Treatment-Resistant High Output Ileostomy Secondary to Subtherapeutic Valproic Acid

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Divalproex sodium is an enteric-coated tablet that becomes valproate in aqueous solution.[1] Bioavailability of these 2 formulations is equivalent; however, time to peak is different, with valproate taking 1 hour and divalproex sodium taking 3 hours.[1] Clinically, both of these formulations are equally efficacious[2]; however, there are notable differences between side effects. Enteric-coated valproate preparations are thought to have fewer gastrointestinal side effects.[1,3] Despite this, diarrhea is a common side effect from divalproex sodium, reported in up to 23% of patients.[4] In some patients, especially geriatric patients, this side effect may quickly become life threatening and could exacerbate comorbid conditions. Here, we present a geriatric case of divalproex sodium causing a high output despite numerous pharmacologic interventions.

Case Report

A 66-year-old woman with a history of bipolar disorder and chronic kidney disease and a complicated surgical history resulting in an end-ileostomy placement was admitted to the hospital a fourth time in 3 months (January 2018–March 2018) for acute kidney injury secondary to high outflow ileostomy. She had difficulties maintaining volume and electrolytes resulting in deterioration of kidney function. No neurologic changes occurred. Multiple attempts at simultaneous use of opium tincture, somatostatin, cholestyramine, and loperamide to slow ileostomy output failed.

Ten years prior, she was diagnosed with bipolar disorder during her only psychiatric hospitalization and was stabilized on divalproex sodium 250 mg daily, venlafaxine 150 mg daily, and aripiprazole 10 mg nightly. This regimen was continued indefinitely, and no subsequent hospitalizations occurred. She never experienced diarrhea as a side effect from these medications.

During her most recent hospitalization, ileostomy output was averaging 2.1 L/d (normal < 1.2 L/d). Valproic acid level was subtherapeutic at 21 mcg/mL. Divalproex sodium was discontinued, and ileostomy output decreased to 1.2 L/d. Her condition improved with a return to baseline creatinine level (2.5 mg/dL), and she was discharged home. No further hospitalizations for this problem were required. In follow-up 4 months postdischarge, the ileostomy had been reversed and her creatinine level had improved to 1.5 mg/dL. Psychiatrically, she has remained stable.

Discussion

A PubMed search using the terms *depakote*, *valproic acid*, *valproate* plus *high output ileostomy*, *ileostomy*, or *diarrhea* revealed no similar case reports, which may in part be due to the side effect of diarrhea being easily confounded with a high output ileostomy. This lack of literature is especially concerning since without discontinuation of divalproex sodium, this patient would have certainly continued to decline and potentially expired.

The mechanism of action of divalproex sodium causing diarrhea or a high output ileostomy is speculative, but we hypothesize that both are related. Local irritation of gastrointestinal mucosa likely plays a part, as this may result in indigestion, diarrhea, and eructation.[1] Our case suggests that this irritation may be more prominent in the upper gastrointestinal and small bowel areas since she did not complain of diarrhea as a side effect in the 10 years that she was taking divalproex sodium prior to the placement of the ileostomy.

This case highlights the negative effects that psychiatric medications can have on geriatric patients. Pharmacokinetic and pharmacodynamic changes are common in the elderly.[5] These changes may make a particular medication intolerable and should be considered as patients age. Furthermore, geriatric patients on average take more medications resulting in more interactions and subsequently may have more conditions that can be affected negatively by polypharmacy.[5] The most important clinical point this case makes is the necessity to consider medication interactions in the geriatric population prior to ordering a possible unnecessary workup or adding additional medications. In this case, not even simultaneous use of 4 antidiarrheal agents could overcome the combination of age and a small but significant dose of divalproex sodium.

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