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Carnitine in the treatment of valproic acid-induced toxicity.

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Abstract

INTRODUCTION: Valproic acid (VPA) is a broad-spectrum antiepileptic drug that is now used commonly for several other neurological and psychiatric indications. VPA is usually well tolerated, but serious complications, including hepatotoxicity and hyperammonemic encephalopathy, may occur. These complications may also arise following acute VPA overdose, the incidence of which is increasing. Intoxication usually only results in mild central nervous system depression, but serious toxicity and death have been reported.

VALPROIC ACID AND CARNITINE: As a branched chain carboxylic acid, VPA is extensively metabolized by the liver via glucuronic acid conjugation, mitochondrial beta- and cytosolic omega-oxidation to produce multiple metabolites, some of which may be involved in its toxicity. Carnitine is an amino acid derivative that is an essential cofactor in the beta-oxidation of fatty acids. It is synthesized endogenously from the essential amino acids, methionine and lysine. VPA inhibits the biosynthesis of carnitine by decreasing the concentration of alpha-ketoglutarate and may contribute to carnitine deficiency. It is postulated that carnitine supplementation may increase the beta-oxidation of VPA, thereby limiting cytosolic omega-oxidation and the production of toxic metabolites that are involved in liver toxicity and ammonia accumulation. VPA-induced hepatotoxicity and hyperammonemic encephalopathy may be promoted either by a pre-existing carnitine deficiency or by deficiency induced by VPA per se.

CARNITINE SUPPLEMENTATION: Some experimental and clinical data suggest that early intravenous supplementation with l-carnitine could improve survival in severe VPA-induced hepatotoxicity. Carnitine administration has been shown to speed the decrease of ammonemia in patients with VPA-induced encephalopathy although a correlation between ammonia concentrations and the clinical condition was not always observed. As it does not appear to be harmful, l-carnitine is commonly recommended in severe VPA poisoning, especially in children, although the clinical benefit in terms of liver protection or hastening of recovery from unconsciousness has not been established clearly. Prophylactic carnitine supplementation is also advocated during VPA therapy in high-risk pediatric patients.

CONCLUSION: Further controlled, randomized, and probably multicenter trials are required to better delineate the therapeutic and prophylactic roles of l-carnitine and the optimal regimen of administration in the management of VPA toxicity.

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