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ACUTE PAIN SECTION

Review Article

Perioperative Intravenous Acetaminophen and NSAIDs

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Abstract

Background. Unrelieved postoperative pain may result in pain/suffering, as well as multiple physiological and psychological consequences (e.g., splinting, impaired gastrointestinal motility/ileus, and impaired wound healing) which may adversely affect perioperative outcomes and contribute to increased length of stay. Multimodal or balanced analgesia, utilizing regional analgesic techniques (where possible) and nonopioid analgesics appear to represent a viable strategy to decrease systemic opioid consumption and improve postoperative analgesia. The use of multimodal analgesic strategies may result in reduced frequency and severity of unwanted opioid-related adverse effects, better clinically meaningful pain relief, diminished opioid consumption, and an overall improvement of patient satisfaction as well as health outcomes (e.g., earlier ambulation and discharge).

Objectives. Review key aspects of intravenous (i.v.) acetaminophen (APAP) use in the postoperative setting.

Design. Focused literature review.

Results. Intravenous APAP is safe, effective for mild-to-moderate postoperative pain, well-tolerated, and has a very favorable side effect profile with no clearly demonstrated clinically significant drug–drug interactions. It does not exhibit any significant effects on platelet aggregation and therefore may be the preferred nonopioid analgesic when surgical bleeding is an issue.

Conclusion. The i.v. formulation of APAP represents a safe and effective first-line analgesic agent for the treatment of acute mild-to-moderate pain in the perioperative setting when oral agents may be impractical or when rapid onset with predictable therapeutic dosing is required.

Key Words. Intravenous Acetaminophen; Postoperative Pain; Opioid-Sparing; Multimodal Balanced Analgesia

Introduction

One of the primary goals of postoperative pain relief is to provide subjective comfort, inhibit trauma-induced afferent pain transmission, and to blunt the autonomic and somatic reflex responses to pain, leading to enhanced restoration of function and enhancing recovery of the ability to breath, cough, and ambulate without limitations. Despite our increased knowledge in the last decade of the pathophysiology and pharmacology of nociception, acute postoperative pain still remains a major problem [1]. Patients continue to report that one of their primary preoperative concerns is the severity of postoperative pain [1,2]. This appears to be justified, as it has been reported that 31% of patients suffer from severe or extreme pain and another 47% from moderate pain [1].

Unrelieved postoperative pain may result not only in suffering and discomfort, but may also lead to multiple physiological and psychological consequences, which can contribute to adverse perioperative outcomes [3]. Inadequate perioperative analgesia can potentially contribute to a higher incidence of myocardial ischemia, impaired wound healing [4,5], and delayed gastrointestinal (GI) motility resulting in prolonged postoperative ileus [6]. Furthermore, unrelieved acute pain may lead to poor respiratory effort and splinting which can result in atelectasis, hypercarbia, or hypoxemia, contributing to a higher incidence of postoperative pneumonia [3]. In addition, unrelieved perioperative pain may contribute to psychological distress, anxiety, sleeplessness and helplessness, impaired postoperative rehabilitation, and potentially long-term psychological consequences [7], as well as the possibility of chronic postsurgical pain [8–10].

Unimodal postoperative analgesic techniques cannot be expected to provide sufficient pain relief allowing normal

function without the risks of adverse effects (AEs) [11,12]. The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events [11]. The rationale for this strategy is to achieve sufficient analgesia due to the additive or synergistic effects between different analgesics. This allows for a reduction in the doses of these drugs and, thus, a lower incidence of AEs. Unfortunately, much of the existing literature in acute pain management has utilized single analgesic techniques and failed to address the issue of pain during daily function (cough, ambulation, physical therapy, etc.). In addition to a lower incidence of AEs and improved analgesia, it has been demonstrated that multimodal analgesia techniques may provide for shorter hospitalization times, improved recovery and function, and decreased health care costs following surgery [13,14]. Currently, the American Society of Anesthesiologists Task Force on Acute Pain Management [15] and the Agency for Health Care Research and Quality [16] advocates a multimodal analgesic approach for the management of acute pain. The practice guidelines for acute pain management in the perioperative setting specifically state "unless contraindicated, all patients should receive around-the-clock regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), selective **C**yclo**ox**ygenase-2 **I**nhi**b**itor**s** (COXIBs), or acetaminophen" [15].

Thus, postoperative pain management often includes the use of nonopioid analgesics in conjunction with opioids [17]. While these agents are typically not sufficient to treat moderate-to-severe pain by themselves, they are useful adjuncts to opioids that may result in significant reductions in opioid consumption and possible avoidance of opioid-related adverse events. NSAIDs and COXIBs have antipyretic, analgesic, and anti-inflammatory effects, while acetaminophen (APAP) has antipyretic and analgesic effects but limited peripheral anti-inflammatory activity. The use of NSAIDs is associated with an increased risk of specific adverse events, including GI bleeding, GI mucosal damage, renal impairment, and postoperative bleeding [17]. In contrast, APAP has been demonstrated to be well-tolerated [18] with minimal adverse events [19,20]. In 2008, Toms and colleagues [21] updated the original 2004 Cochrane review by Barden et al. [19], and observed that a single dose of APAP provided effective postoperative analgesia for about half of patients for about 4 hours and was associated with few, mainly mild, AEs.

The difference in safety profiles between APAP and NSAIDs is likely due to mechanistic differences in how they produce analgesia. NSAIDs primarily act through inhibition of prostaglandin (PG) synthesis [22]. This is mediated by inhibiting the function of cyclooxygenase (COX) isoenzymes. In 1971, Sir John Vane discovered the central role of COX in the mode of action of NSAIDs [23]. COX-1 is considered a "housekeeping" enzyme, as the PGs it produces help to maintain normal organ function, such as gastric mucosa protection, renal function support, and stimulation of platelet (PLT) aggregation; whereas COX-2 is expressed during inflammation and cell damage, and the PGs it produces accelerate the inflammatory process. The majority of NSAIDs act on both COX-1 and COX-2 isoforms; however, COXIBs that are selective for COX-2 are also available for oral use in the United States [24].

While APAP, NSAIDs, and COXIBs are widely used for pain relief, there are a limited number of studies comparing the efficacy of the intravenous (i.v.) formulations of these drugs. As i.v. APAP was not available when most of these studies were done and i.v. parecoxib is still not available in the United States, the published i.v. data come primarily from studies conducted at sites outside the United States, where there are also multiple commercialized i.v. NSAIDs. This paper discusses the available data evaluating the relative efficacy and safety of i.v. formulations of APAP and NSAIDs/COXIBs. Furthermore, in some instances, i.v. and oral preparations have been studied in head-to-head evaluations, despite differences in onset of efficacy and blood plasma levels. Finally, it is important to note that comparisons to established NSAIDs are most appropriately made using postsurgical pain models. Therefore, the studies discussed will be limited to these models.

The analgesic efficacy of anti-inflammatory agents and oral COX-2 inhibitors may be related in part to blood-brain barrier penetration [25]. Buvanendran and colleagues have shown that cerebrospinal fluid (CSF) rofecoxib levels are approximately15% of plasma levels and that repeated daily dosing more than doubles the area under the curve (AUC) in CSF [26]. As APAP's primary analgesic effect appears to be due to a central nervous system (CNS) site of action, the i.v. route is likely to have a significant advantage over the oral route due in the perioperative period to earlier and higher peak CSF levels.

Permeability of the blood-brain barrier to currently used NSAIDs and COXIBs may be pharmacodynamically important [27]. The main process by which a drug passes from the blood stream to the CNS is passive diffusion, for which degree of protein binding, lipophilicity, and ionization are critical determinants of transfer [28]. When peripheral inflammation is not a significant factor, agents that rapidly penetrate the blood-brain barrier may represent better analgesics, especially in the perioperative period. The COXIBs have been demonstrated to rapidly reach the CNS in humans in concentrations sufficient to inhibit central COX-2 activity [27]. The CNS penetration of NSAIDs is relatively rapid, but high protein binding may cause central analgesic efficacy to be delayed until sufficient CNS levels are achieved. Studies of CNS penetration have been performed for indomethacin [29], ibuprofen [30], and ketoprofen [31,32].

