

The Disulfiram-Morphine Combination Increases Morphine Efflux by Enhancing P-Glycoprotein-Dependent ATP Hydrolysis

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Abstract

Background: Disulfiram has recently resurfaced as a potential drug for combating opioid-induced hyperalgesia. However, the knowledge on the possible pharmacokinetic interactions of disulfiram in morphine pain management is lacking. Disulfiram is a potent P-glycoprotein (P-gp) inhibitor and therefore could influence with gut and blood-brain barrier (BBB) permeability of P-gp substrates, such as morphine. Thus, this investigation is aimed towards determining whether the potential antihyperalgesic effect of disulfiram could be related to the modulation of morphine efflux by P-gp.

Materials and Methods: Morphine and morphine-3-glucuronide (M3G) concentrations in the plasma of rats given either morphine (10 mg/kg, i.g) alone or in combination with disulfiram (25 mg/kg, i.g) for 14 days, were assessed with LC/MS/MS. The expression of Abcb1a and Abcb1b genes in the BBB endothelial cells and in the ileal epithelial cells was assessed by qPCR. P-gp activity was measured in differentiated Caco-2 cells using the rhodamine assay. ATP hydrolysis was investigated in the Malachite Green Assay.

Results: In rats, disulfiram significantly decreased plasma morphine concentrations by twofold, following a 14-day treatment. Brain levels of morphine and M3G were below detection level. The concentrations of M3G were not altered. Additionally, in rats treated with the morphine-disulfiram combination, Abcb1a mRNA levels increased 3-fold, while the expression of Abcb1b remained unchanged. There was also a significant increase in P-gp activity upon disulfiram-morphine exposure in Caco-2 cells when compared to morphine alone. Disulfiram alone decreased ATP hydrolysis, while increasing it in combination with morphine.

Conclusions; The disulfiram-morphine combination decreases plasma morphine concentration by enhancing P-gp and expression in the ileum and ATP hydrolysis. We thus consider the possibility that the antihyperalgesic effect of disulfiram stems from the increased intestinal efflux of morphine.

Keywords

P-glycoprotein, disulfiram, morphine, hyperalgesia.