PREDICTED INTERACTIONS OF SELECTED NSAIDS WITH hERG POTASSIUM CHANNEL USING VIRTUALTOXLAB.

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Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are a clinically useful class of drugs whose therapeutic use is currently limited by adverse drug reactions, such as myocardial infarctions and cerebrovascular accidents, which are thought to be secondary to haemodynamic changes such as blood pressure increases. Interaction between hERG and the widely used NSAID, celecoxib is noted in the literature (Frolov, Ignatova & Singh, 2011).

Methods: Here we present data from the VirtualToxLab (Vedani, Dobler & Smiesko, 2012) which predicts whether a range of NSAIDs may interact with hERG. The VirtualToxLab uses an automated, flexible, docking protocol coupled with 4D Boltzmann scoring to predict ligand-protein interactions. We also present data showing the frequency of post-market arrhythmia's gathered from section 4.8 undesirable effects of the individual Summary of Product Characteristics.

Results: Arrhythmias were reported as very common (≥1/10) in relation to tenoxicam, meloxicam and dexibuprofen use and common (≥1/100 to <1/10) in relation to lornoxicam, piroxicam and alminoprofen use. VirtualToxLab did not predict interactions with hERG for any of these NSAIDs. Frequency of arrhythmia's for celecoxib and etoricoxib were rare (≥1/10,000 to <1/1000) and common (≥1/100 to <1/10), respectively. Arrhythmias were not reported in relation to any other NSAIDs included. Rofecoxib, valdecoxib, floctafenine and celecoxib were predicted to interact with hERG with respective predicted IC50 values of 8.15 µM, 3.55 µM, 1.62 µM and 4.81 µM. All other NSAIDs included were not predicted to interact with hERG.

Discussion: The prediction that celecoxib interacts with hERG is in agreement with previous studies by Frolov, Ignatova & Singh (2011), where electrophysiological methods showed celecoxib inhibited hERG channels expressed in HEK-293 cells with an IC50 of 6.0 µM. These *in silico* predictions suggest a similar investigation may be warranted in relation to rofecoxib, valdecoxib and floctafenine. The post-market arrhythmias reported in relation to those NSAIDs where a hERG interaction was not predicted may be occurring secondary to hypertensive changes (Drazner, 2011). Such hypertensive changes could explain the arrhythmia's that are occurring commonly with etoricoxib use.

Future work: These in silico predictions will be followed up by way of FLIPR assay and/ or electrophysiological investigation and provide insight into the cardiovascular safety profiles of a group of drugs for whom the safety profile seems prolifically difficult to establish in a way that is agreeable to the scientific community.

References:

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