NSAID-Induced Adverse Drug Reaction: Mechanism and Management

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs to reduce pain or swelling. The use of these drugs in high doses or long-term can cause side effects or hypersensitivity problems, also known as Adverse Drug Reaction (ADR). A literature review was carried out using the PubMed database by inserting the keywords 'NSAID', 'adverse drug reaction', and 'hypersensitivity'. All studies related to NSAIDs and their adverse drug reactions were included in this review, while genetic or pharmacogenomics studies and NSAIDs' effectiveness were excluded. The results showed that gastrointestinal (GI) problems such as duodenal ulcers or erosive gastritis are the most common diclofenac effects (2.05%). Cardiovascular issues, such as acute myocardial infarction, were mostly caused by rofecoxib (2.12%). Hypersensitivity, both respiratory and skin, is commonly caused by ibuprofen with prevalence 50% and 67%, respectively. The most frequent kidney problem related to NSAIDs use is acute kidney injury. In comparison, the common hypersensitivity problems are asthma, urticaria, and angioedema. Adverse drug reactions can be prevented or treated by lowering the dose, reducing the duration of treatment, adding companion drugs, or changing the type of NSAID. In conclusion, it can be seen that ibuprofen severely caused kidney problems and hypersensitivity. On the other hand, diclofenac caused digestive issues, and rofecoxib caused cardiovascular problems.

Keywords: *NSAIDs, ADR, side effects, hypersensitivity*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) work by inhibiting the Cyclooxygenase (COX) enzymes [(1)]. COX-1 is responsible for platelet aggregation, renal artery vasodilation, and gastric mucosal protection beneficial to the body, while COX-2 is an enzyme that will increase during the inflammatory process[(2)].

Adverse Drug Reactions (ADR) can arise due to the body's response to a harmful and undesirable drug. Adverse Drug Reaction occurs at doses usually used in humans to prevent, diagnose, and treat disease or modify physiological functions [(3)]. ADRs are commonly categorized into two types, which are type A and type B, based on their respective mechanism. Type A ADR is the most common (85-90%) and predictable, resulting from high doses or long-term use. Meanwhile, Type B ADR occurs as much as 10-15% in ADR cases and is an idiosyncratic reaction [(4)].

The extensive use of NSAIDs causes many problems, including gastrointestinal diseases (ranging from

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dyspepsia to ulcers), kidney, cardiovascular disorders, and hypersensitivity problems [1, 2, 5]. The prevalence of ADR due to NSAIDs is 22%, with a considerable risk of gastrointestinal diseases 1-5%, cardiovascular 7.2%, renal toxicities 1-5%, and hypersensitivity 0.6-5.7% [6-9].

The literature search was carried out to update data about the NSAID class of drugs that commonly cause hospitals' problems globally. The mechanism of side effects, prevalence, and treatment or prevention of ADR due to NSAIDs are written in this review.

Methods

The literature search was performed using the PubMed database with the keywords 'NSAID', 'adverse drug reaction', 'hypersensitivity', and 'mechanism of action'. A total of 1008 studies were obtained in the initial search. Review articles, non-human studies, non-English studies, unrelated studies (genetic or pharmacogenomics), studies with no information related to the drugs used, and studies assessing the efficacy of NSAIDs with other anti-inflammatory drugs were excluded. Only 24 studies focusing on NSAIDs and the adverse drug reactions met the criteria and were included in the review.

Results and Discussion

General Classification of Adverse Drugs Reactions (ADRs)

Adverse Drug Reaction (ADR) is an unwanted and potentially dangerous response that may arise after consuming a drug or a combination of medications in regular doses [10]. The classification of ADR reactions is very complicated. In general, there are approximately five types of responses. ADR type A reaction is the most common reaction; this reaction is caused by a dose and tends to be predictable, which arises due to the pharmacological response. Type B ADR reaction is a rare but unpredictable reaction. Hypersensitivity reactions are included in type B because they are idiosyncratic and depend on each person. The other types of reactions (C, D, and E) are not caused by mechanisms but more likely to be clinical manifestations. Type C reaction is closely related to dose and time of administration. In contrast, type D reaction is commonly associated with the delayed response, so it is difficult to be diagnosed. Type E reaction is a reaction due to the cessation of drug use. However, type A and type B reactions are the most commonly acknowledged in the clinical setting and have been used for a long time [10, 11]. This review is focused on type A and B reactions.

