REVIEWED BY
Haixia Xu, Wang Liu

Introduction

Epileptic seizures are a common clinical feature of Angelman syndrome (AS). Up to 90% of AS patients will suffer from epilepsy, among which the most common is in those with gene deletions. Although evidence is lacking, experience suggests that patients may benefit from medications that are effective in treating myoclonic seizures, such as levetiracetam, clobazam, and clonazepam [1]. Epileptic seizures often require long-term anti-epileptic treatment.Medication reconciliation should be throughout the entire medical process. Drugs that may cause adverse reactions and special groups need special attention. Pharmacists communicate with patients to understand whether the overall medication situation before and after medical handover is consistent, work with the medical team to adjust inappropriate medication, and make detailed and comprehensive records to prevent adverse drug events during the medical process and ensure patient medication safety. The most common adverse reactions of clonazepam are abnormal excitement and muscle weakness. However, cases of severe drowsiness and muscle weakness caused by the combination of sodium valproate and clonazepam are rarely reported. This article reports a case of severe drowsiness and muscle weakness caused by the combination of sodium valproate and clonazepam. This case also reflects the importance of pharmacists' Medication reconciliation the diagnosis and treatment process.

Materials and Methods

Case presentation

An 11-year-old girl who weighed 48kg,was admitted to the hospital with the chief complaints of "limb weakness for 1 week, worsening with fever and rales for 1 day". She was diagnosed with "Angelman Syndrome" in 2017 at another hospital and has been taking oxcarbazepine, sodium valproate, levetiracetam, clonazepam, clobazam, and lamotrigine due to epileptic seizures. From August 7, 2024 to August 12, 2024, she was administered levetiracetam (0.5g p.o.) plus clonazepam (1mg p.o.), clobazam (15mg

p.o.), and sodium valproate sustained-release tablets (I) (0.5g p.o.) every 12h. The parents of the girl complained that after starting sodium valproate sustained-release tablets on August 7, 2024, the girl experienced drowsiness and weakness in the limbs, and intermittent irritability. On August 11, 2024, she developed an unsteady gait, appeared drunk, and was unwilling to move. On August 12, 2024, she presented paralysis of her limbs, unable to stand, restless, unwilling to open her eyes, and accompanied by the sound of phlegm in her throat. She was given diazepam (5 mg) intravenously and fluid replacement and then her symptom of restlessness was relieved.

Admission auxiliary examination: Blood ammonia 52.00 umol·L^{-1}. Arterial blood gas analysis: Lactate 3.8 mmol·L^{-1}, oxygen partial pressure 67.7 mmHg, actual base excess -3.1 mmol·L^{-1}. Glucose measurement and electrolytes: Glucose 6.04 mmol·L^{-1}, potassium 3.43 mmol·L^{-1}, sodium 148 mmol·L^{-1}, chloride 112 mmol·L^{-1}. Valproic acid blood concentration (sampled 8 hours after medication): 120.00 ug·mL^{-1}. Creatine kinase 470 U·L^{-1}. No other abnormalities were found.

Treatment process: The patient experienced weakness in her limbs and severe drowsiness after taking sodium valproate. So the use of sodium valproate was suspended at the night of August 12, 2024. The patient had recurrent fever, weak cough reflex, and rales in the throat. She had excessive phlegm that was not easily expectorated, and was treated with cefoperazone-sulbactam for infection. Clinical pharmacists took medication reconciliation for children (Table 1).

