Increase in bilirubin plasma concentration in patients taking sodium valproate

Dear Editor,

In plasma of healthy individuals, bilirubin is mostly unconjugated and bound to albumin (95%), while the rest of it (5%) is conjugated with glucuronic acid and free[1]. Uptake of bilirubin in hepatocytes is mediated by a carrier protein, and after conjugation it is excreted in bile. The carrier protein is a member of the organic anion-transporting polypeptide (OATP) family, which have been found capable of transporting a large array of structurally divergent endogenous substances and drugs[2]. It is being increasingly recognized that many of the bilirubin – drug interactions could take its place at the level of transportation through the membrane of hepatocytes.

Sodium valproate compete with bilirubin for its high affinity binding sites on albumin, which results in displacement of unconjugated bilirubin from albumin[3,4]. The displaced bilirubin, due to its lipid solubility, enters tissues, and plasma bilirubin concentration decreases, but only marginally[5].

However, elevated bilirubin concentrations could be observed as an isolated phenomenon in some patients receiving valproate[6], confusing practitioners who are uncertain whether this was sign of liver toxicity of the drug. It could be explained by competition between bilirubin and valproate for common organic anion transporting polypeptide (OATP) in the membrane of hepatocytes. It was shown for one of the OATPs, the OATP 1B1, that it transported both bilirubin and several drugs, like indinavir, saquinavir, cyclosporine A, and rifamycin. In this study, those drugs inhibited transport of bilirubin, confirming the hypothesis that inhibition of OATP1B1 is an important mechanism for drug-induced unconjugated hyperbilirubinemia[7]. Other drugs are also transported into hepatocytes by OATPs, like pravastatin and temocaprilat[8], suggesting that sodium valproate uses the same transporters. Functional polymorphism of OATP 1B1 (high and low transport activity) was also proved, and linked to single nucleotide polymorphism of a gene encoding OATP 1B1[9]. This could explain why valproate induces elevation of serum bilirubin in only some of the patients using that drug.

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