What anesthesiologists should know about paracetamol (acetaminophen)

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ABSTRACT

Paracetamol is widely used in the management of acute and chronic pain. The purpose of this review is to give anesthesiologists answers to some of the most common questions about paracetamol, specifically the following questions. What is the mechanism of action of paracetamol? Is paracetamol a NSAID? Which endogenous analgesic systems are influenced by paracetamol? Are the perceived concerns about paracetamol use real? What new research is there into paracetamol-induced liver failure? Is paracetamol safe for use by patients with liver disease or those taking anticoagulants? How effective is paracetamol for the management of postoperative pain? Does paracetamol have any opioid-sparing effects? Which formula has the best analgesic efficacy? Which route of administration has the better pharmacokinetic profile? Is the concentration of paracetamol in blood or cerebrospinal fluid relevant to the analgesic effect? Which starting dose should be administrated in intravenous infusion? *(Minerva Anestesiol 2009;75:644-53)*

Key words: Acetaminophen - Cyclooxygenase - Serotonin - Cannabinoids - Analgesics, opioid - Drug toxicity - Liver failure - Blood platelets - Pain, postoperative - Infusion, intravenous

Paracetamol, also known as acetaminophen, was synthesized in 1878 by Morse [1] and introduced for medical usage in 1893.[2] However, until the 1950s, when it was identified as the active metabolite of the two well-known antipyretic drugs acetanilide and phenacetin, it had only limited use. Since its reintroduction into clinical medicine in the United States in 1955 as an analgesic replacement for phenacetin (which was withdrawn from the market for its nephrotoxicity), paracetamol has become one of the most popular and widely used drugs for the first-line treatment of fever and pain.[3] It has been used perioperatively in oral, rectal, and parenteral formulations. The recent introduction to the market of a ready-to-use intravenous paracetamol formulation has increased the interest of anesthesiologists in the use of this old drug in the postoperative setting. However, questions and concerns still exist among physicians over its mechanism of action, its potential toxicity, and its analgesic potency. The aim of this review is to give anesthesiologists an update on these three key issues.

Mechanism of action

More than 100 years after its synthesis, the mechanism of action of paracetamol remains unknown. In particular, it is still under discussion as to whether it acts peripherally and/or centrally and which analgesic pathway is mainly affected by its administration.[4] Potential mechanisms include an inhibition of cyclooxygenase isoenzymes,[5] interaction with the endogenous opioid pathway,[6] activation of the serotoninergic bulbospinal pathway,[7] involvement of the nitric oxide (NO) pathway,[8] and an increase in cannabinoid/vanilloid tone.[9]

As the analgesic actions of paracetamol resemble those of non-steroid anti-inflammatory drugs (NSAIDs), the first effort to explain its mechanism of action was directed at demonstrating that paracetamol also inhibits cyclooxygenase (COX). Flower and Vane showed that the antipyretic effect of paracetamol is related to the inhibition of prostaglandin synthetase in the brain.[10] In the 1990s a major advance in physiology and pharmacology was the discovery of the two cyclooxygenase isozymes (COX-1 and COX-2), which catalyze the conversion of arachidonic acid to prostaglandins, thromboxanes, and prostacyclin and represent the targets of NSAIDs. Prostaglandins (PGs) are mediators of fever, pain and inflammation. Both of the COX enzymes have cyclooxygenase and peroxidase activity. The cyclooxygenase activity converts arachidonic acid to prostaglandin G_2 (PGG_2), which is a hydroperoxide, and then the peroxidase part of the enzyme catalyzes the metabolism of PGG_2 to prostaglandin H_2 (PGH_2).[11] Cyclooxygenase is sensitive to the local oxidation environment, which is influenced by organic peroxides and by reducing or oxidizing agents. A reducing agent is required to convert the COX enzyme from the active oxidized form (Fe^{4+}) to the inactive resting form (Fe^{3+}). In broken cell preparations, a phenol that is commonly added to the cells represents the reducing agent.[12] Paracetamol (para-acetyl-amino-phenol) is a substituted phenol; therefore, it acts as a reducing agent.[13] Although it has no affinity for the active site of COX, it blocks its activity by reducing the active oxidized form of the enzyme to an inactive form. In intact cells, when the levels of the substrate arachidonic acid are low (less than 5 μmol/L), paracetamol is a potent inhibitor of PG synthesis, because it blocks the physiological regeneration of peroxidases; thus, the process is stopped. However, in broken cells, when the concentration of hydroperoxides is high, paracetamol is a weak inhibitor of PG synthesis.[14] The details of the hypothetical mechanism by which paracetamol inhibits prostaglandin synthesis are presented in Figure 1. The inhibitory effect of paracetamol on prostacyclin production is completely blocked by butyl-hydroperoxide.[15] This peroxide-dependent COX inhibition explains why paracetamol is not active at peripheral sites of inflammation where peroxide concentrations are high, whereas it is active in the brain where peroxide concentrations are low. Paracetamol selectively inhibits COX activity in cells with a low oxidant status (endothelial cells), rather than cells with a high oxidant status (platelets).[12] The selective inhibition of COX in the central nervous system explains why paracetamol is not associated with gastric side effects and inhibition of platelet activity that are typically observed with NSAIDs. On the other hand, these findings support the hypothesis that paracetamol does not possess anti-inflammatory efficacy similar to NSAIDs, but rather it has only analgesic and antipyretic actions. However, due to the similarity of some of its in vivo effects to those of selective COX-2 inhibitors, some authors maintain that paracetamol has some anti-inflammatory activity; however, it clearly does not suppress the types of severe inflammation that accompany diseases such as rheumatoid arthritis.[5] A second hypothesis posits that paracetamol acts by selectively inhibiting a particular isoform of the COX enzyme; this isoform, which was characterized and cloned in dog brain, was designated COX-3.[16] COX-3 is highly expressed in specific tissues, such as the brain and the heart. The presence of COX-3 could explain the pharmacological actions of paracetamol and other drugs that are weak inhibitors of COX-1 and COX-2.[17] However, COX-3 is simply a variant of COX-1 that is derived from the same gene on chromosome 9 and retains intron 1. The retained intron sequence could alter folding and may affect the active site of the enzyme; this might lead to altered enzymatic properties, as shown by the lower potency (about 1/5) in generating PGE2.[18] Therefore, as COX-3 is unlikely to be the elusive target of paracetamol in human tissues, the mystery as to how paracetamol exerts an analgesic effect without affecting COX-1 and COX-2 remains unsolved.