On the second day after discontinuing sodium valproate, the patient could open her eyes but remained somnolent. The physician instructed to change the clonazepam dosage to 0.5 mg, p.o., every 12h. Clinical pharmacists and physicians conducted case discussions. The clinical pharmacist considered that the patient's symptoms of drowsiness and limb weakness might be due to the interaction between sodium valproate and clonazepam, which exacerbated the central nervous system depressant effects of clonazepam, leading to limb weakness and a significant increase in creatine kinase to 470U·L^{-1}. The third day after discontinuing sodium valproate, the patient's valproic acid concentration in blood was measured at 21.60 μg/ml, and creatine kinase had decreased to 160U·L^{-1}. The patient could grasp objects with her hands but still felt weak and was unable to sit or stand. On August 16, 2024, the patient stopped taking clonazepam and added sodium valproate (0.25g, p.o., q12h) for anti-epileptic treatment. The dosage of levetiracetam and clobazone remained the same as before. The parents reported that the patient slept deeply after taking sodium valproate in the morning and was able to play after waking up. The parents did not give the patient sodium valproate at night, and the patient slept again at 3:00 a.m. She was able to stand for a short period and her muscle strength had recovered compared to before. Her body temperature was normal, the cough reflex was still weak, and the phlegm in the throat had also decreased. Considering the patient's drowsiness after taking 0.25g of sodium valproate in the morning, the sodium valproate regimen was adjusted to 0.125g, p.o., q12h on August 19, 2024. On August 20, 2024, the patient slept for 7 hours at night and was in good mood. She could sit up independently and eat a small amount by herself. Additionally, her coughing and phlegm had weakened. On August 23, 2024, the valproic acid concentration in blood was 37.80 μg/ml. Considering that the patient has no epileptic seizures, the anti-epileptic regimen should be continued. Upon discharge, the patient could walk with support and was in mood.

Literature Review

We searched the PubMed database with the keywords "sodium valproate", "clonazepam", "toxic","Benzodiazepines", "CK" (creatine kinase), and "Limb weakness". One literature with one case report was retrieved on the report of myotoxicity caused by the combination of sodium valproate and clonazepam [2]. Another case was reported on the case of elevated muscle enzymes caused by clonazepam [3]. In addition, the third case with the adverse effects of clonazepam overdose was reported, including drowsiness, falls, syncope, systemic hypotonia, and periodic coma [4].

Results

Literature Case 1 [2]. Xiaonian Han et al. reported on a 24-year-old female with a 2-year history of epilepsy who experienced severe adverse reactions during oral administration of clonazepam (2 mg, bid) combined with sodium valproate (0.5 mg, bid) for 21 days. Symptoms included muscle weakness, pain, inability to rise from bed, and elevated creatine phosphokinase levels. Two weeks after discontinuing clonazepam, her muscle weakness gradually improved and she was able to stand but not walk. Upon re-admission, blood tests including complete

Table 1. Patient's anti-epileptic medication history.

Drug	Weight (kg)	Oral dosage	Start and End Time	Remarks (Reasons for Adjustment, Medication Compliance, Efficacy, Adverse Reactions, etc.)
Oxcarbazepine	NA	NA	2015-2017	Medications for epileptic seizures. She showed clenched fists with both hands at night, had poor sleep and slept only three hours each night. After taking medications, the symptoms and sleep quality improved.
Levetiracetam	NA	0.5 mg q12h	2017-To present	In 2017, she had symptoms of skewed mouth and strabismus. Levetiracetam was switched to treat these conditions.
Clonazepam	NA	Starting from 0.25mg, q12h and gradually increasing to 1mg, q12h	2019-05/31/2023	In 2019, she experienced tremors in both feet while defecating and dressing, lasting from more than 10 seconds to about 1 minute. The symptoms were significantly relieved after the addition of clonazepam. In 2021, she had convulsions once when she had a fever, which was characterized by unresponsiveness, eyes turning up, and tonic shaking of the whole body, which resolved spontaneously in about 1 minute.
Clonazepam	NA	0.5mg, am 0.25mg,pm	05/31/2023-04/08/2024	
Sodium valproate oral solution	NA	15ml, q12h	05/31/2023-11/30/2023	Since the seizures couldn't be controlled, her sleep increased after adding sodium valproate. Before taking valproate, she slept about 5 to 6 hours a day. After taking valproate, her sleep duration generally was around 9 to 10 hours. At first, the tremors in her both feet improved for a few days. Later, after adjusting the dosage several times, the effect was not satisfactory. In November 2023, after discontinuing "sodium valproate", she had frequent tremors in both feet, which lasted for 20 to 30 minutes, and occasionally accompanied by tremors in both upper limbs.
Clobazam	41.5	5mg-15mg, q12h	04/08/2024-To present	Her feet trembled when defecating and dressing. On April 10, 2024, she suddenly had a convulsion, which was characterized by unresponsiveness, staring eyes, and rigid shaking of the limbs, which lasted for about 10 minutes. She switched to clobazam and initially the number of shaking of her feet and hands was significantly reduced, which lasted for more than 10 seconds. The shaking symptoms impro ved for 1 month, with attacks occurring 1-2 times a day. Later, the effect was not good, and the shaking of the feet and hands increased and lasted for 20-30 minutes.
Clonazepam	47	1mg,q12h	07/15/2024-08/08/2024	She tend to have shaking feet and occasionally shaking hands when defecating, dressing, stimulating the lower limbs, and falling asleep. After adding lamotrigine, she became excited and her sleep worsened significantly. She slept about 3 hours a day. The duration of her shaking was shortened, but the frequency of her attacks increased. She had recurring attacks throughout the day, which could be relieved on her own.
Lamotrigine	47	12.5mg,q12h	07/15/2024-08/08/2024	
Levetiracetam	48	0.5mg ,q12h	08/08/2024-08/12/2024	
Clobazam	48	15mg,q12h	08/08/2024-08/12/2024	After she stopped taking lamotrigine and added sodium valproate, she began to experience drowsiness, limb weakness, and intermittent irritability. Since August 11, she has had an unsteady gait, appeared drunk, and was unwilling to move. Since August 12th, she had symptoms of limb paralysis, inability to stand, restlessness, and unwillingness to open her eyes.
Clonazepam	48	1mg,q12h	08/08/2024-08/12/2024	
divalproex sodium extended-release tablets	48	0.5g ,q12h	08/07/2024-08/12/2024	

