Relationship Between Structural Alerts in NSAIDs and Idiosyncratic Hepatotoxicity: An Analysis of Spontaneous Report Data from the WHO Database

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Abstract
Background Idiosyncratic drug reactions such as hepatotoxicity and blood dyscrasias represent one of the major causes of drug withdrawal from the market. According to the reactive metabolite (RM) concept, this may be due to the metabolic activation of structural alerts (SAs), functionalities in the drug molecule that are susceptible to bioactivation resulting in RMs. The relationship, however, between metabolic activation of SAs in drugs with in vivo toxicity measured as disproportionate reporting of adverse drug reactions (ADRs) to the WHO VigiBase database has never been studied.

Objective
The objective of this study was to investigate whether reported associations of hepatotoxicity between NSAIDs with SAs and NSAIDs with mitigated SAs are disproportionately present in the ADR reporting VigiBase database of the WHO collaborating center (the Uppsala Monitoring Centre). The extent of disproportionality of these associations is compared with associations of NSAIDs and hemorrhage, an ADR not associated with the forming of RMs.

Methods
We calculated the reporting odds ratios for five NSAIDs [bromfenac (withdrawn), lumiracoxib (withdrawn), diclofenac, ibuprofen, and naproxen] associated with the MedDRA preferred terms: hepatic failure, hepatic function abnormal, hepatic necrosis, and hepatitis. The disproportionality of the association of these ADRs is compared with the preferred term hemorrhage.

Results
The results show that hepatotoxicity is more disproportionately reported in the WHO database for NSAIDs with SAs (bromfenac, lumiracoxib, diclofenac) than for NSAIDs where SAs are mitigated (ibuprofen and naproxen). This difference in reporting between NSAIDs with SAs and with mitigated SAs is not observed for the ADR hemorrhage, an ADR not associated with the forming of RMs.

Conclusions
This study shows that although spontaneous reports have many limitations, the findings are in line with previous research on the reactive metabolite concept. Whether SAs and the number of SAs in the NSAIDs actually play a role in the observed hepatotoxicity must be investigated in future studies.