Nonsteroidal Anti-Inflammatory Drugs

61

Kimberlie A. Graeme

Contents

Biochemistry and Clinical Pharmacology 1220

Pathophysiology of Toxic Effects 1220

Clinical Presentation and Life-Threatening Complications 1220
Acute Allergic Reactions 1220
Adverse Effects and Clinical Toxicity Due to Chronic Use 1221
Adverse Effects and Clinical Toxicity Due to Acute Overdosage 1229

Diagnosis of Acute Overdose 1229

Treatment of Acute Overdose 1232

Special Populations 1233

References 1234

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse class of compounds that share anti-inflammatory, analgesic, and antipyretic properties. Both therapeutic and adverse effects of NSAIDs are primarily due to cyclooxygenase (COX) inhibition. There are different types of COX, denoted as COX-1, COX-2, and COX-3 (which is considered a variant of COX-1) [1].

NSAIDs are commonly utilized and comprise up to 2.5% of all prescription dollars spent, globally. A National Health Interview Survey in 2010 revealed that 12.8% of adults in the United States were taking NSAIDs at least three times a week for 3 months, which represented a more than 40% increase in use since 2005. Further, telephone surveys reveal that 26% of users of over-the-counter NSAIDs take more than the recommended dose [2]. These factors explain the finding that adverse effects from NSAIDs are among the most common drug side effects reported in the United States and worldwide [3]. In 2005, the US Food and Drug Administration released a statement stressing "the importance of using the lowest effective dose for the shortest duration possible if treatment with a NSAID is warranted for an individual patient" [2]. This thought is echoed throughout current literature.

Despite the significant number of reports of toxicity from chronic use and overuse, intentional acute overdosage of NSAIDs is rarely life-threatening and death from acute NSAID overdose is quite rare.

The author would like to thank Anthony "Tony" Morkunas who contributed to the first edition of this chapter.

K.A. Graeme (✉)
Medical Toxicology, Banner – University Medical Center, Phoenix, AZ, USA
e-mail: Kimberlie.Graeme@bannerhealth.com

J. Brent et al. (eds.), *Critical Care Toxicology*,
DOI 10.1007/978-3-319-17900-1_96

Biochemistry and Clinical Pharmacology

Metabolism of phospholipids by the enzyme phospholipase A_2 produces arachidonic acid, a 20 carbon unsaturated fatty acid which is embedded in cellular membranes. During inflammatory processes, arachidonic acid is converted into prostaglandins and thromboxanes. This conversion is mediated by COX, lipoxygenase, and cytochrome P450 enzymes. Nonsteroidal anti-inflammatory drugs prevent the substrate arachidonic acid from binding to the active site of COX enzymes (Fig. 1).

Pathophysiology of Toxic Effects

In general, the COX-1 isoform performs housekeeping functions, such as gastric mucosal protection. Due to its function in maintaining homeostasis, COX-1 is found in high concentrations in many cells and tissues, including endothelial cells, platelets, renal collecting tubules, and the gastrointestinal (GI) tract. Conversely, COX-2 is inducible by mediators of inflammation, such as tumor necrosis factor and cytokines. Nonsteroidal anti-inflammatory drugs can downregulate COX-2 pathways, thereby inhibiting inflammation. These differences in COX isoenzymes has led to classifying various NSAIDs by strength of inhibition of each isoenzyme, with nonselective NSAIDs inhibiting both COX-1 and COX-2 enzymes and selective NSAIDs inhibiting COX-2 more than COX-1 enzyme. Despite these classifications, both COX-1 and COX-2 are expressed in many tissues and there is overlap in COX-1 and COX-2 function. For instance, COX-2 derived prostaglandins play a role in maintenance of GI mucosal integrity and COX-1 derived prostaglandins contribute to inflammation [1, 4–7]. Further, we are discovering that there is significant similarity in the clinical toxicity produced by nonselective and selective NSAIDs. It appears that dose may be more important than laboratory-defined COX selectivity. At higher doses, COX selectivity blurs [1].

While some continue to classify by COX selectivity ("nonselective" if the NSAID inhibits both COX-1 and COX-2 well and "selective" if it primarily inhibits COX-2; selective is also sometimes denoted as COXIB), others prefer to classify NSAIDs by chemical composition (See Tables 1 and 2). Most reviews include both classifications and both can be useful clinically; however, NSAIDs classified as selective do not always share common adverse effect profiles with each other, even at therapeutic doses. For instance, regardless of selectivity, GI side effects may occur with most NSAIDs, particularly in the lower GI tract [1]. The same is true for adverse cardiovascular effects, especially at high doses [1]. Some propose that solubility and partition coefficients, pH, and pKa may determine the distribution of various NSAIDs into various body tissues, contributing to differing toxic effects from different NSAIDs. Table 3 lists pharmacokinetic parameters of some NSAIDs. Others have suggested that NSAIDs target Ca^{++} induced K^{+} channels but differ in their ability to affect the channels and produce toxicity [1]. Still others suggest that differential transport of NSAIDs with transporters such as the organic anion transporting polypeptide 2A1 (OATP2A1) may account for varying toxicity of various NSAIDs [1].

Clinical Presentation and Life-Threatening Complications

Adverse effects and clinical toxicity may occur from: drug-drug interactions (Table 4), acute allergic reactions, chronic use and overuse, and acute overdosage. While the focus of this textbook is acute overdose and associated toxicity, drug-drug interactions and chronic toxicity are so common with NSAIDs due to the prevalence of their use that these adverse effects are discussed. Allergic reactions are less common, but can be life-threatening, and are also discussed.

Acute Allergic Reactions

Nonsteroidal anti-inflammatory drug hypersensitivity reactions have been reported with diclofenac, ibuprofen, naproxen, ketoprofen, phenylbutazone, and oxyphenbutazone [17].

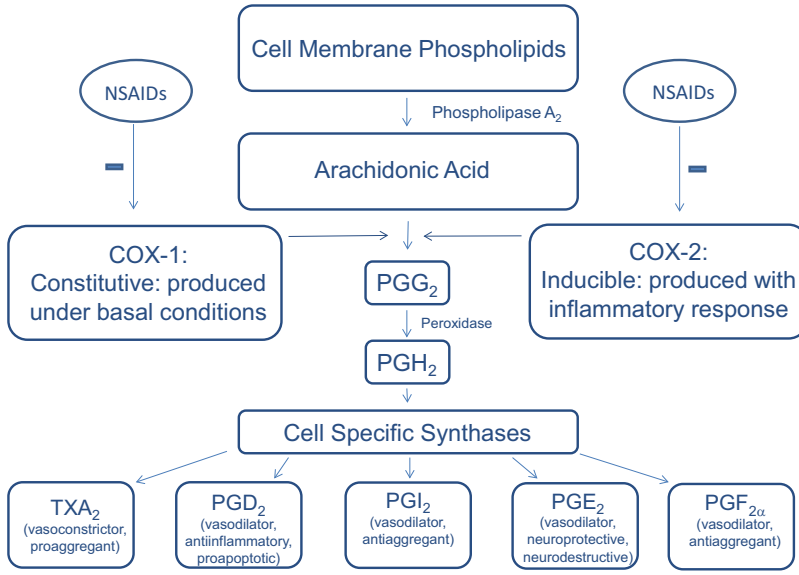

Fig. 1 **Actions of NSAIDs**. In normally functioning cells, phospholipase converts phospholipids in the cell membrane into arachidonic acid, which begins the arachidonic acid cascade. Arachidonic acid is further converted to PGG_2 by COX enzymes. PGG_2 is then converted PGH_2 by peroxidase. Under normal circumstances, the action of COX enzymes on arachidonic acid eventually produce prostaglandins D_2, E_2, $F_{2\alpha}$ (PGD_2, PGE_2, PGF_2), prostacyclin I_2 (PGI_2), and thromboxane A_2 (TXA_2), needed for gastrointestinal mucosal protection, maintenance of renal perfusion, and regulation of platelet aggregation. NSAIDs limit the production of PGG_2, by inhibiting COX enzymes, which subsequently results in less PGH_2. Since NSAIDs reduce the amount of PGH_2 that can be acted upon by cell specific synthases to produce prostaglandins (PGD_2, PGE_2, PGF_2), prostacyclins (PGI_2), and thromboxanes (TXA_2), many cell functions are altered. The reduced production of prostaglandins, prostacyclins, and thromboxanes can affect vasoconstriction/vasodilation, platelet aggregation, neuroprotection, neurodestruction (e.g., apoptosis), inflammatory responses, and carcinogenesis

Acetaminophen and salicylates, which are discussed in other chapters, have also been associated with hypersensitivity reactions. Nonsteroidal anti-inflammatory drugs are amongst the most likely drugs to induce anaphylaxis. Single oral administration of a NSAID may result in anaphylaxis. Nonsteroidal anti-inflammatory drug-induced anaphylaxis is likely due to an IgE-mediated response, may occur rapidly, and may be life-threatening [17–19]. Retrospective analysis of an allergy service in the Netherlands found that 17% of hospitalizations were related to NSAID hypersensitivity, 30% of which were secondary to diclofenac. The most common reaction was anaphylaxis, in this hospitalized group [18]. Of note, nonallergic drug hypersensitivities, commonly called pseudoallergic or idiosyncratic reactions, may result from NSAID use as well.