Recent findings have shown that the analgesic effect of paracetamol involves a "self-synergistic" interaction between spinal and supraspinal sites, with recruitment of endogenous opioid pathways. Intrathecal (spinal) administration of paracetamol to mice produced dose-related antinociception that was insensitive to the opioid antagonist naloxone, whereas intracerebroventricular (supraspinal) administration had no effect. However, combined

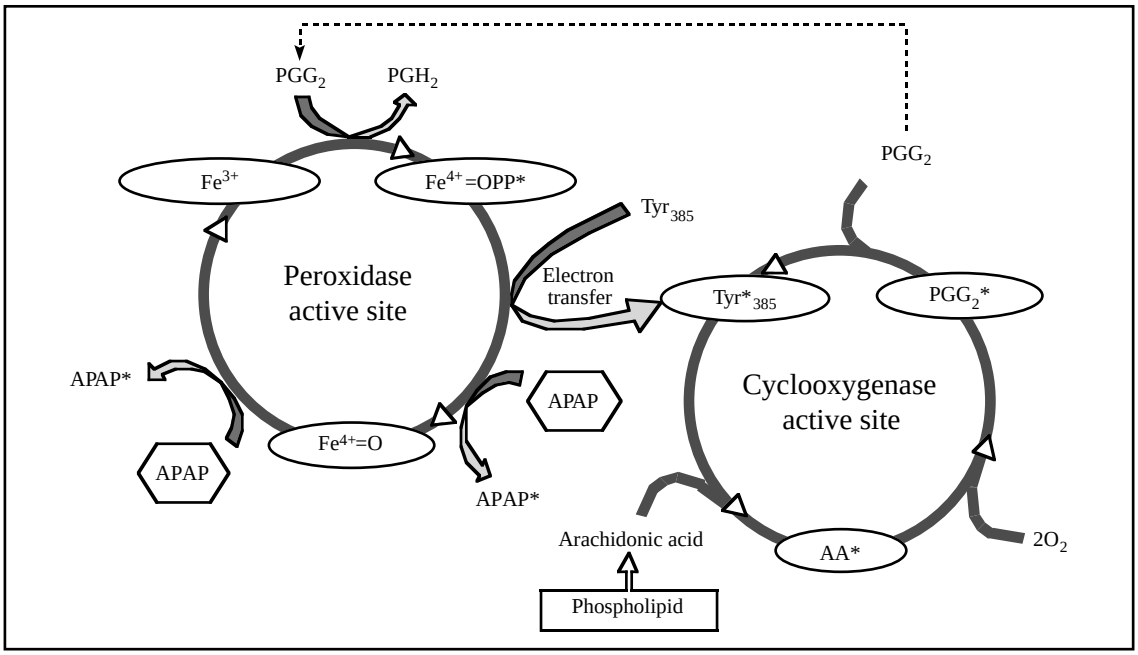

Figure 1.—Hypothetical mechanism of the paracetamol-mediated inhibition of prostaglandin synthesis. A cyclooxygenase monomer shows two distinct catalytic sites: a cyclooxygenase active site and a peroxidase active site. The cyclooxygenase activity converts the arachidonic acid to prostaglandin G2 (PGG_2), which is a hydroperoxide, and then the peroxidase part of the enzyme catalyzes the metabolism of PGG_2 to prostaglandin H2 (PGH_2). The Tyrosyl radical (Tyr*385) initiates the oxygenation of arachidonic acid (AA) by removing the 13-pro(S) hydrogen of the molecule, and generating a radical species (AA*) that is further oxidized by two molecules of oxygen (O_2), to yield PGG_2. PGG_2 then diffuses (dotted line) to the peroxidase active site and undergoes a two-electron reduction to the equivalent alcohol, PGH_2. The reduction of PGG2 in the peroxidase active site yields an oxidized heme radical, which generates the tyrosil radical. The ferryl protoporphyrin IX radical cation (Fe4+=OPP*) can then be transferred to the neighboring tyrosine residue (Tyr385) in the cyclooxygenase active site; this yields the requisite Tyr*385 and a partially reduced form of the heme, named Ferryl protoporphyrin IX (Fe4+=O); this must be further reduced by one electron to regenerate the resting enzyme (Fe3+). Therefore, an endogenous reductant is required to convert the enzyme from the active oxidized form (Fe4+) to the inactive resting form (Fe3+). This heme reduction is performed by any number of reducing cosubstrates. Cyclooxygenase is sensitive to the local oxidation environment. When the levels of the substrate arachidonic acid are low, paracetamol (para-acetyl-aminophenol = APAP), which is a substituted phenol, acts as a reducing agent and inhibits prostaglandin synthesis by reducing the higher oxidative state of the enzymes. When the concentration of the arachidonic acid substrate increases and the concentration of hydroperoxides (PGG_2) become higher, paracetamol is a weak inhibitor of prostaglandin synthesis. This might explain why paracetamol is not active at sites of inflammation, where the concentrations of peroxides are high. Modified from Chandrasekharan NV *et al.*[11] and Arnoff *et al.*[13]

