Raltegravir-based Postnatal HIV Prophylaxis Therapy in a Neonate After in Utero Dolutegravir Exposure

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Abstract: We present a case report of a neonate receiving raltegravir-based postnatal HIV prophylaxis after in utero dolutegravir exposure. High levels of raltegravir and dolutegravir can potentially cause bilirubin toxicity as they compete for albumin binding and follow the same metabolic pathway through UGT1A1. This case suggests delaying initiation of raltegravir-based postnatal prophylaxis by 24–48 hours after in utero dolutegravir exposure.

Key Words: dolutegravir glucuronide, raltegravir, neonates, wash-out, UGT1A1

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RALTEGRAVIR IS ONE OF FEW ANTIRETROVIRAL AGENTS TO BE USED FOR POSTNATAL HIV PROPHYLAXIS (PNP) DIRECTLY AFTER BIRTH.1 Raltegravir readily crosses the placenta and its metabolism in neonates is prolonged.2 Hence, neonatal raltegravir-based PNP should be initiated 24–48 hours if mothers have received raltegravir 2–24 hours before delivery to prevent accumulation of raltegravir. This recommendation has not been adopted for neonates born to mothers who received dolutegravir during pregnancy, while dolutegravir also crosses the placenta and follows similar metabolism.3 To our knowledge, we present the first reported case of a neonate receiving raltegravir-based PNP after in utero dolutegravir exposure.

Raltegravir is predominantly metabolized by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), as are dolutegravir and bilirubin. Activity of UGT1A1 is very low at birth, posing a risk of competition between raltegravir, dolutegravir, and bilirubin for UGT1A1. Hence, simultaneous high raltegravir and dolutegravir exposure in neonates increases the risk of neonatal hyperbilirubinemia. A 33-year-old woman with HIV-1 presented to the hospital pregnant while using elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in October 2019. She had an HIV-RNA viral load (VL) <40 copies/mL and CD4+ cell count of 820 cells/μL. Her antiretroviral therapy was switched to raltegravir 400 mg twice daily (BID) <40 copies/mL and CD4+ cell count of 820 cells/μL. Her antiretroviral therapy was continued for 8 weeks after gestation and the neonate (boy) weighed 3.500 g at birth. Other than atrial flutter, the neonate had no medical conditions. The last maternal dolutegravir dose was taken 14 hours before delivery. Neonatal presumptive HIV treatment was initiated 3.5 hours after birth consisting of raltegravir (1.5 mg/kg OD), lamivudine (2 mg/kg BID), and zidovudine (4 mg/kg BID). Other medication included sotalol 2 mg/kg/day for prenatal arrhythmia. A cord blood sample was taken at delivery and a neonatal blood sample was drawn 6 days later. Results for raltegravir, dolutegravir, and bilirubin concentrations are shown in Table 1. Physical examination of the neonate did not show marked jaundice. The neonate was bottle-fed with formula and not breast-fed. Neonatal presumptive HIV treatment was discontinued after 4 weeks. HIV PCR tests at 7 and 18 weeks of life were negative; hence, no vertical HIV transmission occurred.

At birth, dolutegravir cord plasma concentration was well above the 90% maximal effective concentration (EC90: 0.32 mg/L), which is comparable with findings in clinical studies and PK simulations.3,5 However, dolutegravir wash-out half-life was substantially prolonged in this neonate (about 140 hours) compared with an average of 32 hours for neonates not receiving raltegravir-based PNP.4 The dolutegravir metabolic glucuronidation rate (dolutegravir glucuronide/dolutegravir molar plasma concentration) was about 10-fold lower compared with findings from other studies due to reduced UGT1A1 activity.6 We were unable to compare dolutegravir metabolic rate with other neonates as this has not yet been reported in literature. Total bilirubin at day 6 after birth (9.9 mg/dL) was above population means, but well below the phototherapy treatment threshold of 21 mg/dL (local protocol).7 The observed findings suggest that raltegravir, dolutegravir, and bilirubin metabolism has been reduced, probably due to competition for UGT1A1. Moreover, pharmacologically active unbound concentrations of these compounds might have been increased as in vitro studies suggest that they compete with each other for albumin-binding sites.8,9 Together with reduced drug metabolism, this could result in increased risk of raltegravir, dolutegravir, or bilirubin induced toxicity.10

The reported case, along with other studies, show that neonatal dolutegravir levels after in utero exposure are mostly therapeutically relevant and thus set for >24 hours.3,5 In this period dolutegravir and raltegravir and bilirubin are competing for UGT1A1 metabolism and possibly albumin binding, which is still immature in the neonate. We propose to delay neonatal raltegravir-based PNP initiation until 24–48 hours after birth if the mother has received dolutegravir within 24–48 hours before delivery to prevent potential toxicity. It should be noted that this strategy can only be applied when the mother is adherent to ART. Poor maternal adherence to dolutegravir could result in low neonatal dolutegravir exposure.
and therefore suboptimal HIV prophylactic activity during the first hours of life.

In summary, this case suggests that neonates born from mothers who have received dolutegravir 2–24 hours before delivery should be started on raltegravir-based PNP 24–48 hours after birth. This case is consistent with the assumption that dolutegravir glucuronidation metabolic rate is very low during the first days of life. If available, application of therapeutic drug monitoring of dolutegravir and raltegravir is encouraged in future cases of raltegravir-based PNP after in utero dolutegravir exposure to better understand what happens in these neonates. Larger datasets are needed to assess the impact of delayed initiation of raltegravir-based PNP after birth on clinical toxicity and efficacy.

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