Topical NSAID application, such as topical ketoprofen use, may produce contact and photocontact allergic reactions as well as anaphylaxis [17, 19].

Adverse Effects and Clinical Toxicity Due to Chronic Use

Generally, higher doses, longer duration of use, and comorbidities of the patient are associated with increased risk of adverse drug effects from NSAIDs. Additionally, genetic susceptibility may contribute to variable toxicity. The major adverse effects of NSAIDs involve the GI, renal, and cardiovascular systems; however, other systems may also be affected [1]. These adverse effects will be discussed systematically.

Table 1 Classification by chemical structure[a]

Chemical class	Examples of drugs: generic name (brand name)
Acetic acids	**Bromfenac (Duract®)** – a benzene acetic acid; withdrawn from US market due to severe hepatotoxicity, resulting in death and transplantation [8–10] **Diclofenac (Voltaren®, Cataflam®)** – a phenylacetic acid; associated with DILI [10] **Etodolac (Lodine®, Lodine XL®)** – an indole acetic acid **Indomethacin (Indocin®)** – an indole acetic acid **Sulindac (Clinoril®)** – an indene acetic acid **Tolmetin (Tolectin®) –** a heteroaryl acetic acid
Butanones (Ketones)	**Nabumetone (Relafen®)** – a prodrug
Diarylheterocyclics (also, COXIBs or COX-2 selective inhibitors)	**Rofecoxib (Vioxx®)** – a furanone; a sulfone; withdrawn from US and other markets due to risk of myocardial and cerebral infarctions **Celecoxib (Celebrex®)** – a sulfonamide derivative; a pyrazole; occasional DILI [10] **Valdecoxib (Bextra®)** – a isoxazole; a sulfonamide derivative; withdrawn from US and other markets **Paracoxib (Dynastat®)** – injectable prodrug of valdecoxib; not on US market **Etoricoxib (Arcoxia®)** – a bipyridine; a sulfone; not on US market **Lumaricoxib (Prexige®)** – a phenylacetic acid; never on US market; analog of diclofenac; highly COX-2 sensitive; associated with liver toxicity (severe hepatic necrosis, requiring transplantation or resulting in death) [9–12]
Fenamic acids (anthranilic acids)	**Meclofenamic acid (Meclomen®)** **Mefenamic acid (Ponstel®)**
Oxicams (enolic acids)	**Meloxicam (Mobic®)** **Piroxicam (Feldene®)**
Propionic acid derivatives	**Fenoprofen (Nalfon®)** **Flurbiprofen (Ansaid®)** **Ibuprofen (Motrin®) –** occasional DILI [10] **Ketoprofen (Orudis®)** **Naproxen (Naprosyn®)** **Oxaprozin (Daypro®)** **Suprofen (Suprol®)** – off US and other markets
Pyrazolones	**Oxyphenbutazone** **Phenylbutazone**
Pyrrolo-pyrroles	**Ketorolac (Toradol®)** – a carboxylic acid; banned from many European markets; significant gastrointestinal toxicity
Salicylates (discussed in a separate chapter)	**Acetyl salicylic acid (Aspirin®)** **Sulfasalazine (Azulfidine®)** **Diflusinal (Dolobid®)**
Sulphonanilides	**Nimesulide** (never on US market; severe hepatotoxicity) [10]

Key: *DILI* drug-induced liver injury, *US* United States, *COX* cyclooxygenase

[a]This table is a composite of many works [1, 4, 10, 13]. Of note, there is some variation in classification by chemical structure amongst different authors. The brand names given are examples of those used in the United States. These may differ in other countries

Neurological and Neurovascular Effects from Chronic Exposure

Cerebrovascular accidents: There is controversy regarding the risk of stroke with NSAID use [1, 15]. Studies are historical and contradictory. For instance, one retrospective cohort study revealed an increased risk of stroke among users of rofecoxib and valdecoxib but not diclofenac, ibuprofen, naproxen, and indomethacin; however, another retrospective cohort study revealed both nonselective (naproxen, indomethacin, piroxicam, meloxicam, diclofenac) and selective (celecoxib and rofecoxib) NSAIDs were associated with increased risk of stroke. In the later study, ibuprofen was the only NSAID that did not increase the risk of stroke [1]. Most clinical trials suggest an association of increased thromboembolic events with NSAID use, regardless of COX-2 selectivity. In general, meloxicam appears to present less risk than rofecoxib and celecoxib

Table 2 Classification by COX-1 and COX-2 isoform selectivity[a]

COX 1 selective (Low COX-2 inhibition: COX-1 inhibition ratios; lowest listed at top)	Unselective (Progressing from more COX 1 selective to more COX-2 selective)	COX 2 selective[b] (High COX-2 inhibition: COX-1 inhibition ratios; highest listed at top)
Ketorolac[c]	Meclofenamate	Etodolac
Flurbiprofen	Sulindac	Celecoxib
Ketoprofen	Naproxen	Meloxicam
Indomethacin	Piroxicam	
Tolmetin	Ibuprofen	
Aspirin (Acetylsalicylic acid)	Acetaminophen	
Nabumetone	Sodium salicylate	
Fenoprofen	Diflunisal	

This table was generated from multiple sources [1, 4, 5, 13]
Key: *COX* cyclooxygenase
[a]Note: COX 1 selective and unselective are generally called "nonselective" and COX 2 selective is generally referred to as "selective" or "COXIB"
[b]Others that are typically classified as COX-2 selective but that are not available on the US market include: rofecoxib (thrombotic disease), nimesulide (liver toxicity), valdecoxib (thrombotic disease), lumiracoxib (liver toxicity), etoricoxib, and paracoxib
[c]Off the market in France, Germany, and some other countries for bleeding complications, primarily perioperatively, and for renal failure, especially in the elderly or those with impaired renal function. Ketorolac has a higher relative risk of GI bleeding than most NSAIDs

Table 3 Pharmacokinetics of some NSAIDs[a]

NSAID	Bioavailability (%)	Half-life (h) (therapeutic; may differ in overdose)[b]	Volume of distribution (L/kg, unless otherwise stated)	Clearance (L/h; unless otherwise stated)	Primarily renally eliminated (Y/N)	Peak (h) (therapeutic; may differ in overdose)	Protein binding (%)
Celecoxib	Solution: 64–88 Capsule: 22–40	6–12	400 L	27.7	N (hepatic metabolism; inhibits CYP2D6)	2–4	97
Diclofenac	50–60 (first-pass effect)	1–2	0.1–0.2	21.0	Y	2–3	99
Ibuprofen	>80	2–4	0.15	3–3.5	Y	0.5	99
Ketoprofen	90	2	0.1	6.9	Y	1–2	99
Meloxicam	89	15–20	10 L	0.4–0.5	half	4–10	99
Naproxen	95	12–17	0.16	0.13 ml/min/kg	Y	1	99

Many sources were used to develop this table [7, 13, 14]
[a]Generally, most NSAIDs are acidic, have high bioavailability, and are highly protein bound. Most are metabolized by the liver. Some (such as, naproxen, ibuprofen, and ketoprofen) are also glucuronidated by renal enzymes [1]
[b]While NSAIDS (excluding Aspirin) reversibly inhibit the COX enzyme, drugs with long half-lives, such as piroxicam with its half-life of 30–86 h, will appear to irreversibly inhibit COX enzyme. Further, in overdose half-lives of all NSAIDs may be prolonged. Aspirin irreversibly inhibits COX enzyme; thus, new COX enzyme must be made to restore function

and most studies indicate that ibuprofen does not present a significant stroke risk [1].

