PARACETAMOL (ACETAMINOPHEN)

Indications

Paracetamol is recommended for the following conditions:

1) Fever: it is used as an antipyretic in adult and pediatric patients for the treatment of influenza syndromes, exanthematous diseases, acute respiratory tract infections, and more. In cases of influenza syndromes, paracetamol may be combined with sympathomimetics, salicylates, antihistamines, barbiturates, and caffeine.
2) Symptomatic pain relief: paracetamol is indicated for the symptomatic relief of mild to moderate pain associated with acute otitis media (AOM), headaches, neuralgia, dysmenorrhea, surgical procedures, knee and hip osteoarthritis (it is considered a first-line treatment for pain associated with knee and hip osteoarthritis, in accordance with the EULAR recommendations of 2003 and 2005). In analgesia, paracetamol may be combined with codeine and tramadol:
    - With codeine: recommended for the treatment of acute pain (postoperative pain, headache, migraine, acute musculoskeletal pain/lower back pain) and persistent chronic pain (osteoarthritic pain, chronic lower back pain, knee/hip osteoarthritis, rheumatoid arthritis, ankylosing spondylitis).
    - With tramadol: indicated for the symptomatic treatment of mild to moderate acute pain.

Dosage

Monotherapy

Analgesia

Oral, rectal administration.

Adults: 0.5-1 g every 4-6 hours; do not exceed a maximum daily dose of 4 g or 2.6 g for long-term therapies.

Children: 10-15 mg/kg/dose; do not exceed a total daily dosage of 90 mg/kg/day when administered in close succession (24, 48, and 72 hours) (Marchetti et al., 2004; AIFA, 2010).

Acute Otitis Media

Oral, rectal administration.

Children: 10-15 mg/kg/dose every 4-6 times/day.

Symptomatic Treatment of Pediatric Headache

Oral.

Children (<18 years): 15-20 mg/kg up to 3 times/day. paracetamol is the first-line therapeutic agent for the acute treatment of migraine attacks in children under 12 years of age.

Knee Osteoarthritis (Gonarthrosis)

Oral administration.

Adults: equal or less than 3 g/day, even for prolonged treatments. At this dosage, paracetamol can be administered in combination with other drugs with a good safety profile (EULAR Recommendations 2003) (Jordan et al., 2003).

Hip Osteoarthritis (Coxarthrosis)

Oral administration.

Adults: up to 4 g/day (American College of Rheumatology and EULAR 2005 guidelines) (Zhang et al., 2005). The Italian Consensus on EULAR 2005 Recommendations for hip osteoarthritis has set the maximum dose of paracetamol to be used as a first-line drug for pain treatment at 3 g/day, which can be administered for a long time (Punzi et al., 2006). To enhance analgesic action, paracetamol can be combined with codeine.

Combinations

Analgesic-Antipyretic Preparations

Paracetamol plus Acetylsalicylic Acid

Oral administration.

Adults: 125-400 mg/day (paracetamol) plus 200-800 mg/day (acetylsalicylic acid) divided into 1-4 administrations, taken with a full stomach.

Rectal administration.

Adults: 500-1000 mg/day (paracetamol) plus 700-1400 mg/day (acetylsalicylic acid) divided into 2-4 administrations.

Adolescents (12-16 years): 250-750 mg/day (paracetamol) plus 350-1050 mg/day (acetylsalicylic acid) divided into 1-3 administrations.

Paracetamol plus Acetylsalicylic Acid plus Ascorbic Acid

Oral administration.

Adults: 200-800 mg/day (paracetamol) plus 300-1200 mg/day (acetylsalicylic acid) plus 300-1200 mg/day (ascorbic acid) divided into 1-4 administrations, taken with a full stomach.

Paracetamol plus Acetylsalicylic Acid plus Caffeine

Oral administration.

Adults: 125-900 mg/day (paracetamol) plus 100-1500 mg/day (acetylsalicylic acid) plus 25-150 mg/day (caffeine) divided into 1-6 administrations, taken with a full stomach.

Adolescents (12-16 years): 62.5-375 mg/day (paracetamol) plus 125-750 mg/day (acetylsalicylic acid) plus 12.5-75 mg/day (caffeine) divided into multiple administrations, taken with a full stomach.