APAP

APAP, known as paracetamol outside the United States, has been available as an analgesic and antipyretic agent in the United States and the United Kingdom since the 1950s [33,34]. Since that time, it has developed an

established record of tolerance, safety, and efficacy for both adults and children [17]. Currently, APAP is the most commonly prescribed analgesic and antipyretic in children [34] and is indicated for the short-term management of mild-to-moderate pain and the reduction of fever in both children and adults [17]. Intravenous APAP has been approved in approximately 80 countries in Europe, Asia-Pacific, Middle East, Africa, and other regions outside the United States primarily as Perfalgan and other trade names (Bristol-Myers Squibb Company, New York, NY, USA). Over 440 million units (1,000 mg equivalent) have been distributed since its first commercialization in Europe in 2002 through April 2010, representing over 65 million estimated patient exposures. OFIRMEV (APAP for injection; Cadence Pharmaceuticals, Inc., San Diego, CA, USA) received approval by the U.S. Food and Drug Administration (FDA) in 2010.

APAP—Mechanisms of Action

The mechanism of APAP-mediated pain relief is still not completely understood. However, it has been shown that APAP rapidly enters the intact CNS and the majority of the mechanisms involved in analgesia occur in the CNS [34,35]. APAP has been demonstrated to centrally inhibit PGs via the COX pathway [24,29,36], reinforce the descending serotonergic inhibitory pain pathways [37–39], trigger indirect activation of cannabinoid CB_1 receptors [38,40], and inhibit nitric oxide pathways [41,42] through *N*-methyl-D-aspartate or substance P [22,43,44]. Despite the fact that APAP inhibits COX-1 and COX-2 [44], it has weak peripheral anti-inflammatory activity, limited GI effects, and a slight, clinically insignificant impact on PLT function [45]. Hinz and colleague postulated that APAP functions in part via preferential COX-2 blockade [46]. *Ex vivo* COX inhibition and pharmacokinetics (PKs) of APAP were assessed in five volunteers receiving single 1,000 mg doses orally. Coagulation-induced thromboxane B_2 and lipopolysaccharide-induced prostaglandin E_2 (PGE_2) were measured *ex vivo* and in vitro in human whole blood as indices of COX-1 and COX-2 activity. In vitro, APAP elicited a 4.4-fold selectivity toward COX-2 inhibition (IC_{50} = 113.7 μmoles/L for COX-1; IC_{50} = 25.8 μmoles/L for COX-2 [46]). It has also been postulated that APAP is only able to inhibit COX isoforms at sites where peroxide levels are low, such as the CNS [36,47]. Therefore, at sites of high peroxide concentration, such as sites of inflammation, APAP has reduced activity against COX [34,36,47].

The introduction of an i.v. formulation of APAP has provided a convenient and fast-acting analgesic that results in rapid onset of pain relief, reduced time to meaningful pain relief, and reduced time to maximal pain relief compared to the oral formulation [17,35,48,49]. Double-blind clinical trials have shown that i.v. APAP was significantly better at providing analgesia than placebo in patients undergoing orthopedic [50] or gynecological surgery [17] and it has been demonstrated to reduce opioid requirements following surgery. Intravenous APAP 1 g every 6 hours following orthopedic surgery resulted in a 33% reduction in morphine consumption over 24 hours [50]. Intravenous APAP also reduced the need for rescue medication following tonsillectomy or endoscopic sinus surgery, with administration of i.v. APAP resulting in fewer doses of meperidine or oxycodone [51]. In the United Kingdom, i.v. APAP is currently indicated for the short-term treatment of moderate pain or fever when the rapid onset of analgesia is clinically justified (i.e., following surgery) or when oral administration is not possible for both adults and children (weighing more than 33 kg) [52].

APAP Dosing

APAP is available worldwide in rectal, oral, and i.v. formulations. Peak APAP plasma concentrations occur 3.5–4.5 hours after rectal administration, 45–60 minutes after oral administration, and at the end of the 15-minute i.v. infusion [44,49,53]. Rectal formulations have been associated with lower bioavailability and increased interpatient variability than oral formulations, with the likelihood of obtaining subtherapeutic plasma concentrations unless a loading dose is used [54–56]. While oral bioavailability is typically quite high (85–93%), early plasma concentrations are variable and concentrations may remain subtherapeutic (<10 μg/mL) in many patients for a significant period (as long as 60 to 80 minutes) [49,53]. When oral administration is not possible or rapid onset of relief is needed, i.v. administration is the method of choice [48,53]. Intravenous APAP allows for convenient administration with a rapid onset of pain relief that may be particularly useful in a postoperative setting [57].

For oral and i.v. APAP dosing, adult and adolescent patients weighing at least 50 kg may receive a dose of 1 g every 4 to 6 hours to a maximum of 4 g/day or a dose of 650 mg every 4 hours (3,900 mg/day). The minimum duration between doses is 4 hours; for those patients with severe renal impairment (creatinine clearance rates of ≤30 mL/min), the minimum duration between doses is 6 hours [17]. For adults and adolescents weighing less than 50 kg, and all children and newborns, weight-based dosing (e.g., 10 to 15 mg/kg) should be used to calculate the APAP dose.

APAP PKs

The mean C_{max} is higher, and T_{max} occurs sooner for i.v. APAP compared to per os (PO) at equivalent doses. However, other PK parameters, such as metabolism, distribution, and elimination, are similar, indicating that APAP disposition is unchanged by the route of administration. In a randomized, four-period, crossover study undertaken in 38 healthy male volunteers, each subject was serially assigned in random order to receive four treatment sessions with either i.v. APAP 1 g or oral APAP 1 g, dosed at q4h (to a maximum of 4,000 mg daily) or q6h over a 48-hour treatment period with each session separated by a 72-hour washout period [58]. Intravenous APAP demonstrated an approximately 75% higher mean first-dose C_{max} (i.v. q4h: 26.0 ± 7.7 μg/mL; i.v. q6h: 28.4 ± 21.2 μg/mL vs oral q4h: 15.1 ± 5.4 μg/mL; oral

q6h: 15.1 ± 4.4 μg/mL) and a T_{max} that occurred at the end of the 15-minute i.v. infusion which was approximately 30 minutes prior to the T_{max} observed for oral APAP. Distribution and mean clearance values at steady state were comparable between the two formulations. No accumulation occurred after 12 hours of repeated dosing for either formulation regardless of dosing schedule. The route of administration did not appear to have a significant impact on fractional excretion in urine of free (unconjugated) APAP or APAP metabolites.

The putative therapeutic APAP threshold concentration for analgesia and antipyresis is 10 μg/mL and 7 μg/mL, respectively [55,59]. In part, because of its negligible protein binding and relatively high lipid solubility [60], APAP penetrates readily through an intact blood-brain barrier, and APAP concentrations in the CSF appear to be linearly dose proportional with plasma levels [61]. Therefore, the analgesic profile of the drug parallels its concentration–time curve in the CSF, which is somewhat delayed but parallel to the plasma concentration–time curve [62].

Demonstrating the importance of CSF levels of APAP, Kokki and colleagues at the University of Kuopio, Finland, studied 32 children who were undergoing lower body surgery with spinal anesthesia [35]. After i.v. dosing, APAP rapidly penetrated the intact CNS with earliest detectable levels occurring at 5 minutes. The authors noted that while oral or rectal APAP is effective, i.v. APAP leads to faster onset of efficacy with analgesic action within 15 minutes and fever reduction within 30 minutes [35].

Similar to the findings of Kumpulainen et al., the onset of analgesia after i.v. APAP occured within 15 minutes when administered to adults [17,48,63]. This faster onset may confer a clinical benefit over oral dosing with an onset ranging from 0.55 to 1.4 hours [64–66]. For example, following oral surgery, i.v. APAP had a faster onset of analgesia and was more effective in reducing pain intensity in the first hour of treatment than oral APAP [49]. Similar results were observed following orthopedic surgery [67]. Additionally, Royal et al. demonstrated faster onset of antipyresis with i.v. vs oral APAP in a fever trial [68]. Therefore, in clinical situations where rapid onset of action is desired or where the patient is unable to reliably tolerate oral intake, an i.v. formulation of APAP may be quite useful.

