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SHORT COMMUNICATION

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Methods We calculated the reporting odds ratios for five NSAIDs [bromfenac (withdrawn), lumiracoxib (withdrawn), diclofenac, ibuprofen, and naproxen] associated with the MedDRA preferred terms: hepatic failure, hepatic function abnormal, hepatic necrosis, and hepatitis.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.

Key Points

In the WHO, VigiBase™ database, NSAIDs with structural alerts (SAs) are more often associated with hepatotoxicity than NSAIDs with mitigated SAs. This difference is not observed for the adverse drug reaction (ADR) hemorrhage, an ADR not associated with the bioactivation of SAs to reactive metabolites (RMs).

This observation shows that although databases with spontaneously reported ADRs have many limitations, these outcomes are in line with previous studies and the RM concept.

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1 Introduction

Adverse drug reactions (ADRs) are the most common cause of pharmaceutical product recalls and labeling changes. They are categorized as predictable and unpredictable (idiosyncratic) reactions. Idiosyncratic ADRs cannot be explained by the known pharmacology of the drug and although they are dose dependent in susceptible individuals, they can occur at any dose within the usual therapeutic range. Certain ADRs are not recognized as potential medical problems prior to approval due to the insufficient number of patients in clinical trials as the incidence rate can be extremely low [1]. Some drugs are known to elicit ADRs prior to metabolism. However, most drugs that elicit an ADR are first metabolized to proximate and ultimate toxic species, a process referred to as metabolic activation or bioactivation [1, 2].

It is generally thought that reactive, electrophilic compounds, formed either from the parent drug (e.g., a reactive quinone-imine from paracetamol) or as a consequence of increased cellular production of reactive oxygen and and/or nitrogen species (hydroxyl radical, superoxide, and peroxynitrite) are responsible for initiating toxicity [3, 4].

The NSAID bromfenac was withdrawn in 1998 after less than a year on the market. The US FDA received 20 reports of serious hepatotoxicity; of these reports, four patients died of liver failure and eight required liver transplants [5]. Bromfenac possesses arylacetic acid, aniline, and bromobenzene motifs that through enzymatic activation processes can undergo bioactivation to reactive epoxides, quinone metabolites, reactive nitroso compounds, acyl glucuronides and acyl-coenzyme A (CoA) thioesters [6].

NSAIDs are a widely used drug class and a major class of drugs associated with toxicity. Depending on the NSAID structure, both cytochrome P450 (CYP)-dependent and glucuronosyltransferase-dependent metabolic pathways may be involved in the formation of metabolites that can react with proteins [7].

Although the chemical structures of NSAIDs differ considerably, many of them contain arylacetic acid, 2-arylpropionic acid, or anthranilic acid derivatives. A number of examples of metabolic activation of carboxylic acid drugs have been documented that may serve as circumstantial evidence with regard to the toxicological relevance of acyl glucuronides and acyl-CoA thioesters [3, 8, 9].

Lumiracoxib is an arylacetic acid derivative whose metabolism in humans is mostly catalyzed by CYP enzymes [10]. Hydroxylumiracoxib, the major circulating metabolite of lumiracoxib in humans, is oxidized to a reactive quinone-imine intermediate in human liver microsomes that can be trapped by glutathione [11, 12]. Lumiracoxib is structurally related to diclofenac, a drug itself known to induce a rare but severe hepatotoxicity in exposed patients. Diclofenac undergoes CYP-catalyzed hydroxylation at the 4′ and 5′ positions, the products of which are also oxidized to reactive quinone-imine intermediates and characterized as their corresponding thiol adducts in humans [13].

Carboxylic acids with a methyl substitution at the α-carbon of the arylacetic group, such as in ibuprofen and naproxen, exhibit lower reactivity with protein nucleophiles probably due to steric hindrance; these two drugs belong to the safest NSAIDs [14].

Although there are countless examples of drugs that are hepatotoxic or cause idiosyncratic drug toxicity for which bioactivation pathways are described, not all drugs possessing functionalities susceptible to bioactivation are bioactivated and, in addition, not all drugs that are bioactivated lead to toxicity [1].

The careful use of structural alerts (SAs) within new chemical entities is one approach to minimize drug-induced toxicity; minimizing body burden is another. Drugs containing SAs might be considered safer if the dose does not exceed 100 mg/day [14]. Drug-induced hepatotoxicity and drug-induced autoimmune disease are more frequently associated with compounds administered at a high daily dose: for two compounds possessing the same SA, it is frequently the case that the low-dose compound will not cause toxicity, whereas a higher-dose compound will [1].