Paracetamol plus Caffeine

Oral administration.

Adults, children (age > 15 years): 1-3 g/day (paracetamol) plus 130-390 mg/day (caffeine) divided into 2-3 daily administrations. Do not exceed recommended doses.

Paracetamol plus Caffeine plus Chlorphenamine plus Isopropamide

Oral administration.

Adults: 1000 mg/day (paracetamol) plus 50 mg/day (caffeine) plus 16 mg/day (chlorphenamine maleate) plus 0.4 mg/day (isopropamide iodide) divided into 2 administrations, every 12 hours.

Paracetamol plus Caffeine plus Chlorphenamine plus Isopropamide plus Ascorbic Acid

Oral administration.

Adults: 1000 mg/day (paracetamol) plus 50 mg/day (caffeine) plus 16 mg/day (chlorphenamine maleate) plus 0.4 mg/day (isopropamide iodide) plus 1000 mg/day (ascorbic acid) divided into 2 administrations, every 12 hours.

Paracetamol plus Ascorbic Acid

Oral administration.

Adults: 330-3000 mg/day (paracetamol) plus 50-1200 mg/day (ascorbic acid) divided into multiple administrations.

Adolescents (13-15 years): 330-495 mg/day (paracetamol) plus 200-300 mg/day (ascorbic acid) divided into 1-3 administrations.

Children (7-13 years): 165-990 mg/day (paracetamol) plus 100-600 mg/day (ascorbic acid) divided into 1-3 administrations.

Paracetamol plus Ascorbic Acid plus Propyphenazone

Oral administration.

Adults: 900-1200 mg/day (paracetamol) plus 450-600 mg/day (ascorbic acid) plus 450-600 mg/day (propyphenazone) divided into multiple administrations.

Paracetamol plus Chlorphenamine

Oral administration.

Adults: 300-600 mg/day (paracetamol) plus 2-4 mg/day (chlorphenamine) divided into 1-2 administrations.

Children: 2.5-5 ml of solution (containing 2400 mg/100 ml paracetamol plus 15 mg/100 ml chlorphenamine) every 4-6 hours, depending on body weight.

Rectal administration.

Adults: 300-600 mg/day (paracetamol) plus 2-4 mg/day (chlorphenamine).

Children (over 5 years): 300 mg/day (paracetamol) plus 2 mg/day (chlorphenamine) divided into 2 administrations.

Children (3-5 years): 150-300 mg/day (paracetamol) plus 1-2 mg/day (chlorphenamine) divided into 1-2 administrations.

Paracetamol plus Chlorphenamine plus Caffeine.

Oral administration.

Adults: 400 mg (paracetamol) plus 2 mg (chlorphenamine maleate) plus 25 mg (caffeine) every 6 hours.

Paracetamol plus Chlorphenamine plus Sodium Ascorbate

Oral administration.

Adults: 600 mg/day (paracetamol) plus 4 mg/day (chlorphenamine maleate) plus 560 mg/day (sodium ascorbate) divided into two daily administrations, taken with a full stomach.

Paracetamol plus Ibuprofen

Oral administration.

Adults: 500-1000 mg (paracetamol) plus 150-300 mg (ibuprofen) every 6 hours. Maximum daily dose: 3000 mg (paracetamol) plus 900 mg (ibuprofen). The fixed combination of paracetamol and ibuprofen should be used at the lowest effective

dose and for the shortest possible time to relieve painful symptoms. The combination is not recommended in children and adolescents under 18 years of age.

Paracetamol plus Pseudoephedrine

Oral administration.

Adults: 300-1200 mg/day (paracetamol) plus 30-120 mg/day (pseudoephedrine) divided into 1-4 administrations with a full stomach. Do not exceed the recommended dose.

Paracetamol plus Diphenhydramine plus Pseudoephedrine

Oral administration.

Adults, children (age >12 years): 2000 mg/day (paracetamol) plus 180 mg/day (pseudoephedrine hydrochloride) plus 25 mg/day (diphenhydramine hydrochloride) as prescribed.