Table 1. Article Review Results

No	Sites of Reaction	Types of Reaction	Name of drugs	Prevalence (%)	Ref
1.	Gastrointestinal	Peptic ulceration and unspecified gastrointestinal bleeding site	Diclofenac Loxoprofen Celecoxib Mefenamic acid	2.05 1.72 1.66 1.51	(12)
		Colorectal cancer	Aspirin	0.88	(13)
		Stomach cancer	Aspirin	0.14	
		Pancreas cancer	Aspirin	0.14	
		Small bowel injury	Celecoxib	N/A	(14)
		Gastrointestinal bleeding	Etoricoxib	N/A	(15)
		Small bowel lesion (erythema, erosions, ulcers, edema)	Diclofenac	N/A	
		Esophagitis and gastric/duodenal ulcers	Aspirin	N/A	

Cont... **Table 1. Article Review Results**

2.	Cardiovascular	Stroke	Ibuprofen Rofecoxib Celecoxib Diclofenac	3.36 1.14 0.87 0.58	(8, 16, 17)
		Myocardial infarction	Lumiracoxib Rofecoxib Celecoxib Diclofenac	2 0.89 0.86 0.54	
		Cardiovascular death	Rofecoxib Celecoxib	0.86 0.85	
		Acute Myocardial Infarction (AMI)	Ketorolac Indomethacin Diclofenac Rofecoxib Etoricoxib	2.31 1.66 1.33 1.33 1.32	
		Cardiovascular death	Etoricoxib Diclofenac	4.07 3.98	
3.	Renal Injury	Acute Kidney Injury (AKI)	Ibuprofen Naproxen Diclofenac 25 mg with acetaminophen Ketorolac Combination of ibuprofen and naproxen Combination of ibuprofen and ketorolac Rofecoxib	67 11 7.7 7 7 7 N/A	(18-22)

Cont... **Table 1. Article Review Results**

4.	Hypersensitivity (Respiratory)	NSAID-exacerbated respiratory disease (NERD)	Ibuprofen Acetaminophen Mefenamic acid Diclofenac Aspirin Naproxen	60 59 40 20 20 20	(23-27)
		Asthma	Aspirin Mefenamic acid Diclofenac Ibuprofen	50 20 20 10	
		Nasal rhinorrhea, wheezing	Ibuprofen	N/A	
		Nasal Polyps	Aspirin	9.7	
		Rhinitis	Aspirin	8.7	
	Hypersensitivity (Skin)	Urticaria	Ibuprofen Aspirin Metamizole	50 15 10	(28-33)
		Angioedema	Ibuprofen Aspirin Metamizole	37 20 10	
		Maculopapular eruption	Celecoxib	N/A	
		Exanthema	Ibuprofen	4.6	
		NSAID-exacerbated cutaneous disease (NECD)	Ibuprofen Diclofenac Acetylsalicylic acid Ketoprofen	24 15 14 8	

Note: Prevalence is expressed in percentage (%) and sorted from highest to smallest, which causes ADR

N/A: Not available

Type A Adverse Drugs Reactions and Its Clinical Manifestations

Type A was a reaction caused by most ADRs (85-90%). Usually, this type was predictable and could arise due to high doses or long-term use [(4)]. Type A reactions can be divided into three sites of reactions: gastrointestinal, cardiovascular, and renal injury due to reactions that arise due to the pharmacological effects of the drugs[(4, 5)].