The WHO Global Individual Case Safety Report (ICSR) database, VigiBase™, contains over 8.5 million spontaneously reported ADRs [15]. Although limited details about each suspected adverse reaction are sent, this is the largest database of spontaneously reported drug toxicity. Despite the evidence that metabolic activation of SAs leads to ADRs manifested as in vivo toxicity being well established [4], the reactive metabolite (RM) concept has never been linked to in vivo toxicity measured as spontaneously reported ADRs reported to the WHO database.

The objective of this research was to study whether reported associations of hepatotoxicity between NSAIDs with SAs (the bromobenzene ring, the arylacetic acid group, and the aniline ring) and NSAIDs with mitigated SAs (introduction of a methyl group on the α-C-atom in the arylacetic acid group) are disproportionally present in the ADR reporting VigiBase™ database of the WHO collaborating center [the Uppsala Monitoring Centre (UMC)]. The extent of disproportionality of these associations is compared with associations between NSAIDs and hemorrhage, an ADR not associated with the formation of RMs.

2 Methods

Study data were obtained from the WHO Global ICSR database, VigiBase™, which is maintained by the UMC. As of May 2014, this database contained over 8.5 million

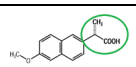
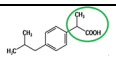
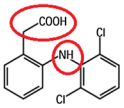
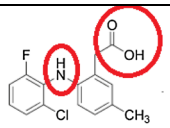
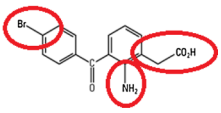
Naproxen DD: 1000 mg	Ibuprofen DD: 2400 mg	Diclofenac DD: 150 mg	Lumiracoxib (W) DD: 400 mg	Bromfenac (W) DD: 150 mg
				

Fig. 1 Researched NSAIDs, structural alerts, and daily dose. Structural features *circled in red* are chemical structures within the drug molecules prone to be bioactivated into reactive features and finally reactive metabolites. Structural features *circled in green* are mitigated structural alerts that are less prone to be bioactivated into reactive features and reactive metabolites. *DD* daily dose, *W* withdrawn

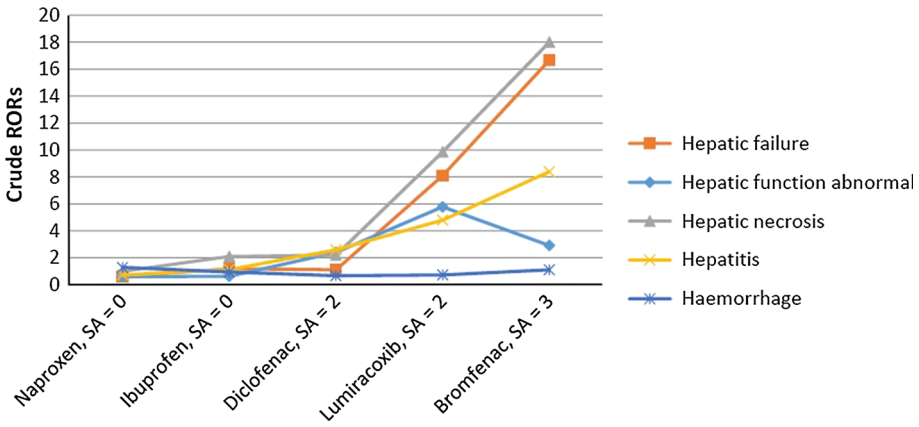


Fig. 2 NSAIDs, ordered by number of structural alerts and daily dose, and the crude reporting odds ratio for the five researched preferred terms. *RORs* reporting odds ratios, *SA* structural alert

case reports of suspected ADRs [15]. For this study, all suspected ADRs reported to VigiBase™ were taken into account. To study the relationship between SAs in NSAIDs we determined the crude reporting odds ratios (RORs) for five NSAIDs (bromfenac, lumiracoxib, diclofenac, ibuprofen, and naproxen) associated with four *Medical Dictionary for Regulatory Activities* (MedDRA®[1]) Preferred Terms (PTs) for hepatotoxicity: hepatic failure, hepatic function abnormal, hepatic necrosis, and hepatitis. Choices for PTs are based on expert opinion. Three NSAIDs (bromfenac, lumiracoxib, diclofenac) contain SAs, whereas in ibuprofen and naproxen the arylacetic SA is mitigated. The strength of the association of these ADRs is compared with the crude RORs for the same five NSAIDs and the PT hemorrhage, an ADR not associated with the forming of RMs. The chemical structures, SAs, and daily dose of the NSAIDs are summarized in Fig. 1.