Paracetamol plus Propyphenazone

Oral administration.

Adults: 400-1200 mg/day (paracetamol) plus 572-1716 mg/day (propyphenazone) divided into 2-3 administrations.

Children: 200-600 mg/day (paracetamol) plus 286-858 mg/day (propyphenazone) divided into 2-3 administrations.

Paracetamol plus Propyphenazone plus Caffeine

Oral administration.

Adults: 250-1000 mg/day (paracetamol) plus 150-600 mg/day (propyphenazone) plus 25-100 mg/day (caffeine) divided into multiple administrations.

Paracetamol plus Propyphenazone plus Caffeine plus Thiamine

Oral administration.

Adults, adolescents (over 12 years): 610-930 mg/day (paracetamol) plus 300-450 mg/day (propyphenazone) plus 50-75 mg/day (caffeine) plus 30-45 mg/day (thiamine).

Paracetamol plus Propyphenazone plus Ascorbic Acid

Oral administration.

Adults: 300-1200 mg/day (paracetamol) plus 150-600 mg/day (propyphenazone) plus 150-600 mg/day (ascorbic acid) divided into 1-4 administrations for no more than 7 days.

Paracetamol plus Sobrerol

Oral administration.

Adults: 600-1200 mg/day (paracetamol) plus 300-600 mg/day (sobrerol). Or 4-6 teaspoons/day of syrup (containing 1280 mg/100 ml paracetamol plus 800 mg/100 ml sobrerol).

Children (less than 1 year): 45-60 drops/day of solution (containing 133 mg/ml paracetamol plus 83 mg/ml sobrerol) divided into 3-4 administrations.

Children (1-4 years): 45-120 drops of solution (containing 133 mg/ml paracetamol plus 83 mg/ml sobrerol) divided into 3-4 administrations.

Children (over 4 years): 90-180 drops of solution (containing 133 mg/ml paracetamol plus 83 mg/ml sobrerol) divided into 3-4 administrations.

Rectal administration.

Adults: 1000 mg/day (paracetamol) plus 400 mg/day (sobrerolo).

Children: 500 mg/day (paracetamol) plus 200 mg/day (sobrerol).

Paracetamol plus Dextromethorphan plus Doxylamine

Oral administration.

Adults, adolescents (over 12 years): 30 ml/day of solution (containing 2 g/100 ml paracetamol plus 0.05 g/100 ml dextromethorphan plus 0.025 g/100 ml doxylamine). Do not exceed 3 days of therapy; administer before bedtime and with a full stomach.

Paracetamol plus Pheniramine plus Phenylephrine

Oral administration.

Adults: 250-1250 mg/day (paracetamol) plus 20-120 mg/day (pheniramine) plus 10-60 mg/day (phenylephrine) divided into multiple administrations. Do not exceed the maximum daily dose.

Paracetamol plus Phenylephrine plus Ascorbic Acid

Oral administration.

Adults: 600-1800 mg/day (paracetamol) plus 10-30 mg/day (phenylephrine hydrochloride) plus 40-120 mg/day (ascorbic acid) divided into 2-3 daily administrations.

Paracetamol plus Ascorbic Acid plus Dimethofrine plus Caffeine plus Chlorpheniramine plus Isopropamide

Oral administration.

Adults, children (age >12 years): 125-375 mg (paracetamol) plus 30-90 mg (ascorbic acid) plus 25-75 mg (dimethofrine) plus 15-45 mg (caffeine) plus 2.5-7.5 mg (chlorpheniramine) plus 0.2-0.6 mg (isopropamide) to be divided into 2-3 administrations.

Paracetamol plus Codeine

Oral, rectal administration.

Adults: 500-3000 mg/day (paracetamol) plus 30-180 mg/day (codeine).

Children (age <18 years): 10-20 mg/kg/dose (paracetamol) plus 0.5-1 mg/kg/dose (codeine) (Marchetti et al., 2004).

Paracetamol plus Oxycodone

Oral administration.

Adults: 1300 mg/day (paracetamol) plus 20-80 mg/day (oxycodone) divided into 4 daily administrations, every 6 hours. Do not exceed a maximum dose of 4 g/day for paracetamol and 80 mg/day for oxycodone.