Aseptic meningitis: Aseptic meningitis generally presents with fever, headache, photophobia, and meningeal signs (e.g., neck stiffness). Less commonly, confusion, lethargy, and seizures are seen. Aseptic meningitis is a rare complication of NSAID use, but NSAIDs are the most common cause of drug-induced aseptic meningitis. Aseptic meningitis has been reported following

Table 4 Drug-drug interactions producing toxicity and critical illness

Drug or drug class that interacts with NSAIDs	Effect	Some specific interactions
Angiotensin-converting enzyme inhibitors[a]	Increase risk of renal compromise, hyperkalemia, and hypertension	Indomethacin (and probably other NSAIDs) inhibits the antihypertensive response of captopril; however, sulindac has a small opposing effect of the antihypertensive efficacy of captopril and enalapril
Angiotensin inhibitors	Increased risk of renal compromise and hyperkalemia	
Anticoagulants	GI side effects (e.g., bleeding)	NSAIDs can produce hypoprothrombinemia, but the effect is variable and dependent on the specific NSAID COX-2 selective agents can have platelet-aggregating effects and compete with warfarin for albumin binding sites NSAIDs increase the incidence of bleeding in patients receiving heparin therapy
Antidiabetic agents (Sulfonylureas and insulin)	Increased risk of hypoglycemia	Phenylbutazone enhances the hypoglycemic response of antidiabetic agents
Beta-blockers	Increased risk of hypertension	NSAIDs (indomethacin, flurbiprofen, piroxicam) reduce the antihypertensive effects of beta-blockers Sulindac is less likely to interfere with beta-blockers Calcium channel blockers have lesser interactions with NSAIDs than do beta-blockers
Corticosteroids	GI side effects (e.g., ulceration, bleeding)	
Cyclosporine	Increased risk of cyclosporine toxicity (nephrotoxicity)	Sulindac increased cyclosporine concentrations and serum creatinine (2- to 3-fold) within 3 days Indomethacin increases nephrotoxicity in animals Mefenamic acid increases serum creatinine and cyclosporine concentrations within 1 day
Diuretics	Increased risk of renal compromise and hypertension	Concomitant administration of indomethacin, diclofenac, or ibuprofen with triamterene has produced hyperkalemia Indomethacin may inhibit the formation of prostaglandins, which protect against drug-induced nephrotoxicity
Ethanol	Increased risk of GI bleeding	A two- to threefold increase in incidence of minor gastric bleeding has been reported with co-ingestion of ethanol and NSAIDs
Hydralazine	Increased risk of hypertension	Indomethacin increases blood pressure through inhibition of prostaglandin synthesis
Lithium	Increased risk of lithium toxicity	NSAIDs (including COXIBs) increase serum lithium levels to varying degrees (12–448%), depending on the NSAID Elevations in lithium levels may occur in as few as 3 days Diclofenac, ibuprofen, indomethacin, ketorolac, mefenamic acid, naproxen, phenylbutazone, and piroxicam reportedly interfere with renal prostaglandins that are involved in the excretion of lithium

(*continued*)

Table 4 (continued)

Drug or drug class that interacts with NSAIDs	Effect	Some specific interactions
Methotrexate	Increased risk of methotrexate toxicity (hematologic toxicity)	NSAIDs may increase methotrexate levels Toxicity is generally seen at higher (antineoplastic) doses of methotrexate and less commonly with lower doses Diclofenac prior to high-dose methotrexate therapy has resulted in serious methotrexate toxicity Flurbiprofen, co-administered with low-dose methotrexate, has reportedly produced neutropenia, thrombocytopenia, and GI bleeding Ibuprofen decreases the renal clearance of methotrexate by 50% and doubles the methotrexate area under the curve Death has occurred with concomitant use of indomethacin, ketoprofen, naproxen, and phenylbutazone
Serotonin reuptake inhibitors (SSRIs)	Increase adverse GI effects (e.g., GIB)	SSRIs increase bleeding risk by inhibiting platelet adhesion and function Conversely, tricyclic antidepressants do not appear to increase GI risks as much

This table was generated from many sources [1, 4, 15, 16]
Key: *GIB* gastrointestinal bleed, *COXIBs* COX-2 selective
[a]Increases in blood pressure with NSAIDs are most pronounced when co-administered with angiotensin II receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEIs) and lowest with calcium channel blockers and loop diuretics [16]

therapeutic doses of ibuprofen, naproxen, sulindac, piroxicam, diclofenac, ketoprofen, and tolmetin. It occurs most commonly in women with systemic lupus erythematosus. The cause may be direct chemical irritation of the meninges by the NSAID but may also involve a hypersensitivity reaction. Laboratory findings include pleocytosis, primarily neutrophils, in the CSF, with associated elevations of protein; however, the cultures will be negative for infectious agents [20–22]. The differential diagnosis should include medication overuse headache, a refractory, chronic headache that resolves following cessation of the NSAID.

Hearing loss: Transient and persistent sensorineural hearing loss have been reported to occur after therapeutic doses of ketorolac [23, 24].

Pulmonary Effects from Chronic Exposure

Asthma: There is nearly complete cross-reactivity between aspirin-induced asthma and nonselective NSAID-induced asthma. Selective NSAIDs do not often appear to exacerbate asthma, although there are a few case reports of cross-reactivity with aspirin-induced asthma [15, 16, 18]. Patients with nasal polyps, a marker of arachidonic acid metabolism abnormalities, are more likely to experience NSAID-exacerbated respiratory disease. Genetic susceptibility contributes to this risk [18].

Cardiovascular Effects from Chronic Exposure

Myocardial infarction: Once it was discovered that rofecoxib increased the risk of serious cardiovascular events (e.g., myocardial infarctions, congestive heart failure, and cardiac failure events), the cardiovascular risks of other NSAIDs were investigated. Meta-analyses revealed that other NSAIDs are associated with adverse cardiovascular events, such as myocardial infarction. This risk appears to be dose dependent, but some agents are more strongly associated with cardiovascular events. Low-dose ibuprofen has cardioprotective effects, similar to aspirin; however, high-dose ibuprofen increases cardiovascular risks [1, 15]. Diclofenac use presents a 40–60% higher relative risk of serious

cardiovascular events, compared to no NSAID use. This risk appears to be at least equivalent to rofecoxib, which has been withdrawn from the US market [1, 6, 15]. Despite this, diclofenac is the most commonly used NSAID worldwide [1]. Etoricoxib, which is not available in the United States, also appears to increase the risk of adverse cardiovascular events. Conversely, celecoxib and etodolac (both selective NSAIDs), and naproxen (a nonselective NSAID), have very low risks of adverse cardiovascular events [1, 6]. Patient factors, such as previous myocardial infarction, contribute to the risk of myocardial infarction, especially when taking higher doses of NSAIDs [1].

Dysrhythmias: Multiple studies indicate an increased risk of atrial fibrillation associated with NSAID use, especially long-term use [1].

Gastrointestinal Effects from Chronic Exposure

Dose- and duration-dependent adverse effects range from mild (dyspepsia, nausea) to severe (duodenal ulcers, gastrointestinal bleeding and stricture of the lumen, occasionally complicated by obstruction and perforation) [2]. In general, the most severe adverse effects involve the distal (lower) GI tract, while the more mild effects are more proximal (upper GI tract). Patients taking NSAIDs have a relative risk of 4.7 for upper GI bleeding and perforation, compared with nonusers; however, this risk varies depending on the agent [2] (See Table 5). Enteric-coated and sustained release products may decrease upper GI symptoms; however, these preparations increase the risk of distal GI toxicity, which is more serious [1].

Some measures can be taken to limit the GI toxicity induced by NSAIDs. Patient risk factors, such as advanced age; previous GI injury; and concurrent therapy with anticoagulants, aspirin, corticosteroids, and selective serotonin reuptake inhibitors (SSRIs) also contribute to toxicity; therefore, other agents should be considered [2]. When topical, rather than oral, NSAIDs can be utilized, this should be done to limit the GI side effects [1]. Protective strategies, such as the co-administration of misoprostol, are recommended to limit GI toxicity (Grade I evidence) [2]. Modeling suggests that a proton pump inhibitor may reduce upper GI adverse effects [15]. Meta-analysis of nine randomized clinical trials comparing celecoxib with nonselective NSAIDs found less GI side effects associated with celecoxib [1]. However, this data cannot be extrapolated to other selective NSAIDs, as rofecoxib does not appear to provide this advantage [1].