In 2003, a study showed that NSAIDs such as naproxen and indomethacin could cause small intestinal injury [(33)]. In 2007, COX-2-specific NSAIDs such as celecoxib and rofecoxib were considered to increase the incidence of myocardial infarction and heart failure [(34)]. Aspirin, ibuprofen, ketorolac can cause interstitial nephritis, nephrotic syndrome, and papillary necrosis; the effects on the kidneys are generally caused by dosage, type of drug, and duration of use [(35)].

a. Gastrointestinal toxicities

According to Lai [(12)], problems related to gastrointestinal problems occurred due to the use of diclofenac (2.05%), celecoxib (1.66%), loxoprofen

(1.72%) (in Japan and Korea), and mefenamic acid (1.51%). In the use of aspirin, 1.4% could cause several types of gastrointestinal cancer during the treatment period. Common cancers were colorectal (0.88%), stomach (0.14%) and pancreas (0.14%). Meanwhile, the use of nonselective NSAIDs of 0.61% could cause colorectal (0.36%), pancreas (0.09%) and gastric (0.05%) cancers. On the other hand, COX-2 selective NSAIDs of 0.56% could develop several types of gastrointestinal cancer, especially colorectal (0.33%), pancreas (0.07%), stomach (0.04%), and oesophageal (0.04%) cancers [13].

The well-known mechanism regarding NSAIDs causing gastrointestinal toxicity was suppressing COX enzyme activity, where non-selective NSAIDs could induce injury to the gastric mucosa due to topical erosive effects combined with systemic effects characterized by the depletion of prostaglandins synthesized by COX-1 [5, 36].

b. Cardiovascular Disorder

The occurrence of cardiovascular-related NSAIDs included heart failure, myocardial infarction, ischemic stroke, and cardiac death. Of all patients who received treatment with NSAIDs, 7.2% experienced cardiovascular events during the treatment period. The use of ketorolac was also identified as increasing cases of acute myocardial infarction (AMI), followed by indomethacin, etoricoxib, rofecoxib, diclofenac [8, 16].

The increasing cardiovascular risk was demonstrated by COX-2 selective NSAID. Rofecoxib was often associated with the incidence of myocardial infarction, ibuprofen, and diclofenac for the risk of stroke, and etoricoxib and diclofenac for the risk of death from cardiovascular (myocardial infarction, arrhythmia, pulmonary embolism, and stroke) [17, 37].

COX-2 selective NSAIDs inhibited vascular prostacyclin synthesis (PGI2), where PGI2 functioned as an anti-platelet aggregation with vasodilator properties. PGI2 was a protective mediator for the cardiovascular system, which worked through IP receptors, and was expressed in various cell types. The increased risk was caused by a decrease in the formation of PGI2. However, this risk could be reduced by inhibiting COX-1 since COX-1 had an activity in the formation of thromboxane A2 (TXA2), which caused vasoconstriction[5].

The combination of these two effects could lead to a "pro-thrombotic state" with a significant risk of developing myocardial infarction or stroke. However, except for naproxen, none of the non-selective NSAIDs (apart from aspirin) could affect COX-1 platelets in a significant way needed for the inhibitory effect of platelets [5, 38]. In terms of cardiovascular safety, naproxen, and ibuprofen at the lowest effective dose were the best first choice with the lowest risk [8, 39-41].

c. Renal toxicity

In the event of kidney toxicity caused by NSAIDs, drugs with a high level of toxicity were ibuprofen (67%), naproxen (11%), ketorolac (7%), the combination of ibuprofen and naproxen (7%), and ibuprofen and ketorolac (7%). The combination of diclofenac with acetaminophen was also known to induce Acute Kidney Injury (AKI) occurrence, especially for patients with accompanying diseases such as liver cirrhosis or hypertension. COX-2 selective NSAID, rofecoxib, also showed an increased risk for AKI, although according to studies, selective NSAIDs showed a smaller risk compared to nonselective [18-20].

