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CLINICAL PHARMACOLOGY OF PARACETAMOL

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ABSTRACT

Paracetamol is the active metabolite of phenacetin and has analgesic and antipyretic effects but has only weak anti-inflammatory effects. Paracetamol is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme. In adults, the oral dose of paracetamol is 325 to 650 mg thrice-daily or 4 times-daily and in children it is 10 to 15 mg/kg not more than five doses per day. Paracetamol has been found efficacy and safe and the prophylaxis and treatment with paracetamol and the trials conducted with paracetamol have been reviewed. Different cytochromes P-450 isozymes metabolize paracetamol into N-acetyl-p-benzoquinone-imine a toxic reactive intermediate metabolite. Paracetamol is also conjugated with glucuronic acid by different isoforms of 5'-diphosphate-glucuronosyltransferases. The pharmacokinetics of 1,000 mg paracetamol (Panadol) and 1,000 mg paracetamol plus 60 mg caffeine (Panadol extra) have been studied in healthy volunteers following oral administration. Panadol and Panadol extra are rapidly absorbed as the mean absorption half-life is about 0.35 hours and are rapidly eliminated as the mean elimination half-life is 2.25 hours (Panadol) and 3.60 hours (Panadol extra) (P-value > 0.05). The interactions of paracetamol with drugs, the toxicity induced by paracetamol, and the treatment of paracetamol poisoning have been reviewed. The aim of this study is to review paracetamol efficacy and safely, prophylaxis, treatment and trials conducted with paracetamol. In addition, paracetamol metabolism and pharmacokinetics, the interactions of paracetamol with drugs, the toxicity induced by paracetamol, and the treatment of paracetamol poisoning have been reviewed.

KEYWORDS: Drug-interactions, efficacy-safely, metabolism, pharmacokinetics, poisoning, prophylaxis, toxicity, treatment, and trials.

INTRODUCTION

Paracetamol (acetaminophen) is the active metabolite of phenacetin. Paracetamol raises the threshold to painful stimuli, thus exerting an analgesic effect against pain due to a variety of aetiologies. Paracetamol is available without a prescription and is used as a common household analgesic by children and adults. It also is available in fixed dose combination containing narcotic and non-narcotic analgesics (including aspirin and other salicylates), barbiturates, caffeine, vascular headache remedies, sleep aids, toothache, antihistamines, antitussives, decongestants, expectorates, cold and flu preparations, and sore throat treatments. Paracetamol is well-tolerated, however, overdose-two-thirds of which are intentionally induced-can cause severe hepatic damage, it leads to nearly 80,000 emergency department visits and 30,000 hospitalizations annually in the United States. The maximum U.S. Food and Drug Administration-recommended dose of paracetamol is 4 grams daily.[1]

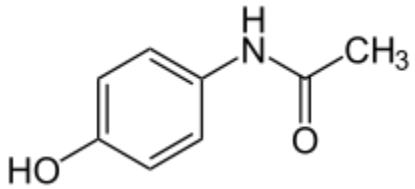
Mechanism of action of paracetamol

Paracetamol has analgesic and antipyretic effects like those of aspirin. But only weak anti-inflammatory effects at commonly used doses (1,000 mg daily). It is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. The presence of high concentrations of peroxides, as occur at sites of inflammation, reduces its cyclooxygenase-inhibitory activity.[1]

Therapeutic uses of paracetamol

Paracetamol is suitable for analgesic and antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (e.g. those with aspirin hypersensitivity, children with a febrile illness, and patients with blending disorders). The conventional oral dose of paracetamol is 325 to 650 mg thrice-daily or 4 times-daily, total daily doses of paracetamol should not exceed 4 grams (2,000 mg daily for patients with a history of heavy alcohol use). Single doses for children 2 to 11 years old depend on age and weight (about 10 to 15 mg/kg), not more than five doses should be administered

in 24 hours. An injectable preparation is typically used in combination with narcotic analgesics for its opioid-soaring effect. Particular attention is warranted due to the availability of a wide variability of prescriptions and non-prescriptions multi-ingredient medications that represent potentially toxic overlapping sources of paracetamol.[1]



Paracetamol molecular structure (molecular weight = 151,163 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "paracetamol efficacy, safely", "paracetamol prophylaxis", "paracetamol treatment", "paracetamol trials", "paracetamol metabolism", "paracetamol pharmacokinetics", "paracetamol drug interactions", "paracetamol toxicity", and "treatment of paracetamol poisoning". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics[1] has been consulted.

RESULTS

Efficacy and safely of paracetamol

Of 296 patients undergoing third molar surgery, 132 patients (44.6%) received a single intravenous dose of 2,000 mg of paracetamol and 164 patients (55.4%) received a single intravenous dose of 1,000 mg of paracetamol. The analgesic efficacy of 2,000 mg of paracetamol was superior to the recommended dose of 1,000 mg in terms of magnitude and duration of analgesic effect and both treatments were safe.[2] It was compared the efficacy and safely of a single oral doses of 60 mg/kg or 90 mg/kg of paracetamol which were administered to 20 patients undergoing third molar extractions. Paracetamol was administered 30 min prior the surgical extraction of teeth and there were no significant differences in pain scores between 60 mg/kg or 90 mg/kg dose of paracetamol. A 90 mg/kg dose of paracetamol does not offer any advantages over 60 mg/kg dose in patients undergoing third molar surgery.[3] Thirty patients undergoing third molar surgery received either a single oral dose of 2,000 mg of paracetamol (N = 15) or a single oral dose of 2,000 mg of ibuprofen (N = 15). Despite there was no statistically difference between paracetamol and ibuprofen, paracetamol had better analgesic efficacy than ibuprofen and both treatments were safe.[4] Seven studies enrolled 2,947 patients who underwent surgery and received three fixed-dose-combinations of 75 to 100 mg ibuprofen/250 mg paracetamol, or 150 to 200 mg ibuprofen/500 mg paracetamol (U.S. Food and Drug Administration approved dose level) or 292 to 400 mg ibuprofen/975 to 1,000 mg paracetamol. Ibuprofen plus paracetamol fixed-dose-combination effectively and safely treated moderated, acute, and severe pain in patients who underwent surgery and the highest fixed-dose-combination of 292 to 400 mg ibuprofen/975 to 1,000 mg paracetamol was well-tolerated.[5] It was compared the effectiveness and safely of paracetamol administered intravenously at the daily dose of 1,000 mg (N = 25) to those of tramadol administered intravenously at the daily dose of 1 mg/kg (N = 25) to women during labour. One hour after administration, the Visual Analogue Pain Score was 4.60 and 5.82 (P-value < 0.05) in women treated with paracetamol and tramadol, respectively. Paracetamol is preferred over tramadol as it is associated with better analgesic efficacy and induces lower adverse-effects in women at labour.[6] Paracetamol was administered intravenously at the daily dose of 1,000 mg (N = 30) and tramadol was administered intravenously at the daily dose of 1,000 mg (N = 29) to women during labour and paracetamol relieved pain more effectively than tramadol.[7] Paracetamol due to its efficacy, safely, and the poor interaction with drugs is the first-choice treatment of pain.[8] One-hundred-fifty-one patients who underwent major orthopaedic surgery had moderate to severe pain and received either 1,000 mg of paracetamol intravenously (N = 49, 32.4%), or 2,000 mg of paracetamol intravenously (N = 50, 33.1%) or placebo (N = 52, 34.4%) 4 times-daily. Patients who received paracetamol had relief of pain more effectively (P-value < 0.05) than placebo and paracetamol was well-tolerated.[9] Paracetamol has a unique role in children because it is the first-line treatment of fever and pain. When paracetamol was administered orally at the dose of 10 to 15 mg/kg 4 times-daily effectively treated severe pain and offered a significant additive analgesic effect to opiates and paracetamol remains the first-choice treatment of analgesia and antipyresis in children.[10]