APAP Analgesic Efficacy

I.V. APAP vs Propacetamol

An i.v. prodrug of APAP, propacetamol, had been available in Europe for over 20 years [17]. Propacetamol is converted by plasma esterases immediately to APAP and diethylglycine, with 2 g propacetamol yielding approximately 1 g APAP. However, due to paracetamol's poor water solubility and low stability in solution, it is formulated as a lyophilized powder that must be dissolved in glucose or saline prior to infusion, and is associated with injection site pain in more than 50% of patients [48]. The development of a ready-to-use i.v. APAP formulation that does not require reconstitution [48], and is not associated with injection site pain as compared to placebo [17] rapidly replaced propacetamol. The reduced infusion site AEs observed with APAP is likely a reflection of pH and osmolarity values that are closer to or within physiologic ranges [48,63].

Overall, i.v. APAP demonstrated comparable efficacy to a bioequivalent dose of propacetamol in both children (15 mg/kg i.v. APAP ~ 30 mg/kg propacetamol) and adults (1 g i.v. APAP ~ 2 g propacetamol). The onset of efficacy for i.v. APAP and propacetamol was similar, occurring at approximately 15 minutes for both adults and children [48,63–66].

Macario and Royal performed a literature review of randomized clinical trials of i.v. APAP for acute postoperative pain [69]. Sixteen articles from nine countries published between 2005 and 2010 met inclusion criteria and had a total of 1,464 patients (Macario 2010). Four of the 16 articles had three arms in the study. One article had four arms. As a result, 22 study comparisons were analyzed: i.v. APAP to an active comparator (n = 8 studies) and i.v. APAP to placebo (n = 14 studies) [69]. The randomized controlled trials (RCTs) were of high methodological quality with Jadad median score = 5. In seven of eight active comparator studies (i.v. parecoxib [n = 3 studies], i.v. metamizol [n = 4], oral ibuprofen [n = 1]), i.v. APAP had similar analgesic outcomes as the active comparator [69]. Twelve of the 14 placebo studies found that i.v. APAP patients had improved analgesia. Ten of those 14 studies reported less opioid consumption, a lower percentage of patients rescuing, or a longer time to first rescue with i.v. APAP [69]. Macario and Royal concluded that in aggregate, these data indicate that i.v. APAP is an effective analgesic across a variety of surgical procedures [69].

I.V. NSAIDs

In a regional audit of six target National Health Service Hospitals within the south of the United Kingdom, i.v. NSAID administration was the preferred route of anti-inflammatory analgesics in the perioperative period largely because of its reliability and speed of onset [70]. Additionally, it was preferred in appropriate patients who were not permitted to take anything by mouth early in the perioperative period. The results of this audit also indicated significant use of i.v. NSAIDs not in accordance with manufacturers' recommendations.

Ketorolac

Ketorolac (Toradol) was the first parenteral NSAID for clinical analgesic use introduced in the United States. Studies have revealed that ketorolac is less effective as the sole postoperative analgesic in the management of moderate-to-severe postoperative pain [71,72]. Thus, as is the case with other i.v. nonopioids, its efficacy as analgesic monotherapy is usually insufficient particularly for severe pain after major surgery.

Keterolac Dosing

Since ketorolac has been marketed, there have been reports of death due to GI and operative site bleeding [73]. In the first 3 years after ketorolac was approved in the United States, 97 fatalities were reported [74]. As a consequence, the drug's license was suspended in Germany and France [75]. In a response to these events, the drug's manufacturer recommended reducing the dose of ketorolac from 150 to 120 mg per day [76]. The European Committee for Proprietary Medicinal products recommended a further maximal daily dose reduction to 60 mg for the elderly and to 90 mg for the nonelderly [77]. Currently, there is consensus that the maximum daily dose should be as low as 30 to 40 mg [78]. Furthermore, ketorolac is contraindicated as a preemptive analgesic before any major surgery and is contraindicated intraoperatively when hemostasis is critical because of its potential for prolonged PLT effects and increased risk of perioperative bleeding [71].

Ketorolac PKs

Ketorolac is almost entirely bound to plasma proteins (>99%), which results in a small apparent volume of distribution with extensive metabolism by conjugation and excretion via the kidney [79]. The mean plasma half-life is approximately 5.5 hours. The analgesic effect occurs within 30 minutes with maximum effect between 1 and 2 hours and duration of 4–6 hours [79].

Ketoralac—Analgesic Efficacy

Cassinelli and colleagues studied 25 patients who underwent a primary multilevel lumbar decompression procedure and were randomly assigned to receive either ketorolac or placebo in a double-blinded fashion [80]. There were no significant differences in available patient demographics, intraoperative blood loss, or postoperative Hemovac drain output between study groups. Morphine equivalent requirements were significantly less at all predetermined time points in addition to the overall hospital morphine requirement in patients randomized to receive ketorolac. Visual analog pain scores were significantly lower in patients randomized to receive ketorolac immediately postoperative in addition to 4, 12, and 16 hours postoperative. There were no identifiable postoperative complications associated with the use of ketorolac [80]. Cassinelli et al. concluded that i.v. ketorolac seems to be a safe and effective analgesic agent following multilevel lumbar decompressive laminectomy [80].

Ibuprofen

Ibuprofen, named from the now outdated nomenclature iso-butyl-propanoic-phenolic acid, is the most commonly used oral NSAID in the United States (primarily as an over-the-counter pain reliever). An i.v. formulation of ibuprophen (Caldolor; Cumberland Pharmaceuticals, Nashville, TN, USA) [81] was FDA approved in 2009. Ibuprofen is a racemic mixture of [–]R- and [+]S-isomers. *In vivo* and *in vitro* studies indicate that the [+]S = isomer is responsible for clinical activity. The [–]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The enzymatic chiral inversion of ibuprofen is a three-step mechanism involving the formation of the acyl-CoA thioester by stereoselective activation of R-(–)-enantiomer in the presence of acyl-CoA sythetase (CoA) and enzymatic epimerization of the R-thioester to the S-(+)-thioester followed by the formation of S-(+)-enantiomer by hydrolysis of S-(+)-thioester [82,83]. Compounds demonstrating the same chiral inversion mechanisms as that of R-(–)-ibuprofen may inhibit the ibuprofen inversion and result in a decrease in the amount of S-(+)-ibuprofen formed [83]. The [–]R-isomer serves as a circulating reservoir to maintain levels of active drug.

Ibuprofen Dosing

The i.v. formulation is available in the United States as a 400 mg/4 mL or 800 mg/8 mL vial. Inactive ingredients include water and arginine (to increase its water solubility) (the lysine salt of ibuprofen—ibuprofen lysine [a different formulation], was released for i.v. use earlier in Europe). The concentration of arginine is 78 mg/mL and is present at a molar ratio of 0.92:1 (arginine : ibuprofen) [81]. The solution pH is approximately 7.4. Intravenous ibuprofen must be diluted with 0.9% or normal saline, 5% dextrose with water, or lactated Ringer's solution to a final concentration of 4 mg/mL or less prior to infusion, resulting in the following:

- 400 mg dose: dilute 4 mL in no less than 100 mL of diluent (Albany Medical Center uses 200 mL)
- 800 mg dose: dilute 8 mL in no less than 200 mL of diluent (Albany Medical Center uses 400 mL)

Diluted solutions are stable for up to 24 hours as ambient temperature (approximately 20 to 25°) and room lighting. Infusion time must be no less than 30 minutes [81].

