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Rifampin-divalproex drug-drug interaction in an adult patient: A case report

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Abstract

The divalproex (DVP) package insert states that rifampin may increase the oral clearance of valproate by 40% and that valproic acid derivative dose adjustments may be required when starting or stopping rifampin. However, the overall clinical significance of this drug-drug interaction remains unclear given that limited clinical outcome data has been published. This case describes a 52-year-old female with bipolar disorder, borderline personality disorder, and PTSD who was previously stable on a medication regimen consisting of DVP delayed-release 500 mg every morning and 1500 mg every evening (baseline steady-state trough 99.8 mcg/mL). Throughout rifampin therapy for latent tuberculosis treatment, she required an increase in both the frequency of DVP administration, from 2 to 3 times daily, and DVP dose by 75% to maintain clinical stability. Valproic acid trough concentrations ranged from 56.4 to 75.9 mcg/mL during the 4-month course of rifampin. This report supports that the DVP-rifampin interaction may be clinically significant and of a greater magnitude than suggested by the package insert.

Keywords: rifamycin, rifabutin, rifapentine, valproate, pharmacokinetic, valproic acid

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Background

Rifampin is a bactericidal antibiotic commonly used for the treatment of latent TB. Short-course rifamycin-based regimens are preferred over a longer course of isoniazid monotherapy due to the lower toxicity risk and higher treatment completion rates.[1] Rifampin is a strong inducer of several drug-metabolizing enzymes, yielding many drug interactions.[2] The suspected mechanism of the interaction between rifampin and divalproex (DVP) is rifampin-mediated induction of DVP metabolism through induction of uridine diphosphate glucuronosyltransferase (UGT) enzymes, CYP2C9, and CYP2C19.[2,3]

The DVP package insert states that rifampin increases the oral clearance of valproate products by 40% and that DVP dose adjustments may be required when starting or stopping rifampin.[3] This is based on 1 unpublished study in which valproate 7 mg/kg × 1 dose was given 36 hours after a rifampin 600 mg/d × 5-day course was completed. Two other published cases[4,5] were identified that provide additional clinical context to this interaction. The Dutch patient originally described by Hanrath and Swart,[5] described in English by DeLucia and Mahon,[4] experienced a decrease in serum valproic acid concentration from 82 mcg/mL at a maintenance dose of 2500 mg/d to subtherapeutic (<12 mcg/mL) 10 days after initiation of rifampicin. The patient described by DeLucia and Mahon[4] required significant dose escalation of DVP following 3 months of rifampin therapy. However, this patient had not apparently been previously stable on DVP as the patient

required inpatient psychiatric admission due to treatment nonadherence. As such, guidance surrounding the management of this interaction for patients on stable DVP dosing and in the English language remains limited. The patient described in this report was stable on DVP and then decompensated within 2 weeks of starting rifampin for latent TB infection.

Case Report

This case report describes a 52-year-old Cuban female with a past medical history significant for bipolar disorder, borderline personality disorder, PTSD, alcohol use disorder in full sustained remission, migraines, RA, fibromyalgia, obstructive sleep apnea, severe obesity, fatty liver, hypothyroidism, hypertriglyceridemia, acne, allergic rhinitis, and herpes simplex. The patient was previously stable on DVP delayed-release (DR) 500 mg every morning and 1500 mg every evening (19.5 mg/kg/day). Her most proximal valproic acid trough concentration was 99.8 mcg/mL 6 weeks prior to rifampin initiation. Refill history using proportion of days covered indicated at least 80% medication adherence throughout DVP therapy—above the threshold at which most medications are expected to achieve the most clinical benefit.[6] The patient was also prescribed gabapentin 900 mg 3 times daily, acyclovir 400 mg twice daily, levothyroxine 25 mcg daily, 2 fluticasone nasal sprays in each nostril daily, loratadine 10 mg every morning, montelukast 10 mg daily, albuterol inhaler 1 to 2 puffs every 4 to 6 hours as needed, and potassium chloride 10 mEq/d. Rifampin 600 mg daily × 4 months was started by an infectious disease physician to treat latent TB infection, an incidental finding during workup for etanercept initiation for RA treatment.