Table 5 Relative risk of GI bleeding with NSAIDs [7]

Low risk:	Ibuprofen (RR = 2.23)
Moderate risk:	Diclofenac (RR = 3.61)
	Naproxen (RR = 4.46)
	Indomethacin (RR = 5.12)
High risk:	Ketorolac (RR = 14.54)

RR Relative risk

Hepatic Effects from Chronic Exposure

NSAIDs (when acetaminophen is included) are third, following antibiotics and anticonvulsants, as causes of drug-induced liver injury (DILI) [10]. Up to 10% of cases of DILI are felt to be attributable to NSAIDs and nearly all NSAIDs have been implicated in causing liver injury [9, 12] (Table 6). A higher incidence of DILI has been described with diclofenac and sulindac compared to other NSAIDs. Most DILI caused by NSAIDs is minor; rarely, severe hepatotoxicity develops, occasionally resulting in death or the need for liver transplantation [10]. Nonsteroidal anti-inflammatory drug-induced liver diseases include: acute hepatitis, cholestasis (ibuprofen), cholestatic hepatitis (sulindac), chronic hepatitis (diclofenac), granulomatous hepatitis (phenylbutazone), and acute liver failure (bromfenac, lumiracoxib; neither are on US market) [12].

A genetic predisposition to DILI has been noted with diclofenac and lumiracoxib (not on US market) [10]. Lumiracoxib is structurally similar to diclofenac. The hepatotoxicity is generally idiosyncratic [10]. However, nongenetic risk factors are involved in NSAID-induced DILI as well, including use of other hepatotoxic drugs and chronic liver disease [10]. The hepatotoxicity of both diclofenac and lumiracoxib can be delayed for 1–3 months and has been associated with hepatotoxic metabolites and glutathione adduct

Table 6 NSAID-induced liver injury

NSAID	Type of liver injury seen	% of reported NSAID-induced hepatotoxicity[b]
Diclofenac	Hepatocellular injury	34.1%
Ibuprofen[a]	Hepatocellular injury (some cases may occur with hepatitis C) Cholestasis Vanishing bile duct syndrome	14.6%
Sulindac	Cholestatic Hepatocellular injury Mixed pattern Generalized hypersensitivity reactions (associated with most of the fatal cases)	12.4%
Naproxen	Hepatocellular injury Cholestasis Rarely, immune-allergic hypersensitivity reactions Cross-hepatotoxicity with fenoprofen	11.1%
Piroxicam	Cholestatic jaundice Hepatocellular injury Rarely, hypersensitivity (rash, fever, eosinophilia)	9.3%

Note: While this table is unique, much of the data is derived from the text, graphs, and tables found in the article by Unzueta A, et al. [10]

[a]Ibuprofen has one of the best hepatotoxic safety profiles of the NSAIDs; however, because it is one of the most frequently used NSAIDs, it is responsible for a significant number of cases

[b]Acetylsalicylic acid is responsible for 12% of reported NSAID-induced hepatotoxicity; acetaminophen-induced hepatotoxicity was not included in the data used to populate this table

formation, with glutathione depletion, oxidative stress, and mitochondrial injury [12, 25]. With lumiracoxib use, severe hepatocellular necrosis associated with positive auto-antibodies (antinuclear antibodies) has resulted in the need for transplantation and in death [9, 12].

Renal Effects from Chronic Exposure

Kidney injury: It is estimated that 2.5 million people in the United States experience NSAID-mediated renal disease annually [5]. Acute and chronic renal failure, with an associated reduction in glomerular perfusion and filtration rate, are seen [1]. Understanding blood flow to the kidney helps elucidate this disease process (See Fig. 2). Prostaglandins normally dilate the afferent arteriole bringing blood to the glomerulus. Nonsteroidal anti-inflammatory drugs limit prostaglandin production, producing vasoconstriction of the afferent arteriole, thereby limiting blood flow to the glomerulus [1, 26].

Risk factors for NSAID-mediated renal disease include: high doses, concomitant use of medications that alter renal autoregulation, age greater than 65 years, male gender, intravascular volume depletion, cardiovascular disease, diabetes, and pre-existing chronic renal disease [1, 5, 15]. Nonsteroidal anti-inflammatory drugs may produce renal papillary necrosis, acute interstitial nephritis (AIN), and the nephrotic syndrome. Renal papillary necrosis may result from medullary ischemic injury [1, 5]. The nephrotic syndrome is characteristic, with edema, oliguria, foamy urine, hematuria, and proteinuria. Acute interstitial nephritis is generally reversible [1, 5, 26]. Chronic renal failure (CRF) secondary to NSAIDs is rare but may occur secondary to interstitial nephritis or papillary necrosis [1]. While regular doses of NSAIDs are unlikely to produce CRF, high doses of NSAIDs increase the risk significantly [1].

Electrolyte abnormalities: Generally, all NSAIDs are associated with sodium retention, edema, and weight gain, regardless of COX selectivity. Hyponatremia is the most common electrolyte abnormality seen with NSAID use. Hyperkalemia, likely secondary to potassium retention, also occurs, regardless of COX selectivity; however, hypokalemia may also occur [1, 5, 27]. Hypocalcemia, hypomagnesemia, and hypophosphatemia are also reported [27]. Renal tubular acidosis, type 4, with associated electrolyte abnormalities may be seen [5].

Hypertension: Hypertension may worsen in previously hypertensive patients once placed on NSAIDs. In one study, rofecoxib was associated

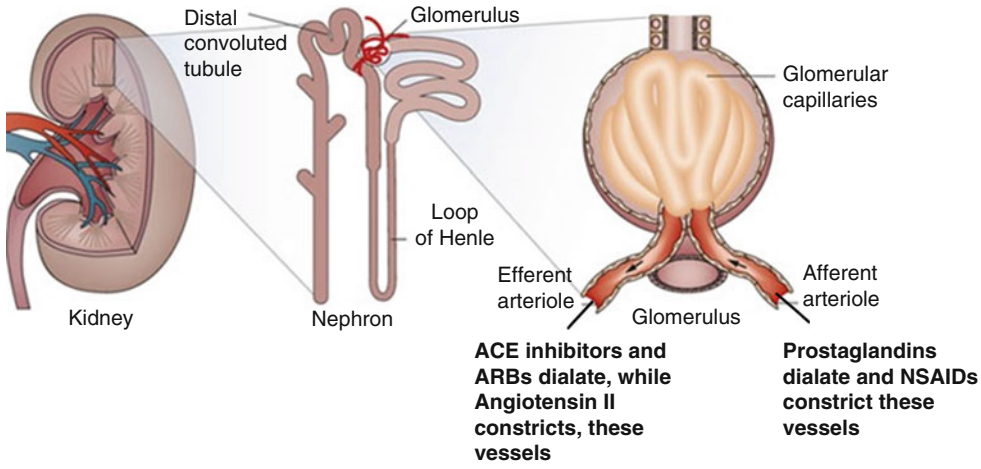

Fig. 2 NSAID effects on the kidney. The afferent arteriole normally dilates in response to prostaglandins; this results in an increased GFR. NSAIDs inhibit this effect by reducing the production of prostaglandins. This produces relative vasoconstriction of the afferent arteriole and decreases GFR. Conversely, angiotensin II normally constricts the efferent arteriole to increase GFR. However, ACE inhibitors inhibit this effect and produce a relative dilation of the efferent arteriole; this decreases GFR. Administration of ARBs also leads to vasodilation of the efferent system. By acting at different sites to reduce GFR, NSAIDs (afferent vasoconstriction) and ACE inhibitors/ARBs (efferent vasodilation) can significantly limit GFR when administered concomitantly. This explains the increased risk of renal insufficiency and failure seen when these agents are used together [5]. *GFR* glomerular filtration rate, *ACE* angiotensin-converting-enzyme, *ARBs* angiotensin II receptor blockers

with worsening hypertension, while celecoxib was associated with a lower risk, revealing that this adverse effect is independent of COX selectivity, although this is not uniformly found in all studies [1]. The mean increase in systolic blood pressure is 2–3 mmHg, but it can be much greater, especially if the patient is co-ingesting angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or diuretics [15]. This effect has been demonstrated in randomized controlled trials.

Immunologic Effects from Chronic Exposure

NSAIDs (with acetylsalicylic acid included) are the most frequent drugs involved in hypersensitivity drug reactions. Hypersensitivity may be mediated by immunoglobulin E (IgE), by T cells, or by activation of pathways that release vasoactive mediators (histamine, prostaglandins, sufidopeptide leukotrienes) [17, 18]. Immunologic disease includes NSAID-induced respiratory disease (e.g., anaphylaxis, which is discussed above), cutaneous disease (e.g., delayed fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis), renal disease (e.g., nephritis, which is discussed above), and hepatic disease (which is discussed above) [9, 17, 18]. A multisystem hypersensitivity syndrome characterized by fever, rash, hepatic injury, and lymphadenopathy has been reported as well [28].