Using a randomized, double-blind, placebo-controlled, single-dose, crossover study, Pavliv and colleagues found that the maximum plasma concentration (C(max)) of i.v. ibuprofen was approximately twice that of oral ibuprofen, and the (t(max)) of i.v. ibuprofen was 0.11 hour compared with 1.5 hours for oral ibuprofen. However, the elimination half-life of i.v and oral ibuprofen did not differ, both of which were approximately 2 hours. Oral ibuprofen was 100% bioavailable; therefore, the area under the concentration–time curve did not differ between i.v and oral ibuprofen. In addition, i.v. ibuprofen infused over 5 to 7 minutes did not differ in terms of safety or tolerability when compared with oral ibuprofen [84]. Although the package insert states to infuse over no less than 30 minutes, rapid infusion of i.v. ibuprofen over 5 to 7 minutes has also been shown to be safe and effective [84]. Thus, i.v. ibuprofen, when administered over 5 to 7 minutes in healthy subjects, achieved a higher C(max) and a more rapid t(max) than did oral ibuprofen and was found to be safe and well tolerated [84].

Table 1 Pharmacokinetic parameters of intravenous ibuprofen [82]

	400 mg* Caldolor Mean (CV%)	800 mg* Caldolor Mean (CV%)
Number of patients	12	12
AUC (mcg·h/mL)	109.3 (26.4)	192.8 (18.5)
C_{max} (mcg/mL)	39.2 (15.5)	72.6 (13.2)
KEL (1/h)	0.32 (17.9)	0.29 (12.8)
T1/2 (h)	2.22 (20.1)	2.44 (12.9)

* 60 minute infusion time.
C_{max} = Peak plasma concentration; CV = coefficient of variation; KEL = First-order elimination rate constant; T1/2 = elimination half-life.

Although there are no suggested restrictions on the duration of therapy with i.v. ibuprofen, however, like all NSAIDs, it is recommended to use the lowest effective dose for the shortest possible duration. It is also recommended to use caution when initiating treatment with i.v. ibuprofen in patients with considerable dehydration.

Ibuprofen PKs

The PK parameters of i.v. ibuprofen determined with volunteers are presented in Table 1 [81]. Ibuprofen, like most NSAIDs, is highly protein bound: >99% bound at 20 mcg/mL, and at concentrations >20 mcg/mL, binding is nonlinear [81]. The high degree of protein binding observed with NSAIDs limits the ability of these agents to enter the CNS. The metabolism of ibuprofen is predominantly via CYP2C9, and its primary route of clearance is renal excretion.

Ibuprofen Analgesic Efficacy

Southworth et al. conducted a multicenter, randomized double-blind, placebo-controlled trial in 406 patients scheduled to undergo elective, single-site orthopedic or abdominal surgery, and suggested that ibuprofen 800 mg i.v. q6h was effective for postoperative pain management and was generally well tolerated with dizziness being the main AE [85].

Diclofenac

Diclofenac, a nonselective NSAID, is a weak acid (a phenylacetic acid derivative), with a pka of 4.0 and a partition coefficient into n-octanol from aqueous buffer, pH 7.4, of 13.4 [86]. After i.v. injection, plasma levels of diclofenac fell rapidly and were below the limits of detection at 5.5 hours postdosing. Individual drug profiles were described by a triexponential function, and mean half-lives of the three exponential phases were 0.05, 0.26, and 1.1 hours. After i.v. dosing, plasma levels, peak levels, and AUC were significantly reduced, and the volume of distribution was increased, as was the plasma clearance with coadministration of aspirin [87]. These observations were felt to be due in part to decreased protein binding and increased bilary excretion of diclofenac in the presence of salicylate. There are two i.v. diclofenac formulations available in Europe. The older parenteral formulation of diclofenac sodium (Voltarol ampoules) contains propylene glycol and benzyl alcohol as solubilizers (termed propyleneglycol-benzyl alcohol [PG-BA] diclofenac) but is still relatively insoluble. For i.v. use in postoperative pain, PG-BA diclofenac requires reconstitution for each patient, dilution to ≥100 mL, buffering and slow infusion over ≥30 minutes to minimize irritation. Despite these limitations, PG-BA diclofenac is used extensively as a result of its proven efficacy [88]. A newer formulation of diclofenac suitable for i.v. bolus injection (Dyloject) has been developed by complexing diclofenac sodium with hydroxypropyl β-cyclodextrin as a solubility enhancer (termed HPβCD diclofenac). This newer bolus diclofenac formulation was shown to be bioequivalent to the prior propylene glycol-based version which required an i.v. infusion over 30 minutes [89].

Diclofenac Dosing

HPβCD diclofenac may be given intramuscularly (IM) or i.v. Usual perioperative dosing is HPβCD diclofenac 37.5–75 mg i.v. every l2 hours after an initial bolus dose of 75 mg i.v./IM. HPβCD diclofenac is available as a pre-prepared formulation (solution) in a 2-mL vial (75 mg/2 mL) ready for immediate injection.

Diclofenac PKs

Following i.v. administration, a C_{max} of 21, 524 ng/mL (including one aberrant value, approximately 10-fold higher than expected) for HPβCD diclofenac was attained at a median T_{max} of 3 minutes (first assessment point) and a C_{max} of 5,668 ng/mL for PG-BA was attained at a T_{max} of 30 minutes (duration of the infusion) [90]. Diclofenac is highly bound (99.7%) to serum proteins, mainly albumin, and has a volume distribution of about 0.12–0.17 L/kg in healthy subjects [91,92]. Diclofenac is eliminated principally by metabolism and subsequent urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites [92]. The mean elimination half-life ($t_{1/2}$) of HPβCD diclofenac was 1.17 hours after both i.v. bolus and intramuscular injection, while that for PG-BA diclofenac was 1.23 hours after i.v. infusion and 1.71 hours after intramuscular injection [90].

Diclofenac Analgesic Efficacy

Single-dose HPβCD diclofenac at a dose of 3.75, 9.4, 18.74, 25, 37.5, 50, and 75 mg administered by bolus injection produced significantly greater responses than placebo for total pain relief over 6 hours or pain intensity at 4 hours in the treatment of moderate or severe postoperative dental pain in randomized, double-blind trials. In this study, HPβCD diclofenac 37.5 and 75 mg were similar in efficacy to i.v. ketorolac 30 mg [89].

Other I.V. Nonselective NSAIDs

A number of other i.v. NSAIDs, such as ketoprofen, lornoxicam, and metamizol, are approved for use in Europe, but not in the United States. Metamizole (dipyrone) was available widely, including in the United States, but in the 1970s, it was discovered to be associated with the potential for agranulocytosis and was removed from the U.S. market [93]. It is still available in many countries in Europe and elsewhere. Generally, the efficacy of these products has been determined to be similar to more commonly used i.v. NSAIDs and i.v. COXIBs in postoperative clinical trials [94–98].

I.V. Selective COX-2 Inhibitors

While not available in the United States, i.v. parecoxib, a selective COX-2 inhibitor, was approved for use in Europe for short-term perioperative treatment of acute pain. Parecoxib is an inactive amide prodrug that undergoes rapid hydrolysis in vivo by liver esterase to valdecoxib [99]. It is not approved for use after cardiac surgery due to its risk of increased cardiovascular events. Parecoxib has no effect on PLT function and is not associated with increased postsurgical or GI bleeding.

Parecoxib Dosing

Parecoxib may be given IM or i.v. Usual perioperative dosing is parecoxib 20 mg-40 mg i.v. every 12 hours after an initial dose of 40 mg i.v./IM.

Parecoxib PKs

Following administration, parecoxib is rapidly and fully converted within 10 to 30 minutes to the active COX-2-specific moiety, valdecoxib, in vivo [100–103]. Previous studies in healthy subjects showed that single doses of up to 200 mg i.v. parecoxib are well tolerated and follow predictable PKs with a short plasma half-life ($t_{1/2}$) of 0.3–0.7 hours for parecoxib and a terminal half-life of approximately 10 hours for the active moiety, valdecoxib [101]. Peak plasma levels of valdecoxib are achieved approximately 30 minutes after administration of parecoxib i.v. and roughly 1–1.5 hours after IM administration [101]. Valdecoxib is a substrate for hepatic cytochrome P450 3A4.

