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CYP3A time-dependent inhibition risk assessment using inactivation rate

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Time dependent inhibition (TDI) has become the focus of drug designers much more than reversible inhibition because of the higher safety risk this mode of inhibition carries with it. The IC50 shift is the most commonly used method to risk assess TDI because it can be easily tested with modification of the standard, readily automated, reversible CYP3A inhibition testing procedures. This particular inhibition mechanism was indeed the source of a few documented late stage failures and is strongly suspected to participate in the frequently disqualifying liver toxicities in pre-clinical species. We measured kinetic inactivation parameters K_I and k_{inact} for 63 known CYP3A inactivators using a single robust method and validated a miniaturised screening assay based on inactivation rate (k_{obs}) at 10 µM test article concentration versus the current gold standard assay. The inactivation rate constant of a large set of registered drugs (400) has been used to highlight the specific advantages of this method versus the IC_{50} shift. Using an empirically defined positive/negative k_{obs} bin of 0.02 min-1, 4% of registered drugs only were found positive. This proportion increased to more than 20% when in-house lead optimization molecules were considered, emphasizing the importance of filtering this property out when selecting promising drug candidates. Finally, we suggest that the data and technology described here may be a good basis for building structure activity relationships and *in silico* modelling.

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Management of cross-reactivity among sulfonamides: A case report

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A patient developed agranulocytosis after introduction of sulfonylurea agent. According to the Regional Pharmacovigilance Center (CRPV) it was a true hypersensitivity reaction. A month later, the patient is hospitalized for a bronchial infection where multidrug-resistant bacterium is highlighted. The antibiogram shows the interest of sulfamethoxazole and the physician asked pharmacists for the management strategy. Sulfonamides are classified into 3 distinct groups based on their chemical structure: the sulfonylarylamines (including sulfonamide antibiotics), non sulfonylarylamines (including the sulfonylureas) and the sulfonamide derivatives. Analysis of the literature indicated that cross-reaction among different classes of sulfonamide drugs is unlikely to occur, especially between antibacterial sulfonamide and non-sulfa antibiotics because of their difference in structure. An immunoallergic response usually occurs within the first 48 hours in the re-entry of the causal treatment or in case of cross-reaction with a drug of similar chemical structure. In the absence of potential therapeutic alternative, the sulfamethoxazole was introduced with a close biological monitoring. The clinical and biological evolution has been favorable. Among the antibiotics, sulfa allergy is the most common allergy after the beta-lactams. 3% of patients treated with sulfonamides antibiotics develop a severe allergy. In contrast the risk is very rare with non-antibiotic sulfonamides. This case illustrates the collaboration between physicians, pharmacists and the CRPV in the management of complex therapeutic issues. The risk of cross-reactivity between different sulfonamides exists but it is very rare and reintroduction is discussed depending on the severity of the adverse event occurred previously and the risks and benefits of the therapy.

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