Both nonselective and selective (e.g., valdecoxib) NSAIDs may produce serious skin reactions [12]. The most frequent dermal reactions are exanthemas that are maculopapular and are commonly due to ibuprofen or naproxen. Contact dermatitis and photosensitivity may occur, generally triggered by ketoprofen and diclofenac. Severe reactions such as toxic epidermal necrolysis or Stevens-Johnson syndrome have been only rarely reported with NSAID use; these syndromes can prove fatal [15, 17, 18]. Chronic propionic acid-NSAID use has also produced pseudoporphyria, with bullous photosensitivity and similarities to porphyria cutanea tarda [29].

Hematopoietic Effects from Chronic Exposure

Phenylbutazone can produce serious blood dyscrasias, including aplastic anemia, agranulocytosis, and thrombocytopenia [30]. Phenylbutazone is sometimes referred to as "bute" and has been taken illicitly by jockeys and other racetrack workers [30]. Oxyphenbutazone, a metabolite of phenylbutazone, can produce similar toxicity.

Adverse Effects and Clinical Toxicity Due to Acute Overdosage

NSAIDs are generally well tolerated in overdose, with acute poisonings most commonly producing minimal morbidity and very rarely death. However, large overdosage may produce toxic encephalopathy, seizures, respiratory failure, cardiovascular arrest, renal failure, and hepatic injury. In the United States, ibuprofen is one of the most frequently ingested NSAIDs in acute overdose. Several deaths have been reported [27]. Lodise et al. report of a 51-year-old man who presented after intentional, isolated ibuprofen ingestion, confirmed by gas chromatography/mass spectrometry (GC/MS). The patient presented with coma, hypotension, metabolic acidosis, and respiratory depression. Despite vigorous supportive care, he died 4 h after arrival to the ED. Postmortem examination revealed edema of the brain, heart, and lungs, with unspecified myocardial injury. Postmortem ibuprofen concentrations were approximately 25 times greater than therapeutic concentrations [27]. Naproxen is also commonly ingested. Al-Abri et al. report of a 28-year-old man who ingested 70 g of naproxen and ethanol. He was drowsy, tachycardic, and developed metabolic acidosis that was treated with continuous venovenous hemofiltration (CVVH). He had recurrent seizures and respiratory failure requiring intubation. His naproxen concentration was approximately 40 times greater than therapeutic concentrations [31].

While many NSAIDs share a similar clinical appearance in overdose, there are notable distinctions. Clinical findings of acute NSAID overdoses found in the literature are summarized in Table 7, and the unique features of different classes of agents are further delineated in the footnotes of Table 7 and in the discussion that follows.

Some important points to remember when caring for patients with large overdoses of NSAIDs, reviewed by system, include:

Neurologic: Acute psychosis and auditory hallucinations have been reported with overdosage of indomethacin, diclofenac, sulindac, and mefenamic acid [4]. Seizures, including status epilepticus, may occur, especially after overdosage of mefenamic acid [4, 32]. A retrospective review of single-agent exposures resulting in seizures from 1997 to 2010 in Switzerland revealed that mefenamic acid was the most prevalent cause of drug-induced seizures; however, due to its current infrequent use, this is not likely the case now [45]. Nystagmus, diplopia, miosis, and blurred vision have also been reported following overdosage of NSAIDs [4, 32]. The pupils may be fixed in miosis, but this should not be utilized as a prognosticator, since patients with this finding have made full neurological recoveries [56].

Pulmonary: Pulmonary edema and respiratory distress syndrome (ARDS) in conjunction with multiple organ failure have occurred in overdose [4, 50].

Renal: A profound, anion-gap, metabolic acidosis can occur with massive overdoses, occasionally with pH less than 7 [48, 49].

Complications of overdosage: Complications of toxic encephalopathy and hypotension may occur and occasionally prove fatal. These can include: aspiration pneumonia, respiratory failure, rhabdomyolysis, ischemia, and sepsis [27, 56, 61]. Rarely, dysrhythmias, such as ventricular fibrillation, and cardiac arrest have been reported [27]. Ischemic necrosis of the extremities may ensue [36].

Diagnosis of Acute Overdose

Blood studies: Symptomatic patients warrant the following basic blood studies: complete blood count, electrolytes, renal function tests, and liver

Table 7 Reported clinical findings with acute NSAID overdosage[a]

NSAID	Clinical findings in overdose
General NSAID overdosage [4, 32–35]	*Neurological*: headache, dizziness, toxic encephalopathy (irritability, agitation, or coma), seizures, blurred vision *HEENT*: tinnitus *Pulmonary*: hyperventilation, respiratory alkalosis (rarely respiratory failure) *Cardiovascular*: mild hypotension and tachycardia (rarely cardiovascular collapse or dysrhythmias) *Gastrointestinal*: GI distress (nausea, vomiting, diarrhea, abdominal pain), rarely GI bleeding, rarely pancreatitis *Hepatic*: hepatic injury, generally mild *Renal*: sodium and water retention, rarely acute renal failure, hematuria, proteinuria *Heme*: hypoprothrombinemia (prolonged prothrombin time), rarely: neutropenia, aplastic anemia, agranulocytosis, leukocytosis, thrombocytopenia
Acetic acids (diclofenac, etodolac, indomethacin, sulindac) [33, 36–40]	*Neurological*: headache, dizziness, toxic encephalopathy (disorientation, irritability, agitation, hallucinations, coma), quadriplegia with interspersed choreiform movements (rare), extensor reflexes on plantar stimulation (rare), fixed gaze (without doll's eye movements; rare) *HEENT*: tinnitus *Pulmonary*: respiratory arrest (rare) *GI*: GI distress (vomiting, abdominal pain); colonic perforation (with diclofenac; rare) *Hepatic*: falsely elevated bilirubin (due to the phenolic metabolites of etodolac); hyperbilirubinemia (with normal liver enzymes in patient with sulindac overdose) *Renal*: acute kidney injury, proteinuria, hematuria, renal failure (anuria) *Hematopoietic*: hypoprothrombinemia, bone marrow aplasia and cytopenias, granulocytosis (transient, with acute sulindac overdose) *Integument*: skin necrosis (ischemic)
Diarytheterocyclics (celecoxib) [41]	*Neurological*: drowsiness, irritability, agitation *GI*: GI distress, abdominal pain *Integument*: rash
Fenamic acids (flufenamic acid, meclofenamic acid, mefenamic acid, tolfenamic acid) [26, 32, 42–45]	*Neurological*: toxic encephalopathy (agitation, coma) seizures,[b] dyskinesia, muscle twitching, hyperreflexia, extensor plantar response, miosis *Cardiovascular*: cardiopulmonary arrest (rare) *GI*: GI distress (vomiting, diarrhea) *Renal*: acute renal failure *Hematopoietic*: hypoprothrombinemia
Propionic acid derivatives[c] (fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin) [27, 31–33, 46–60]	*Neurological*: dizziness, headache, drowsiness, toxic encephalopathy (agitation, coma), seizures (rare; may be recurrent), muscle twitching (rare), nystagmus (rare), diplopia (rare), blurred vision, miosis, unreactive pupils (rare; with eventual full neurological recovery), ataxia, vertigo *HEENT*: tinnitus, decreased hearing *Pulmonary*: hyperventilation (respiratory alkalosis with metabolic acidosis; generally, less severe than is seen with salicylate), respiratory depression (rarely, respiratory arrest) *Cardiovascular*: tachycardia, bradycardia (rare), hypotension, congestive heart failure (rare), dysrhythmias (rare), cardiac arrest (ventricular tachycardia/fibrillation; very rare) *GI*: GI distress (nausea, vomiting, abdominal pain, hematemesis); pancreatitis (rare) *Hepatic*: liver failure (very rare); hyperbilirubinemia[d] *Renal*: hematuria and proteinuria; polyuria; acute renal insufficiency; acute renal failure (tubular necrosis, nephritic syndrome); metabolic acidosis (common, though generally mild; however, may be severe in large overdosage); hyperkalemia; hypokalemia; hypernatremia; hyponatremia *Hematopoietic*: hypoprothrombinemia, thrombocytopenia *Metabolic/endocrine*: hypothermia (rare, but more often than hyperthermia);[e] adrenal insufficiency

