Severe Anemia Secondary to a Probable Drug Interaction between Zidovudine and Valproic Acid

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A 42-year-old man with human immunodeficiency virus (HIV) infection and a history of complex partial seizures developed severe anemia after the addition of valproic acid to his stable antiretroviral regimen of zidovudine, lamivudine, and abacavir. The inhibition of zidovudine glucuronidation by valproic acid and the resultant zidovudine hematologic toxicity is the proposed mechanism of the interaction.

Anemia is a well-described adverse effect of zidovudine therapy, occurring in 2% and 9.7% of patients receiving 500 mg q.d. and 1500 mg q.d., respectively [1]. Given the dose-dependent nature of this adverse effect, the concomitant administration of medications that impair the glucuronidation of zidovudine to its inactive derivative, 5′-glucuronidyl zidovudine (GZDV), may inadvertently increase the risk of zidovudine-mediated anemia. Because the enzyme responsible for the biotransformation of zidovudine has been identified as the UGT2B7 isoenzyme of the uridine diphosphate glucuronosyltransferase system, it may be possible to anticipate drug interactions between zidovudine and clinically significant inhibitors of this enzyme [2]. Valproic acid—often used for both its anticonvulsant and mood-stabilizing properties in HIV-positive patients due to its low propensity for cytochrome P450-mediated drug interactions—is a well-described inhibitor of drug glucuronidation, and it has demonstrated the potential for competitive inhibition of UGT2B7-mediated zidovudine metabolism [3, 4]. Concomitant administration may therefore increase the risk of dose-related adverse effects of zidovudine therapy, including hematologic toxicity. We describe a case of profound anemia related to a drug interaction between zidovudine and valproic acid.

Case report. A 42-year-old HIV-positive male patient began therapy with zidovudine (300 mg b.i.d.), lamivudine (150 mg b.i.d.), and abacavir (300 mg b.i.d.) in July 2002. The patient’s past medical history was significant for chronic hepatitis B and childhood-onset complex partial seizures with secondary generalization. His antiseizure regimen consisted of carbamazepine (600 mg b.i.d.), clobazam (20 mg b.i.d.), and gabapentin (400 mg in the morning and 800 mg at bedtime). At the time antiretroviral therapy was initiated, the patient’s hemoglobin level was 105 g/L (130–170 g/L), hematocrit was 30.6% (39%–49%), and mean corpuscular volume (MCV) was 103.1 fl (82.0–97.0 fl). Immediately before starting antiretroviral therapy, viral load was 34,796 copies/mL and CD4+ cell count was 16 cells/mm³. Despite receiving therapeutic dosages of 3 anticonvulsants, the patient continued to experience at least 1 seizure per month. Valproic acid was therefore added to his existing regimen at a dosage of 500 mg b.i.d. in April 2003. At the time valproic acid therapy was initiated, the hemoglobin level measured 126 g/L, hematocrit was 35.8%, and MCV was 118.7 fl. Viral load was 319 copies/mL, and CD4+ cell count was 298 cells/mm³.

In June 2003, the patient presented to the emergency department of our hospital following a seizure at home. At the time of presentation, his hematologic parameters were as follows: hemoglobin level, 22 g/L; hematocrit, 6.3%; and MCV, 115.7 fl. Findings of an MRI of the head were normal. The level of valproic acid level was slightly subtherapeutic, measuring 281 μmol/L (350–700 μmol/L). There was no evidence of gastrointestinal bleeding or hemolysis, and vitamin B₁₂, ferritin, and RBC folate levels were all within normal limits. The patient’s antiretroviral therapy was discontinued, but the anticonvulsant therapy was maintained at unchanged dosages. The patient received a transfusion of 4 units of packed RBCs, and his hemoglobin level 4 weeks after the discontinuation of antiretroviral therapy was stable at 93 g/L. In July 2003, antiretroviral therapy with stavudine, lamivudine, and abacavir was resumed, and, in October 2003, the patient’s hemoglobin level measured 143 g/L, and his CD4+ cell count measured 621 cells/mm³. Stavudine was chosen as a substitute for zidovudine because it does not undergo glucuronidation and is not associated with bone-marrow suppression.