administration produced synergistic antinociception that was reversed when naloxone was given either spinally or subcutaneously.[19] Moreover, each of the subtype-selective opioid receptor antagonists (β-FNA (μ), naltrindole (δ), and nor-BNI (κ)) attenuated the site/site synergy produced by paracetamol; thus, each of the opioid receptor subtypes and endogenous pathways (endorphin, enkephalin, and dynorphin) were implicated to some degree in this synergy.[6] As paracetamol does not bind to opioid receptors [20] and naloxone does not reverse its analgesic effect at a single site but only attenuates the spinal/supraspinal synergy,[19] these findings support the hypothesis that the analgesic activity of paracetamol includes the activation of descending opioid pathways and a synergistic interaction at the level of the spinal cord.

Many studies support the hypothesis that serotonin (5-hydroxytryptamine; 5-HT) participates in the central antinociceptive effect of paracetamol. Serotonin and noradrenaline are the two main neurotransmitters implicated in the endogenous descending pain inhibitory pathway, known as the "analgesic system", which originates at the level of the midbrain in the periaqueductal gray and in the magnus raphe nucleus that lies within the medulla.[21] In rat brain, the antinociceptive action of paracetamol is associated with changes in

the serotoninergic system. A significant down-regulation of 5-HT_{2A} binding sites in the frontal cortex in response to 5-HT release was demonstrated in rats after the administration of paracetamol; this indicates that the serotoninergic system plays a major role in the mechanism underlying analgesia produced by this drug.[22] The antinociceptive activity of intraperitoneally-administrated paracetamol in the hot-plate test in mice was increased by the selective blockade of 5-HT_{1A} and 5-HT_{1B} receptors, whereas it was antagonized by the administration of selective agonists for these receptors.[7] Following intrapalmar injection of formalin, the intravenous and oral administration of paracetamol in rats reduced nociceptive behaviors (biting and licking) in both phases of the typical biphasic nocifensive response to the test. The antinociceptive activity of paracetamol was completely blocked by the intrathecal administration of a 5-HT_{1A} receptor antagonist. Conversely, the intraplantar injection of paracetamol failed to induce any anti-inflammatory effect and reduced nociceptive behavior only at high doses in the early phase of the test; this suggested a lack of relevant local activity.[23] The potent 5-HT_3 receptor antagonist tropisetron has been reported to reverse the antinociceptive effect of paracetamol in the paw pressure test in rats.[24] However, intrathecal injection of other 5-HT_3 receptor antagonists, such as ondansetron and granisetron, was unable to block its activity. This suggested that a specific spinal tropisetron-sensitive receptor could be involved in the antinociceptive mechanism of action of paracetamol.[25] All these findings reinforce the evidence for a centrally-acting component of paracetamol that involves the serotoninergic inhibitory descending pathway.

Among various mechanisms proposed to account for the analgesic action of paracetamol is the nitric oxide pathway. The L-arginine-NO pathway is activated by substance P and N-methyl-D-aspartate (NMDA), and its activation results in the facilitation of nociception transmission. Paracetamol inhibited substance P-mediated hyperalgesia. Moreover, inhibitors of nitric oxide synthase (NOS) activity produced antinociception and markedly increased the analgesic action of paracetamol.[8]

Recent investigations have demonstrated that the analgesic effect of paracetamol is due to the indirect activation of cannabinoid CB1 receptors.[3] In the brain and spinal cord, paracetamol, following deacetylation to its primary amine (p-aminophenol) and conjugation with arachidonic acid by the action of fatty acid amide hydrolase (FAAH), is converted to the bioactive metabolite N-acylphenolamine (AM404).[26] As it is an inhibitor of the cellular reuptake of anandamide (the first recognized endocannabinoid), AM404 can indirectly activate CB1 receptors by increasing the levels of endogenous cannabinoids in the brain. Moreover, AM404 is a potent activator of vanilloid subtype 1 receptor (TRPV1).[27] The antagonism of CB1 receptor activity completely prevents the analgesic efficacy of paracetamol.[9] AM404 inhibits in a dose-dependent manner both COX-1 and COX-2, and because of the consumption of arachidonic acid, it reduces the production of prostaglandins.[27] This could explain why paracetamol inhibits prostaglandin production in the brain. Moreover, besides inhibiting nociception, cannabinoids markedly lower body temperature via activation of CB1 receptors. Therefore, the potential involvement of the cannabinoid system could also help explain the antipyretic effect of paracetamol. Finally, the well-known effects of cannabinoids (relaxation, euphoria and feelings of wellness) are shared by aniline analgesics, such as paracetamol, acetanilide, and phenacetin.[3]

