Hypothermia in an Adolescent Due to Probable Drug-Drug Interaction Involving Clobazam

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We report on a 16-year-old female who developed hypothermia as a result of a drug-drug interaction that produced supratherapeutic serum concentrations of clobazam. Although clobazam and its active metabolite (*N*-desmethyloclobazam) are metabolized by cytochrome 2C19 (CYP2C19), literature suggests that clobazam-associated drug interactions involving this isoenzyme are not clinically relevant because of its wide therapeutic index. This report describes clobazam-associated hypothermia due to supratherapeutic serum concentrations of clobazam that resulted from the combination of 2 CYP2C19 inhibitors.

ABBREVIATIONS CLB, clobazam; CYP, cytochrome; NCLB, *N*-desmethyloclobazam

KEYWORDS clobazam; CYP2C19; drug interaction; hypothermia; omeprazole; oxcarbazepine; pediatric

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Introduction

Pharmacologic agents, including sedatives such as benzodiazepines, have been implicated as a cause of central thermoregulatory failure resulting in hypothermia.¹ Clobazam (CLB) is a 1,5-benzodiazepine approved for use in Lennox-Gastaut syndrome.² It is often used as adjunct therapy in the management of patients with refractory seizures.² A review of the literature found published case reports of clobazam-associated hypothermia that occurred in one adult and 2 pediatric patients.^{3,4}

CLB is metabolized primarily by cytochrome (CYP) 3A4 to an active metabolite (i.e., *N*-desmethyloclobazam [NCLB]), which represents about 20% of its activity (Figure 1).^{2,5,6} NCLB is further metabolized by CYP2C19 to an inactive metabolite.^{5,6} Factors that affect CYP3A4 or CYP2C19 activity have the potential to produce changes in CLB and/or NCLB concentrations, which can cause a loss of therapeutic benefit (induction of CYP3A4), produce adverse effects (inhibition of CYP2C19), and complicate therapeutic drug monitoring of CLB. However, drug-drug interaction studies⁷ evaluating CLB and CYP3A4 or CYP2C19 inhibitors or inducers have concluded that the interactions are not generally clinically relevant. Conversely, experts argue that the long half-life of both CLB (36–42 hours) and NCLB (71–82 hours) may make the effect of the drug interaction during steady state more clinically relevant than are effects elucidated in one-dose drug-interaction studies.^{8,9}

A review of the literature was performed using the keywords “CLB” and “hypothermia.” Select references from identified articles were also used. None of the previously reported cases of CLB-associated hypothermia reported serum concentrations of CLB or NCLB at the time of the adverse effect. We report a case of CLB-

associated hypothermia in a pediatric patient believed to be secondary to increased concentrations of NCLB that resulted from a drug interaction with omeprazole and oxcarbazepine.⁶

Case Report

A 16-year-old, 34-kg Caucasian female with a past medical history significant for developmental delay, schizencephaly, ventriculoperitoneal shunt, and seizure disorder was brought to the emergency department with decreased responsiveness, altered mental status, and inability to take her medications. Over the prior 2 months, the patient had demonstrated a decrease in activity, including oral intake, and an increase in nasal congestion. In the emergency department, the patient was found to have a temperature of 31.3°C, a heart rate of 55 beats per minute, and a blood pressure of 73/44.

Three months prior to admission, oxcarbazepine was initiated and titrated to 450 mg by mouth every 12 hours (26 mg/kg/day). Two months prior to admission, the patient's CLB total daily dose had been increased by 5 mg, from 7.5 mg/day (0.22 mg/kg/day) to 12.5 mg/day (0.37 mg/kg/day). During the month prior to admission, the patient had experienced decreased energy and oral intake that were attributed to a viral illness. Other pertinent home medications included levetiracetam 1000 mg in the morning and 1500 mg every evening (73 mg/kg/day). She had also been receiving chronic omeprazole (20 mg daily) for an unknown period of time.

Upon arrival to the emergency department, the patient was warmed with intravenous normal saline and blankets. She was started on piperacillin-tazobactam (3.4 g every 8 hours) and vancomycin (700 mg; 20 mg/kg every 6 hours) empirically, given her history of frequent urinary tract infections and concerns for

Figure 1. Metabolism of clobazam.

sepsis based on the hypothermia and elevated serum C-reactive protein. The patient was admitted to the pediatric intensive care unit as a result of concern for sepsis.

Antibiotics were discontinued at 48 hours when sepsis was ruled out following a negative lumbar puncture and urine analysis. Thyroid-stimulating hormone and cortisol concentrations were within normal limits. During the first day of admission, the patient developed respiratory failure and was intubated and placed on dopamine and norepinephrine due to cardiovascular compromise. The patient underwent a computed tomography of the head that was unchanged from her scan the previous week.

Her home seizure medications of levetiracetam, oxcarbazepine, and CLB were continued at the preadmission doses, and her omeprazole was switched to intravenous pantoprazole (40 mg daily). Antiepileptic serum concentrations were obtained the week prior to admission; randomly obtained concentrations were noted as follows: NCLB 8430 ng/mL (reference range: 300–3000 ng/mL), CLB 135 ng/mL (reference range: 30–300 ng/mL), oxcarbazepine 33 (reference range 10–35 ng/mL), and levetiracetam 24.6 mcg/mL (10–40 mg/L).

On the second day of hospitalization, CLB was discontinued as a result of the patient's elevated NCLB serum concentration, and oxcarbazepine was discontinued as a result of the serum concentration at the upper end of the reference range. The following day the patient began to improve, with increased alertness and ability to maintain her body temperature (Figure 2).