Prophylaxis with paracetamol

Paracetamol is the most commonly used agent for the prophylaxis of post-immunization fever and pain in children who receive the vaccination.[11] A total of 834 patients undergoing surgery were enrolled and 408 patients (48.9%) received paracetamol orally at the daily dose of 1,000 mg and 426 patients (51.1%) received placebo for prophylaxis of postsurgical pain. Relief of pain was reported in 35.1% of patients with no significant difference in patients who received paracetamol or placebo.[12] The administration of vaccine is associated with adverse-effects and fever in hospitalized preterm infants and prophylactic paracetamol prevented adverse-effects and fever. The prophylaxis with paracetamol is recommended in preterm infants who receive vaccine to prevent adverse-effects and fever.[13] Prophylactic administration of paracetamol, started at the time of vaccination and repeated 6 and 12 hours later, reduced the post-immunization fever and irritability in infants.[14] The administration of benzodiazepines along with paracetamol to children is not superior in efficacy to

paracetamol alone in preventing the recurrence of febrile seizures.[15] Twenty-nine extreme premature infants aged 23 to 26 weeks and with post-natal age ≤ 12 hours were enrolled. Minimum effective dose of paracetamol to close the patent ductus arteriosus was 25 mg/kg loading dose followed by 10 mg/kg 4 times-daily for 5 days. Paracetamol was well-tolerated and closed the patent ductus arteriosus in these infants.[16] Prophylactic paracetamol use in extremely premature infants decreases the likelihood of patent ductus arteriosus.[17]

Treatment with paracetamol

Paracetamol is included in the World Health Organization essential drug list and caffeine enhances the analgesic effect of paracetamol. Paracetamol/caffeine administered at the oral dose of 1,000 mg/130 mg effectively treats acute migraine.[18] The oral dose of paracetamol to treat dental pain is 1,000 mg thrice-daily.[19] Fixed-dose-combination of oral tramadol/paracetamol 37 mg/650 mg offers an improved method of treating the newly recognized multi-mechanistic nature of pain.[20] Three premature infants with a gestational age of 31, 27, and 29 weeks and with the patent ductus arteriosus received paracetamol intravenously at the dose of 15 mg/kg, the total dose of paracetamol ranged from 101 to 360 mg/kg, and paracetamol closed the patent ductus arteriosus in all infants.[21] Paracetamol was administered intravenously at the dose of 15 mg/kg 4 times-daily for 3 to 7 days to 11 premature infants with patent ductus arteriosus weighing from 415 to 1,580 grams and this treatment closed the patent ductus arteriosus in all infants.[22] Forty-seven units in United Kingdom used paracetamol for closing the patent ductus arteriosus. The dose and the duration of paracetamol treatment varied greatly among the units and a dose of 15 mg/kg 4 times-daily was used in 62% of units and the duration of treatment of 3 and 5 days was used in 33% and in 31% of units, respectively. Paracetamol efficaciously and safely close the patent ductus arteriosus and is being used increasingly in United Kingdom centres.[23]

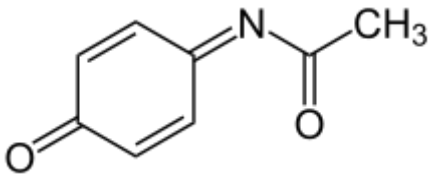
Trials conducted with paracetamol

A randomized, controlled trial was conducted in 103 women on delivery who received either 1,000 mg of paracetamol intravenously (N = 65, 63.1%) or 1,000 mg of tramadol intravenously (N = 38, 36.9%). The pain was assessed by Visual Analogue Pain Scale and was significantly lower in women who received paracetamol. The mean duration of the 1st stage of labour was 211±70 min and the mean duration of delivery was 4.34 hours and both were significantly lower in women who received paracetamol. Paracetamol was more efficacious than tramadol in relieving delivery pain, in shortening the duration of labour, and caused fewer maternal adverse-effects than tramadol.[24] A single, placebo-controlled, double-blind, randomized trial was conducted in 103 patients undergoing cardiac surgery. Fifty-six patients (54.4%) received 1,000 mg of paracetamol intravenously administered 15 min before the end of surgery and also it was administered 6 and 72 hours after the end of surgery and 47 patients (45.6%) received placebo. Analgesic tramadol and anti-emetic ondansetron were administered to both groups of patients. At 12, 18, and 24 hours after the end of surgery, patients who received paracetamol had significantly less pain at rest (P-value = 0.0041, 0.0039, and 0.004, respectively) than patients who received placebo. On the next day, the analgesia was similar in two groups of patients. Patients who received paracetamol required less cumulative morphine than patients who received placebo (48 versus 97 mg) even if the difference did not reach statistical significance (P-value = 0.247). In patients undergoing cardiac surgery, intravenous paracetamol combined with tramadol provides affective pain control.[25] A randomized, clinical trial was conducted in 62 patients and evaluated the efficacy of a single intravenous dose of 1,000 mg of paracetamol to control post-orthognathic surgery pain and to reduce morphine consumption. The patients were randomized into two groups. The study group received 1,000 mg of paracetamol intravenously (N = 31, 50.0%) and the control group (N = 31, 50.0%) received a placebo. The Visual Analogue Pain Scale (VAS) was assessed at 1, 4, 8, 12, 16, 20, and 24 hours postoperatively, morphine consumption, adverse-effects caused by morphine, and patient satisfaction were also analysed. The postoperative VAS was lower in treated patients than in patient who received placebo (P-value < 0.001), the total postoperative morphine consumption was 45.1±21.2 µg/ml in treated patient and was 136±49.9 µg/ml (P-value < 0.001) in patients who received the placebo, and the patient satisfaction was 4.7±0.5 in treated patients and was 4.1±0.5 (P-value < 0.001) in patients who received the placebo. A single intravenous dose of 1,000 mg of paracetamol effectively relieved postoperative surgery pain, provided benefits to patients including reduced pain score, decreased morphine consumption, and improved satisfaction.[26] A prospective, randomised, placebo-controlled, double-blind trial was conducted in women scheduled for elective termination of pregnancy who received 1,000 mg paracetamol intravenously, or 8 mg lornoxicam intravenously, or placebo orally 60 min before anaesthesia. Postoperative pain was assessed by Visual Analogue Pain Scale at 30 and 60 min after the end of surgery. The overall pain intensity was low in treated patients and no difference in relieving pain was observed in women who received paracetamol and in those who received lornoxicam.[27] Randomized, clinical trials were conducted to assess the efficacy of paracetamol in treatment of osteoarthritis. Ten randomized, controlled trials which included 1,712 patients with either symptomatic osteoarthritis of the knee (6 trials) or hip/knee (3 trials) or multiple joints (1 trial) were conducted. Paracetamol administered intravenously at the daily dose of 1,000 mg was effective in relieving pain due to osteoarthritis. For safety reasons paracetamol is the first-line treatment of osteoarthritis in patients who do not respond to other nonsteroidal anti-inflammatory drugs.[28] A double-blind, parallel-group, multicentre,