Potential toxicity and safety profile

Paracetamol has been used safely and effectively for many years. At therapeutic doses, it is considered to be safer than NSAIDs, especially for chronic pain management;[28] indeed it is currently recommended by several international guidelines as the first line treatment for chronic conditions, such as osteoarthritis pain.[29, 30] However, in a small minority of patients paracetamol is responsible for life-threatening liver injury. This potential hepatotoxicity could still represent a perceived barrier to its use among some physicians. The liver is the organ that is most affected by acute paracetamol toxicity. Damage to the liver following paracetamol ingestion is not due to the drug itself, but to the toxic metabolite N-acetyl-p-benzoquinine imine (NAPQI). Once absorbed, approxi-

mately 90% of paracetamol is metabolized by conjugation (mainly glucoronidation) via UDP-glucuronosyltransferase (isoform UGT1A6) and sulfation via two sulfotransferases (SULT1A1 and SULT1A3); the end-products are inactive metabolites that are eliminated in urine. A small fraction (5%) is eliminated unchanged. The remaining 5% is oxidized by the CYP2E1 subfamily of cytochrome P450, which leads to the formation of NAPQI.[31] Other human cytochrome P450 isoforms, including CYP1A2, CYP3A4, and CYP2A6, have been reported to form NAPQI in vitro, but their contributions in vivo seem negligible.[32] Paracetamol is also oxidized by CYP2A6 to form inert catechols, such as methoxyacetaminophen. In the liver, NAPQI is quickly combined with the endogenous antioxidant glutathione to form non-toxic conjugates that are eliminated in the urine. However, after an overdose (when glutathione stores in the liver become depleted), free NAPQI begins to accumulate and causes centrilobular necrosis of the liver.[3] Critical events that lead to cell death include the oxidation of enzymes, DNA fragmentation, and mitochondrial injury. Hepatic injury can be limited through administration of N-acetylcysteine, which replenishes the levels of glutathione in the liver.[31] Risk factors that may predispose patients to paracetamol-induced hepatotoxicity are excessive dosing, increased P450 activation (as in patients treated with anticonvulsants and isoniazid, etc.), decreased gluthatione availability, and chronic severe ethanol abuse.[3]

Paracetamol overdose remains a significant clinical problem, accounting for as many as 40% of acute liver failure cases in the United States and the United Kingdom. Furthermore, recent data suggest an increase in paracetamol intoxications in recent years. Besides suicide attempts, unintentional overdoses constitute at least half of paracetamol-related hospitalizations. It is important to emphasize that the median dose ingested by individuals who developed acute liver failure was 24 g (equivalent to 48 500 mg tablets).[33] Risk factors include repeated dosing in excess of package labeling, use of multiple paracetamol-containing products, simultaneous use or abuse of alcohol and narcotics, age, and comorbidities that include liver diseases and depression.[34]

Conversely, when used at an appropriate dosage, paracetamol is a safe drug for both acute and chronic pain management. The maximum daily dosage is 4 g; this is consistent with the decline in analgesic activity, which normally occurs over a period of 6 hours. The recommended dose for intravenous paracetamol injection in adults is 1 g. A randomized controlled trial compared the analgesic efficacy and safety of i.v. paracetamol at starting doses of 1 and 2 g in a total of 164 patients undergoing third molar surgery. Regarding hepatic function, no significant adverse events were recorded. Only one patient included in the i.v. paracetamol 1 g group showed a transient increase in aminotransferases.[35] Another study evaluated the effects of one large dose of 3 g of i.v. paracetamol in 35 patients that were undergoing tonsillectomy under local anesthesia. Only one patient displayed a subclinical disturbance of hepatocellular integrity as indicated by a reversible increase in GSTA1-1 and aminotransferases; however these levels returned to normal within 2-4 days.[36] Finally, a recent study evaluated the tolerability of paracetamol at 4, 6, and 8 g/day for three days in healthy young adults. Paracetamol plasma concentrations did not accumulate during three days of repeated supratherapeutic doses, and, at steady state, they were significantly lower than would be expected from single-dose data. As expected, sulfate formation clearance was lower, whereas glucuronide formation clearance was unexpectedly higher. These results suggested possible saturation of the sulfate pathway, but also the induction of glucuronosyltransferase, UTG1A6, by paracetamol itself (especially at higher dosage). The activity of serum hepatic aminotransferases remained within the expected ranges during the study, and the incidence of adverse events was similar for both paracetamol and placebo.[31] These results may have important implications when reconsidering the safety profile and tolerability of paracetamol.

The perception that paracetamol should be avoided in patients with chronic liver disease arose from an awareness of the association between massive paracetamol overdose and acute liver failure. However, there is no evidence in the literature of an increased risk of hepatotoxicity in these patients with the recommended doses.[37] Alcoholic patients treated with the maximum recommended daily dose of paracetamol (4 g per day for three consec-

utive days) did not develop increases in serum transaminases or other measures of liver injury.[38] Therefore, paracetamol can also be used safely in patients with liver disease.