Discussion. We believe, for several reasons, that the precipitous and serious decline in hemoglobin levels in this patient occurred as a result of an interaction between valproic acid and...
zidovudine. First, the patient had been hematologically stable until the time valproic acid therapy was initiated and was receiving no other drug therapy aside from his anticonvulsant and antiretroviral regimens. Second, although anticonvulsants are rarely associated with various hematologic abnormalities, the patient’s hemoglobin level has remained stable despite the continued administration of valproic acid, carbamazepine, gabapentin, and clobazam [5, 6]. Although rapid declines in hemoglobin levels have been reported with the combination of zidovudine and lamivudine, such changes generally occur within the first 3–4 months of combined use [7, 8]. Finally, a pharmacokinetic basis for a drug interaction between valproic acid and zidovudine exists. In a study of 6 HIV-infected male volunteers with normal renal and hepatic function, the pharmacokinetics of zidovudine and GZDV were determined after 4 days of zidovudine monotherapy (100 mg q8h) and after 4 days of coadministration of zidovudine and valproic acid (250 mg q8h). The addition of valproic acid resulted in an 80% increase in the area under the concentration-time curve (AUC) of zidovudine (from 0.65 to 1.17 μg/h/mL; P < .05), with a corresponding decrease in mean GZDV levels (from 4.12 to 3.22 μg/h/mL; P < .05) relative to the administration of zidovudine alone [9]. In addition, oral clearance of zidovudine and the GZDV:zidovudine urinary excretion ratio were reduced by approximately 60% and 50%, respectively, with concomitant valproic acid administration. Although limited by the small sample size, the aforementioned findings suggest that valproic acid acts as an inhibitor of zidovudine glucuronidation in vivo. The steady state concentrations of valproic acid attained among the study patients were similar to that in our patient, ranging from 221 to 471 μmol/L. Although no changes were found in hematologic parameters in this study, the 4-day duration of combined valproic acid and zidovudine use was likely too short for clinically meaningful changes to become apparent.

The mechanism whereby the risk of hematologic cytotoxicity increases with increasing zidovudine dosages may be related to the intracellular accumulation of the toxic metabolite zidovudine monophosphate (AZTMP) [10]. Specifically, AZTMP interferes with both cellular DNA synthesis and exonuclease-catalyzed removal of zidovudine from host cell DNA [11, 12]. In addition, at clinically relevant concentrations, AZTMP acts as a potent inhibitor of the transport of pyrimidine nucleotide sugars into the Golgi complex, thereby inhibiting protein glycosylation and altering glycosphingolipid synthesis [13]. Therefore, AZTMP may elicit cytotoxic effects on rapidly growing erythrocyte precursors, both by interfering with nuclear DNA replication and by compromising the function of membrane receptors involved in the receiving of extracellular stimuli required for cell growth and differentiation.

The phosphorylation of AZTMP to zidovudine diphosphate by the enzyme thymidylate kinase is the rate-limiting step in the generation of the virologically active triphosphate derivative [14]. As a consequence, AZTMP accounts for ~95% of all phosphorylated zidovudine products [15]. Theoretically, as the plasma concentration of zidovudine increases due to upward dosage adjustments or competing drug interactions, further increases in intracellular AZTMP pools are probable, with little change in either diphosphate or triphosphate metabolite production expected [14]. These findings were confirmed in a small trial of 10 HIV-positive male patients in whom the intracellular AUC0–12 h of AZTMP increased >2-fold when the dosage of zidovudine was increased from 300 mg q.d. to 600 mg q.d. In contrast, no significant change in the AUC0–12 h of the triphosphate metabolite was observed [16]. Since AZTMP incorporation into the DNA of human bone-marrow cells increases linearly with the dose of zidovudine [11], and the generation of the diphosphate metabolite from AZTMP is rate-limiting and inefficient, we hypothesize that the increased AUC of zidovudine attained with the addition of valproic acid to our patient’s drug regimen was associated with an accumulation of intracellular AZTMP, which precipitated a severe decrease in the hemoglobin level. Unfortunately, an assay for intracellular zidovudine metabolite concentrations was not available at our institution to fully verify this hypothesis.

In summary, we describe an interaction between zidovudine and valproic acid that was a probable cause of severe anemia in our patient, according to the Naranjo probability scale [17]. To our knowledge, this is the first description of a clinically significant patient outcome attributable to valproic acid–mediated inhibition of zidovudine glucuronidation. The degree of change in hemoglobin level and timing relative to the initiation of valproic acid in this case warrant the conclusion that clinicians should be aware of the potential for this interaction and monitor complete blood counts closely when valproic acid and zidovudine are coadministered. Alternatively, nucleoside analogues that do not undergo glucuronidation and/or do not cause significant hematologic toxicity (e.g., stavudine, tenofovir, and abacavir) can be substituted for zidovudine in regimens for patients receiving concomitant valproic acid.

References

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