(*continued*)

Table 7 (continued)

NSAID	Clinical findings in overdose
Pyrazolones (oxyphenbutazone,[f] phenylbutazone[f]) [30, 33, 61]	*Neurological*: toxic encephalopathy (irritability, agitation, coma), seizures (may include status epilepticus) *Cardiovascular*: tachycardia, hypotension, cardiovascular collapse *Pulmonary*: respiratory depression and failure, respiratory alkalosis, pulmonary edema *GI*: GI irritation, ulceration and GIB *Hepatic*: hepatic injury (hepatocellular, cholestasis) *Renal*: hematuria, acute renal failure (may require weeks of hemodialysis), electrolyte and fluid imbalances, metabolic acidosis (may be profound) *Endocrine*: Hyperglycemia, acutely *Hematopoietic*: acute leukocytosis (granulocytosis)[g] hypoprothrombinemia, thrombocytopenia, hypocellularity of bone marrow (if biopsied)
Sulfonanilides (nimesulide) [62]	Metabolic/endocrine: hypothermia[e]; hypoglycemia[h]

[a]Table 7 comprises primarily data from case reports, case series, and retrospective reviews. Often, only severe or unusual cases are reported in the literature
[b]Mefenamic acid is more likely to produce seizures, compared with other NSAIDs, with >1/3 of patients overdosing on mefenamic acid having seizures [32]
[c]Generally, dose of >400 mg/kg of ibuprofen are required to produce significant toxicity [32]
[d]Bilirubin may be falsely elevated due to NSAID metabolites that interfere with the assays for bilirubin [63, 64]
[e]NSAIDs are known to uncouple oxidative phosphorylation in laboratory studies, so one would expect to see hyperthermia, but this is not generally seen clinically. In severe overdose, hypothermia following coma is more commonly reported than hyperthermia. Hypothermia has also been reported with nimesulide, even at therapeutic doses, in young children
[f]Tend to be more toxic than most other NSAIDs; Phenylbutazone is used in veterinary medicine and by equine racetrack workers; oxyphenbutazone is a metabolite of phenylbutazone [30, 33]
[g]Bone marrow dyscrasias are more characteristic of chronic use
[h]Both hypoglycemia and hypothermia may occur after a single therapeutic dose, as well

function tests. Bilirubin may be falsely elevated after overdosage of some NSAIDs [38].

In the older literature, many acute NSAID overdose cases occurred with significant co-ingestion of salicylate, and in the reported fatalities involving NSAIDs, significant salicylate toxicity was often noted; therefore, it is important to assess for concomitant salicylism [33]. Similarly, acetaminophen levels and liver function tests should be assessed to assess for concomittent acetaminophen toxicity (See chapters on Salicylate and Acetaminophen). Diflunisal, a salicylic acid derivative, cross-reacts with some salicylate assays and may produce a false positive for salicylate. Laboratory studies for NSAID concentrations are not generally available and are not likely to be of clinical utility in the acute management. Further, the once advocated nomogram to assess severity of ibuprofen toxicity, based on ibuprofen concentrations, is not useful [4].

Urine studies: Urinalysis may reveal proteinuria and hematuria. Phenylbutazone toxicity has been associated with red-discoloration of the urine, due to a rubazonic acid metabolite [65]. Generally, rapid urine drug screens (enzyme-linked immunoassays) are of limited value. Further, many rapid urine drug screens may produce false positive cannabinoid screens after the use of NSAIDs. If a patient is critically ill, GC/MS may be helpful at detecting co-ingestants as well as NSAIDs.

Imaging studies: Computed tomography (CT) may be useful in the patient with altered mental status of uncertain etiology but is not uniformly necessary for patients known to have overdosed on NSAIDs. Chest radiographs may be helpful for patients with suspected pulmonary edema, ARDS, or aspiration pneumonitis or pneumonia. Ultrasound of the kidneys or liver may be helpful in assessing renal or hepatic failure, respectively, but are not uniformly required.

Treatment of Acute Overdose

Treatments for salicylate and acetaminophen toxicity are not included in this chapter; the treatment of these toxicities differs significantly from what is described below, please refer to these chapters, specifically, if a patient suffers from salicylate or acetaminophen poisoning.

General: Treatment is primarily supportive and expectative. Watch for respiratory compromise. Patients with significant NSAID ingestions may show evidence of GIBs due to the risk of GI irritation, ulceration, and bleeding which may be attenuated by employing an H_2-receptor antagonists [1, 34] (Grade I recommendation). Hypotension generally responds to intravenous fluids, but occasionally vasopressors are employed [56, 57]. Wood et al. report a case of vasopressor-resistant hypotension, eventually resulting in cardiac arrest and death, after massive ibuprofen overdosage [47]. Since functional adrenal insufficiency has been reported in a patient with massive NSAID overdose, hypotension with a concomitant low cortisol level could be treated with systemic steroids [57]. Extracorporeal membrane oxygenation has been utilized for cardiovascular support in the treatment of massive ibuprofen overdose with cardiac failure [56]. Severe metabolic acidosis can be treated with fluid resuscitation and bicarbonate; occasionally, renal replacement therapy is necessary (see below) [47, 57]. Liver transplantation has been utilized to treat fulminant hepatic failure from NSAIDs [46, 66].

Elimination: Oral administration of activated charcoal, without gastric emptying, may reduce NSAID absorption if patients present within 1 h of ingestion and if the airway is protected (e.g., patient is alert or endotracheally intubated for depressed mental status). However, it is unknown if charcoal administration alters the outcome in these patients. Because most NSAIDs are highly protein bound and extensively metabolized, forced diuresis, urinary alkalization, and hemodialysis are generally not indicated to enhance drug elimination. When studied, these methods do not appear to alter clearance significantly [31, 32, 55]. However, patients with severe acid/base abnormalities, severe electrolyte abnormalities, or acute renal failure may benefit from renal replacement therapy (e.g., high-flux hemodialysis, sustained low efficiency dialysis, continuous hemofiltration, etc.) [30–32, 35, 47, 55]. When renal failure occurs, hemodialysis may be required for weeks to months, but it is generally reversible [52]. Virji, et al. report on a case of severe phenylbutazone poisoning treated with plasmapheresis, but this is not generally performed [61].

Intravenous lipid emulsion therapy (LET) has been used to treat naproxen and ibuprofen toxicity in dogs (case report and series in veterinary literature) [67, 68]. Since most cases of human overdose are not life-threatening, LET is generally unnecessary; however, LET could be tried if cardiac arrest resulted from an overdosage of a lipophilic NSAID, such as ibuprofen or naproxen. Its benefit, if any, following NSAID overdose is strictly theoretical. There are no data indicating that it is beneficial or improves outcome in these patients.

Indications for ICU Admission After NSAID Overdose (Patients May Be Transferred Out of the ICU, Once These Resolve)

Seizures
Encephalopathy (agitation, psychosis, coma)
Angioedema with impending airway compromise
Respiratory failure
Pulmonary edema or ARDS
Hemodynamic instability (hypotension, shock, dysrhythmias)
Gastrointestinal hemorrhage
Fulminant hepatic failure
Renal failure with clinical compromise
Significant electrolyte or acid/base disturbances (e.g., severe metabolic acidosis)
Multiple organ failure

Special Populations

Geriatric: Elderly patients are known to be more susceptible to the adverse effects of NSAIDs, such as renal toxicity and central nervous system effects. Rarely, NSAIDs produce confusion, hallucinations, and psychoses [69].

Pediatric: Although the rate of life-threatening and fatal events from overdosage of ibuprofen (1.6%) is much less than that of acetaminophen (5.6%) and aspirin (5.9%) in adults; these rates are similar and much lower (approximately 0.4% of reported overdoses for each agent are life-threatening) in children [16]. This is likely due to the higher frequency of unintentional overdoses in children compared with adults. Adolescents may be more susceptible to seizures after mefenamic acid overdose, compared to adults [45]. Randomized controlled trials show an increased risk of renal failure in children taking ibuprofen for fever [16].