Recognizing the rifampin-DVP interaction and general timeline for enzyme induction (eg, 1 to 4 weeks after initiation),[2,7] close monitoring occurred during this period. Telephone follow-up was scheduled weekly for 6 weeks after starting rifampin to assess psychiatric stability. Valproic acid steady-state trough concentrations were scheduled at 2, 4, and 6 weeks to provide objective data to supplement subjective assessments. Proactive DVP regimen adjustments were not planned given the limited information around the clinical significance of this drug-drug interaction. Any DVP dose or frequency adjustments that occurred were promptly in response to subjective reports of hypomanic symptoms, such as pressured speech, decreased need for sleep, impulsive spending, psychosis, increased irritability, distractibility, and flight of ideas, and not primarily in response to reduced valproic acid steady-state trough concentrations. See the Figure for timing of dose adjustments and total daily dose prescribed. The patient first reported symptoms within 2 weeks after starting rifampin. Approximately 6 weeks after rifampin initiation, DVP frequency of administration was adjusted from 2 to 3 times daily while maintaining the same total daily dose to provide more frequent DVP DR dosing in the presence of a potent inducer expected to significantly increase DVP clearance. Additional medication exposures during this time included etanercept initiation for RA, a 10-day benzonatate course for upper respiratory infection–associated cough, and a short course of ziprasidone 40 mg daily during weeks 12 to 14, none of which were expected to significantly interact with DVP. Ziprasidone was added because of continued symptoms despite an ~50% increase of DVP dose. However, the patient refused to continue ziprasidone, so DVP dose adjustments continued as clinically indicated. Ultimately, the patient no longer reported hypomanic symptoms 4 days after increasing DVP DR to 1000 mg every morning, 1000 mg every afternoon, and 1500 mg nightly.

Recognizing the potential for DVP side effects or toxicities to occur as rifampin induction effects dissipate over 1 to 4 weeks,[7] the treatment team planned a gradual dose reduction after her rifampin course was completed: a decrease in DVP DR by 500 mg/d every week until the pre-rifampin DVP regimen was reached. Additionally, weekly valproic acid steady-state trough concentrations (Figure), ALT, and CBC were ordered to monitor for DVP-related toxicities. Facility protocol is to check ALT first and then complete additional tests if indicated. ALT and CBC labs were within normal limits throughout DVP and rifampin therapy; therefore, further liver panel tests were not ordered. All valproic acid steady-state trough concentrations were <100 mcg/mL. A drug interaction probability scale calculation was performed and resulted in a score of 5, indicating a probable drug-drug interaction.[8]

Discussion

This case report describes a patient who was stable on DVP and then decompensated within 2 weeks of starting rifampin. A literature review revealed limited clinical guidance on the interaction between DVP and rifampin. This is the second case describing the clinical course associated with a pharmacokinetic DVP-rifampin interaction written in the English language.[4]

The first report describes a 54-year-old female with epilepsy who experienced breakthrough seizures after starting rifampicin while previously stable on carbamazepine, valproic acid 2500 mg/d, and clonazepam.[5] Valproic acid concentrations decreased from 82 mcg/mL to <12 mcg/mL 10 days after rifampicin initiation. Unfortunately, further information is not available as the case report is written in the Dutch language.