clinical trial involving 168 patients with symptomatic osteoarthritis of the knee was conducted. Patients received either aceclofenac intravenously at the dose of 100 mg twice-daily (N = 82, 48.8%) or paracetamol intravenously at the dose of 1,000 mg thrice-daily (N = 86, 51.2%). Both treatments showed significant improvement of osteoarthritis of the knee and the adverse-effects were similar in both treatments. At 6 weeks of treatment, aceclofenac had greater improvement in pain and in functional capacity than paracetamol and both treatments were well-tolerated.[29] A blind, randomized, comparative, parallel, clinical trial was conducted in 99 febrile children, aged 6 months to 12 years, who were allocated into three groups. The first group of children received paracetamol orally at the daily dose of 15 mg/kg, the second group of children received ibuprofen orally at the daily 10 mg/kg, and the third group of children received both paracetamol and ibuprofen. The mean tympanic temperature after 4 hours of drug administration was significantly lower in children who received paracetamol and ibuprofen than in those who received paracetamol or ibuprofen alone (P-value < 0.05). The rate of temperature falling and the number of afebrile children were higher (P-value < 0.05) in children who received paracetamol and ibuprofen. The highest fall of temperature was noted in the 1st hour of drug administration in all groups of children and treatments were well-tolerated. Paracetamol and ibuprofen combination caused a quicker reduction of temperature than either paracetamol or ibuprofen alone thus the combination of paracetamol plus ibuprofen is advocated in febrile children.[30] A double-blind, parallel, randomized, placebo-controlled trial was conducted in 58 preterm infants born at < 29-week gestation and with a postnatal age of 6 hours who had a ductus arteriosus larger than 0.9 mm. Infants were randomized to receive either intravenous paracetamol (a loading dose of 15 mg/kg followed by 7.5 mg/kg 4 times-daily) or intravenous dextrose and treatments lasted 5 days. The primary outcome was the need for surgical intervention in infants with patent ductus arteriosus after 5 days of treatment and the secondary outcomes included ductal closure at 5 days, ductal size at 48 hours, ductal reopening, mortality, and significant morbidities. Infants treated with paracetamol had less open ductus arteriosus at 5 days than infants who received dextrose (P-value = 0.003). Infants who received paracetamol had a higher-rate of ductal closure (P-value = 0.002) and smaller ductal size (P-value = 0.04) than infants who received dextrose. Two deaths occurred in infants treated paracetamol and 1 death occurred in infant who received dextrose and deaths were not attributed to the intervention and no other adverse-effects were reported. Early paracetamol treatment reduced the number of infants requiring surgical intervention for patent ductus arteriosus.[31] A multicentre, randomized, controlled trial was conducted in 49 preterm infants with patent ductus arteriosus who were randomized to receive either intravenous paracetamol at the dose of 15 mg/kg 4 times-daily for 3 days or intravenous ibuprofen administered at the daily dose of 10 mg/kg on the first day of life followed by 5 mg/kg on the successive second and third days. Paracetamol was less effective in closing the patent ductus arteriosus than ibuprofen (52% versus 78%, respectively, P-value = 0.026), but the constriction-rate of the ductus arteriosus was similar in infants who received paracetamol and in those who received ibuprofen (81% versus 90%, respectively, P-value = 0.202), as confirmed by logistic regression analysis. The re-opening-rate, the need for surgical closure, and the occurrence of adverse-effects were also similar in infants who received paracetamol and ibuprofen. Paracetamol was less effective in closing the patent ductus arteriosus than ibuprofen, but due to the similar constriction effect, paracetamol and ibuprofen were associated with the same patent ductus arteriosus outcomes. These results support the use of intravenous paracetamol as a first-choice treatment of patent ductus arteriosus.[32]

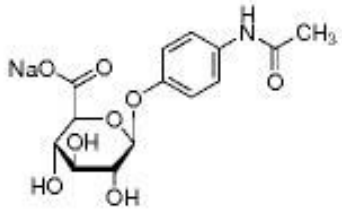
Metabolism of paracetamol

Paracetamol is metabolized into NAPQI a toxic, reactive, intermediate compound which is formed by the following human cytochromes P450: CYP 2D6, 2E1, 1A2, 2A6, 3A4.[33]



N-acetyl-p-benzoquinone imine molecular structure (molecular weight = 149.149 grams/mole)

Paracetamol is conjugate with glucuronic acid by uridine 5'-diphosphate-glucuronosyltranferases UDP 1A1, 1A6, 1A9, and 2B15.[34]



Paracetamol glucuronide (molecular weight = 327.29 grams/mole)

Bakare-Odunola and Abubakar[35] studied the pharmacokinetics of paracetamol and paracetamol plus caffeine which have been administered to 6 healthy volunteers weighing 65±30 kg. A single oral dose of 1,000 mg of paracetamol (Panadol) and a single oral dose of 1,000 mg of paracetamol plus 60 mg of caffeine (Panadol extra) were administered to 6 healthy volunteers. Table 1 summarizes the pharmacokinetic parameters of Panadol and Panadol extra which have been obtained in 6 healthy volunteers.

Table 1: Pharmacokinetic parameters of Panadol and Panadol extra which have been obtained in 6 healthy volunteers. Values are the mean±SEM, by Bakare-Odunola and Abubakar.[35]

Parameter	Panadol	Panadol extra	%Change	*P-value
Lag of time (h)	0.26±0.04	0.32±0.06	23.00	> 0.05
Kab (h^{-1})	2.26±0.48	2.82±1.04	24.48	> 0.05
$T_{1/2}$ ab (h)	0.35±0.05	0.39±0.09	1.43	< 0.05
Tmax (h)	0.27±0.028	0.47±0.028	74.00	> 0.05
Peak conc. (mg/ml)	26.00±2.55	23.36±0.85	10.15	< 0.05
AUC_{0-4h} (mg*h/ml)	62.45±10.02	54.80±11.09	12.25	< 0.05
Kel (h^{-1})	0.36±0.045	0.30±0.11	16.67	= 0.05
$T_{1/2}$ el (h)	2.25±0.48	3.60±0.99	60.00	> 0.05
TBC (ml/h)	16.80±5.26	22.68±3.15	35.00	> 0.05

Kab = absorption-rate constant. $T_{1/2}$ ab = absorption half-life. Tmax = time to reach the peak concentration. AUC_{0-4h} = area under the concentration-time curve. Kel = elimination-rate constant. $T_{1/2}$ el = elimination half-life. TBC = total body clearance. *Student t test.

This table shows that Panadol is rapidly absorbed as the mean absorption-rate constant and the mean absorption half-life are 2.26 h^{-1} and 0.35 hours, respectively, and Panadol is rapidly eliminated as the mean elimination-rate constant and the mean elimination half-life are 0.36 h^{-1} and 2.25 hours, respectively. Caffeine prolongs the absorption half-life and reduces the peak concentration and the area under concentration-time curve of paracetamol.