Acetaminophen-induced nephrotoxicity occurs in 1-2% of patients with paracetamol overdose, and this becomes evident after hepatotoxicity. It can be differentiated from hepatorenal syndrome, which may complicate fulminant hepatic failure. The pathophysiology of renal toxicity in paracetamol poisoning has been attributed to cytochrome P-450 mixed function oxidase isoenzymes that are present in the kidney. The role of N-acetylcysteine therapy in the setting of acetaminophen-induced renal failure is unclear. Paradoxically, glutathione conjugates have been implicated in the formation of nephrotoxic compounds.[39] Generally, paracetamol is thought to have only minor effects on renal function, as it does not affect constitutively expressed COX-1. Transient increases in urine sodium, potassium, albumin, and alpha-1-microglobulin have been observed in elderly patients undergoing orthopedic surgery, but no significant differences were noted between groups that were treated with paracetamol (1 g q.i.d.) and those given either COX-2 inhibitor or placebo. In such patients, these results suggest that transient glomerular and tubular dysfunctions are not related to the studied analgesic therapies, and as such they are not clinically relevant.[40]

In contrast to traditional NSAIDs, paracetamol is usually not considered to influence platelet function. However, recent investigations have shown that intravenous paracetamol is a weak inhibitor of platelet COX-1, with a dose-dependent antiaggregatory effect observed in healthy volunteers for at least 90 min after its administration.[41] Paracetamol causes a mild degree of COX-1 inhibition when associated with parecoxib,[42] and it potentiates the antiaggregatory effects of aspirin and diclofenac.[43] Platelet aggregation is more impaired by diclofenac than paracetamol, even when administrated at the loading dose of 3 g.[36] The antiaggregatory effect of paracetamol does not seem to be clinically relevant, and surgical bleeding attributable to paracetamol seems unlikely.[41] However, in chronic treatment, although paracetamol is considered the analgesic of choice in patients receiving anticoagulants, the combination of paracetamol and warfarin is not as safe, as is generally believed. A recent international study showed a significant increase in the normalized ratio (INR) and significant reductions in vitamin K-dependent clotting factors in patients receiving a stable treatment of warfarin who received 4 g paracetamol per day for 14 days. These results suggest that an intensified INR monitoring in patients treated with oral anticoagulants and paracetamol is advisable.[44] The identification of drug-drug interactions is an important aspect of patient care. Paracetamol is widely metabolized by UDP-glucuronosyltransferase (UGT) enzymes that play a key role in drug-drug interactions, as they catalyze the conjugation of various endogenous and exogenous substances. Experimental evidence indicates that ranitidine, propanolol, and cisapride inhibit paracetamol glucuronidation, whereas estrogen-containing oral contraceptives increase it. The effects of carbamazepine, phenytoin, phenobarbital, and rifampin on paracetamol glucuronidation remain to be determined. Finally, as genetic polymorphisms have been identified for many UGT isoenzymes, pharmacogenetic studies could have a role in identifying patients that possess allelic variants with either enhanced or reduced glucuronidation activity.[45]

Analgesic efficacy in postoperative pain

The perioperative use of paracetamol by different routes of administration has been widely studied.[46] The onset and duration of the analgesic effect is determined by the route of administration of paracetamol. After oral administration, a large variability in individual plasma levels of paracetamol has been observed for a period of 80 min post-dose.[47] The use of effervescent tablets speeds up oral absorption by reducing the time to maximum plasma concentration (Tmax) from 45 min for ordinary tablets to 27 min with effervescent tablets.[48] A faster onset of analgesia is obtained when paracetamol is given intravenously. Therapeutic plasma concentrations are achieved within 20 min of intravenous administration. The analgesic effect lasts around 2 hours post-dose.[49] Intravenous administration is the route of choice when oral administration is not possible or when

rapid analgesia is required, as in the postoperative setting. Even though the rate of absorption is slower and more variable than either intravenous or oral administration, rectal administration is widely used in children. The plasma concentration in adults receiving 1 g rectal paracetamol following cardiac surgery was only 1.2 mcg/ml, compared to 2.7 mcg/ml when given orally.[50]

A systematic review of 51 studies concluded that a single dose of oral paracetamol is an effective analgesic treatment for acute postoperative pain in at least 50% of participants (n = 5762), and it is associated with infrequent, mild, and transient adverse events. The number needed to treat (NNT) values for at least 50% pain relief over four to six hours following a single dose of oral paracetamol were as follows: 500 mg NNT 3.5; 600 to 650 mg NNT 4.6; 975 to 1000 mg NNT 3.6.[51] A meta-analysis of eight randomized controlled trials (RCTs) that compared rectal paracetamol with a placebo showed a clinically-relevant analgesic effect at doses higher than 20 mg/kg.[52] Single or multiple doses of intravenous paracetamol (1 g) generally provided significantly better analgesic efficacy than the placebo. The ready-to-use paracetamol intravenous formulation (1 g) showed similar efficacy to a bioequivalent dose of 2 g propacetamol.[53] Propacetamol is the parenteral prodrug of paracetamol. After injection, it is rapidly and completely converted by plasma esterase into 50% paracetamol. Therefore, after hydrolysis and bioequivalence has been established, 1 g of propacetamol provides 0.5 mg paracetamol.[54]

Although its opioid-sparing effect is still controversial, paracetamol is also used in multimodal analgesia. In a meta-analysis of seven RCTs, including 265 patients, paracetamol combined with patient controlled analgesia (PCA) morphine after major surgery induced a significant morphine-sparing effect (in the range of 20%); although this was lower than that obtained with NSAIDs, the incidence of morphine-related adverse events did not change in the postoperative period.[55]These data were confirmed by another meta-analysis which comprised 52 RCTs (4893 adults). The following results were reported: with a NSAID regimen, morphine sparing was approximately 40%; with other COX-2 inhibitors, it was approximately 25%; and with paracetamol, it was below 20%. Although the differences in the extent of morphine-sparing between different classes of non-opioid drugs did not reach statistical significance, a reduction in morphine-related adverse events only occurred with NSAIDs.[56] In a recent clinical trial conducted in patients after lumbar laminectomy and discectomy, intravenous paracetamol (1 g at 6-hour intervals) improved the quality of postoperative analgesia and increased patient satisfaction, but it did not decrease opioid requirements.[57] A meta-analysis evaluated the possible additive analgesic effects of the combination of paracetamol with NSAIDs for postoperative pain management. Adding an NSAID to paracetamol increases its analgesic efficacy, whereas there is no evidence of a superior analgesic effect of this combination when compared to the NSAID alone.[52]