CLB and NCLB serum concentrations repeated 2 days following discontinuation of CLB showed an NCLB concentration of 5750 ng/mL and a CLB concentration of 143 ng/mL. Concentrations of levetiracetam were not repeated since previous tests were within the desired range. Likewise, oxcarbazepine concentrations were not measured, as previous values were within the reference range and this drug had been stopped. The patient's respiratory and cardiovascular systems continued to improve, and she was weaned off vasopressors and extubated on day 7 of admission. On day 9 of admission, the parents reported that the patient had returned to her baseline neurological status. She was transferred to the pediatric floor on day 10.

Out of concern for drug-drug interaction, pantoprazole was changed to oral ranitidine on discharge, which was to replace omeprazole. Oxcarbazepine was restarted at a dose of 300 mg every 12 hours (~18 mg/kg/day). Neurology did not resume the CLB during the patient's hospitalization because of the lack of seizures she experienced while on monotherapy levetiracetam. The patient was discharged on hospital day 12 with a plan for follow-up with neurology. There was no documentation of a CYP2C19 genotype or phenotype in her medical record. To date, these tests have not been performed.

Discussion

Our case is similar to previous reports of CLB-associated hypothermia; however, unlike previous

Figure 2. Temperature during admission.

reports, we report serum drug concentrations. In one previously published case,⁴ there is some indication that hypothermia from CLB may be related to dose. A 3-year-old with a history of epilepsy secondary to diffuse cerebral dysgenesis experienced hypothermia (36.1°C) at a dose of 0.6 mg/kg/day.⁴ Following resolution of hypothermia and a brief interruption of therapy, CLB was reintroduced. She is reported to have taken CLB at a dose of 0.15 mg/kg/day for 1 year following the initial hypothermic episode with no further issues in temperature regulation. This suggests that hypothermia associated with CLB could be dose or concentration related.

The second pediatric case involved a 4-year-old with seizures secondary to encephalomalacia, developed following a case of bacterial meningitis in the newborn period.⁴ She demonstrated a temporal relationship, with onset of hypothermia (32.8°C) at day 10 of therapy. The authors did not rechallenge this patient with CLB and she remained euthermic 1 year following discontinuation of CLB.

Another patient case of CLB-associated hypothermia has been described³ in a 58-year-old patient with a history of severe developmental delay and seizure disorder since the age of 3. This patient experienced 9 episodes of hypothermia over the course of 1 year. Infection and metabolic etiologies were initially considered but were ruled out. Upon review of his medication list, it was noted that CLB 10 mg twice a day had been added most recently, and initiation correlated with the onset of hypothermic episodes. CLB was discontinued. He was followed for 6 months and had no further hypothermic episodes.

Our case is unique in that the hypothermia was due to supratherapeutic serum concentrations of CLB that resulted from the combination of two CYP2C19 inhibitors. Although the dose was lower than that reported by DiFazio et al,⁴ our patient had an increased serum

concentration of NCLB that was associated with a drug-drug interaction of CLB with oxcarbazepine and omeprazole. Prior to initiation of omeprazole our patient had been receiving CLB without episodes of hypothermia. However, oxcarbazepine had recently been added, and CLB was increased in the months leading up to the hospital admission. Serum drug concentrations were measured and NCLB was found to be 2.8 times the upper limit of normal, whereas CLB was within the therapeutic range.

Figure 1 depicts the metabolism of CLB. In phase 1 of CLB metabolism, CYP3A4 is a major isoenzyme responsible for conversion to NCLB. Oxcarbazepine induces CYP3A4, which may lead to higher CLB conversion to NCLB. Both CYP2C19 and 2B6 have minor effects on conversion from CLB to NCLB; however, CYP2C19 is the major enzyme responsible for metabolism of NCLB to an inactive moiety. Both omeprazole and, to a lesser degree, oxcarbazepine inhibit CYP2C19, thereby increasing serum concentrations of both CLB and NCLB.^{6–9} Articles^{5,6} describing drug interaction between CLB and omeprazole have described these CYP interactions as clinically insignificant. We propose that NCLB is elevated from 2 separate interactions resulting from oxcarbazepine induction of CYP3A4 increasing CLB conversion to NCLB, resulting in normal CLB concentrations, and omeprazole and oxcarbazepine inhibition of CYP2C19 leading to a decreased conversion from NCLB to the inactive metabolite, indicating a high NCLB concentration. Because the patient had been on CLB prior to the dose increase/addition of interacting medications, it could be argued that it was the elevated serum concentration that is associated with the onset of hypothermia in this case. The exact mechanism of hypothermia has not been elucidated.

Based on the Naranjo¹⁰ method of assessing probability that a reaction is related to the medication, this adverse event can be categorized as probable. Our

case demonstrated a clear temporal association that is specifically related to the initiation of a medication proposed to cause increased serum concentrations of CLB as well as its active metabolite. NCLB serum concentration was well above the accepted reference range. Hypothermia is an established adverse effect of psychoactive medications, and a few published case reports^{3,4} specifically link CLB to hypothermia. Hypothermia resolved upon rewarming and discontinuation of the medication. Hypothermia was not a likely symptom of our patient's other diseases, since temperature regulation is a function of the hypothalamus and would not be affected by schizencephaly.¹ A CYP3A4 or CYP2C19 genotype or phenotype is not likely, as our patient had received CLB before without adverse effects. No NCLB concentrations were obtained prior to the ones we reported.

Conclusions

This case represents an example of a clinically significant adverse event in an adolescent due to a probable drug-drug interaction between CLB, omeprazole, and oxcarbazepine that led to CLB toxicity. Based on our experience, we recommend clinicians consider the potential clinical significance of CLB drug-drug interactions when initiating CLB or other therapy or when titrating CLB to avoid clinically significant adverse effects.

ARTICLE INFORMATION

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