Case Report of Valproate-Induced Hypothermia in a Patient With Schizoaffective Disorder

To the Editor: Valproate is widely used to treat seizure disorders and prevent migraine headaches and is used as a mood stabilizer in patients with bipolar disorder. Valproate has an established adverse event profile. Two well-known valproate-induced adverse events are thrombocytopenia and hyperammonemia, which can lead to hematopoietic complications and delirium, respectively. However, hypothermia is another serious but significantly less documented adverse reaction to valproate treatment. While hypothermia is a serious medical emergency, a review of the limited published cases suggests that prompt discontinuation of valproate therapy results in restoration of normothermia. Return to thermal homeostasis typically occurs without ongoing medical complications arising from the period of drug-induced hypothermia. We report on such a case, in which prompt valproate discontinuation along with aggressive rewarming resulted in a full recovery for the patient.

Case report. Ms A, a 48-year-old African American woman with a history of schizoaffective disorder (*DSM-IV*), hypertension, congestive heart failure, and type II diabetes mellitus, presented to the emergency department (ED) from the local state psychiatric facility in July 2008 having been found lethargic and hypothermic (axillary temperature 30°C [86°F]). The patient had a history of compulsive hand washing, water consumption, and showering. The psychiatric facility had noticed that, during the days prior to admission, the patient was abnormally docile. For at least 6 weeks prior to ED presentation, the patient had been on treatment with the following medications at stable doses: valproate (500 mg po qam, 1000 mg po qhs), risperidone (3 mg po bid, long-acting injection 50 mg IM every 2 wk), benztropine (0.5 mg po bid), haloperidol (5 mg/d po prn), furosemide (20 mg/d po), and magnesium (to treat furosemide-induced hypomagnesemia). The state psychiatric facility had suspected that the patient was "cheeking" her medicines, particularly the valproate, given lack of observed clinical efficacy. Approximately 3 weeks before the patient developed hypothermia, this suspicion was confirmed by the patient's valproate level, which was barely detectable at < 1 ng/mL. More recently, the patient had been refusing valproate doses several times a week.

Upon presentation to the ED, routine laboratory studies revealed low white blood cells at 1,700/μL and low platelets at 32,000/μL. The patient's plasma valproate level was 28 μg/mL (normal range, 50–100 μg/mL) and plasma ammonia level was 50 μmol/L. In the ED, the rectal temperature was initially 30.5°C (86.9°F). At the time of presentation the patient was obtunded and her hypothermia was treated with a forced air warming device and warmed intravenous fluids. Following these interventions in the ED, her temperature improved to 33.3°C (91.9°F). At that time the patient was transferred to the medical intensive care unit (MICU) for further evaluation and monitoring. Upon admission to the MICU, all the patient's antipsychotic medications were suspended due to concern for medication-induced adverse events. Given the patient's current blood dyscrasias and altered mental status in the context of longstanding psychiatric illness, hematology/oncology and psychiatry consultations were obtained. Based on these consultations, the most likely diagnosis was drug-induced hypothermia and thrombocytopenia. Other investigatory studies that would have suggested disseminated intravascular coagulation or adrenal insufficiency were negative. Furthermore, the patient's temperature continued to improve on day 2, to 36.8°C (98.2°F), following cessation of valproate therapy.

The patient remained normothermic and became responsive by the third hospital day. The patient's pancytopenia also improved following discontinuation of medications. Valproate was added to the patient's allergy list after the psychiatry consult team reviewed the limited literature on valproate and hypothermia. For control of the patient's primary psychiatric symptoms, risperidone 1 mg po bid was reinitiated, and she returned to her facility in stable condition.

Upon return to her facility, the patient was placed on close staff monitoring to prevent her excessive water utilization. Routine surveillance of the patient's vital signs showed that her temperature remained slightly low, but not hypothermic, at around 36°C (96.7°F). During this same period, laboratory studies demonstrated a platelet count within normal limits. Since the patient's return to the state mental health facility, she has been maintained psychiatrically on treatment with risperidone, fluvoxamine, and lorazepam prn.