Parecoxib Analgesic Efficacy

Studies have generally demonstrated that i.v. parecoxib 40 mg q12h produced similar pain relief over 48 hours as conventional NSAIDs (metamizole) after open hysterectomy [104], and that single doses produced superior pain relief to placebo in same-day surgery cases [105]. In clinical trials, parecoxib has demonstrated analgesic efficacy in patients following laparotomy [106], orthopedic (knee) surgery [107], or oral surgery [108]. Furthermore, in clinical trials, parecoxib and valdecoxib had no effect on PLT aggregation in healthy elderly and nonelderly volunteers [109–111] and were associated with significantly lower incidences of gastroduodenal ulcers than standard doses of the nonspecific NSAIDs ketorolac, diclofenac, and naproxen [112–115].

Comparative Studies

I.V. APAP vs I.V. Nonselective NSAIDs

A few studies directly compared the efficacy of i.v. APAP to specific i.v. NSAIDs, and these studies will be discussed in the sections that follow (Table 2). Preliminary data indicate that analgesic efficacy of APAP is similar to NSAIDs and COXIBs when peripheral inflammation or inflammatory pain models are not being considered [124]. When peripheral inflammation is a significant component of pain, NSAIDs and COXIBs appear to be conferred a significant advantage over APAP.

APAP vs Ketorolac

Lee et al. [116] was a randomized, active- and placebo-controlled, double-blind, parallel-group, 6-hour, single-dose study in 80 American Society of Anesthesiologists (ASA) I–II adult females (20–60 years old) scheduled for elective total thyroidectomy under standardized general anesthesia. Thirty minutes prior to the end of surgery, the patients were randomized into four groups of 20: i.v. APAP 1,000 mg, ketorolac 30 mg, i.v. APAP 700 mg plus morphine 3 mg, and saline (control group). A visual analog scale (VAS) was used to assess pain intensity and side effects (nausea, vomiting, headache, sedation, dizziness, and respiratory depression) at 0.5, 1, 2, 4, and 6 hours after study drug dosing. All three active groups had better pain scores and used less rescue at 0.5 and 1 hour than the control group ($P < 0.05$). Satisfaction was similar in the three active treatment groups compared to control. The authors concluded that i.v. APAP 1,000 mg produced similar analgesic efficacy to i.v. ketorolac 30 mg after thyroidectomy and may represent "an alternative to ketorolac for pain prevention after mild to moderately painful surgery in situations where the use of NSAIDs is unsuitable."

In Ko et al. [125], 60 patients undergoing elective hand or forearm surgery were randomly assigned to one of three groups: the control group (C) received 0.5% lidocaine diluted with normal saline to 40 mL volume (n = 20) as an i.v. regional anesthesic block (IVRA); the APAP group (P for paracetamol) received IVRA lidocaine and APAP 300 mg admixture with saline to 40 mL (n = 20); and the ketorolac group (K) received IVRA lidocaine and ketorolac 10 mg admixture with saline to 40 mL (n = 20). The operative arm was elevated for 2 minutes and then exsanguinated with an Esmarch wrap and the double pneumatic tourniquet proximal cuff was inflated to 250 mm Hg and the study medications were administered. Sensory and motor block onset time, tourniquet pain, and analgesic use were assessed during operation. After tourniquet deflation, VAS (0–10) scores were assessed at 5, 10, 20, 30, and 40 minutes after deflation. Intermittent bolus fentanyl 1 μg/kg was used for pain treatment with VAS 3 or greater. The onset time of tourniquet pain (>3) was recorded as was

Table 2 Comparative studies of perioperative nonopioid analgesics

Author/year	Type of study	Drugs compared	Surgical procedure	Sample size	Results
Lee et al., 2010 [116]	Prospective R, DB, PC/AC parallel	Placebo IV APAP Ketorolac IV APAP + MS04	Total Thyroidectomy	20 20 20 20	All AC groups better pain scores and less rescue than control, satisfaction similar in all AC groups, IV APAP had similar analgesic efficacy to IV ketorolac
Koppert et al., 2006 [117]	Prospective R, PC	Placebo Acetaminophen Parecoxib	Orthopedic surgery	25 25 25	IV APAP equivalent analgesic efficacy to IV parecoxib with significant decreased opioid use in first 24 hours
Ng et al., 2004 [118]	Prospective R, DB, C	Parecoxib Ketorolac	Laparoscopic Sterilization	18 17	Early evaluation in PACU at waking and 1 hour post-operative ketorolac had better analgesic efficacy
Leykin et al., 2008 [119]	Prospective R, DB, C	Parecoxib Ketorolac	Nasal surgery	25 25	Parecoxib equal to ketorolac in analgesic efficacy, side effects, and patient satisfaction
Grundmann et al., 2006 [120]	Prospective R, DB, PC	Placebo APAP Parecoxib Metamizol	Lumbar Discectomy	20 20 20 20	Metamizol superior to parecoxib, APAP, and placebo for pain relief in PACU with infrequent side effects ($P < 0.05$)
Kampe et al., 2006 [121]	Prospective R, DB, C	Acetaminophen Metamizol	Breast Cancer Surgery	20 20	IV APAP clinically equivalent to metamizol
Landwehr et al., 2005 [122]	Prospective R, DB, PC	Placebo Acetaminophen Metamizol	Retina Surgery	13 12 13	IV APAP produced better pain relief than placebo and was comparable to IV metamizol
Tiippana et al., 2008 [123]	Prospective R, DB, C	Intraop IV Parecoxib followed by PO Valdecoxib x7d Intraop IV APAP followed by PO APAP x7d Intraop IV Parecoxib followed by PO Valdecoxib x7d + IV Dexamethasone 10 mg Intraop IV APAP followed by PO APAP x7d + IV Dexamethasone 10 mg	Laparoscopic Cholecystectomy	40 40 40 40	IV APAP followed by oral APAP was as effective as IV parecoxib followed by oral valdecoxib but IV APAP reduced rescue use on first day ($P < 0.001$)

AC = active comparator; APAP = acetaminophen; C = controlled; DB = double-blind; i.v. = intravenous; PO = per os (oral); PC = placebo-controlled; R = randomzied.

total fentanyl consumption. After surgery, pain was assessed every 30 minutes for 2 hours in the postanesthesia care unit (PACU). Tramadol 50 mg was given for pain scores >3. Total tramadol consumption was recorded for the 2 hours in the PACU [125].

Sensory block onset time was shorter and tourniquet pain onset time was longer in the P group (APAP) compared to the control group ($P < 0.05$). The duration of sensory block and amount of fentanyl consumption were not different among the groups. Tourniquet pain scores were not different among the groups. Postoperative VAS scores were better in the K and P groups compared to control ($P < 0.05$) as was the number of patients who required supplemental tramadol and the total consumption of tramadol ($P < 0.05$ for each). The side effect profile was not significantly

different among the groups. The authors observed that i.v. APAP added to a standard IVRA block could shorten onset time to sensory block, but APAP or ketorolac produces comparable postoperative pain relief [125].

APAP vs Ibuprofen

Published, peer-reviewed data comparing the efficacy of i.v. APAP and i.v. ibuprofen for analgesia are not available. Unlike the situation with NSAIDs, APAP's analgesic effect is due to a central site of action, resulting in the potential for the i.v. route to have a significant advantage over oral due to the earlier and higher peak CSF levels. As a result, the oral APAP data will not be predictive of outcome if head-to-head i.v. studies were to be conducted.

Similar to other NSAIDs, the use of i.v. ibuprofen is contraindicated in patients with known hypersensitivity to ibuprofen or NSAIDS and during the perioperative setting of coronary artery bypass graft surgery [81]. Patients with a history of ulcers, GI bleeding, fluid retention, heart failure, or patients that have renal impairment, heart failure, liver impairment, and patients taking diuretics or ACE inhibitors should be monitored closely due to an increased risk for cardiovascular or GI risks.