Interaction of paracetamol with drugs

Paracetamol reduced the dissolution-rate of propranolol hydrochloride and propranolol hydrochloride reduced the dissolution-rate of paracetamol. The time to reach the peak concentration of propranolol hydrochloride was prolonged and an extension of the elimination half-life of propranolol hydrochloride was observed when propranolol hydrochloride was co-administered with paracetamol. A delay in the time to reach the peak concentration of paracetamol and a shortness of the elimination half-life of paracetamol were observed when paracetamol was co-administered with propranolol hydrochloride.[36] Twelve healthy male volunteers received lamotrigine at the daily dose of 100 mg for 36 days and also received paracetamol at the dose of 1,000 mg 4 times-daily. The co-administration of lamotrigine with paracetamol decreased the area under the plasma concentration-time curve of lamotrigine from 166 to 127 µmol/L (P-value < 0.001), increased the clearance of lamotrigine glucuronide from 1.7 to 2.8 L/h (P-value = 0.005), and the trough concentration of lamotrigine was reduced from 5.3 to 3.9 µmol/L (P-value = 0.003) when lamotrigine was co-administered with paracetamol. Paracetamol altered the steady-state of lamotrigine glucuronidation resulting in a 20% decrease in total systemic exposure and a 25% decrease in trough concentration of lamotrigine and this interaction is of clinical relevance.[37] Eight healthy volunteers received cimetidine at the daily dose of 400 mg and also received paracetamol at the daily dose of 1,000 mg. The peak salivary concentration and the absorption-rate constant of cimetidine were significantly reduced (P-value < 0.05), while the time to reach the peak concentration, the absorption half-life constant, the lag-time, and the elimination half-life of cimetidine were increased (P-value < 0.05). These results indicate that paracetamol affects the pharmacokinetic parameters of cimetidine.[38] Two flavonoids, luteolin and quercetin, were evaluated as potential inhibitors of human cytochrome P-450 (CYP) isoforms and UDP-glucuronosyltransferase isoforms. Luteolin and quercetin inhibited human CYP isoforms to varying degrees, with the greatest potency was observed towards CYP1A2 and CYP2C8 which are the CYPs that metabolize paracetamol. These results indicate that luteolin and quercetin inhibit human CYP isoforms and UDP-glucuronosyltransferase isoforms which metabolize paracetamol thus luteolin and quercetin alters the metabolism of paracetamol.[39] The metabolism of paracetamol is mediated by UDP-glucuronosyltransferases and by CYP2E1 and CYP1A2. The drugs that induce CYP2E1 and CYP1A2 and the drugs that inhibit UDP-glucuronosyltransferases increase the exposure of NAPQI resulting in elevated risk of hepatotoxicity.[40]

Toxicity caused by paracetamol

Of 181 cases of paracetamol intoxication 143 cases (79.0%) were intentional intoxications. Patients with intentional intoxication were more often female than males (85% versus 45%, P-value < 0.001) and younger than older patients (median age 23.0 versus 43.5 years, P-value < 0.001). The median daily ingested dose was lower in the unintentional than in the intentional intoxication (8.2 versus 12.9 grams, P-value < 0.001) and cases of acute liver failure occurred in 24% of intoxicated patients.[41] It was compared the characteristics of old and young patients with suspected intoxication by paracetamol and 25 patients were aged ≥ 65 years and 50 patients were aged 20 to 30 years. Old patients were more likely to be associated with chronic paracetamol use (71% old patients, 6% young patients, P-value < 0.001), or with accidental toxic exposure (90% old patients, 29% young patients, P-value < 0.001), while young patients were more likely to have a deliberate high-dose exposure (10% old patients, 71% young patients, P-value < 0.001).[42] The hepatotoxicity caused by paracetamol overdose, both intentional and non-intentional, is the most common cause of drug-induced

liver injury in the United States of America and remains a global issue.[43] Paracetamol is a widely used analgesic and is more toxic than other analgesics which are available without prescription. It was estimated that paracetamol is involved in 6% of poisonings, 56% of acute liver failures, and 7% of drug-induced liver injuries.[44] Paracetamol induces hepatotoxicity, is the leading cause of acute liver failure, and paracetamol is glucuronidated, sulfated, and oxidised and the sulfation is of critical importance in understanding the risk of liver toxicity secondary to paracetamol overdose.[45]

Treatment of paracetamol poisoning

Treatment of paracetamol intoxication consists in the administration of N-acetylcysteine preferably shortly after paracetamol ingestion. Some authors do not recommend treatment with N-acetylcysteine at low paracetamol plasma concentrations since unnecessary adverse-effects can occur. But no treatment with N-acetylcysteine at high paracetamol plasma concentrations may lead to unnecessary severe morbidity and mortality.[46] Fifteen patients with paracetamol poisoning were treated with intravenous N-acetylcysteine at the dose of 300 mg/kg given 20 hours after paracetamol ingestion. The plasma concentrations of paracetamol were 262 and 369 µg/ml at hospital admission and after 4 hours, respectively. Liver-function tests remained normal or were only slightly disturbed in 11 of 12 patients (91.7%) 10 hours of paracetamol ingestion. Severe liver damage developed in three patients (20.0%) in whom treatment was started more than 10 hours after paracetamol ingestion. N-acetylcysteine was well-tolerated and had the advantage of being available as a pharmaceutical preparation.[47] Paracetamol overdose remains the leading cause of death or liver transplantation due to acute liver failure and N-acetylcysteine has long been recognized as an effective antidote minimizing the risk and severity of acute liver injury if administered early after paracetamol ingestion.[48] The only treatment approved by the U.S. Food and Drug Administration for acute paracetamol poisoning is a 72-hour protocol of oral N-acetylcysteine administration. Clinical experience suggests that this protocol may be excessive for many episodes of acute paracetamol poisoning. Hepatotoxicity from paracetamol poisoning is preventable when intravenous administration of N-acetylcysteine initiated within 8 to 10 hours after paracetamol ingestion and continued for 20 hours.[49] Paracetamol poisoning continues to be a worldwide problem and, despite the availability of an effective antidote, N-acetylcysteine, the optimal way to use this antidote, particularly following very large doses of paracetamol ingested, has not been yet established. Clinical trials support a shorter N-acetylcysteine administration and allow the possibility for intensifying treatment without the risk of high-rates of adverse-effects.[50] Charcoal is the best choice to reduce the absorption of paracetamol and N-acetylcysteine should be given to people presenting intoxication due high dose of paracetamol ingested. Current management of paracetamol poisoning involves the administration of intravenous or oral N-acetylcysteine. The treatment with N-acetylcysteine decreases in morbidity and mortality of patients intoxicated with paracetamol.[51]

