OFFICIAL ABSTRACT and CERTIFICATION

Co-administration of Atorvastatin Blocks CYP3A4: Exacerbated Risk of Interstitial Lung Disease

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Drug-drug interactions (DDIs) involving statins, which are prescribed to more than 40 million individuals annually, often lead to deadly adverse drug events (ADEs), including interstitial lung disease (ILD). The objective of this study was to elucidate the molecular basis of ILD caused by the co-administration of statins and cytochrome P450 (CYP) drug inhibitors. Using the FDA Adverse Event Reporting System (FAERS), proportional reporting ratios (PRRs) were calculated to determine statistical associations between ILD and the co-administration of statins. Molecular docking was applied to determine compounds, from the ZINC library, that may cause ILD when administered with statins. A mechanism underlying the pathology of statin-induced ILD was determined using off-targets of statins, key proteins/genes in the lung surfactant metabolism, protein/gene interaction data, and tissue-specific protein expression levels. PRRs calculated from statistical analyses demonstrated the direct involvement of CYP3A4 in atorvastatin-induced ILD due to DDIs ($p=0.031$), indicating the co-administration of atorvastatin with CYP3A4 drug inhibitors should be avoided. Molecular docking identified diphenhydramine, whose association to ILD is currently unknown, may bind to CYP3A4 and cause ILD when co-administered with atorvastatin. ABCB1 and SLCO2B1 were identified as off-target proteins of atorvastatin, suggesting an off-target binding of atorvastatin to ABCB1 or SLCO2B1 causes a disruption in protein-protein interactions that ultimately causes ILD. This study revealed the mechanistic connection between atorvastatin and ILD through CYP3A4 activity, presenting a novel statistical and bioinformatic approach to determine the molecular basis and pathology mechanism of ADEs resulting from DDIs, and to offer safer drug prescription to prevent ADEs.

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