Paracetamol is also available in fixed combinations with other molecules (codeine, tramadol, oxycodone). Combining drugs from different classes with different modes of action may present the opportunity to optimize efficacy and tolerability, meaning that lower doses of each drug may be required to achieve the same degree of pain relief. Although these drug associations are available only in oral formulations, they have been studied both in chronic and in acute postoperative pain management. A recent systematic review confirms previous findings that combining paracetamol with codeine provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain. The NNT values were 2.2 for 800 to 1000 mg paracetamol plus 60 mg codeine, 3.9 for 600 to 650 m g paracetamol plus 60 mg codeine, and 6.9 for 300 mg paracetamol plus 30 mg codeine.[58] A paracetamol/tramadol combination (325 mg/37.5 mg) has been used for postsurgical pain after orthopedic surgery, especially in day surgery patients. The analgesic efficacy of this combination was significantly superior to the placebo and comparable to that obtained with codeine/paracetamol; not only there was better tolerability but there was also a lower incidence of constipation. The mean daily dose of paracetamol/tramadol was 4.3-4.5 tablets/day.[59] The efficacy of coadministered oxycodone/paracetamol for postsurgical pain following oral surgery has also been studied. The analgesic efficacy of oxycodone/paracetamol (5 mg/325 mg) in patients

suffering from dental pain after a third molar surgery was significantly lower than that obtained with either the association of oxycodone/ibuprofen (5 mg / 400 mg) [60] or the sole administration of rofecoxib 50 mg.[61] The analgesic efficacy of the new combination of oxycodone/paracetamol (10 mg/325 mg) was significantly superior to both the placebo and to the controlled-release formulation of oxycodone (20 mg).[62]

The optimal dose of paracetamol is a controversial issue. The minimum plasma paracetamol level required for analgesia and anti-pyresis is thought to be 10-20 mg/L, whereas the threshold for potential hepatotoxicity is considered 150 mg/L.[46] Recent investigations underlined that it is the concentration in the affected compartment rather than in the plasma itself that relates to the effect. Although the concentration in the affected compartment may mirror the plasma concentration, it is subject to a time delay.[63] Paracetamol readily penetrates into the cerebrospinal fluid after only a single intravenous injection (15 mg/kg) and rises to concentrations of about 7 mg/L. It is detectable in cerebrospinal fluid within 5 minutes of i.v. injection.[64] In children, the analgesic efficacy of rectal paracetamol increases in a linear manner as the dose is increased from 0 to 60 mg/kg. However, rectal doses greater than 30 mg/kg are not recommended.[65] The dose required for analgesia is greater than that required for an anti-pyretic effect. The recommended dose of intravenous paracetamol in pediatric surgical patients is 15 mg/kg.[52] Neonates and infants have a reduced clearance of paracetamol and are capable of forming the reactive intermediate metabolite that causes hepatocellular damage, particularly after multiple doses. They have an immature glucuronide conjugation system; therefore the sulfation metabolic pathway is the most important route of metabolism.[66] In adults, the standard dose of paracetamol is 1 g every 6 hours, with a maximal daily dose of 4 g/day, either p.o. or i.v., in a 15-minute infusion. However, several studies investigated the benefits of increasing the loading dose. The analgesic efficacy of a 2 g starting dose of i.v. paracetamol following a third molar surgery was superior to the recommended dose of 1 g in terms of both the magnitude and the duration of the effect; moreover, there was no significant difference regarding side effects.[35] After intravenous administration of paracetamol (2 g starting dose and 5 g during the first 24 hours) in healthy subjects, the pharmacokinetics of the drug remained unchanged. After the administration of 2 g paracetamol, the peak plasma concentration did not raise the toxic threshold, and it was approximately 35% lower after the repeated 1 g infusions than with the concentration measured after 2 g. The dosage of 5 g daily was shown to be both safe and well tolerated.[67] However, when a single i.v. dose of 3 g of paracetamol was administrated to patients undergoing tonsillectomy, the observed opioid-sparing effect was similar to that reported after conventional doses of paracetamol and lower than that obtained with 75 mg of diclofenac. The authors concluded that although no hepatotoxicity was observed, the administration of paracetamol at higher doses than recommended might increase the risk of hepatic side effects, without any improvements in analgesic efficacy.[36]

Conclusions

Paracetamol is a safe and effective drug for acute and chronic pain management, although its mechanism of action is still a controversial issue. It is a centrally-acting analgesic that interacts with the cyclooxygenase system, the endogenous opioid pathway, the serotoninergic inhibitory descending system, the NO pathway, and the endocannabinoid system. Paracetamol-induced hepatotoxicity is a rare event that is usually related to either intentional or accidental overdose. At the recommended doses (up to 4 g daily), paracetamol can also be safely used in patients with alcoholic liver disease. Caution should be exercised when administrating paracetamol to patients who are taking anticoagulants. The antiaggregatory effect of paracetamol seems not to be clinically relevant with regard to postoperative surgical bleeding. The ready-to-use intravenous formulation shows the best pharmacokinetic profile in postoperative pain management. Furthermore, it penetrates readily into the cerebrospinal fluid and provides rapid and predictable analgesia in the postoperative setting. A 2 g loading dose may be more efficient than the conventional 1 g, but further studies are needed to confirm this hypothesis. Although high-

er doses are not associated with hepatotoxicity, the recommended dose at present is 1 g in a 15-min infusion every 6 hours. The morphine-sparing effect of paracetamol is about 20%; therefore, it does not significantly reduce the incidence of opioid-related adverse events.