DISCUSSION

Paracetamol is the active metabolite of phenacetin and is available without prescription and has analgesic and antipyretic effects but has weak anti-inflammatory effects at commonly used doses of 1,000 mg. Paracetamol is available in fixed dose combination containing narcotic and non-narcotic analgesics (including aspirin and other salicylates) barbiturates, caffeine, vascular headache remedies, sleep aids, toothache, antihistamines antitussives, decongestants, expectorates, cold and flu preparations, and some throat treatments. Paracetamol is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among other nonsteroidal anti-inflammatory drugs. Paracetamol is particularly valuable for patients in whom aspirin is contraindicated such as patients with aspirin hypersensitivity, children with a febrile illness, and patients with blending disorders. The conventional oral dose of paracetamol is 325 to 650 mg thrice-daily or 4 times-daily and the total daily dose of paracetamol should not exceed 4 grams daily and 2,000 mg daily in patients with a history of heavy alcohol use. In children, aged 2 to 11 years, the paracetamol oral dose is 10 to 15 mg/kg not more than five dose per day.[1] The efficacy and safely of paracetamol have been reviewed. Patients undergoing third molar surgery received either a single intravenous dose of 2,000 mg or 1,000 mg of paracetamol and the dose of 2,000 mg has higher analgesic effect and both treatments are safe[2], paracetamol was administered at the single oral dose of 60 or 90 mg/kg to patients who underwent third molar extraction and the dose of 90 mg/kg does not offer any advantages to the dose of 60 mg/kg[3], patients undergoing third molar surgery received either 2,000 mg of paracetamol orally or 2,000 mg of ibuprofen orally and paracetamol has better analgesic efficacy than ibuprofen[4], patients undergoing surgery received three fixed-dose-combinations of 75 to 100 mg ibuprofen/250 mg paracetamol, or 150 to 200 mg ibuprofen/500 mg paracetamol (U.S. Food and Drug Administration approved dose level) or 292 to 400 mg ibuprofen/975 to 1,000 mg paracetamol. These treatments effectively and safely treat moderate, acute, and severe pain and the highest dose of ibuprofen/paracetamol is well-tolerated[5], paracetamol was administered intravenously at the daily dose of 1,000 mg and tramadol was administered intravenously at the dose of 1 mg/kg to women during labour and paracetamol is preferred over tramadol and induces lower adverse-effects than tramadol[6], paracetamol was administered intravenously at the daily dose of 1,000 mg and tramadol was administered intravenously at the daily dose of 1,000 mg to women during labour and paracetamol reliefs pain more effectively than tramadol[7], paracetamol due to its

efficacy, safely, and the poor interaction with drugs is the first-choice treatment of pain[8], patients undergoing major orthopaedic surgery had moderate to severe pain and received either paracetamol intravenously at the dose of 1,000 mg, or 2,000 mg, or placebo 4 times-daily and paracetamol is more effective (P-value < 0.05) than placebo in relieving pain and is well-tolerated[9], paracetamol was administered orally at the daily dose of 10 to 15 mg/kg 4 times-daily to children with fever and pain and paracetamol remains the first-choice treatment of analgesia and antipyresis in children.[10] These results indicate that paracetamol effectively and safely reliefs pain in patients undergoing third moral surgery, the fixed-dose-combination of ibuprofen/paracetamol treats moderate, acute, and severe pain and is well-tolerated, paracetamol treats pain in women during labour more effectively than tramadol, paracetamol treats pain more effectively than placebo, and paracetamol is the first-choice treatment of pain and fever in children. The prophylaxis with paracetamol has been reviewed. Prophylaxis with paracetamol reduces fever and pain in children who receive the vaccination[11], patients undergoing surgery received either 1,000 mg of prophylactic paracetamol orally or placebo and relief of pain is observed in 35.1% of patients with no significant difference in patients who received paracetamol or placebo[12], prophylaxis with paracetamol is recommended in preterm infants who receive vaccine to prevent adverse-effects and fever[13], prophylaxis with paracetamol reduces post-immunization fever and irritability in infants who receive the vaccine[14], the administration of benzodiazepines with paracetamol is not superior to paracetamol alone in preventing recurrence of febrile seizures in children[15], prophylaxis with paracetamol administered at a loading dose of 25 mg/kg followed by 10 mg/kg 4 times-daily for 5 days close the patent ductus arteriosus in infants and paracetamol is well-tolerated[16], and the prophylaxis with paracetamol decreases the likelihood of patent ductus arteriosus in extremely preterm infants.[17] These results indicate that the prophylaxis with paracetamol reduces fever and pain in children who receive the vaccination, patients who underwent surgery received paracetamol orally at the daily dose of 1,000 mg or placebo and relief of pain is observed in 35.1% of patients with no significant difference in patients who received paracetamol or placebo, prophylaxis with paracetamol reduces the post-immunization fever and irritability in infants who received the vaccine, benzodiazepines plus paracetamol prevents febrile seizures as paracetamol alone, and prophylactic paracetamol close the patent ductus arteriosus in preterm infants. The treatment with paracetamol has been reviewed. Paracetamol/caffeine administered orally at the dose of 1,000 mg/130 mg treats acute migraine[18], paracetamol administered orally at the dose of 1,000 mg thrice-daily treats dental pain[19], tramadol/paracetamol administered orally at the dose of 73 mg/650 mg treats pain[20], paracetamol administered intravenously at the dose of 15 mg/kg to premature infants closes the patent ductus arteriosus[21], paracetamol administered intravenously at the dose of 15 mg/kg 4 times-daily for 3 to 7 days close the patent ductus arteriosus in premature infants[22], the dose of paracetamol for closing the patent ductus arteriosus varies in United Kingdom and the dose of 15 mg/kg 4 times-daily and is used in 62% of units and the duration of treatment of 3 and 5 days is used in 33% and in 31% of units, respectively.[23] These results indicate that paracetamol/caffeine treats acute migraine, paracetamol treats dental pain, tramadol/paracetamol treats pain, paracetamol closes the patent ductus arteriosus in premature infants, and the therapeutic schedules to close the patent ductus arteriosus varies among the units of the United Kingdom and a dose of 15 mg/kg 4 times-daily is used in 62% of units in the United Kingdom. The trials with paracetamol have been reviewed. A randomized, controlled trial was conducted in women on delivery who received either 1,000 mg of paracetamol intravenously or 1,000 mg of tramadol intravenously and paracetamol is more efficacious than tramadol in relieving pain, in shortening the duration of labour, and causes fewer adverse-effects than tramadol[24], a single, placebo-controlled, double-blind, randomized trial was conducted in patients undergoing cardiac surgery who received either 1,000 mg of paracetamol intravenously or placebo before and after the surgery and all patients also received the analgesic tramadol and the anti-emetic ondansetron. Shortly after surgery, patients who received paracetamol have less pain and require less cumulative morphine than patients who received placebo and the day after surgery the analgesia is similar in patients who received paracetamol and those who received placebo[25], a randomized, clinical trial evaluated the efficacy of a single intravenous dose of 1,000 mg of paracetamol versus that of placebo in controlling orthognathic surgery pain and in reducing morphine consumption. A single intravenous dose of 1,000 mg of paracetamol reliefs postoperative pain and decreases morphine consummation more effectively than placebo[26], a prospective, randomized, placebo-controlled, double-blind trial assessed the postoperative pain in women who underwent elective termination of pregnancy who received 1,000 mg of paracetamol intravenously, or 8 mg of lornoxicam, or placebo. The surgical pain is lower in treated women and no difference in relieving pain is observed in women who received paracetamol or lornoxicam[27], randomized, clinical trials assessed the efficacy of paracetamol in treating osteoarthritis. Paracetamol was administered intravenously at the daily dose of 1,000 mg and effectively treats pain due to osteoarthritis. Paracetamol is the first-line treatment of osteoarthritis reserved for those who do not respond to other nonsteroidal anti-inflammatory drugs[28], a double-blind, parallel-group, multicentre, clinical trial was conducted in patients with symptomatic osteoarthritis of the knee who received either aceclofenac intravenously at the dose of 100 mg twice-daily or paracetamol intravenously at the dose of 1,000 mg thrice-daily. Both treatments improve osteoarthritis of the knee, the adverse-effects are similar