APAP vs Metamizol

Dipyrone (metamizole) is a NSAID used in some countries to treat pain (postoperative, colic, cancer, and migraine); it is banned in other countries including the United States because of an association with life-threatening blood agranulocytosis. Edwards and colleagues performed a 2010 Cochrane Review on single-dose dipyrone for acute postoperative pain which was updated from a 2001 Cochrane review [126]. There were no relevant new studies identified, but additional outcomes were sought [126]. Fifteen studies tested mainly 500 mg oral dipyrone (173 participants), 2.5 g i.v. dipyrone (101), 2.5 g intramuscular dipyrone (99), with fewer than 60 participants receiving any other dose [126]. Over 70% of participants experienced at least 50% pain relief over 4 to 6 hours with oral dipyrone 500 mg compared to 30% with placebo in five studies (288 participants; number needed to treat [NNT] 2.4 [1.9 to 3.2]) [126].

Grundmann and colleagues conducted a prospective, double-blind, randomized, placebo-controlled study comparing the efficacy of three i.v. non-opioid analgesics for postoperative pain relief after lumbar microdiscectomy [120]. Eighty healthy patients were randomly divided into four treatment groups (n = 20 each) to receive either parecoxib 40 mg, paracetamol 1 g, metamizol 1 g, or placebo i.v. 45 minutes before the end of surgery. In the metamizol group, the pain score at arrival in the PACU was significantly lower compared with the paracetamol, parecoxib, and placebo groups. In addition, in the metamizol group, significantly fewer patients required additional patient-controlled analgesia compared with the other groups studied. The incidence of adverse side effects was infrequent in all groups [120].

Kampe and colleagues assessed the clinical efficacy of i.v. APAP 1 g and i.v. dipyrone 1 g on a 24-hour dosing schedule in this randomised, double-blinded study of 40 ASA I–III (American Society of Anesthesiologists classification of physical status) patients undergoing surgery for breast cancer [121]. Regarding pain scores at rest, the 90% confidence interval (CI) of the mean differences between the treatment groups over 30 hours postoperatively was found to be within the predefined equivalence margin [+7.5/–6.2], and the CI values for pain scores on coughing [+7.3/–9.0] were similar [121]. The two groups did not differ in cumulative opioid rescue consumption (Dipy Group 14.8 +/– 17.7 mg vs Para Group 12.1 +/– 8.8 mg, $P = 0.54$) nor in piritramide loading dose (Dipy Group 0.95 +/– 2.8 mg vs Para Group 1.3 +/– 2.8 mg, $P = 0.545$). Five patients in the Dipy Group experienced hypotension in contrast to none in the APAP Group ($P = 0.047$). There were no significant between-treatment differences for other adverse events, patient satisfaction scores ($P = 0.4$), or quality of recovery scores ($P = 0.3$) [121].

Landwehr and colleagues assessed clinical efficacy of i.v. APAP 1 g and i.v. metamizol 1 g on a 24-hour dosing schedule in this randomized, double-blinded, placebo-controlled study of 38 ASA physical status I–III patients undergoing retinal surgery [122]. They concluded that i.v. APAP 1 g has similar analgesic potency as i.v. metamizol 1 g for postoperative analgesia after retinal surgery [122].

I.V. Parecoxib vs I.V. APAP

Due to the specificity of COXIBs, parecoxib is associated with fewer bleeding complications than nonspecific NSAIDs, but potential risks for renal and cardiovascular events remain. For example, in a study comparing the renal effects of i.v. parecoxib and i.v. APAP vs placebo on elderly, post-orthopedic surgery patients, parecoxib demonstrated a significant transient reduction in creatinine clearance during the 2 hours following administration [117]. Clinically relevant decreases in glomerular filtration rate (GFR) may be experienced by patients suffering from concomitant diseases affecting renal function or aggravated by changes to the effective or actual circulating volume in an acute situation. Comparatively, as a result of its weak peripheral PG inhibition, i.v. APAP demonstrated no effect on GFR in patients with normal renal function and is recommended for use in patients with renal dysfunction. Secondary end points of the study (pain intensity and opioid consumption) illustrated that i.v. APAP 1 g and i.v. parecoxib 40 mg produced equivalent pain reductions over the 3 days treatment period; however, there was a numerical trend over 72 hours to decreased opioid consumption in the patient cohort treated with APAP with significant results in the first 24 hours [117].

One hundred sixty patients who underwent elective laparoscopic cholecystectomy were randomized by Tiippana and colleagues to four groups of 40 patients [123]. Groups 1 and 3 received parecoxib 40 mg i.v. during surgery and valdecoxib 40 mg × 1 PO for 7 postoperative days. Groups 2 and 4 received APAP 1 g × 4 i.v. during surgery and

1 g × 4 PO for 7 days. In addition, Groups 3 and 4 were given dexamethasone 10 mg i.v. intraoperatively. The patients were given oxycodone 0.05 mg/kg i.v. in phase 1 PACU (PACU 1) or 0.15 mg/kg PO in phase 2 PACU (PACU 2) as needed to keep VAS <3/10 [123]. Pain intensity, nausea, and the need of oxycodone in PACU 1 were similar in all groups [123]. Dexamethasone reduced the need of oral oxycodone in PACU 2 (7.0 +/– 1.0 mg vs 9.1 +/– 1.0 mg, $P < 0.05$). Pain intensity was similar in all groups at home. More patients in the parecoxib/valdecoxib groups needed rescue medication on the 1st postoperative day ($P < 0.001$) than paracetamol-treated patients [123]. Tiippana et al. concluded that APAP was as effective as parecoxib/valdecoxib for pain after laparoscopic cholecystectomy (LCC). Dexamethasone decreased the need of oxycodone in PACU 2. The effect of dexamethasone was similar in APAP and parecoxib/valdecoxib patients [123].

I.V. COXIBs vs I.V. Nonselective NSAIDs

Parecoxib vs Ketorolac

In short surgical procedures, rapid onset of analgesia is desired. While i.v. parecoxib may have a reduced risk of bleeding, the onset of analgesia may take longer than nonselective active NSAIDs because it requires 0.6 hour to achieve a therapeutic concentration [99]. To evaluate this effect, a double-blind, randomized, controlled trial was conducted to compare the efficacy of ketorolac and parecoxib following laparoscopic sterilization [118]. Thirty-six patients were randomized to receive either i.v. parecoxib (40 mg) or i.v. ketorolac (30 mg) at induction of anesthesia, and assessed for 3 hours postoperatively. At waking and 1 hour, pain scores were significantly higher for patients who received parecoxib. However, the number of patients requiring rescue analgesia was similar in the two treatment groups. The median time to rescue was numerically lower in, but clinically similar to, the parecoxib group [118]. Based upon these data, ketorolac may be preferable to parecoxib when rapid onset of analgesia is required (i.e., following a short surgical procedure). However, ketorolac use is limited due to bleeding complications especially when ketorolac is used at high doses or for more than 5 consecutive days [73,127]. In a different study, the two agents appeared to have equal analgesic efficacy.

Leykin and colleagues conducted a prospective, randomized, double-blind comparison between parecoxib (40 mg i.v. q8h) and ketorolac (3 mg i.v. q8h) for early postoperative analgesia following nasal surgery [119]. The AUC of the VAS calculated during the study period was 635 (26–1,413) in the parecoxib group and 669 (28–1,901) in the ketorolac group ($P = 0.54$). Rescue morphine analgesia was required by 12 patients (48%) in the parecoxib group and 11 patients (44%) in the ketorolac group ($P < 0.05$), while mean morphine consumption was 5 +/– 2.5 mg and 5 +/– 2.0 mg in ketorolac and parecoxib groups, respectively ($P < 0.05$). No differences in the incidence of side effects were recorded between the two groups [119]. Leykin et al. concluded that in patients undergoing endoscopic nasal surgery and local infiltration with 1% mepivacaine, parecoxib administered before discontinuing general anesthesia is as effective in treating early postoperative pain as ketorolac [119].

