Hepatocellular toxicity of clopidogrel: Mechanisms and risk factors

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Clopidogrel is a prodrug used widely as a platelet aggregation inhibitor. After intestinal absorption, approximately 90% is converted to inactive clopidogrel carboxylate and 10% via a two-step procedure to the active metabolite containing a mercapto group. Hepatotoxicity is a rare but potentially serious adverse reaction associated with clopidogrel. The aim of this study was to find out the mechanisms and susceptibility factors for clopidogrel-associated hepatotoxicity. In primary human hepatocytes, clopidogrel (10 and 100muM) was cytotoxic only after cytochrome P450 (CYP) induction by rifampicin. Clopidogrel (10 and 100muM) was also toxic for HepG2 cells expressing human CYP3A4 (HepG2/CYP3A4) and HepG2 cells co-incubated with CYP3A4 supersomes (HepG2/CYP3A4 supersome), but not for wild-type HepG2 cells (HepG2/wt). Clopidogrel (100muM) decreased the cellular glutathione content in HepG2/CYP3A4 supersome and triggered an oxidative stress reaction (10 and 100microM) in HepG2/CYP3A4, but not in HepG2/wt. Glutathione depletion significantly increased the cytotoxicity of clopidogrel (10 and 100microM) in HepG2/CYP3A4 supersome. Co-incubation with 1muM ketoconazole or 10mM glutathione almost completely prevented the cytotoxic effect of clopidogrel in HepG2/CYP3A4 and HepG2/CYP3A4 supersome. HepG2/CYP3A4 incubated with 100muM clopidogrel showed mitochondrial damage and cytochrome c release, eventually promoting apoptosis and/or necrosis. In contrast to clopidogrel, clopidogrel carboxylate was not toxic for HepG2/wt or HepG2/CYP3A4 up to 100microM. In conclusion, clopidogrel incubated with CYP3A4 is associated with the formation of metabolites that are toxic for hepatocytes and can be trapped by glutathione. High CYP3A4 activity and low cellular glutathione stores may be risk factors for clopidogrel-associated hepatocellular toxicity.
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