Paracetamol plus Tramadol

Oral administration.

Adults, children (age > 12 years): 650 mg/day (paracetamol) plus 75 mg/day (tramadol). Doses may be increased up to 2600 mg/day for paracetamol and up to 300 mg/day for tramadol. The interval between administrations should not be less than 6 hours.

Children (age ≤12 years): the combination of paracetamol and tramadol is not recommended.

Elderly patients: dosage adjustment is not required, but consider that in patients over 75 years of age, the elimination half-life of tramadol increases by 17%. Nephropathic patients (CrCl: 10-30 ml/min): increase the dosing interval to 12 hours. In patients undergoing dialysis, no additional post-dialysis dose is required. Nephropathic patients (CrCl <10 ml/min): The combination of paracetamol and tramadol is not recommended due to the presence of tramadol.

Hepatic patients (Child-Pugh class B, moderate liver failure): administer the combination of paracetamol plus tramadol with caution; consider extending the dosing interval.

Hepatic patients (Child-Pugh class C, severe liver failure): the pharmacological combination is not recommended due to the presence of paracetamol.

Sedative Cough Preparations

Paracetamol plus Promethazine plus Dextromethorphan

Oral administration.

Adults: 20 ml/day of syrup containing (2.5 g/100 ml paracetamol plus 100 mg/100 ml promethazine hydrochloride plus 75 mg/100 ml dextromethorphan hydrobromide) once a day, in the evening, with a full stomach. Do not exceed 3 days of treatment.

Children (12-16 years): 10 ml/day of syrup containing (2.5 g/100 ml paracetamol plus 100 mg/100 ml promethazine hydrochloride plus 75 mg/100 ml dextromethorphan hydrobromide) once a day, in the evening, with a full stomach. Do not exceed 3 days of treatment.

Decongestant Preparations

Paracetamol plus Tripolidine plus Pseudoephedrine

Oral administration.

Adults, adolescents (over 12 years): 600-900 mg/day (paracetamol) plus 5-7.5 mg/day (tripolidine) plus 120-180 mg/day (pseudoephedrine) divided into 2-3 administrations. Or 24-36 ml/day of syrup (containing 2.5 g/100 ml paracetamol plus 0.021 g/100 ml tripolidine plus 0.5 g/100 ml pseudoephedrine) divided into 2-3 administrations.

Children (6-12 years): 12-18 ml/day of syrup (containing 2.5 g/100 ml paracetamol plus 0.021 g/100 ml tripolidine plus 0.5 g/100 ml pseudoephedrine) divided into 2-3 administrations.

Antispasmodic Preparations

Paracetamol plus Butylscopolamine

Oral administration.

Adults: 500-3000 mg/day (paracetamol) plus 10-60 mg/day (butylscopolamine) divided into multiple daily administrations. Do not exceed the recommended maximum doses.

Rectal administration.

Adults: 800-3200 mg/day (paracetamol) plus 10-40 mg/day (butylscopolamine) divided into 1-4 daily administrations. Do not exceed the recommended maximum doses.

Contraindications

Paracetamol is contraindicated in the following cases:

1) Hypersensivity;
2) Severe hepatic insufficiency.

Warnings

Fever: the guidelines from the National Institute for Clinical Excellence (NICE) regarding the use of antipyretics in pediatric patients recommend against administering these drugs solelyfor the purpose of lowering fever in the absence of other symptoms. Antipyretics, including paracetamol, do not reduce the risk of febrile seizures and should only be given if the fever exceeds 38.5°C and/or is accompanied by other symptoms such as fatigue, discomfort, headache, or pain.