blood count, urine tests, liver and kidney function tests, electrolytes, and blood ammonia were all normal, but her serum creatine kinase was significantly elevated to 4261 $U{\cdot}L^{-1}$ (normal range 38-174 $U{\cdot}L^{-1}$), while her serum sodium valproate concentration was 101.89$\mu g{\cdot}mL^{-1}$ (normal range 50-100$\mu g{\cdot}mL^{-1}$).

Literature Case 2 [3] . Gupta et al. reported a case of elevated muscle enzymes in a 15-year-old male patient after oral administration of clonazepam. He developed symptoms of anxiety, irritability, ataxia, and vomiting after taking clonazepam (1 mg, tid) for 1 day, accompanied by elevated muscle enzymes reaching 5969 $U{\cdot}L^{-1}$ (upper limit of normal: 195 $U{\cdot}L^{-1}$). One month after discontinuing clonazepam, the symptoms disappeared, and muscle enzymes returned to normal levels.

Literature Case 3 [4]. Uçar etal. reported a case of a 30-month-old baby girl who suffered secondary poisoning due to accidental clonazepam overdose. She was presenting with symptoms of somnolence, stumbling, falling, syncope, weakness, decreased muscle tone, reduced reflexes, periodic coma pattern, sinus tachycardia, and prolonged QTc interval. Fifteen hours after presentation, her serum clonazepam concentration was 241.8 ng/mL (reference range: 10-75 ng/mL). The girl's neurological condition improved after treatment with flumazenil, and her clinical symptoms resolved after 72 hours of treatment.

Discussion and conclusion

Valproate is a weak inhibitor of certain cytochrome P450 isoenzymes [5], and cytochrome P450 may play a significant role in the reduction and oxidation of clonazepam [6], which may explain the enhanced central nervous system depressant effects of clonazepam and the resulting severe drowsiness and limb weakness observed when valproate is added. Severe somnolence, unsteady gait, and significant weakness can all be symptoms of clonazepam overdose. Additionally, the patient received 5 mg of diazepam injection intravenously once on the day of admission.Diazepam belongs to the class of benzodiazepines. When it is used in combination with two other benzodiazepines, namely clonazepam and clobazam, the central inhibitory effect is enhanced.Therefore, the patient's drowsy state was significantly more pronounced after admission compared to before. However, cases of myopathy caused by sodium valproate have been reported in children. Ahmed et al. [7] reported an 8-year-old boy who developed progressive weakness in both lower limbs after taking sodium valproate for 6 months. He had difficulty getting up from a sitting position, climbing stairs, running or playing games, but he had no pain in his legs. Routine examinations included serum lactate, creatine kinase, and serum valproic acid levels, and nerve conduction results were normal. However, needle electromyography of his lower limb muscles showed that the action potential had a short duration and a low amplitude, which was in line with the characteristics of myopathy. Further examinations revealed a low level of serum carnitine. After discontinuing sodium valproate and taking carnitine orally for three weeks, the patient's muscle strength recovered. However, the patient in this case did not have symptoms of progressive weakness of the limbs after taking sodium valproate again, so the possibility of myopathy caused by valproic acid was not considered.

