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Case report

A young child with HIV and unsteady gait: A case report

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ABSTRACT

Background: We would like to raise awareness about the toxicities related to the added excipients present in the oral solution of Liponavir/ritonavir in particular alcohol and propylene glycol.
Case presentation: In this case report, we describe an 18 month-old child with a newly diagnosed HIV infection on antiretroviral therapy (ART). She developed shortly after starting the ART unsteady gait and imbalance.
Conclusions: The excipient-excipient interaction in Lopinavir/ritonavir may contribute to major toxicities not only in premature neonates and infants; but also in older children specifically from Asian ethnicity.

Background

It is important to raise awareness about the added excipients present in the liquid formulations of ART [1], in particular alcohol and propylene glycol as in the Kaletra oral solution. The excipient-excipient interaction may contribute to major toxicities not only in premature neonates and infants; but also in older children specifically from Asian ethnicity. Propylene glycol toxicity in particular in preterm neonates may lead to cardiomyopathy, elevated lactic acid, acute renal failure, and respiratory complications [2].

Case presentation

An 18 month-old girl presented to the clinic with bilateral submandibular enlarged lymphadenopathy of three months duration associated with intermittent low-grade fever and weight loss. Her mother was diagnosed one week prior to presentation with HIV infection. The patient's workup was significant for an elevated HIV viral load of 514.000 copies per mL with a $CD4^{+}T$ cells count of 1233 cells/mm^3 (21.5%).

The results of complete blood count, liver and kidney functions were within normal ranges except for mild elevation of AST and ALT at 211 and 215 IU/L respectively.

The patient did not receive breast milk or previous blood transfusion; thus she was diagnosed with perinatal HIV infection. The mother was not screened prenatally for HIV. The child had normal growth up until her recent weight loss. She had attained appropriate developmental milestones for age.

We initiated antiretroviral therapy (ART) with a dual nucleoside/nucleoside reverse transcriptase inhibitors backbone [Zidovudine (AZT)/Lamivudine (3TC)] and a boosted protease inhibitor (PI) [Lopinavir/ritonavir (LPV/r)] according to weight-directed dosing [1]. The parents were instructed in the clinic about all the medications and the appropriate administration to minimize dosing errors.

After three days of starting the ART, we received a call from the father concerned that his daughter was acting "weird" after taking her morning doses; she was having unsteady gait (changed from the baseline) around one hour after taking the medications, walking holding on furniture and walls, sleepy most of the time "as if she was drunk". These symptoms would resolve after she takes a nap. This was not noticed after the evening doses since she would go directly to sleep. The patient presented to the clinic the next day before she took her ART; physical exam was normal, appropriate gait for her age, good muscle tone and power. The parents denied ingestion of any other medication by the patient. As the patient was doing well, we did not any blood testing

We decided to stop one of the medications and observe. The patient was back to normal, with no recurrent changes in the gait and behavior.

Abbreviations: ART, antiretroviral therapy; AZT, Zidovudine; 3TC, Lamivudine; PI, protease inhibitor; LPV/r, Lopinavir/ritonavir; CNS, central nervous system; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; WHO, World Health Organization.

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Discussion and conclusions

The medication that was discontinued was Lopinavir/ritonavir (LPV/r) (Kaletra oral solution = 80 mg LPV +20 mg r per mL). She was receiving a dose of 12 mg per Kg per dose by mouth twice daily.

The oral solution of Kaletra is highly concentrated; each one mL contains 356.3 mg of alcohol (42.4% v/v) and 152.7 mg of propylene glycol (15.3% v/v) in addition to other excipients [2].

There is a risk of toxicity related to the amount of alcohol and propylene glycol contained in Kaletra oral solution, particularly in neonates younger than 14 days (mainly preterm) and infants. Toxicities include hyperosmolality, with or without lactic acidosis, renal toxicity, central nervous system (CNS) depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias, ECG changes, and hemolysis [2–4].

The oral solution should not be used in the immediate postnatal period, including neonates age <14 days or preterm neonates until 14 days after their due date, unless the infant is carefully monitored and benefits outweigh the risks [3].

Ethanol competitively inhibits propylene glycol metabolism as both are metabolized by alcohol dehydrogenase (ADH) in the liver; this may lead to propylene glycol toxicity due to impaired elimination in neonates, in patients with renal dysfunction and in some patients of Asian origin [2,3,5].

Ethanol is rapidly absorbed and metabolized to acetaldehyde by ADH and subsequently oxidized to acetate by aldehyde dehydrogenase (ALDH) [6].

In addition to the immature activity of ADH and ALDH in infants and children (ADH reaches adult activity at nearly five years of age) [7]; there are genetic polymorphisms of ADH and ALDH mainly affected by ethnicity and sex [8].

An isozyme of ADH (β2β2) is found more frequently in Asians, and an ALDH isozyme (ALDH2), although present in Asians, often is in an inactive form [8]. Also, females have lower amounts of gastric ADH compared with males, which lead to increased risk of alcohol and possibly propylene-glycol associated adverse events [9].

To note that our patient's mother is Filipino and the father is Lebanese.

We suspect that she developed a lack of coordination and unsteady gait due to acute ethanol exposure from Kaletra. We were not able to measure blood alcohol concentration in our patient and did not want to expose her again to the Kaletra solution. Although the patient received the correct dose prescribed of Kaletra; her ethnicity and sex may have affected the metabolism of the excipients and resulted in the described side effects.

We discontinued Kaletra solution and started Nevirapine in addition to AZT/3TC.

The World Health Organization (WHO) introduced in 2015 in some African countries LPV/r oral pellets that do not contain ethanol or propylene glycol [10]. The new heat-stable and taste-masked oral pellet formulation of LPV/r seems to be promising and more acceptable by caregivers [11].

It is important to raise awareness about the added excipients present in the liquid formulations of ART, in particular alcohol and propylene glycol as in the Kaletra oral solution. The excipient-excipient interaction may contribute to the major toxicities not only in premature neonates and infants; but also in older children specifically from Asian ethnicity.

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Authors' contributions

All authors (N.Y., Y.Y., and R.H.W.) contributed to the literature search and writing the case report.

All authors meet the ICMJE authorship criteria

Declaration of Competing Interest

None.

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