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Structural alert/reactive metabolite concept as applied in medicinal chemistry to mitigate the risk of idiosyncratic drug toxicity: a perspective based on the critical examination of trends in the top 200 drugs marketed in the United States.

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Because of a preconceived notion that eliminating reactive metabolite (RM) formation with new drug candidates could mitigate the risk of idiosyncratic drug toxicity, the potential for RM formation is routinely examined as part of lead optimization efforts in drug discovery. Likewise, avoidance of "structural alerts" is almost a norm in drug design. However, there is a growing concern that the perceived safety hazards associated with structural alerts and/or RM screening tools as standalone predictors of toxicity risks may be over exaggerated. In addition, the multifactorial nature of idiosyncratic toxicity is now well recognized based upon observations that mechanisms other than RM formation (e.g., mitochondrial toxicity and inhibition of bile salt export pump (BSEP)) also can account for certain target organ toxicities. Hence, fundamental questions arise such as: When is a molecule that contains a structural alert (RM positive or negative) a cause for concern? Could the molecule in its parent form exert toxicity? Can a low dose drug candidate truly mitigate metabolism-dependent and -independent idiosyncratic toxicity risks? In an effort to address these questions, we have retrospectively examined 68 drugs (recalled or associated with a black box warning due to idiosyncratic toxicity) and the top 200 drugs (prescription and sales) in the United States in 2009 for trends in physiochemical characteristics, daily doses, presence of structural alerts, evidence for RM formation as well as toxicity mechanism(s) potentially mediated by parent drugs. Collectively, our analysis revealed that a significant proportion (~78-86%) of drugs associated with toxicity contained structural alerts and evidence indicating that RM formation as a causative factor for toxicity has been presented in 62-69% of these molecules. In several cases, mitochondrial toxicity and BSEP inhibition mediated by parent drugs were also noted as potential causative factors. Most drugs were administered at daily doses exceeding several hundred milligrams. There was no obvious link between idiosyncratic toxicity and physicochemical properties such as molecular weight, lipophilicity, etc. Approximately half of the top 200 drugs for 2009 (prescription and sales) also contained one or more alerts in their chemical architecture, and many were found to be RM-positive. Several instances of BSEP and mitochondrial liabilities were also noted with agents in the top 200 category. However, with relatively few exceptions, the vast majority of these drugs are rarely associated with idiosyncratic toxicity, despite years of patient use. The major differentiating factor appeared to be the daily dose; most of the drugs in the top 200 list are administered at low daily doses. In addition, competing detoxication pathways and/or alternate nonmetabolic clearance routes provided suitable justifications for the safety records of RM-positive

drugs in the top 200 category. Thus, while RM elimination may be a useful and pragmatic starting point in mitigating idiosyncratic toxicity risks, our analysis suggests a need for a more integrated screening paradigm for chemical hazard identification in drug discovery. Thus, in addition to a detailed assessment of RM formation potential (in relationship to the overall elimination mechanisms of the compound(s)) for lead compounds, effects on cellular health (e.g., cytotoxicity assays), BSEP inhibition, and mitochondrial toxicity are the recommended suite of assays to characterize compound liabilities. However, the prospective use of such data in compound selection will require further validation of the cellular assays using marketed agents. Until we gain a better understanding of the pathophysiological mechanisms associated with idiosyncratic toxicities, improving pharmacokinetics and intrinsic potency as means of decreasing the dose size and the associated "body burden" of the parent drug and its metabolites will remain an overarching goal in drug discovery.

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