References

1. Morse HN. Ueber eine neue Darstellungsmethode der Acetylamidophenole. Ber Deutscher Chem Ges 1878;11:232-3.
2. Von Mering J. Beitrage zur Kenntniss der Antipyretica. Ther Monatsch 1893;7:577-87.
3. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. CNS Drug Reviews 2006;12:250-75.
4. Smith HS Potential analgesic mechanisms of acetaminophen. Pain Physician 2009;12:269-80.
5. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Therapeutics 2005;12:46-55.
6. Raffa RB, Walker EA, Sterious SN. Opioid receptors and acetaminophen (paracetamol). Eur J Pharmacol 2004;503:209-10.
7. Roca-Vinardell A, Ortega-Alvaro A, Gilbert-Rahola J, Micò JA. The role of 5HT1A/B autoreceptors in the antinociceptive effect of systemic administration of acetaminophen. Anesthesiology 2003;98:41-7.
8. Bujalska M. Effects of nitric oxide synthase inhibition on antinociceptive action of different doses of acetaminophen. Polish J Pharma 2004;56:605-10.
9. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol 2006;531:280-1.
10. Flower R, Vane JR. Inhibition of prostaglandine synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature 1972;240:410-1.
11. Chandrasekharan NV, Simmons DL. The cyclooxygenases. Genome Biol 2004;5:241.
12. Lucas R, Warner TD, Vojnovic I, Mitchell JA. Cellular mechanisms of acetaminophen: role of cyclooxygenase. FASEB J 2005;19:635-7.
13. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic chracteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther 2006;79:9-19.
14. Ouellet M, Percival MD. Mechanism of paracetamol inhibition of cyclooxygenase isoforms. Arch Biochem Biophys 2001;387:273-80.
15. Boutaud O, Aronoff DM, Richardson JH, Marnett LJ, Oates JA. Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandine H(2) synthases. Proc Natl Acad Sci USA 2002;99:7130-5.
16. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS *et al.* COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA 2002;99:13926-31.
17. Botting R, Ayoub SS. COX-3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins Leukot Essent Fatty Acids 2005;72:85-7.
18. Schwab JM, Schluesener HJ, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol? Lancet 2003;361:981-2.
19. Raffa RB, Stone DJ, Tallarida RJ. Discovery of "self-synergistic" spinal/supraspinal antinociception produced by acetaminophen (paracetamol). J Pharmacol Exp Ther 2000;295:291-4.
20. Raffa RB, Codd EE. Lack of binding of acetaminophen to 5-HT receptor or uptake sites (or eleven other binding-uptake assays). Life Sci 1996;59:PL37-PL40.
21. Coluzzi F, Mattia C. Mechanism-based treatment in chronic neuropathic pain: the role of antidepressants. Curr Pharm Des 2005;11:2945-60.
22. Srikiatkhachorn A, Tarasub N, Govitrapong P. Acetaminophen-induced antinociception via central 5-HT2A receptors. Neurochem Int 1999;34:491-8.
23. Bonnefont J, Alloui A, Chapuy E, Clottes E, Eschalier A. Orally administrated paracetamol does not act locally in the rat formalin test. Anesthesiology 2003;99:976-81.
24. Pelissier T, Alloui A, Caussade F, Dubray C, Cloarec A, Lavarenne J *et al.* 5-HT3 receptors mediate spinal 5-HT antinociception: an antisense approach. J Pharmacol Exp Ther 1996;278:8-14.
25. Libert F, Bonnefont J, Bourinet E, Doucet E, Alloui A, Hamon M *et al.* Acetaminophen: a central analgesic drug that involves a spinal tropisetron-sensitive, non-5-HT3 receptor-mediated effect. Mol Pharmacol 2004;66:728-34.
26. Högestätt ED, Jönsson BA, Edmund A, Andersson DA, Björk H, Alexander JP *et al.* Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem 2005;280:31405-12.
27. Zygmunt PM, Chuang H, Movahed P, Julius D, Hogestatt ED. The anandamide transport inhibitor AM404 activates vanilloid receptors. Eur J Pharmacol 2000;396:39-42.
28. Courtney P, Doherty M. Key questions concerning paracetamol and NSAIDs for osteoarthritis. Ann Rheum Dis 2002;61:767-73.
29. American College of Rheumatology Subcommitte on osteoarthritis guideline: recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905-15.
30. Simon LS, Lipman AG, Jacox AK, Caudill-Slosberg M, Gill LH, Keefe FJ *et al.* Pain in osteoarthritis, reumatoid arthritis and juvenile chronic arthritis. 2nd ed. Glenview, Illinois: American Pain Society; 2002.
31. Gelotte CK, Auiler JF, Lynch JM, Temple AR, Slattery JT. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007;81:840-8.
32. Manyike PT, Kharasch ED, Kalhorn TF, Slattery JT. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolita formation. Clin Pharmacol Ther 2000;67:275-82.
33. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS *et al.* Acetaminophen-induced acute liver failure: results of a United States multi center, prospective study. Hepatology 2005;42:1364-72.
34. Myers RP, Shaheen AA, Li B, Dean S, Quan H. Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose. Clin Gastroenterol Hepatol 2008;6:918-25.
35. Juhl GI, Norholt SE, Tonneses E, Hiesse-Provost O, Jensen TS. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administrated as a 2 g starting dose following third molar surgery. Eur J Pain 2006;10:371-7.
36. Silvanto M, Munsterhjelm E, Savolainen S, Tiainen P, Niemi T, Ylikorkala O *et al.* Effect of 3 g of intravenous paracetamol on post-operative analgesia, platelet function and liver enzymes in patients undergoing tonsillectomy under local anaesthesia. Acta Anaesthesiol Scand 2007;51:1147-54.
37. Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients with liver disease. Am J Ther 2005;12:133-41.
38. Kuffner EK, Green JL, Bogdan GM, Knox PC, Palmer RB,