The patient in this case had previously been on a regimen of "levetiracetam, clonazepam, and valproate" for 6 months. During this period, the patient slept about 10 hours a day, which was more than before but not to the level of severe lethargy, and no limb weakness was observed. However, in this episode, the clonazepam dose was 2.6 times the previous dose, and with the concurrent use of clobazam, the child exhibited severe drowsiness and weakness after adding valproate. The patient's creatine kinase was 168$U{\cdot}L^{-1}$ on August 5, 2024 (normal range 30-135$U{\cdot}L^{-1}$), and it rose to 470$U{\cdot}L^{-1}$ on August 13, 2024, which was significantly higher than before.Although she cannot verbally express myalgias verbally but she was irritable. We used the drug interaction probability scale proposed by Horn [8] to evaluate drug interactions.Our patient scored 7 on this scale, indicating a high likelihood of a drug interaction between valproate and clonazepam.

Clobazam is extensively metabolized in the liver, and the main metabolic pathway is N-demethylation, mainly metabolized by CYP3A4, followed by CYP 2C19 and CYP 2B6 [9]. Walzer et al. [10] conducted a population pharmacokinetic analysis of seven phase II-III clinical studies to examine drug interactions when clobazam was co-administered with commonly used antiepileptic drugs. The analysis results indicate that valproate has no effect on the pharmacokinetics of clobazam and its metabolite N-norclobazam after reaching steady state, and clobazam does not affect the pharmacokinetics of valproic acid. Therefore, the occurrence of adverse

reactions caused by the interaction between clobazam and valproate is not considered in this case.

Valproate encephalopathy is typically associated with hyperammonemia, with typical manifestations of apathy, somnolence, and cognitive impairment. This condition occurs shortly after the use of valproate and the encephalopathy resolves rapidly upon discontinuation of the drug [2]. Our patient's blood ammonia was 52.00 μmol·L^{-1} (normal range 9-30 μmol·L^{-1}) on the sixth day after sodium valproate was added., which was not significantly elevated. Three days after stopping sodium valproate, the patient's symptoms of lethargy and poor muscle strength were not significantly relieved, so the possibility of valproic acid encephalopathy was ruled out.

After discontinuing clonazepam and taking sodium valproate orally again, the patient in this case did not exhibit symptoms of limb weakness or severe lethargy, and her mental state improved significantly. During the course of treatment, although electromyography and muscle biopsy were not completed to confirm the occurrence of myotoxicity, the patient's muscle strength recovered after discontinuing clonazepam. One week later, the patient's creatine kinase value dropped to 47 U·L^{-1}. Therefore,we considered that the patient in this case had adverse reactions of significant central nervous system suppression and myotoxicity after the combined use of sodium valproate and clonazepam. In addition, the patient's weak cough reflex and heavy phlegm sounds during this course of the disease may also be related to the decrease in systemic muscle strength resulting in the inability to cough up sputum.

In conclusion, we described a case of the serious adverse drug reaction of severe drowsiness and limb weakness caused by the combination of sodium valproate and clonazepam. The aim is to enhance clinicians' awareness of the interaction between the two drugs, even though this condition is rare.

Acknowledgments:

We would like to thank our patient and her families for their patience in replying our questions during the follow-up.

Author contributions:

Xiaotong Meng completed the literature review and wrote the article. Bo Wang completed the case presentation. Manqing Deng completed patient's medication reformulation.

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