A search of the archives of *The Journal of Clinical Psychiatry* (as well as *The Primary Care Companion to The Journal of Clinical Psychiatry*) revealed no articles involving valproate-induced hypothermia. Using the search terms *valproate* and *hypothermia* in the National Center for Biotechnology Information's PubMed returned only 17 articles. Only 5 of these articles, all case reports, describe human subjects and discuss the complication experienced by this patient. In 1984, Löscher and Vetter[1] demonstrated a moderate hypothermic effect of valproate in rats in a study investigating the effects of drug-induced increases in γ-aminobutyric acid levels. The first case reports involving thermoregulation and valproate came in 2000 with 4 patients that developed hypothermia on valproate treatment and 1 patient who achieved heat tolerance while on valproate treatment.[2] Three of these patients developed hypothermia shortly after being started on valproate therapy and their hypothermia resolved within days of the drug's discontinuation. The final patient discussed in the series had been taking valproate for 2 years and hypothermia did not develop until shortly after the patient's coadministration of risperidone was discontinued. Nagarajan et al[3] wrote a short response letter to that article adding a case of a child who developed hypothermia on valproate therapy. The child became hypothermic 2 days into valproate treatment and became normothermic within a week of discontinuation.

In 2002, Longin et al[4] reported 2 pediatric cases in which the patients tolerated valproate therapy but became hypothermic when topiramate was added to their medication regimen. Those cases occurred even though topiramate alone is not known to cause temperature regulation problems or exhibit a pharmacokinetic drug-drug interaction with valproate. Those patients also improved when valproate therapy was discontinued. Similarly, 2 cases were reported in which, although valproate levels were subtherapeutic, patients developed hypothermia when the dose of coadministered zotepine (an atypical antipsychotic) was in-

creased.[5] In those patients, gradual discontinuation of the zotepine was sufficient to regain normothermia. Finally, in 2005, the first case of severe hypothermia due to valproate overdose was reported.[6] Contributing factors for the hypothermia in that case included very cold outside temperature and the patient's immersion in cold water by nonmedical personnel due to concerns regarding potential alcohol intoxication. This patient fully recovered after aggressive rewarming.

Since the patient under discussion was also on risperidone treatment, it is important to understand that drug's potential contribution to temperature regulation. In 2000, Oerther and Ahlenius[7] demonstrated dose-dependent hypothermia in rats given risperidone. This effect was thought to be due to risperidone's dopamine (D_1) receptor agonism. A similar PubMed search revealed a single case report of risperidone-induced hypothermia.[8] The authors related the hypothermia to risperidone's preferential occupancy of serotonin-2 ($5\text{-}HT_2$) receptors. Given all of the available data, risperidone, valproate, and compulsive water use all could have played a part in the development of the observed hypothermia in the patient under discussion. On the basis of the fact that her valproate dose was fluctuating leading up to the incident and her significant improvement after discontinuation of the valproate, we suspect that the valproate therapy was the most likely trigger for this patient's hypothermia. This finding is similar to those from previously discussed case reports.

The primary purpose of this report is to emphasize the emerging pattern of hypothermia induced by valproate. As this medication is often prescribed by primary care physicians, these physicians should, therefore, be familiar with this rare, but serious, adverse effect of valproate. This patient was fortunate to be in a long-term inpatient setting and monitored regularly. As such, she was transported promptly to the local ED and rewarming began as soon as possible. While complete recovery seems quite possible, early rewarming is important. The readership of the Companion may benefit from this reminder of the risk of hypothermia in their valproate-treated patients, particularly when valproate is used in combination with other psychotropic medications such as topiramate or risperidone.

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Potential conflicts of interest: None reported. ***Funding/support:*** None reported.
doi:10.4088/PCC.08l00741