Combination Therapy (I.V. APAP/I.V. NSAID)

On occasion, it may be useful to combine APAP and an NSAID in an effort to achieve optimal analgesia while minimizing opioid analgesia (e.g., severe postoperative pain in a patient with obstructive sleep apnea and significant sensitivity to opioids). In a qualitative review, Hyllested and colleagues examined studies of APAP, NSAIDs, or their combination in postoperative pain management—irrespective of their route of administration [127]. They found that the addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone, and the limited data available also suggest that paracetamol may enhance analgesia when added to an NSAID, compared with NSAIDs alone [98]. In a qualitative systematic review of analgesic efficacy for acute postoperative pain, the combination of APAP and NSAID was more effective than APAP or NSAID alone in 85% and 64% of relevant studies, respectively [128]. The combination resulted in a reduction in pain intensity scores and rescue opioid consumption, 35.0 ± 20.9% and 38.8 ± 13.1%, respectively, vs APAP alone, and 37.7% ± 26.6% and 31.3% ± 13.4% lesser, respectively, vs an NSAID alone [128].

Safety/Tolerability of APAP Anti-inflammatory Agents

APAP

Aside from the known potential for hepatotoxicity with excessive dosing, APAP has a long history of safety. Intravenous APAP is safe, with an AE profile similar to placebo [44,48,50,129]. Significant AEs due to i.v. APAP use are rare and occur at an estimated rate of less than 1/10,000 [17]. Children exhibit a similar safety profile to adult populations [63,130–132].

Parra et al. [133] evaluated oral APAP 2,000 mg/day and 4,000 mg/day and found a minor, but still statistically significant, effect on international normalized ratio (INR) with the lower dose by day 7 of dosing compared to placebo in a study of 36 patients on a stable dose of warfarin. The mean maximum increase from baseline INR was approximately 0.6 (week 2) and 0.9 (week 3), respectively, for the 2,000 mg/day and 4,000 mg/day oral APAP groups. No studies have been performed specifically evaluating the short-term (<5 days) use of i.v. APAP in patients anticoagulated with warfarin; however, when taken together, the literature suggests monitoring may be appropriate in patients on warfarin when i.v. or oral APAP treatment is planned for more than several days.

APAP, regardless of route of administration, appears to have only limited potential for drug–drug interactions (Table 3) [134]. These interactions appear to be independent of route of administration. Substances that induce or

Table 3 Literature summary of drug–drug interactions with acetaminophen

Drug	interaction mechanism	Interaction potential
Alcohol	CYP2E1 inducer and substrate	In theory, acetaminophen overdoses during the window of sudden abstinence may produce a risk of acetaminophen-induced hepatotoxicity. However, based upon the literature, it generally appears that therapeutic acetaminophen dosing is safe.
Anticonvulsants	Nonspecific hepatic inducer	Published long-term studies failed to show that anticonvulsants induced acetaminophen-induced hepatotoxicity partly due to anticonvulsant-induced increased metabolism of acetaminophen through nontoxic (non-NAPQI producing) elimination pathways.
Caffeine	CYP1A2 substrate	Enhances early exposure of oral acetaminophen, but is not expected to affect i.v. acetaminophen.
Cimetidine	CYP2E1 inhibitor	May reduce NAPQI formation, but this effect may be minimal at therapeutic acetaminophen doses. Used with N-acetyl cysteine to treat oral acetaminophen overdoses to reduce NAPQI formation.
Diflunisal	Not characterized	Increases acetaminophen levels by 50%, but the clinical significance is unknown.
Isoniazid	CYP2E1 inducer and substrate	In theory, acetaminophen overdoses during the window of sudden abstinence may produce a risk of acetaminophen-induced hepatotoxicity.
Serotonin-3 antagonists	Pharmacodynamic interaction	Potential antagonism of acetaminophen analgesic effect in experimental pain. Not demonstrated to occur in postoperative pain studies.
Warfarin	Pharmacodynamic interaction	Acetaminophen may increase INR in patients taking warfarin.

regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of APAP and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of APAP. The concomitant use of probenecid reduces APAP clearance, and salicylamide prolongs the elimination half-life, but the clinical relevance of these effects are unknown [17]. While older literature suggested that APAP may increase the risk for developing hepatotoxicity in patients already on hepatic inducing medications, such as barbiturates and anticonvulsants, a review of the literature found little evidence to support this assertion [135].

APAP daily maximum dose recommendations have been driven by concerns over hepatotoxicity associated largely with uncontrolled outpatient use [43]. Patients with severe hepatic disease are also at an increased risk for hepatotoxicity, but glutathione deficiency does not appear to be an additional risk factor [44]. Overall, the risk of adverse events or hepatotoxicity is extremely rare with therapeutic use [44]. Patients with high alcohol consumption or are fasting who ingest toxic doses of APAP appear to be at increased risk of developing hepatotoxicity [18,136–141], but those taking appropriate therapeutic doses of APAP do not seem to be at overly excessive clinically significant risks.

NSAIDs

The use of NSAIDS may be associated with renal impairment, GI effects, blood clotting disorders, and cardiovascular events [33,43]. COX-2 is constitutively expressed in kidney and vascular endothelium where it plays a role in the maintenance of vascular integrity [142]. Therefore, NSAIDs that target COX-2 may increase the risk for renal impairment and toxicity. Short-term treatment with ibuprofen or ketorolac results in a minimal impact on normal renal function [143–145]. For example, a systematic review of patients receiving diclofenac, ketorolac, indomethacin, or ibuprofen for 3 days postoperatively did not find an increased incidence of renal failure [146]. Although short-term use of NSAIDs for the management of acute pain does not seem to impair renal function [146], there are numerous reports of NSAID-induced renal failure when these drugs are utilized for the perioperative management of pain [147–152]. A transient reduction in renal function was observed on postoperative day 1 as measured by reduced creatinine clearance, sodium output, and potassium output, although values returned to normal on day 2 [146]. However, patients receiving ketorolac are at a dramatically increased risk of renal failure if treatment is extended beyond 5 days [153]. Additionally, ibuprofen and ketorolac may increase the risk for toxicity when administered concomitantly with aminoglycosides [154] or cyclosporine [155]. The risk of renal toxicity also increases in children with hypovolemia, hypotension, or preexisting renal disease [43].

GI AEs of NSAIDs include ulcer formation and bleeding. Inhibition of COX in the epithelium of the stomach leads to a reduction in PGs and a subsequent increase in sensitivity to gastric acid. This can cause hemorrhages and erosions of the gastric epithelium [118]. Short-term use of NSAIDs (<1 week) has a reduced risk of developing serious GI events, although these events may occur at any time [142,156,157]. There have been multiple reports of

GI ulceration or bleeding associated with brief exposure to NSAIDs for the perioperative management of pain [158–162]. Patients are at an increased risk for developing adverse GI events if they have peptic ulcer disease, *Helicobacter pylori* infection, or if they are of an advanced age [163–165].

Perioperative Issues of Selective COX-2 Inhibitors

Selective COXIBs, such as parecoxib, are associated with less gastric toxicity and fewer bleeding complications than NSAIDs, and are safe for perioperative use in noncardiac surgery [163,165–167]. The risk of renal insult is roughly the same as with traditional NSAIDs; however, of particular concern is the increased risk of cardiovascular adverse events observed in patients treated with COX-2 inhibitors. Patients who received oral rofecoxib had an almost fivefold increased risk of myocardial infarction [133] and an increased risk of atherothrombotic complications after 18 months of rofecoxib intake [168], and this appears to be a class effect, although different agents seem to possess different degrees of risk. Therefore, COX-2 inhibitors should be avoided in the perioperative period of coronary artery bypass graft surgery and those patients who are at an increased risk for thrombotic events [141,163,169,170]. An assessment for the risk of a cardiovascular event should be performed before patients are treated with a COX-2 inhibitor.

Clinicians may prescribe low-dose aspirin in conjunction with COX-2 inhibitors in efforts to interfere with any prothrombotic COXIB tendencies. Rimon and colleagues reported the surprising observation that celecoxib and other COXIBs may bind tightly to a subunit of COX-1 [171]. Although celecoxib binding to one monomer of COX-1 does not affect the normal catalytic processing of arachidonic acid (AA) by the second partner subunit, celecoxib does interfere with the inhibition of COX-1 by aspirin in vitro. X-ray crystallographic results obtained with a celecoxib/COX-1 complex show how celecoxib can bind to one of the two available COX sites of the COX-1 dimer. Administration of celecoxib to dogs interferes with the ability of a low dose of aspirin to inhibit AA-induced *ex vivo* PLT aggregation. Because COXIBs exhibit cardiovascular side effects, they are often prescribed in combination with low-dose aspirin to prevent thrombosis. It is important to know that the cardioprotective effect of low-dose aspirin on COX-1 may be blunted by COXIBs [171].