Neonatal: There are several reports of iatrogenic overdosage of indomethacin in premature infants, due to the use of indomethacin to treat patent ductus arteriosus (PDA) and to prevent intracranial hemorrhage (ICH). There is concern about indomethacin decreasing mesenteric, cerebral, and renal blood flow; altering platelet and renal function; and disrupting gastric mucosal integrity. In fact, there have been anecdotal reports of necrotizing enterocolitis (NEC) and intestinal perforations with suspected causal contribution from indomethacin. Following planned treatment with indomethacin, patients may experience transient renal impairment, with decreased diuresis, edema, hyponatremia, and hyperkalemia. Narayanan et al. performed a retrospective review of iatrogenic tenfold overdoses of intravenous indomethacin to 4 premature infants (secondary to dosing error) and compared the cases to a large population of premature infants who received appropriate intravenous indomethacin dosing [70]. All 4 patients received only one dose of a tenfold dosing error, with 3 patients experiencing transient drops in urine output and 2 experiencing transient increased BUN or creatinine; however, none experienced NEC, ICH, or chronic lung disease [70]. Due to the low number of patients (4 patients, with one dosing error each), this data is similar to a case series of 4, and it is difficult to be completely reassured by this data due to the rarity of NEC. Schuster et al. report on a preterm infant who received a single 100-fold overdose of indomethacin for the treatment of PDA. The infant experienced transient renal failure with oliguria and mild hyponatremia and hyperkalemia, with full resolution by 4 days [71].

Obstetric: A large epidemiological study found that nonselective and selective NSAIDs may lead to abortion in the first trimester, with an odds ratio of 2.4 (95% confidence interval 2.1–2.8), compared with pregnant women not taking NSAIDs. Misoprostol, which is sometimes given with NSAIDs for GI protection, should not be administered to pregnant patients due to the risk of miscarriage [15].

Nonsteroidal anti-inflammatory drugs may delay labor, may prematurely close the ductus arteriosus, and may increase blood loss at delivery. Pregnant patients are at increased risk of fetal ductus arteriosus closure as the pregnancy progresses. Indomethacin, diclofenac, and naproxen are known to produce premature closure of the ductus arteriosus. With closure, fetal ultrasound may reveal dilation of the right ventricle, absence of flow in the pulmonary trunk, tricuspid regurgitation, pulmonary insufficiency, or oligohydramnios. The fetus may develop pulmonary hypertension [72–74]. When severe, fetal hydrops and death ensue [72]. Therefore, NSAIDs generally should not be administered during the last trimester [15, 16]. Intrauterine fetal exposure to NSAIDs may also produce hyponatremia and hyperbilirubinemia, recognized at delivery [72, 75].

Lactating mothers may take nonselective and selective NSAIDs, as levels of celecoxib and ibuprofen have been shown to be very low in breast milk [15].

Key Points in Overdosage

Most NSAID overdoses do not produce life-threatening toxicity.

Phenylbutazone and oxyphenbutazone are more toxic than other NSAIDs.

Mefenamic acid overdoses are commonly associated with seizures (much more so than other NSAIDs).

When massive NSAID overdosage occurs, it may be life-threatening.

Critical care is required when the NSAID overdose results in: encephalopathy, status epilepticus, respiratory failure, hypotension, dysrhythmias, cardiac failure, GI bleeding, GI perforation, hepatic failure, renal failure, significant metabolic acidosis or electrolyte abnormalities, cytopenias, and ischemia.

Severely poisoned patients may acutely have fixed, pin-point pupils yet proceed to a full neurological recovery.

NSAID overdosage may produce psychosis, especially in the elderly.

Some NSAIDs may falsely elevate the serum bilirubin concentrations (assay dependent).

Remember to assess for concomitant salicylate and acetaminophen toxicity, as the treatment for these poisonings differs from the treatment of NSAID poisoning.

Renal replacement therapy can be commenced for severe metabolic acidosis but is unlikely to facilitate significant removal of NSAIDs.

Key Prescribing Points Box [15]

- *High risk for adverse GI effects*: age >65 years; previous ulcer, gastrointestinal bleeding, or perforation; other drugs known to increase gastrointestinal adverse events (anticoagulants, aspirin, serotonin reuptake inhibitors, corticosteroids); and serious comorbidities (hepatic, renal, or cardiac impairment; excessive alcohol intake; heavy smoking).
- *Aspirin sensitive asthma*: Avoid nonselective NSAIDs, due to cross-reactivity. Selective COX-2 inhibitors can generally be taken, although the first dose should be taken under medical supervision.
- *Pregnancy*: Avoid NSAIDs. When NSAID use is essential, limit the dose during early pregnancy because of the risk of miscarriage and in late pregnancy because of the risk of increased blood loss and closure of the ductus arteriosus.

References

1. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal anti-inflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821–47.
2. Goldstein JL, Cryer B. Gastrointestinal injury associated with NSAID use: a case study and review of risk factors and preventative strategies. Drug Healthc Patient Saf. 2015;7:31–41.
3. Sakuma M, Kanemoto Y, Furuse A, et al. Frequency and severity of adverse drug events by medication classes: the JADE study. J Patient Saf. 2015;00:1–6.
4. Graeme K, Morkunas A. Non-steroidal anti-inflammatory agents. In: Brent J, Wallace K, Burkhart K, et al., editors. Critical care toxicology. 1st ed. Philadelphia: Mosby; 2005.
5. Rahman S, Malcoun A. Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2, and the kidneys. Prim Care Clin Office Pract. 2014;41:803–21.
6. Reddy KS, Roy A. Cardiovascular risk of NSAIDs: time to translate knowledge into practice. PLoS Med. 2013;10(2):1–6.
7. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2012;32(6):1491–502.
8. Fontana RJ, Quallich LG. Acute liver failure. Curr Opin Gastroenterol. 2001;17(3):291–8.
9. Pillans PI, Ghiculescu RA, Lampe G, Wilson R, Wong R, Macdonald GA. Severe acute liver injury associated with lumiracoxib. J Gastroenterol Hepatol. 2012;27(6):1102–5.
10. Unzueta A, Vargas HE. Nonsteroidal anti-inflammatory drug-induced hepatotoxicity. Clin Liver Dis. 2013;17(4):643–56.
11. Fok KC, Bell CJ, Read RB, Eckstein RP, Jones BE. Lumiracoxib-induced cholestatic liver injury. Intern Med J. 2013;43(6):731–2.
12. Chitturi S, Farrell GC. Lessons from lumiracoxib: are cyclooxygenase-2 inhibitors less hepatotoxic than non-selective non-steroidal anti-inflammatory drugs? J Gastroenterol Hepatol. 2012;27:991–6.

