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Differences in serum concentration with valproate oral solution versus delayed-release divalproex in an adherent patient

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Abstract

Background: Several different formulations of valproic acid derivatives are available in the United States. Although these formulations have different absorption characteristics, they are believed to be interchangeable, with the exception of the extended-release product.

Case Report: A 31-year-old African American man with schizoaffective disorder was started on fluphenazine concentrate and valproate oral solution on admission to an inpatient unit. A 12-hour steady-state concentration, drawn on 1000 mg/day, resulted in 40.8 mg/L, and the dose continued to be titrated. Despite increasing doses, confirmed medication adherence, and accurate lab sampling, his concentrations remained low: 60.3 and 60.1 mg/L on 1500 mg/day, and 65.6 mg/L on 1750 mg/day. He was switched to divalproex delayed-release tablets, and his dose was increased to 2000 mg/day. Follow-up 12-hour steady-state concentrations were significantly higher, at 126.6 and 113.8 mg/L. It is theorized that the formulation of divalproex/valproic acid is what contributed to these differences in concentrations.

Discussion: Valproic acid formulations are considered to be interchangeable, and several studies have demonstrated that chronic psychiatric inpatients stabilized on delayed-release divalproex may be safely switched to valproate oral solution without changes in psychiatric stability. This case demonstrates a significant difference in serum drug concentrations when switching from valproate oral solution to divalproex delayed-release tablets.

Keywords: valproic acid, divalproex, serum concentrations

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Background

Valproate (VPA) and its derivatives are FDA approved for seizures, migraine prophylaxis, and treatment of manic episodes associated with bipolar disorder.[1] In the United States, several oral formulations are available, including an immediate-release (IR) solution (as valproate sodium), an IR capsule (as valproic acid), a delayed-release (DR) sprinkle capsule (as divalproex sodium), a DR tablet (as divalproex sodium), and an extended-release (ER) tablet (as divalproex sodium). Despite different absorption characteristics, these formulations are considered to be interchangeable, with the exception of the ER product, which requires an adjustment in dose.[2] There are a few reports of changes in serum concentration when converting between divalproex sodium DR and valproate oral solution. The following case will add to the literature by describing a patient who was switched from the oral solution to the DR tablet formulation and had a significant change in the serum valproate concentration.

Case Report

A 31-year-old African American man was admitted to the state psychiatric hospital and started on fluphenazine 10 mg/day and valproate 250 mg twice daily. Fluphenazine

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TABLE: Changes in doses, formulations, and serum concentrations of valproate derivatives during inpatient admission

Hospital Day	VPA Concentration	Dose, mg/day	Formulation	Time After Last Dose, h
36	—	↑ 1000	Oral solution	
42	40.8	1000	Oral solution	11.03
48	—	↑ 1500	Oral solution	
50	60.3	1500	Oral solution	11.85
74	60.1	1500	Oral solution	11.43
82	—	↑ 1750	Oral solution	
95	65.6	1750	Oral solution	10.92
97	—	↑ 2000	DR tablet	
116	126.6	2000	DR tablet	10.70
125	113.8	2000	DR tablet	10.58
153	98.2	2000	DR tablet	10.70
174	124.1	2000	DR tablet	10.83

DR = delayed release; VPA = valproic acid derivatives.

concentrate and valproate oral solution formulations were prescribed because of the patient's history of medication nonadherence. His past medical history included schizoaffective disorder and foot/shoulder pain. On admission, laboratory tests were significant for hypercholesterolemia, but all other panels were within normal limits, including complete metabolic panel (CMP) and complete blood count.

During the next month, fluphenazine was titrated to 40 mg/day, but valproate was increased for the first time on day 36 to 500 mg twice daily. Labs drawn on day 42 indicated no change in CMP values and a VPA concentration of 40.8 mg/L (Table). All medication concentrations were drawn approximately 11 hours after the last dose. The dose was subsequently increased to 500 mg every morning and 1000 mg every evening on day 48, with a level on day 50 of 60.3 mg/L.

Olanzapine was added to target continued psychosis, and VPA concentration on day 74 was 60.1 mg/L. His CMP remained stable and valproate was increased to 750 mg every morning and 1000 mg every evening on day 82, whereas olanzapine continued to be titrated upwards. Fluphenazine was cross-tapered to chlorpromazine, and the VPA concentration on day 95 was 65.6 mg/L. Throughout his admission, the patient did not refuse any doses of his medication, and mouth-checks were used to ensure adherence.

As he stabilized, the patient endorsed his intent to adhere to treatment adjustments; therefore, all his medications were changed from liquid to solid dosage forms. On day 97, valproate oral solution was changed to divalproex DR and the dose increased to 1000 mg twice daily because of the low concentration and continued hypomania. Labs drawn on day 116 revealed normal lipid panel, CMP, and complete blood count, and a steady-state VPA concentration of 126.6 mg/L. At this point, the patient was prescribed divalproex DR 1000 mg twice daily, benztropine 2 mg/day, trazodone 50 mg/day, olanzapine 30 mg/day, melatonin 3 mg/day, caffeine 200 mg/day, chlorpromazine 200 mg/day, and a multivitamin.