in both treatments, and at 6 weeks of treatment aceclofenac has greater improvement in pain and in functional capacity than paracetamol[29], a blind, randomized, comparative, parallel, clinical trial assessed the efficacy of paracetamol administered orally at the daily dose of 15 mg/kg versus that of ibuprofen administered orally at the daily dose of 10 mg/kg and versus that of both paracetamol and ibuprofen in febrile children. The tympanic fever after 4 hours of drug administration is lower (P-value < 0.05) in children who received paracetamol plus ibuprofen than in those who received paracetamol or ibuprofen alone. The rate of temperature falling and the number of afebrile children are higher (P-value < 0.05) in children who received paracetamol and ibuprofen[30], a double-blind, parallel, randomized, placebo-controlled trial was conducted in preterm infants with the patent ductus arteriosus who received either paracetamol intravenously at a loading dose of 15 mg/kg followed by 7.5 mg/kg 4 times-daily or intravenous dextrose and treatments lasted 5 days. At 5 days of treatment, infants who received paracetamol have less open ductus arteriosus (P-value = 0.003) and have smaller ductal size (P-value = 0.04) than infants who received dextrose. Treatment with paracetamol reduces the number of infants requiring surgical intervention for closing the patent ductus arteriosus[31], a multicentre, randomized trial was conducted in preterm infants with patent ductus arteriosus who received either intravenous paracetamol at the dose of 15 mg/kg 4 times-daily for 3 days or intravenous ibuprofen administered at the daily dose of 10 mg/kg on the first day followed by 5 mg/kg on the successive second and third days. Paracetamol is less effective than ibuprofen (P-value = 0.026) but the constriction-rate of the ductus arteriosus is similar in infants who received paracetamol and in those who received ibuprofen (P-value = 0.202). The re-opening-rate, the need for surgical closure, and the occurrence of adverse-effects are similar in both treatments. These results support the use of intravenous paracetamol as the first-choice treatment of infants with the patent ductus arteriosus.[32] The metabolism of paracetamol has been reviewed. Paracetamol is metabolized into NAPQI by CYP 2D6, 2E1, 1A2, 2A6, and 3A4[33] in addition paracetamol is also conjugated with glucuronic acid by UDP 1A1, 1A6, 1A9, and 2B15.[34] Bakare-Odunola and Abubakar[35] studied the pharmacokinetics of paracetamol (Panadol) and paracetamol plus caffeine (Panadol extra). Panadol consists in a single oral dose of 1,000 mg of paracetamol and Panadol extra consists in a single oral dose of 1,000 mg of paracetamol plus a single oral dose of 60 mg of caffeine. Panadol and Panadol extra are rapidly absorbed as the mean absorption half-life is 0.35 and 0.39 hours (P-value > 0.05), respectively, and are rapidly eliminated as the mean elimination half-life is 2.25 and 3.60 hours (P-value > 0.05), respectively. The interaction of paracetamol with drugs has been reviewed. Paracetamol reduces the dissolution-rate of propranolol hydrochloride and propranolol chloride reduces the dissolution-rate of propranolol. In addition, paracetamol alters the pharmacokinetic parameters of propranolol hydrochloride and propranolol hydrochloride afters the pharmacokinetic parameters of paracetamol[36], paracetamol decreases (P-value < 0.001) the area under the concentration-time curve lamotrigine, increases (P-value = 0.005) the clearance of lamotrigine glucuronide and increase (P-value = 0.003) the trough concentration of lamotrigine. Paracetamol alters the steady-state of lamotrigine glucuronidation resulting in a reduction of total systemic exposure and trough concentration of lamotrigine[37], paracetamol reduces the peak salivary concentration and the absorption-rate constant of cimetidine (P-value < 0.05) while increases the time to reach the peak concentration, the absorption half-life constant, the lag-time, and the elimination half-life of cimetidine (P-value < 0.05)[38], the flavonoids luteolin and quercetin inhibit human CYP1A2 and CYP2C8 and UDP-glucuronyltransferase isoforms which metabolize paracetamol[39], and paracetamol is metabolized by CYP2E1 and CYP1A2 and by UDP-glucuronosyltransferases. The drugs that induce CYP2E1 and CYP1A2 and inhibit UDP-glucuronosyltransferases increase the exposure to NAPQI resulting in elevated risk of hepatotoxicity.[40] These results indicate that paracetamol alters the pharmacokinetic parameters of propranolol hydrochloride and propranolol hydrochloride alters the pharmacokinetic parameters of paracetamol, paracetamol alters the pharmacokinetic parameters of lamotrigine, and cimetidine, and luteolin and quercetin inhibit human CYP1A2 and CYP2C8 and UDP-glucuronyltransferase which metabolize paracetamol and the drugs which induce CYP2E1 and CYP1A2 and inhibit UDP-glucuronosyltransferases increase the exposure of NAPQI resulting in elevated risk of toxicity. The toxicity induced by paracetamol has been reviewed. The unintentional intoxication with 8.2 grams of paracetamol and the intentional intoxication with 12.9 grams of paracetamol cause acute liver failure which occurs in 24% of patients[41], old patients are more likely to be associated with chronic paracetamol use than young patients (P-value < 0.001) and young patients are more likely to have deliberate high-dose of paracetamol than old patients (P-value < 0.001)[42], the hepatotoxicity caused by paracetamol overdose is the most cause of drug-induced liver injury in the United States of America[43], paracetamol causes 6% of poisonings, 56% of acute liver failures, and 7% of drug-induced liver injuries[44], paracetamol is glucuronidated, sulfated, and oxidised and the sulfation is of paracetamol is of critical importance in understanding the risk of liver toxicity secondary to paracetamol overdose.[45] These results indicate that the overdose of paracetamol can induce liver failure, old patients assume overdose of paracetamol more frequently than young patients while young patients assume higher dose of paracetamol than young patients, overdose of paracetamol is the most cause of liver injury in United States of America, paracetamol induces 6% of poisoning, 56% of acute liver failures, and 7% of drug-induced liver injuries, and sulfation of paracetamol is a risk of liver toxicity. The

treatment of paracetamol poisoning has been reviewed. Treatment of paracetamol intoxication consists in the administration of N-acetylcysteine shortly after paracetamol ingestion. Low paracetamol plasma concentrations do not require treatment with N-acetylcysteine. No treatment with N-acetylcysteine at high plasma concentrations of paracetamol may lead to severe morbidity and mortality[46], patients with paracetamol poisoning received N-acetylcysteine intravenously at a dose of 300 mg/kg for 20 hours after paracetamol ingestion. Liver-function tests remained normal or only slightly disturbed in most of patients and liver damage developed in 20.0% of patients in whom treatment with N-acetylcysteine was started 10 hours after paracetamol ingestion[47], N-acetylcysteine has been recognized to be an effective antidote for paracetamol intoxication[48], hepatotoxicity from paracetamol poisoning is preventable with intravenous N-acetylcysteine treatment initiated 8 to 10 hours after paracetamol ingestion and continued for 20 hours[49], N-acetylcysteine is the optimal antidote for paracetamol poisoning particularly following large doses of paracetamol ingestion[50], and charcoal is the best choice to reduce the absorption of paracetamol and N-acetylcysteine decreases the morbidity and mortality of patients intoxicated with paracetamol.[51] These results indicate that N-acetylcysteine is the antidote of paracetamol poisoning and charcoal is the best choice to reduce the absorption of paracetamol.