Heard K *et al.* The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in acoholic patients – a multi center randomized study. BMC Med 2007;5:13.
39. Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J Med Toxicol 2008;4:2-6.
40. Koppert W, Frotsch K, Huzurudin N, Boswald W, Griessinger N, Weisbach V *et al.* The effects of paracetamol and parecoxib on kidney function in elderly patients undergoing orthopedic surgery. Anesth Analg 2006;103:1170-6.
41. Munsterhjelm E, Munsterhjelm NM, Niemi TT, Ylikorkala O, Neuvonen PJ, Rosenberg PH. Dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers. Anesthesiology 2005;103:712-7.
42. Munsterhjelm E, Niemi TT, Ylikorkala O, Neuvonen PJ, Rosenberg PH. Influence on platelet aggregation of i.v. parecoxib and acetaminophen in healthy volunteers. Br J Anaesth 2006;97:226-31.
43. Galliard-Grigioni KS, Fehr M, Reinhart WH. Influence of combinations of acetylsalicilic acid, acetaminophen, and diclofenac on platelet aggregation. Eur J Pharmacol 2008;595:65-8.
44. Mahel I, Bertrand N, Drouet L, Bat Dit Sollier C, Simoneau G, Mazoyer E *et al.* Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. Haematologica 2006;91:1621-7.
45. Kiang TKL, Ensom MHH, Chang TKH. UDP-glucuronosyltransferases and clinical drug-drug interactions. Pharmacol Ther 2005;106:97-132.
46. Oscier CD, Milner QJ. Peri-operative use of paracetamol. Anaesthesia 2009;64:65-72.
47. Holmer-Petterson P, Owall A, Jakobsson J. Early bioavailability of paracetamol after oral or intravenous administration. Acta Anaesthesiol Scandinavica 2004;48:867-70.
48. Rygnestad T, Zahlsen K, Samdal FA. Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. Eur J Clin Pharmacol 2000;56:141-3.
49. Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. Intern J Clin Pharmacol Ther 2004;42:50-7.
50. Holmer-Petterson P, Jakobsson J, Owall A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. Acta Anaesthesiol Scandinavica 2006;50:673-7.
51. Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database Syst Rev 2008;CD004602.
52. Romsing J, Moiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. Br J Anesthesia 2002;88:215-26.
53. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). Drugs 2009;69:101-13.
54. Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. Int J Clin Pharmacol Ther 2004;42:50-7.
55. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controller trials. Br J Anesth 2005;94:505-13.
56. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Anesthesiology 2005;103:1296-304.
57. Cakan T, Inan N, Culhaoglu S, Bakkal K, Basar H. Intravenous paracetamol improbe the quality of postoperative analgesia but dose not decrease narcotic requirements. J Neurosurg Anesthesiol 2008;20:169-73.
58. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 2009;CD001547.
59. Mattia C, Coluzzi F, Sarzi Puttini P, Viganò R. Paracetamol/Tramadol association: the easy solution for mild-moderate pain. Minerva Med 2008;99:369-90.
60. Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB *et al.* Analgesic efficacy and tolerability of oxycodone 5 mg / ibuprofen 400 mg compared with those of oxycodone 5 mg / acetanimophen 325 mg and hydrocodone 7.5 mg / acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single dose, parallel-group study in a dental pain model. Clin Ther 2005;27:418-29.
61. Korn S, Vassil TC, Kotey PN, Fricke JR. Comparison of rofecoxib and oxycodone plus acetaminophen in the treatment of acute pain: a randomized, double-blind, placebo-controlled study in patients with moderate to severe postoperative pain in the third molar extraction model. Clin Ther 2004;26:769-78.
62. Gammaitoni AR, Galer BS, Bulloch S, Lacouture P, Caruso F, Ma T *et al.* Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg / acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain. J Clin Pharmacol 2003;43:296-304.
63. Gibbs IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child 2008;93:241-7.
64. Kumpulainen E, Kokki H, Kalonen T, Heikkinen M, Savolainen J, Laisalmi M. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluido f children after intravenous administration. Pediatrics 2007;119:766-71.
65. Varela ML, Howland MA. Single high-dose acetaminophen in children. Ann Pharmacother 2004;38:1935-41.
66. Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. Acta Anaesthesiol Scand 2001;45:20-9.
67. Gregoire N, Hovsepian L, Gualano V, Evene E, Dufour G, Gendron A. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. Clin Pharmacol Ther 2007;81:401-5.

Received on March 23, 2009 - Accepted for publication on May 12, 2009.

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