All NSAIDs could change kidney function by inhibiting COX-1 (which regulated renal hemodynamics and glomerular filtration) and/or COX-2 (which mediated the excretion of salt and water) expressed in the kidney [18, 42]. Although rare, NSAIDs could cause nephropathy due to high doses of some drugs. It was found that indomethacin was associated with more cases of kidney failure [37, 43].

Type B Adverse Drugs Reactions and Its Clinical Manifestations

Type B occurred as much as 10-15% in ADR cases. The reaction was unpredictable, was not dose-dependent, and only appeared in certain patients. Type B reactions were divided into several classifications of causes: excessive sensitivity to drug toxicity, idiosyncratic drug reactions, and hypersensitivity reactions, both nonimmunological and immunological [4].

Nonimmunological immune responses to NSAIDs (cross-reactive) were indicated by hypersensitivity reactions to NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease

(NECD), and NSAID-induced urticarial/angioedema (NIUA). For immunological responses (non-cross-reactive), hypersensitivity reactions that might arise were single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) and single-NSAID-induced delayed HS reaction (SNIDR) (24–48 hours after drug entry) [44].

In 2004, it was found that the leading cause of NSAID hypersensitivity was caused by the use of aspirin or nonselective NSAIDs. In contrast, skin reactions are commonly urticaria or angioedema with the similar use of drugs [45].

a. Respiratory Disease

NSAID-exacerbated respiratory disease (NERD) events were generally caused by ibuprofen (60%); mefenamic acid (40%); diclofenac (20%); acetylsalicylic acid (20%); and naproxen (20%). In Europe, the highest causes were acetylsalicylic acid (82%) and pyrazolones (9%), while in America, the highest causes were acetylsalicylic acid (80%) and ibuprofen (41%). Other studies showed that ibuprofen accounted for 63.8% and was followed by acetaminophen (59%). NSAID-exacerbated respiratory disease (NERD) was present in the form of respiratory symptoms such as asthma, rhinitis, nasal polyps, mild chest tightness, and nasal congestion [23, 24].

The suppression mechanism of COX-1 production influenced the reduction of prostaglandin E2 (PGE2) biosynthesis from arachidonic acid. The induction of COX-2 isoenzymes did not compensate for the lack of this anti-inflammatory mediator. The inflammatory process was more striking when COX inhibitors were used, and the respiratory tract's inflammation would persist even if the drug were no longer used [46-50].

b. Skin Eruption

Skin-related cases, both angioedema and urticaria were mostly induced by ibuprofen (43.5%), aspirin (17.5%), metamizole (10%). In another study sequencing from the most to the least frequently induced, there was ibuprofen (24%); diclofenac (15%); acetylsalicylic acid (14%); ketoprofen (8%). On the other hand, the reaction with a combination of two different NSAIDs showed smaller results. NSAID-exacerbated cutaneous disease (NECD) was indicated by the emergence of urticaria and angioedema (41.4%) and urticaria (28.5%), which could occur in a matter of hours. Skin lesions were commonly found on the face (eyes and lips). On the other hand, the delayed reaction would occur more than 24 hours after exposure. It would develop into specific skin diseases (exanthema, fixed drug eruption, toxic epidermal necrolysis, or Stevens-Johnsons syndrome) [9, 27, 28].

The NECD induction mechanism was the same as NERD because both of them resulted from hypersensitivity reactions. The use of COX-2 selective NSAIDs (celecoxib and etoricoxib) was recommended for patients with this hypersensitivity. Hypersensitivity events were rarely found when using COX-2 selective NSAIDs, but prior testing was needed to ensure tolerability [28, 51, 52].

Management of NSAIDs' Adverse Drugs Reaction in Clinical Settings

It is known that an adverse drug reaction (ADR) is an unexpected reaction from a treatment. Physicians or pharmacists commonly recommend changing the drugs with a similar group or the same mechanism or actions. However, it cannot be applied in general because not all medicines can replace each other. Each drug has its levels of efficacy, toxicity, and side effects [53, 54]. In the case of ADR, because of NSAIDs, there are recommended actions that could be applied to prevent or treated ADRs (Table 2).