In conclusion, paracetamol is the active metabolite of phenacetin. Paracetamol has analgesic and antipyretic effects and has only weak anti-inflammatory activity. Paracetamol is particularly valuable for patients in whom aspirin is contraindicated. Paracetamol is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. The conventional oral dose of paracetamol is 325 to 650 mg thrice-daily or 4 times-daily in adults and in children, aged 2 to 11 years, the oral dose of paracetamol is 10 to 15 mg/kg, not more than five doses per day. The efficacy and safely of paracetamol, the prophylaxis and the treatment with paracetamol and the trials conducted with paracetamol have been reviewed. Paracetamol is metabolized into N-acetyl-p-benzoquinone imine by CYP 2D6, 2E1, 1A2, 2A6, and 3A4 and paracetamol is conjugated with glucuronic acid by 5'-diphosphateglucurosyltransferase UDP 1A1, 1A6, 1A9, and 2B15. The pharmacokinetics of oral Panadol (1,000 mg of paracetamol) and oral Panadol extra (1,000 mg of paracetamol plus 60 mg of caffeine) have been studied in healthy volunteers and both Panadol and Panadol extra are rapidly absorbed (the absorption half-life is about 0.35 hours) and are rapidly eliminated [the elimination half-life Panadol is 2.25 hours and that of Panadol extra is 3.60 hours (P-value > 0.05)]. The interactions of paracetamol with drugs, the toxicity induced by paracetamol, and the treatment of paracetamol have been reviewed. The aim of this study is to review the clinical pharmacology of paracetamol.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

The present manuscript is a comprehensive authoritative and updated review of the published data of the clinical pharmacology of paracetamol. In literature, there is no review of the clinical pharmacology of paracetamol. This manuscript has not been previously published, and is not under consideration for publication elsewhere. Furthermore, no illustrations, structure and tables have been previously published. The literature search was performed electronically using PubMed database as search engine and the following key words were used: "paracetamol efficacy, safely", "paracetamol prophylaxis", "paracetamol treatment", "paracetamol trials", "paracetamol metabolism", "paracetamol pharmacokinetics", "paracetamol drug interactions", "paracetamol toxicity", and "treatment of paracetamol poisoning". In addition, the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics has been consulted.

Conflict of interests

The author declares no conflict of interests, or financial interests, in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

General considerations

The author conceived, wrote and typed the present manuscript. Prof. Gian Maria Pacifici, via Sant'Andrea 32, 56127 Pisa, Italy, is the corresponding author. The author is responsible for the reported research. He conceived and designed the study, executed the analysis, interpreted the results, and he drafted, revised, and approved the manuscript as submitted. The present article is a review and drugs have not been administered to men or animals.

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REFERENCES

1. Grosser T, Ricciotti E, FitzGerald GA. Pharmacotherapy of inflammation, Fever, Pain, and Gout, In Goodman@Gilman's. The Pharmacological Basis of Therapeutics. Brunton LL, Knollmann BC editors. Mc Graw Hill. 14th Edition., 25023; 829-856.
2. Juhl GI, Norholt SE, Tonnesen E, Hiesse-Provost O, Jensen TS. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen)

administered as a 2 g starting dose following third molar surgery. Eur J Pain., 2006; 10(4): 371-7.
3. Zacharias M, De Silva RK, Hickling J, Medlicott NJ, Reith DM. Comparative safety and efficacy of two high dose regimens of oral paracetamol in healthy adults undergoing third molar surgery under local anaesthesia. Anaesth Intensive Care, 2007; 35(4): 544-9.
4. Özkan BT, Durmus E, Kalaycı A, Kurban S, Akça CN. The Evaluation of Safety and Analgesic Efficacy of Paracetamol and Ibuprofen Followed by Impacted Third Molar Surgery. Eur J Gen Med., 2010; 7(3): 310-6.
5. Abushanab D, Al-Badriyeh D. Efficacy and Safety of Ibuprofen Plus Paracetamol in a Fixed-Dose Combination for Acute Postoperative Pain in Adults: Meta-Analysis and a Trial Sequential Analysis. CNS Drugs, 2021; 35(1): 105-20.
6. Jindal S, Goel1 P, Mitra S, Pandher DK, Rani S. Efficacy and safety of intravenous paracetamol versus intravenous tramadol for labour analgesia. 0000 Int J Reprod Contracept Obstet Gynecol, 2024; 13(1): 100-6.
7. Makkar JK, Jain K, Bhatia N, Jain V, Mithrawal SM. Comparison of analgesic efficacy of paracetamol and tramadol for pain relief in active labor. J Clin Anesth, 2015; 27(2): 159-63.
8. Salamone F. Pain: the use of paracetamol in multimorbid patients. Med Acad J., 2022; 1(1): 6-13.
9. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology, 2005; 102(4): 822-31.
10. Cranswick N, Coghlan D. Paracetamol efficacy and safety in children: the first 40 years. Am J Ther., 2000; 7(2): 135-41.
11. Kirubakaran R, Viswanathan A, Kompithra RZ. Prophylactic paracetamol for the prevention of fever in children receiving vaccination as part of a standard childhood immunization schedule. Cochrane Database Syst Rev., 2017; 2017(5): CD012655.
12. Cade L, Ashley J. Prophylactic paracetamol for analgesia after vaginal termination of pregnancy. Anaesth Intensive Care., 1993; 21(1): 93-6.
13. Magali D, Shamez L, Vimal V. Prophylactic Paracetamol After Meningococcal B Vaccination Reduces Postvaccination Fever and Septic Screens in Hospitalized Preterm Infants. Ped Inf Dis J., 2020; 39(1): 78-80.
14. Scheifele D, Ward B. Fever prophylaxis can reduce vaccine responses: A caution. Paediatr Child Health, 2018; 23(4): 245–246.
15. Kesavan AT, Nithya T, Gopinath T. Comparative Study of Intermittent Benzodiazepine Prophylaxis versus Paracetamol Alone for Preventing Recurrence of Febrile Seizures. Kerala Med J., Dec. 30, 2016; 9(4): 135–8.
16. Bouazza N, Cambonie G, Flamant C, Rideau A, Tauzin M, Patkai J, et al. Prophylactic Intravenous Acetaminophen in Extremely Premature Infants: Minimum Effective Dose Research by Bayesian Approach. Paediatr Drugs, 2024; 26(1): 83–93.
17. Silahli M, Gokmen Z, Tekin M. Prophylactic intravenous paracetamol use in extremely premature infants for patent ductus arteriosus. J Basic Clin Physiol Pharmacol, 2020; 32(5): 943-50.
18. Barbanti P, Allais G, Cevoli S, Guerzoni S, Valeriani M, Vernieri F. The Role of the Combination Paracetamol/Caffeine in Treatment of Acute Migraine Pain: A Narrative Review. Pain Ther., 2024; 13(3): 319–46.
19. Debortoli C, Lan R, Lafont J, Campana F, Catherine J-H. Paracetamol misusing to dental pain: a case-report and recommendations for treatment. J Oral Med Oral Surg, 2021; 27(10): 1-5.
20. Pergolizzi JV, van de Laar M, Langford R, Mellinghoff H-U, Merchante IM, Nalamachu S, et al. Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain. J Pain Res., 2012; 5(8): 327-46.
21. Bauer-Rusek S, Samra N, Moore SS, Arnon S. Paracetamol Treatment for Patent Ductus Arteriosus, an Apparent Association with Acute Hemolysis in Three Preterm Infants: Case Series. Neonatology, 2022; 119(4): 530-4.
22. Bardanzellu F, Neroni P, Dessì A, Fanos V. Paracetamol in Patent Ductus Arteriosus Treatment: Efficacious and Safe? Biomed Res Int., 2017; 1438038. doi: 10.1155.
23. Noureldein M, Hu K, Groucutt J, Heaver R, Gurusamy K. Paracetamol for patent ductus arteriosus in preterm infants: a UK national survey. 1. J Matern Fetal Neonatal Med., 2022; 35(7): 1408-11.
24. Marwah M, Mandrelle K, Liddle D. A randomized controlled trial of intravenous paracetamol and intravenous. Indian J Obste Gynecol Res., 2023; 10(3): 259-65.
25. Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillone G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. Eur J Cardiothorac Surg, 2007; 32(3): 527-31.
26. Sumphaongern T, Jansisyanont P. Single Dose Intravenous Paracetamol versus Placebo in Postorthognathic Surgery Pain: A Randomized Clinical Trial. Anesthesiol Res Pract, 2024; 2024: 8898553. doi: 10.1155.
27. Hein A, Norlander C, Blom L, Jakobsson J. Is pain prophylaxis in minor gynaecological surgery of clinical value? a double-blind placebo controlled study of paracetamol 1 g versus lornoxicam 8 mg given orally. Ambul Surg., 2001; 9(2): 91-4.