A follow-up concentration on day 125 was 113.8 mg/L, and divalproex DR was continued at the same dose. Repeat concentrations were 98.2 mg/L (day 153) and 124.1 mg/L (day 174) without changes in dose, formulation, or other laboratory values. He was discharged on day 208 with the same medication regimen as day 116, but with the addition of pantoprazole 40 mg/day.

Interestingly, a review of the records indicate that he was discharged from another state hospital 4 years earlier on divalproex DR 1000 mg twice daily, haloperidol 20 mg/day, olanzapine 40 mg/day, benztropine 2 mg/day, and diphenhydramine 50 mg/day. His VPA concentration prior to discharge was 76.3 mg/L, which is much lower than identified at this same dose during this admission.

Discussion

With the exception of the ER tablets, the different formulations of valproic acid derivatives are thought to be interchangeable on a milligram-by-milligram basis. Studies comparing the pharmacokinetics of the different formulations have found distinct differences in absorption in the first 6 hours after dose, with the oral solution having the most rapid absorption.[2,3] Dutta and Reed[2] compared three pharmacokinetic studies in healthy individuals and found that the IR capsule, sprinkle capsule, and DR tablets had similar rates and extent of absorption when viewed during the entire sampling period. The absolute bioavailability and relative bioavailability were ~100% for all the formulations except ER. Similarly, the mean exposure, apparent oral clearance, and apparent volume of distribution were similar for these 4 formulations. Most importantly for the case

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described above, the oral solution and DR tablets had similar mean VPA concentrations 6 hours after the dose, indicating that any concentration drawn after the first 6 hours should have similar values despite the formulation.

Only 2 reports could be found in the literature of switching between valproate oral solution and divalproex sodium. Using an open-trial design, 47 patients were switched from divalproex to valproate oral solution at the same dosage and frequency.[4] Trough serum concentrations were drawn after 2 weeks and were 14.4% lower than at baseline ($P = .001$). Although this was a statistically significant decrease, the authors concluded that it was not clinically relevant because no changes were observed in seizure occurrence or Clinical Global Impression scores. All the patients except one were able to tolerate the therapeutic substitution. Coffey and colleagues[5] describe a case similar to the one presented where a patient was switched from valproate oral solution to the same dose of divalproex sodium. This patient is again described in a case series by Jackson and colleagues,[6] and additional detail is provided. The serum VPA concentration increased significantly after the formulation change, roughly doubling, which is comparable to the presented case. The authors could find no additional literature supporting this or providing a hypothesis. They proposed that autoinduction was present in this patient only during use of valproate oral solution but not during use of divalproex sodium, which they speculate could have been due to a rare genetic variation unique to this patient.

A review of the literature for additional explanations for the change in concentration observed with the case patient revealed a study comparing the effects of haloperidol and chlorpromazine on the pharmacokinetics of valproic acid.[7] The authors observed that patients receiving valproic acid with concomitant chlorpromazine had significantly higher average minimum concentrations than when those same patients received valproic acid without chlorpromazine, averaging 22.5% higher. There was also a significant increase in the half-life with concomitant chlorpromazine. This was not seen in a different group of patients who received valproic acid with or without haloperidol. This is relevant because the case patient was initiated on chlorpromazine during treatment with valproate. Although it is possible that this may have contributed to the changes in VPA concentration, chlorpromazine was initiated on day 90, and the VPA concentrate on day 95 was not significantly different from those prior to chlorpromazine. In contrast to the study where patients were stabilized on a dose of chlorpromazine (100-300 mg/day), the case patient continued to increase his dose of chlorpromazine, so perhaps the interaction was not noticeable until reaching higher doses. Despite this, an interaction with chlorpromazine would not fully explain the changes observed in the VPA concentration. No other medication interactions were identified in the case patient that could have affected the VPA concentration.

In our institution, we have come across several instances when a patient was switched between divalproex DR tablets and valproate oral solution with significant changes in the serum concentration that are not explained by the timing of levels or adherence concerns. Our hospital purchases valproate oral solution in manufacturer-packaged unit dose cups of 250 and 500 mg, so it cannot be a measurement error. There is also no concern that the incorrect dose is being administered because the pharmacy department sends only enough medication for 7 days at a time and does not receive requests for missing medication, as could be seen if a 250-mg cup was administered instead of a 500-mg cup. Furthermore, this has been seen across multiple inpatient units with a variety of staff and different manufacturers. These significant alterations in serum concentration have not been observed when switching between valproate oral solution and divalproex DR sprinkles. Future research will involve a larger study comparing the serum concentrations of patients who have received the same dose with different formulations in this facility.

Conclusion

This case contributes to the literature on the possibility of certain valproate formulations not being interchangeable as has previously been believed. More research is needed to determine whether this could be related to the formulation of valproate or is a unique characteristic to specific patients.

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