APPLICATION OF THERAPEUTIC DRUG MONITORING IN PEDIATRIC INTENSIVE CARE UNIT: A CASE REPORT

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Introduction: Adverse drug reactions (ADRs) have an incidence of 0,5-16,8% in hospitalized children. Pharmacokinetic and pharmacodynamic drug features can be influenced by several factors as plasma protein binding, renal function and hepatic metabolism. Indeed, in children, the different ability to metabolize drugs may result in more variable plasma drug levels compared to adult patients. Phenytoin (PHT) is a widely used antiepileptic drug with a narrow therapeutic index, metabolized by the P450 enzyme system, mainly CYP2C9 and CYP2C19. Genetic variations in cytochrome P450 produce high drug concentration variability between patients. The CYP2C9 gene is highly polymorphic and the two most common variants in caucasian poor metabolizers are CYP2C9*2 and CYP2C9*3. At low concentration, PHT elimination is proportional to the drug concentration, whereas with higher plasma level, a constant amount of drug is removed with prolonged half-time increasing risk of ADRs. Furthermore, omeprazole induces competitive inhibition of CYP2C19 leading to an impairment of PHT metabolism, with a decrease in plasma clearance of 15% and half-life of 27%. Acute ADRs of PHT include sedation, ataxia, dizziness, nystagmus, nausea, and cognitive impairment. We describe the case of a caucasian 5-year old child admitted to Pediatric Intensive Care Unit (PICU) for head trauma, who reported ADR due to PHT accumulation.

Methods: A 5-years old child with regular psychomotor development was carried to a local hospital for severe head trauma with sleepiness and vomiting (Glasgow Coma Scale = 7). Subsequently, he was sedated, intubated and transferred to Bambino Gesù Hospital PICU. Endovenous PHT (10 mg/kg/day) was administered as neuroprotective agent for the first seven days. Plasmatic levels of PHT were measured by the ClinMass LC-MS/MS Antiepileptic Drugs Complete Kit® (RECIPE+ Instruments GmbH, Munich, Germany). A Next Generation Sequencing (NGS) analysis including more than 200 pharmacogenes was performed to evaluate presence of cytochrome polymorphisms.

Results: Intracranial pressure and vital signs remained normal and stable, with no neurological deficit evidence. A brain CT scan resulted negative for hemorrhage or skull fractures. On the fifth day, patient was awake but without signs of awareness and PHT levels were 50 μg/ml (therapeutic range 10-25 μg/ml, alert >25). Therefore, in suspicion of potential interaction with metabolism of PHT, omeprazole was suspended. Moreover, no brainstem reflex impairment was observed, except for horizontal nystagmus. In the following days, he was still unconscious, despite a lower sedation, with horizontal nystagmus and middle mydriasis. On the ninth day, PHT plasma levels were still high (36,45 μg/ml). Clinical and neurological conditions were progressively improved simultaneously with reduction of plasma PHT concentration. The pharmacogenetic analysis revealed the homozygous variant c.1075A>C (p.Ile359Leu) in the CYP2C9, corresponding to the CYP2C9*3 allele, classifying the patient as poor metabolizer. These results confirmed the diagnosis of ADR, characterized by neurological disorders due to PHT plasma accumulation, worsened by the simultaneous administration of omeprazole.

Discussion and conclusions: This case highlights how a pharmacological interference i.e. CYP450 inhibition, combined with poor metabolizer genetic variant could lead to a worsening of clinical status as well as diagnostic faults. Therefore, therapeutic drug monitoring (TDM) should not only be performed to monitor drugs concentration, helping clinicians during diagnostic process, but also as a first step to predict different pharmacogenetic variants in the population with the purpose to reach a complete personalized therapeutic approach.