28. Zhang W, Jones A, M Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. Ann Rheum Dis., 2004; 63(8): 901-7.
29. Batlle-Gualda E, Ivorra JR, Martín-Mola E, Abelló JC, Ferrando LFL, Molina JT, et al. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. Osteoarthritis Cartilage, 2007; 15(8): 900-8.
30. Vyas FI, Rana DA, Patel PM, Patel VJ, and Bhavsar RH. Randomized comparative trial of efficacy of paracetamol, ibuprofen and paracetamol-ibuprofen combination for treatment of febrile children. Perspect Clin Res., 2014; 5(1): 25-31.
31. Schindler T, Smyth J, Bolisetty S, Michalowski J, Mallitt K-A, Singla A, et al. Early paracetamol (EPAR) Trial: A Randomized Controlled Trial of Early Paracetamol to Promote Closure of the Ductus Arteriosus in Preterm Infants. Neonatology, 2021; 118(3): 274-81.
32. Dani C, Lista G, Bianchi S, Mosca F, Schena F, Ramenghi L, et al. Intravenous paracetamol in comparison with ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a randomized controlled trial. Eur J Pediatr, 2021; 180(3): 807-16.
33. Dong H, Haining RL, Thummel KE, Rettie AE, Nelson SD. Involvement of human cytochrome P450 2D6 in the bioactivation of acetaminophen. Drug Metab Dispos, 2000; 28(12): 1397-400.
34. Mutlib AE, Goosen TC, Bauman JN, Williams JA, Kulkarni S, Kostrubsky S. Kinetics of acetaminophen glucuronidation by UDP-glucuronosyltransferases 1A1, 1A6, 1A9 and 2B15. Potential implications in acetaminophen-induced hepatotoxicity. Chem Res Toxicol, 2006; 19(5): 701-9.
35. Bakare-Odunola MT and Abubakar A. Comparison of paracetamol pharmacokinetics in Panadol® and Panadol extra®. Nig J Pharm Res., 2010; 5(1): 57-61.
36. Thejaswinijc JC, Thejaswini BM, Gurupadayya BM, Venkata SK. In vitro In vivo Drug Interaction Study of Paracetamol and Propranolol Hydrochloride. J Young Pharm., 2015; 7(4): 480-5.
37. Gastrup S, Stage TB, Palle Bach Fruekilde BN, Damkier P. Paracetamol decreases steady-state exposure to lamotrigine by induction of glucuronidation in healthy subjects. Br J Clin Pharmacol, 2016; 81(4): 735-41.
38. Garba M, Odunola MT, B H Ahmed BH. Effect of study protocol on the interactions between cimetidine and paracetamol in man. Eur J Drug Metab Pharmacokinet, 1999; 24(2): 159-62.
39. Cao L, Kwara A, Greenblatt DJ. Metabolic interactions between acetaminophen (paracetamol) and two flavonoids, luteolin and quercetin, through in-vitro inhibition studies. J Pharm Pharmacol, 2017; 69(12): 1762-72.
40. Mohamed N, Maideen P. Drug Interactions of Acetaminophen (Paracetamol) involving CYP and UGT Enzymes. Eur J Med., 2019; 7(1): 30-4.
41. Piotrowska N, Klukowska-Rötzler J, Lehmann B, Krummrey G, Haschke M, Aristomenis K Exadaktylos AK, et al. Presentations Related to Acute Paracetamol Intoxication in an Urban Emergency Department in Switzerland. Emerg Med Int., 2019; 2019: 3130843. doi: 10.1155.
42. Kane A, Mitchell SJ, Carroll PR, Matthews S, Hilmer SN. Characteristics of older and younger patients with suspected paracetamol toxicity. Australas J Ageing, 2012; 31(3): 190-3.
43. Published online 2020 Apr 27. doi: 10.4254/wjh.v12.i4.1Rotundo L, Pyrsopoulos N. Liver injury induced by paracetamol and challenges associated with intentional and unintentional use. World J Hepatol, 2020; 12(4): 125-36.
44. Chidiac AS, Buckley NA, Noghrehchi F, Cairns R. Paracetamol (acetaminophen) overdose and hepatotoxicity: mechanism, treatment, prevention measures, and estimates of burden of disease. Exp Opin Drug Metab Toxicol, 2023; 19(5): 297-317.
45. Li J, Chiew AL, Isbister GK, Duffull SB. Sulfate conjugation may be the key to hepatotoxicity in paracetamol overdose. Br J Clin Pharmacol, 2021; 87(5): 2392-6.
46. Koppen A, van Riel A, de Vries I, Meulenbelt J. Recommendations for the paracetamol treatment nomogram and side effects of N-acetylcysteine. Neth J Med., 2014; 72(5): 251-7.
47. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet, 1977; 2(8035): 432-4.
48. Dart RC. A 20-Hour Treatment for Acute Acetaminophen Overdose. N Engl J Med., 2003; 348: 2471-2.
49. Waring WS. Novel acetylcysteine regimens for treatment of paracetamol overdose. Ther Adv Drug Saf., 2012; 3(6): 305-15.
50. Bateman DN. Large paracetamol overdose - Higher dose acetylcysteine is required. Br J Clin Pharmacol, 2023; 89(1): 34-8.
51. Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev., 2018; 2018(2): CD003328. doi: 10.1002.