Perioperative Bleeding

Perioperative bleeding may be induced or exacerbated by concomitant medications that have the potential for interference with surgical hemostasis. For example, when used as a perioperative analgesic, a single dose of a NSAID with significant COX-1 effect may cause prolonged PLT dysfunction [23,172].

APAP 15 mg/kg may produce a dose-dependent, transient, and minor effect on PLTs due to a weak inhibition of PLT COX-1 [172]. However, PLT dysfunction is far more pronounced with the NSAIDs [45,173]. In a study of 107 patients undergoing elective tonsillectomy [174], the authors reported that a single dose of i.v. APAP of 3,000 mg did not cause a significant effect on PLT aggregation, whereas diclofenac 75 mg caused a profound effect and was associated with one patient who required treatment for postoperative bleeding. Note that a single dose of i.v. ketorolac 0.4 mg/kg, the equivalent of a 30 mg in a 70 kg adult, has the potential to cause PLT dysfunction for at least 24 hours [45].

PLTs are especially vulnerable to COX-1 inhibition because unlike most other cells, they are not capable of regenerating this enzyme. Presumably, this reflects the inability of PLTs to independently synthesize proteins. This means that aspirin, which irreversibly acetylates COX, causes inhibition of PLT aggregation for the lifespan of the PLT which is 10 to 14 days [175]. In contrast, nonselective NSAIDs reversibly inhibit the COX enzyme, causing a transient reduction in the formation of thromboxane A_2 (TXA_2) and inhibition of PLT activation which resolves after most of the drug is eliminated [175]. The use of NSAIDs may result in antiplatelet effects and an increased incidence of perioperative blood loss and blood transfusion requirements, resulting in increased morbidity and mortality following a variety of surgical procedures. COXIBs have no significant effects on PLT function at therapeutic dosages [176,177]. For these reasons, the perioperative administration of COXIBs or APAP may be a safer alternative to NSAIDs in certain surgical procedures where increased bleeding is a concern (e.g., total joint arthroplasty, tonsillectomy) [178–191].

Hong et al. evaluated PLT function in 10 healthy volunteers and performed a population pharmacodynamic modeling of aspirin and ibuprofen-induced PLT aggregation inhibition [192]. The authors showed that at an oral dose of 400 mg, ibuprofen's PLT inhibition was significant, lasting 6 to 8 hours. Therefore, when ibuprofen is dosed q6h, PLT function will remain significantly reduced until the drug is discontinued.

Niemi and colleagues reported on their evaluation of the effect on PLT function in healthy volunteers administered single doses of i.v. ketoprofen 1.4 mg/kg, i.v. ketorolac 0.4 mg/kg, and i.v. diclofenac 1.1 mg/kg [173]. Diclofenac produced mild reversible impairment in PLT aggregation and no prolongation in bleeding time, whereas ketoprofen and ketorolac produced both PLT dysfunction and prolonged bleeding time. The single dose effects of ketorolac continued for 24 hours. The anti-PLT effects of ketorolac were confirmed in a placebo-controlled study in 10 healthy adults given a single dose of i.v. ketorolac 0.4 mg/kg or placebo. Ketorolac caused clinically meaningful PLT dysfunction for 24 hours [45]. In an active-controlled crossover study in 10 volunteers, i.v. ketoprofen 1.4 mg/kg and i.v. ketorolac 0.4 mg/kg caused significant PLT dysfunction and prolonged bleeding time, whereas i.v. diclofenac 1.1 mg/kg had a modest transient effect [193]. NSAID-induced PLT dysfunction is dose proportional. For

example, in a study with oral ibuprofen, doses of 200, 400, 800, and 1,200 mg produced 93, 94, 98, and 99% inhibition, respectively [194].

Under normal circumstances, there is no significant concentration of COX-2 in PLTs; there, COX-2 selective inhibitors are less likely to lead to PLT dysfunction. Knijff-Dutmer and colleagues demonstrated in patients with rheumatoid arthritis that naproxen 500 mg bid for 2 weeks significantly reduced PLT aggregation and prolonged bleeding time compared to meloxicam, an NSAID which at low doses exhibits preferential inhibition of COX-2 over COX-1 [195].

Graff and colleagues studies the effects of parecoxib and dipyrone (metamizol, an NSAID no longer available in the United States) on PLT aggregation in patients undergoing meniscectomy: a double-blind, randomized, parallel-group study [196]. PLT aggregation and thromboxane B_2 (TXB_2) formation were significantly lower for 6 hours in dipyrone-treated patients compared with parecoxib-treated patients [196]. In contrast, TXB_2 formation was increased with parecoxib 6 hours after administration compared with pretreatment values. Thus, parecoxib did not affect PLT aggregation in a population of patients undergoing routine partial meniscectomy (or a similar arthroscopic procedure) under clinical conditions.

Acetylsalicylic acid and ketorolac both substantially disrupted PLT function in contrast to i.v. diclofenac 37.5 mg or oral diclofenac 50 mg control. Diclofenac, with its balanced COX-1 and COX-2 inhibitory profile, may pose less risk of postoperative bleeding than NSAIDs such as ketorolac and ASA, which predominantly inhibit COX-1 [197].

Perhaps, the more important question is whether the measurable impairment in PLT function or increase in bleeding time translates into a problem with surgical hemostasis or a readmission to treat postoperative bleeding. While the published data are conflicting, a recent 15-year audit of post-tonsillectomy bleeding and readmission rates for treatment demonstrated a year-over-year increase in bleeding rates paralleling routine perioperative use of NSAIDs or corticosteroids, such as dexamethasone, used to reduce postoperative nausea and vomiting [198].

Conclusion

Multimodal or balanced analgesia, the combination of nonopioid analgesics and/or regional analgesic techniques with an opioid, has been proposed as a way to decrease systemic opioid consumption and to improve postoperative analgesia after surgeries likely to result in severe pain [11,199–202]. The potential benefits of a multimodal approach include clinically meaningful pain relief with reduced consumption of opioids that may result in a reduced frequency and severity of unwanted opioid-related AEs and an overall improvement of patient satisfaction and health outcomes, such as earlier ambulation and discharge.

APAP is a safe, well-tolerated, and effective analgesic for both adults and children. The introduction of ready-to-use i.v. APAP has provided a formulation that achieves more consistent and more rapid therapeutic levels than orally or rectally administered APAP. Intravenous APAP also has a postoperative opioid-sparing effect. Efficacy of a given drug must always be measured against the safety profile and tolerability of that drug. Specifically, direct comparisons of APAP and NSAIDs and other nonopioid therapeutic agents need to be evaluated in the context of the variables affecting time to peak concentration required for various formulations, interpatient variability, and age-related factors affecting antipyretic effects and for analgesic effects. In addition, the type of procedure studied can affect perceived efficacy [9]. Adverse events associated with APAP are comparable to placebo, with only mild effects on PLT aggregation and no clearly demonstrated, clinically significant drug interactions. With therapeutic dosing, hepatotoxicity is rare. Intravenous APAP is a viable alternative to NSAIDS for rapid analgesia, and is associated with a lower incidence of adverse events. A single dose of a COX-1 NSAID may produce prolonged PLT dysfunction and increased risk of surgical bleeding for up to 24 hours. Therefore, i.v. APAP may be the preferred nonopioid analgesic where surgical bleeding is a concern.

In addition, APAP is not associated with the adverse GI events that occur with nonselective NSAIDs or with the cardiovascular adverse events that occur with the selective COX-2 inhibitors. Intravenous APAP represents a safe and effective first-line agent for the treatment of acute mild-to-moderate pain in the perioperative period when oral agents may be impractical or when rapid onset with predictable therapeutic dosing is required.

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