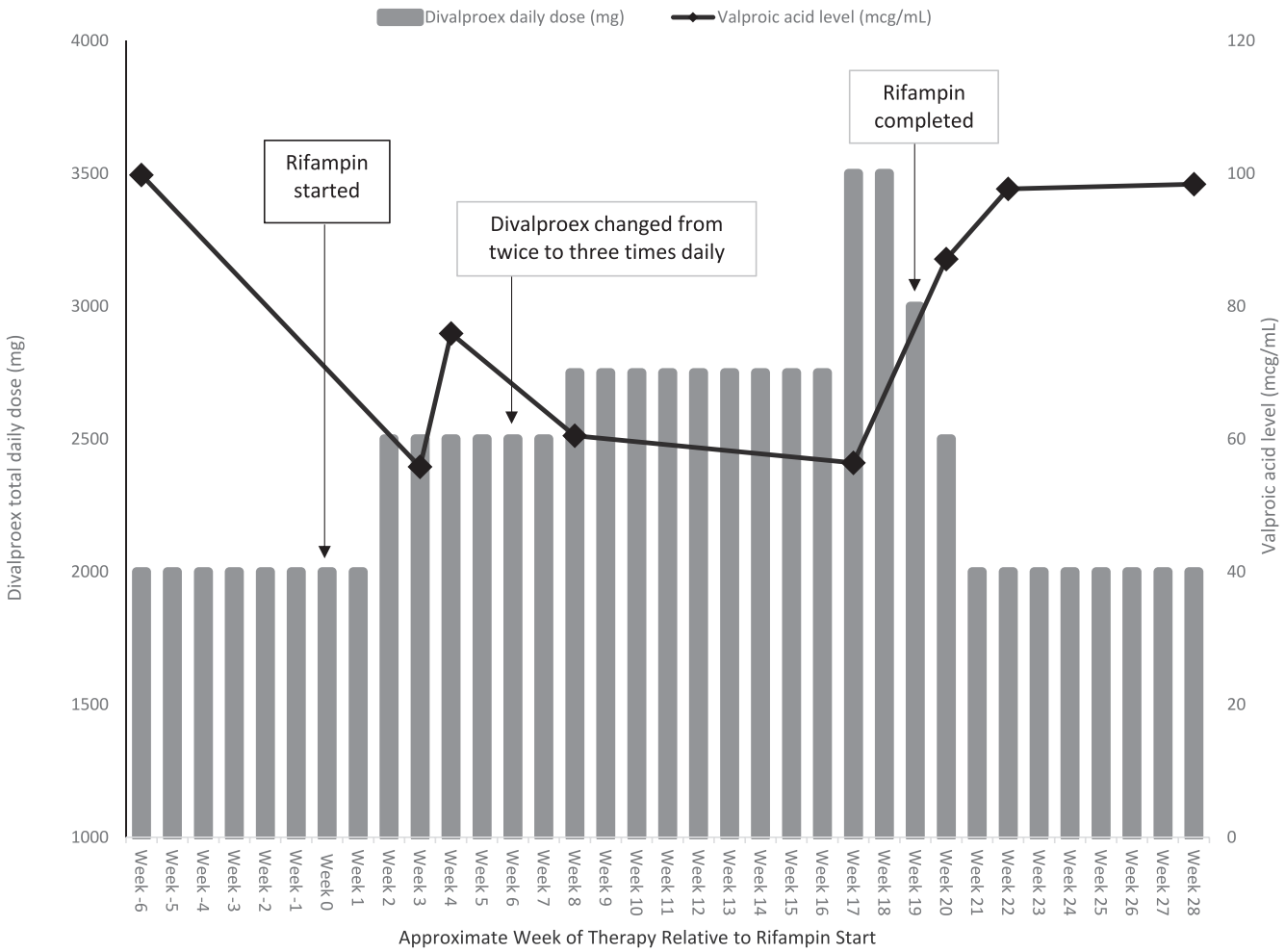

FIGURE: Time course of divalproex regimen adjustments, rifampin use, and divalproex serum concentrations

Another report by DeLucia and Mahon[4] describes the interaction while attempting to stabilize a 58-year-old male patient with acute mania who was nonadherent to valproic acid and 3 months into his rifampin treatment course for latent TB. A comparison to our case report is limited as pre-rifampin valproic acid concentrations are unavailable or not reported and the timeline of pertinent regimen adjustments is unclear. Ultimately, the patient was switched from rifampin to isoniazid to avoid the drug-drug interaction.

In the currently described case report, switching the patient to a 6- to 9-month isoniazid regimen was undesirable given the preference to quickly initiate biological therapy for RA.[1] The baseline steady-state valproic acid trough concentration was 99.8 mcg/mL with mood stability. Over the 4-month course of rifampin, DVP was increased in both dose (75% increase) and frequency (2 to 3 times daily) to maintain clinical stability by treating breakthrough hypomanic symptoms. Our need to increase DVP dose by 75% in this case contrasts with the package insert drug-drug interaction study, which reports a rifampin-mediated 40% increase in valproate clearance.[3] Differences may be related to contrasting valproate derivative dosing (eg, 19.5 mg/kg/d vs 7 mg/kg single dose) and/or continued rifampin dosing (eg, 600 mg daily × 4 months vs 5 days). Notably, valproic acid trough concentrations ranged from 56.4 to 75.9 mcg/mL during rifampin treatment in this patient and did not always correlate with symptom control. As rifampin is highly protein bound, future consideration should also be given to measuring free valproic acid concentrations to observe whether free concentrations offer more congruency with symptoms and dosage adjustments.[2] No DVP-related toxicities occurred post-rifampin discontinuation with the previously described method of gradual DVP dose reduction to pre-rifampin dosing.

DVP metabolism is dependent on glucuronidation, mediated by UGT enzymes, mitochondrial beta-oxidation, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CUP2E1 enzymes.[3] Among these, rifampin is known to induce CYP2A6, CYP2B6, CYP2C9, CYP2C19, and UGT1A1 enzymes.[2] For the rifampin-DVP interaction, rifampin

induction of UGT enzymes, CYP2C9, and CYP2C19 enzymes may be involved. The observed time course of this drug-drug interaction was consistent with the time course of enzyme induction and dissipation.[7]

Conclusion

This report clarifies that the DVP-rifampin interaction may be clinically significant and of a greater magnitude than suggested by the package insert. Although this case may provide a framework for management, specific dosing practices in this setting cannot be recommended given the paucity of data; this interaction should be managed on a case-by-case basis. The clinician should be aware that a more aggressive approach to DVP titration may be warranted when managing this interaction. It is possible that free valproic acid concentration monitoring may offer additional insight. After a rifampin course is completed, DVP dosing should gradually return to pre-rifampin dosing to avoid DVP dose-related toxicities.

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