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Eicosapentaenoic acid ablates valproate-induced liver oxidative stress and cellular derangement without altering its clearance rate: dynamic synergy and therapeutic utility.

El-Mowafy AM[1], Abdel-Dayem MA, Abdel-Aziz A, El-Azab MF, Said SA.

Author information

Abstract

The omega-3 fatty acid eicosapentaenoic acid (EPA) is a superb nature's medicine, with still unfolding health benefits. Because hepatotoxicity is a prominent adverse drug reaction, we currently attempted a new approach in which EPA was challenged to both alleviate hepatotoxicity and provide synergy with anticonvulsant effects of valproate (VPA). Besides, we verified whether EPA may kinetically modulate the clearance rate of VPA. VPA (500mg/kg p.o., for 2weeks) caused rat hepatotoxicity that was manifested as notable (2- to 4-fold) rise in serum liver enzymes (GGT, ALT, and ALP), increased hepatic levels of lipid peroxides and TNF-α (3- and 7-fold) and activity of myeloperoxidase (MPO, 4-fold), lowering of serum albumin (42%), and depletion of liver reduced glutathione (GSH, 36%). Furthermore, histopathologic examination revealed hepatocellular degeneration, focal pericentral necrosis, infiltration of inflammatory cells, and steatosis. Joint treatment with EPA (300mg/kg) blunted the oxidative stress, TNF-α levels and MPO activity, while enhanced levels of serum albumin and hepatic GSH. EPA also ameliorated most of the hepatocellular anomalies evoked by VPA. Additionally, in a mouse PTZ convulsion model, EPA markedly augmented the anticonvulsant effects of VPA far beyond their single responses. On the other hand, pharmacokinetic analyses revealed that joint EPA administration had no effect on serum VPA concentrations. Collectively, results demonstrate for the first time that the ω-3 FA (EPA) markedly alleviated VPA-induced hepatotoxicity, oxidative stress, and inflammation, while enhanced its anticonvulsant effects without altering its clearance. Therapeutically, these protective and synergy profiles for EPA foster a more safe and efficacious drug combination regimen than VPA.

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