13. Grosser T, Smyth E, FitzGerald GA. Anti-inflammatory, antipyretic, and analgesic agents: pharmacology of gout. In: Brunton LL, editor. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw Hill; 2011. p. 959–1004.
14. Paulson SK, Vaughn MB, Jessen SM, et al. Pharmacokinetics of celecoxib after oral administration in dogs and humans: effect of food and site of absorption. J Pharmacol Exp Ther. 2001;297:638–45.
15. O'Day R, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ. 2013;345:f3195.
16. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015;11:1061–75.
17. De Pasquale T, Buonomo A, Illuminati I, et al. IgE-mediated anaphylaxis to ketoprofen: a case report. J Investig Allergol Clin Immunol. 2015;25(1):79–80.
18. Torres MJ, Barrionuevo E, Kowalski M, et al. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Immunol Allergy Clin North Am. 2014;34:507–24.
19. Picaud J, Beaudouin E, Renaudin JM, et al. Anaphylaxis to diclofenac: nine cases reported to Allergy Vigilance Network in France. Allergy. 2014;69:1420–3.
20. Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs – a reminder. Postgrad Med J. 1999;75(890):771–2.
21. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. Arch Intern Med. 1999;159(11):1185–94.
22. Sewell WAC, Jolles S. Drug-induced aseptic meningitis. Adverse Drug React Bull. 2000;205:783–6.
23. Reinhart D. Minimizing the adverse effects of ketorolac. Drug Saf. 2000;22:487–97.
24. Schabb KC, Dickinson ET, Setzen G. Acute sensorineural hearing loss following intravenous ketorolac administration. J Emerg Med. 1995;13:509–13.
25. Boelsterli UA. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Toxicol Appl Pharmacol. 2003;192(3):307–22.
26. Turnball AJ, Campbell P. Mefenamic acid nephropathy – acute renal failure in overdose. BMJ. 1988;296:646.
27. Lodise M, De-Giorgio F, Rossi R, et al. Acute ibuprofen intoxication. Am J Forensic Med Pathol. 2012;33(3):242–6.
28. Anderson DEH, Langworth S, Newman HC, Ost A. Reversible bone marrow granuloma – adverse effect of oxyphenbutazone therapy. Acta Med Scand. 1980;207:131–3.
29. Al-Khenaizan S, Schechter JF, Sasseville D. Pseudoporphyria induced by propionic acid derivatives. J Cutan Med Surg. 1999;3:162–6.
30. Newton TA, Rose SR. Poisoning with equine phenylbutazone in a racetrack worker. Ann Emerg Med. 1991;20(2):204–7.
31. Al-Abri SA, Anderson IB, Pedram F, et al. Massive naproxen overdose with serial serum levels. J Med Toxicol. 2015;11(1):102–5.
32. Smolinske SC, Hall AH, Vandenberg SA, et al. Toxic effects of nonsteroidal anti-inflammatory drugs in overdose. An overview of recent evidence on clinical effects and dose–response relationships. Drug Saf. 1990;5(4):252–74.
33. Vale JA, Meredith TJ. Acute poisoning due to non-steroidal anti-inflammatory drugs: clinical features and management. Med Toxicol. 1986;1:12–31.
34. Bright TP, McNulty CJ. Suspected central nervous system toxicity from inadvertent nonsteroidal anti-inflammatory drug overdose. DICP Ann Pharmacother. 1991;25:1066–7.
35. Kulling PE, Backman EA, Skagius AS, et al. Renal impairment after acute diclofenac, naproxen, and sulindac overdoses. J Toxicol Clin Toxicol. 1995;33(2):173–7.
36. Vaughn JL, Shah KV, Ghossein MM, et al. Acute kidney injury, hyperbilirubinemia, and ischemic skin necrosis due to massive sulindac overdose. Curr Drug Saf. 2015;10:190–2.
37. Sheehan TM, Boldy DA, Vale JA. Indomethacin poisoning. J Toxicol Clin Toxicol. 1986;24(2):151–8.
38. Boldy DAR, Hale KA, Vale JA. Etodolac overdose. Hum Toxicol. 1988;7:203–4.
39. Gross GE. Granulocytosis and a sulindac overdose. Ann Intern Med. 1982;96(6):793–4.
40. Mandegaran R, Conway C, Elton C. Lower gastrointestinal adverse effects of NSAIDS: an extreme example of a common problem. BMJ Case Rep. 2013. doi:10.1136/bcr-2012-008274.
41. Forrester MB. Cases of pediatric ingestion of celecoxib reported to Texas poison control centers in 2000–2007. Hum Exp Toxicol. 2009;28:191–4.
42. McKillop G, Canning GT. A case of intravenous and oral mefenamic acid poisoning. Scott Med J. 1987;32(3):81–2.
43. Balali-Mood M, Proudfoot AT, Critchley JAJH, et al. Mefenamic acid overdosage. Lancet. 1981;317:1354–6.
44. Hendrickse MT. Mefenamic acid overdose mimicking brainstem stroke. Lancet. 1988;2(8618):1019.
45. Reichert C, Reichert P, Monnet-Tschudi F, et al. Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin Toxicol. 2014;25(6):629–34.
46. Laurent S, Rahier J, Geubel AP, et al. Subfulminant hepatitis requiring liver transplantation following ibuprofen overdose [letter]. Liver. 2000;20:93–4.
47. Wood DM, Monaghan J, Streete P, et al. Fatality after deliberate ingestion of sustained-release ibuprofen: a case report. Crit Care. 2006. doi:10.1186/cc4850.
48. Levine M, Khurana A. Polyuria, acidosis, and coma following massive ibuprofen ingestion. J Med Toxicol. 2010;6:315–7. doi:10.1007/s13181-010-0076-8.
49. Holubek W, Stolbach A, Nurok S, et al. A report of two deaths from massive ibuprofen ingestion. J Med Toxicol. 2007;3(2):52–5.

50. Le HT, Bosse GM, Tsai Y. Ibuprofen overdose complicated by renal failure, adult respiratory distress syndrome, and metabolic acidosis. J Toxicol Clin Toxicol. 1994;32:315–20.
51. Martinez R, Smith DW, Frankel LR. Severe metabolic acidosis after acute naproxen sodium ingestion. Ann Emerg Med. 1989;18(10):1102–4.
52. Mattana J, Perinbasekar S, Brod-Miller C. Near-fatal reversible acute renal failure after massive ibuprofen ingestion. Am J Med Sci. 1997;313:117–9.
53. Auriel E, Regev K, Korczyn AD. Nonsteroidal anti-inflammatory drugs exposure and the central nervous system. Handb Clin Neurol. 2014;119:577–84.
54. Menzies DG, Conn AG, Williamson IF, et al. Fulminant hyperkalemia and multiple complications following ibuprofen overdose. Med Toxicol Adverse Drug Exp. 1989;4(6):468–71.
55. Seifert SA, Bronstein AC, McGuire T. Massive ibuprofen ingestion with survival. J Toxicol Clin Toxicol. 2000;38(1):55–7.
56. Marciniak KE, Thomas IH, Brogan TV, et al. Massive ibuprofen overdose requiring extracorporeal membrane oxygenation for cardiovascular support. Pediatr Crit Care Med. 2007;8(2):180–2.
57. Akingbola OA, Singh D, Kleinman JA, et al. Functional adrenal insufficiency complicating an overdose of naproxen and ibuprofen. Clin Pediatr. 2015; 54(1):76–8.
58. Ritter A, Eskin B. Ibuprofen overdose presenting with severe agitation and hypothermia. Am J Emerg Med. 1998;16(5):549–50.
59. Hall AH, Smolinske SC, Conrad FL, et al. Ibuprofen overdose: 126 cases. Ann Emerg Med. 1986;15(11): 1308–13.
60. Aygencel G, Akbuga B, Keles A. Acute pancreatitis following naproxen intake. Eur J Emerg Med. 2006; 13(6):372.
61. Virji MA, Venkataraman ST, Lower DR, et al. Role of laboratory in the management of phenylbutazone poisoning. J Toxicol Clin Toxicol. 2003;41(7):1013–24.
62. Yapakci E, Uysal O, Demirbilek H, et al. Hypoglycemia and hypothermia due to nimesulide overdose. Arch Dis Child. 2001;85:510.
63. Dasgupta A, Langman LJ, Johnson M, et al. Naproxen metabolites interfere with certain bilirubin assays. Am J Clin Pathol. 2010;133:878–83. doi:10.1309/AJCPN6MWATQ3SZTC.
64. Saifee NH, Ranjitkar P, Greene DN. Factors influencing naproxen metabolite interference in total bilirubin assays. Clin Biochem. 2015. doi:10.1016/j.clinbiochem.2015.11.010.
65. Okonek S, Reinecke HJ. Acute toxicity of pyrazolones. Am J Med. 1983;75(5A):94–8.
66. Gulmez SE, Larrey D, Pageaux GP, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen). Drug Saf. 2013;36:135–44.
67. Bolfer L, McMichael M, Ngwenyama TR, et al. Treatment of ibuprofen toxicosis in a dog with IV lipid emulsion. J Am Anim Hosp Assoc. 2014;50(2): 136–40. doi:10.5326/JAAHA-MS-5979.
68. Herring JM, McMichael MA, Corsi R, et al. Intravenous lipid emulsion therapy in three cases of canine naproxen overdose. J Vet Emerg Crit Care. 2015;25 (5):672–8. doi:10.1111/vec.12307.
69. Tavcar R, Dernovsek MZ, Brosch S. Ketoprofen intoxication delirium. J Clin Psychopharmacol. 1999; 19(1):95–6.
70. Narayanan M, Schlueter M, Clyman RI. Incidence and outcome of a 10-fold indomethacin overdose in premature infants. J Pediatr. 1999;135:105–7.
71. Schuster V, von Stockhausen HB, Seyberth HW. Effects of highly overdosed indomethacin. Eur J Pediatr. 1990;149:651–3.
72. Auer M, Brezinka C, Eller P, et al. Prenatal diagnosis of intrauterine premature closure of the ductus arteriosus following maternal diclofenac application. Ultrasound Obstet Gynecol. 2004;23(5):513–6. doi:10.1002/uog.v23:5/issuetoc.
73. Siu KL, Lee WH. Maternal diclofenac sodium ingestion and severe neonatal pulmonary hypertension. J Paediatr Child Health. 2004;40(3):152–3.
74. Talati AJ, Salim MA, Korones SB. Persistent pulmonary hypertension after maternal naproxen ingestion in a term newborn; a case report. Am J Perinatol. 2000;17 (2):69–71.
75. Alun-Jones E, Williams J. Hyponatremia and fluid retention in a neonate associated with maternal naproxen overdosage. J Toxicol Clin Toxicol. 1986;24(3):257–60.