Table 2. Management of NSAID Induced Adverse Drug Reaction

No	Type of Reaction	Reaction	Management	Ref
1.	Type A	Gastrointestinal symptoms (nausea, vomiting, abdominal pain)	Oral or intravenous H2 blockers or antiemetics or PPI	(55, 56)
		Small bowel injury	Conversion from nonselective NSAIDs to selective like celecoxib	(57)
		Acute Myocardial Infarction	Combination of naproxen and ibuprofen in low effective dose	(41)
		Acute kidney injury	Lowering dose	(58)
2.	Type B	AERD	Low salicylate diet	(59)
		Nasal symptoms, such as congestion	Topical nasal decongestants or corticosteroids, oral or nasal antihistamines	(55)
		Bronchospasm	short-acting bronchodilator	
		Urticaria/ angioedema	Addition of antihistamines and leukotriene antagonists	(60)

AERD: Aspirin Exacerbated Respiratory Disease

In type A reaction, it is recommended to reduce the dose or withhold the drug administration until the response disappears [61, 62]. In terms of gastrointestinal symptoms (nausea, vomiting, and abdominal pain), it is suggested to use H2 Blocker or antiemetics to prevent adverse reactions. Guidelines recommend various strategies to avoid problems in those at risk for NSAID-associated GI complications [55, 61]. Patients without gastrointestinal risk factors could use nonselective NSAIDs. On the other hand, patients with gastrointestinal risk could only receive nonselective NSAIDs with PPI. For patients with high gastrointestinal risk factors that needed NSAIDs, including those who had had previous bleeding ulcers or with concomitant anticoagulant therapy, COX-2 plus PPI inhibitors provided the most promising gastrointestinal protection[39, 56].

A recent study found that the use of histamine type-2 receptor antagonists (H2RAs) could prevent GI adverse events in NSAID users. It was recently proved during clinical trials, the use of ibuprofen/famotidine combination could reduce the risk of ulcers by 50% compared with ibuprofen alone [63].

It is recommended to use specific NSAIDs in cardiovascular and kidney disorders such as naproxen and ibuprofen in low doses [37, 41]. Some studies showed that cardiovascular risk has a strong association with cyclooxygenase (COX)-2 selectivity. The low COX-2

selectivity of naproxen results in a lower cardiovascular risk than other NSAIDs [64, 65].

For type B reaction, the identified management was specific for Aspirin Exacerbated Respiratory Disease (AERD), nasal symptoms, bronchospasm, and urticaria. To prevent AERD, patients should limit salicylate use, and it should be closely monitored [59]. To avoid respiratory disorder, especially in the nasal symptoms, topical nasal decongestants or corticosteroids, oral or nasal antihistamines should be administered. A study conducted by Braido [66] showed that inhaled steroids and antihistamine are the primary tools in allergies, rhinitis, and asthma, which are more safe and effective drugs are. A short-acting bronchodilator is recommended to prevent bronchospasm for high-risk patients when they use NSAID [57].

Some studies showed that patients could experience urticaria only after the intake of NSAID. However, if the patients have to use NSAIDs, short-term antihistamines with or without steroids should be administered to prevent exacerbation or control acute urticaria [60, 67]. On the other hand, a recent study revealed that the use of antileukotrienes is more effective in primary cold urticaria delayed pressure urticaria [68].

Conclusion

ADR risks due to the use of NSAIDs were mostly caused by ibuprofen with side effects of kidney problems and hypersensitivity to both breathing and skin, followed by diclofenac with gastrointestinal issues, and rofecoxib, which was not even recommended for patients with cardiovascular problems because it could increase the severity of the disease. Adverse drug reactions could be overcome or prevented by lowering the dose, reducing the duration of treatment, or changing the type of NSAID used.

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