[1] MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.

3 Results

Based on the reported ADRs in VigiBase™, the WHO database, associations with NSAIDs with SAs (bromfenac, lumiracoxib, diclofenac) seem to be reported more disproportionately in three out of four PTs representing hepatotoxicity than in drugs with mitigated SAs (ibuprofen and naproxen). This difference in disproportionate reporting is not observed for the ADR hemorrhage, which is not associated with the forming of RMs (see Fig. 2). NSAIDs, PTs, and the RORs of the separate associations are shown in Table 1.

4 Discussion

The outcomes of this study show a difference in disproportionality in reporting of hepatotoxicity between NSAIDs with SAs and NSAIDs with mitigated SAs in the WHO database, which is in line with the RM concept. Since the number of reported adverse reactions says not that much about the risk of a certain association, measures of disproportionality have been developed that basically compare the numbers of reports on a certain association with the number of reports that would have been expected based on change. Still, this may not be an

Table 1 Number of reports and crude reporting odds ratios for the studied preferred terms

NSAID	Hepatic failure	Hepatic function abnormal	Hepatic necrosis	Hepatitis	Hemorrhage
Naproxen	51 (0.61 [0.5–0.8])	169 (0.59 [0.5–0.7])	21 (1.00 [0.7–1.5])	177 (0.73 [0.63–0.85])	272 (1.29 [1.15–1.46])
Ibuprofen	114 (1.2 [1.0–1.5])	203 (0.63 [0.6–0.7])	50 (2.1 [1.6–2.8])	304 (1.13 [1.0–1.3])	252 (0.95 [0.83–1.08])
Diclofenac	95 (1.11 [0.91–1.36])	672 (2.4 [2.2–2.6])	47 (2.2 [1.7–3.0])	623 (2.6 [2.4–2.8])	146 (0.67 [0.57–0.79])
Lumiracoxib (W)	13 (8.10 [4.7–14.0])	31 (5.78 [4.0–8.3])	4 (9.86 [3.7–26.3])	22 (4.80 [3.1–7.3])	3 (0.73 [0.24–2.28])
Bromfenac (W)	58 (16.7 [12.8–21.6])	35 (2.92 [2.1–4.1])	16 (18.0 [11.0–29.5])	83 (8.4 [6.7–10.4])	10 (1.11 [0.6–2.07])

Data are presented as *n* (ROR [95 % CI])

ROR reporting odds ratio, *W* withdrawn

accurate indication of risk. Spontaneous reports have many limitations: amongst others, they may not contain sufficient pathological information or the reports may be on patients that are highly vulnerable to adverse reactions due to their existing disease state and multiple drug therapies, any or all of which may contribute to the observed liver damage in the reports we included. In addition, ADR spontaneous reports may be subject to various forms of bias and confounding, so the correlation between reported ADRs and the suspected drug does not necessarily have to be based on a truly causal relationship. Beside these limitations, adverse event identification and reporting rates may be higher if there have been warnings about a drug ('notoriety bias') or specific surveillance recommendations [16]. The impact of the withdrawal of bromfenac and lumiracoxib from the market on the disproportionality of the associations of these drugs is unknown. On the other hand, some drugs in our study seem to have a protective effect on the studied ADRs, such as naproxen for hepatitis and diclofenac for hemorrhage, which are well-known adverse effects of NSAIDs. Expected ADRs may have a lower rate of reporting than unexpected, unlabeled serious reactions, which may lead to under-reporting of such cases to pharmacovigilance centers and, consequently, to VigiBase™ [17, 18].

So far, this is one of the first linkages between the RM concept and in vivo toxicity measured as spontaneously reported ADRs in VigiBase™. In this study, the disproportionalities of the associations of NSAIDs seem to increase with the number of SAs and the daily dose for three out of four PTs representing hepatotoxicity. However, no definitive evidence on the relationship between the number of SAs and increased risks can be concluded merely based on the results of this study. A relationship between the number of SAs and the ability to cause toxicities has never been established and needs further research.

5 Conclusion

The outcomes of this study show that the associations between NSAIDs with SAs susceptible for bioactivation and hepatotoxicity are more disproportionally reported than the associations of NSAIDs with mitigated SAs. This difference in reporting is not observed in the reporting of hemorrhage, an ADR not related to the forming of RMs. Additionally, the outcomes show that although spontaneous reports have many limitations, the outcomes are as expected with regard to previous studies on the RM 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.

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