The role of CYP3A4 in amiodarone-associated toxicity on HepG2 cells

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Amiodarone is a class III antiarrhythmic drug with potentially life-threatening hepatotoxicity. Recent in vitro investigations suggested that the mono-N-desethyl (MDEA) and di-N-desethyl (DDEA) metabolites may cause amiodarone's hepatotoxicity. Since cytochrome P450 (CYP) 3A4 is responsible for amiodarone N-deethylation, CYP3A4 induction may represent a risk factor. Our aim was therefore to investigate the role of CYP3A4 in amiodarone-associated hepatotoxicity. First, we showed that 50?M amiodarone is more toxic to primary human hepatocytes after CYP induction with rifampicin. Second, we overexpressed human CYP3A4 in HepG2 cells (HepG2 cells/CYP3A4) for studying the interaction between CYP3A4 and amiodarone in more detail. We also used HepG2 wild type cells (HepG2 cells/wt) co-incubated with human CYP3A4 supersomes for amiodarone activation (HepG2 cells/CYP3A4 supersomes). Amiodarone (10-50?M) was cytotoxic for HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4 supersomes, but not for HepG2 cells/wt or less toxic for HepG2 cells/wt incubated with control supersomes without CYP3A4. Co-incubation with ketoconazole, attenuated cytotoxicity of amiodarone incubated with HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4 supersomes. MDEA and DDEA were formed only in incubations containing HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4 supersomes but not by HepG2 cells/wt or HepG2 cells/wt with control supersomes. Metabolized amiodarone triggered the production of reactive oxygen species, induced mitochondrial damage and cytochrome c release, and promoted apoptosis/necrosis in HepG2 cells/CYP3A4, but not HepG2 cells/wt. This study supports the hypothesis that a high CYP3A4 activity is a risk factor for amiodarone's hepatotoxicity. Since CYP3A4 inducers are used frequently and amiodarone-associated hepatotoxicity can be fatal, our observations may be clinically relevant.
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