Medication-overuse headache (MOH)/Rebound headache: the excessive use of paracetamol for symptomatic treatment of headache may, in predisposed patients, lead to medication-overuse headache (MOH), also known as rebound headache. MOH appears to be limited to patients with preexisting headache disorders, particularly those with migraines or tension-type headaches. MOH may present with the same characteristics as the patient's preexisting headache (exacerbation of preexisting headache) or with different features; typically, it present bilaterally with throbbing or constrictive pain. MOH responds to discontinuation of the implicated drug: the headache completely resolves or returns to its original characteristics within two months following drug cessation. The underlying mechanism of MOH is not fully understood, but there is a suggested genetic predisposition because MOH has developed in migraine patients after treatment with analgesics for painful conditions unrelated to their headaches. Prolonged administration of analgesics may also induce alterations in the expression, sensitization, and activation of involved nerve receptors. In pediatric patients, the abuse of paracetamol (the drug of choice for treating mild to moderate migraine attacks in children under 12 years old) can lead to chronicization of headaches. Therefore, it is recommended to restrict its use to the acute phase while maintaining the recommended dosage range.

Hepatotoxicity: the minimum toxic single dose in healthy adults ranges from 7.5 to 10 grams and is equal to or greater than 150 mg/kg in children. Paracetamol can induce hepatotoxicity, especially when administered at high doses or with a dosing interval shorter than recommended (4-6 hours). Symptoms of hepatotoxicity include nausea, vomiting, sedation, sweating, abdominal pain, elevated transaminases, increased serum bilirubin concentration, and a prolonged prothrombin time exceeding 20 seconds. Subsequent stages may involve liver failure, encephalopathy, coma, and death. Liver failure may be complicated by acidosis, cerebral edema, bleeding, hypoglycemia, hypotension, infection, and renal failure. The risk of liver disease may increase in patients taking drugs that induce the oxidative metabolism of paracetamol; during fasting or low-protein diets (Whitcomb et al., 1994); and in the early days of alcohol cessation in chronic alcoholics (Gomez-Moreno et al., 2008). To reduce the risk of hepatotoxicity, the Food and Drug Administration (FDA) in the United States has recommended, since January 2014, avoiding the prescription of combination drugs containing paracetamol in doses exceeding 325 mg (Food and Drug Administration, 2014). In the United States, approximately half of the cases of paracetamol-induced liver failure are caused by accidental overdose of the drug. Severe cases of liver failure have occurred in patients who took more than the prescribed amount od paracetamol within 24 hours or who took multiple products

containing paracetamol simultaneously, or who consumed alcohol with paracetamol. In some cases, liver failure has required liver transplantation or resulted in the death of the patient (Food and Drug Administration, 2014).

Liver failure: paracetamol should be administered with caution in patients with mild to moderate liver failure due to an increased risk of drug-induced liver toxicity. In patients with severe liver failure, paracetamol is not recommended.

Severe skin reactions: paracetamol can rarely cause severe skin reactions (Halevi et al., 2000; Trujillo et al., 2010; Leger et al., 1998; Bygum et al., 2004). These reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and acute generalized exanthematous pustulosis, can be fatal. If skin reactions (redness, pustules, blisters, patches, etc.) occur while taking paracetamol-containing medications, paracetamol should be discontinued, and the dermatological reactions should be reported to a physician.

Alcoholism: the interaction between alcohol and paracetamol is complex. There may be an increased vulnerability to the toxic effects of paracetamol on the liver, especially when the drug is administered in the early days of alcohol cessation in chronic alcoholics. Therefore, it may be advisable for chronic alcoholics not to discontinue alcohol intake during paracetamol treatment (Gomez-Moreno et al., 2008). While chronic alcohol consumption does not necessarily increase iatrogenic hepatotoxicity when paracetamol is administered at recommended therapeutic doses (Prescott, 2000), the potential risk may increase due to additional predisposing factors such as preexisting liver dysfunction and/or depletion of glutathione reserves (through which the hepatotoxic metabolite of paracetamol, N-acetyl-p-benzoquinone imine, is eliminated).

Chronic malnutrition: patients with chronic malnutrition are at a higher risk of liver damage even with therapeutic doses of paracetamol due to reduced liver metabolic capacity.

Nephropathic/dehydrated patients: in pediatric patients with dehydration or renal failure, paracetamol is the preferred drug over ibuprofen (Jhon et al., 2007).

Chronic kidney disease: in patients with chronic kidney disease, there is no need to reduce the dosage of paracetamol (to diagnose early-stage chronic kidney disease, kidney damage must be present for three months or more, confirmed by pathological abnormalities or markers of kidney damage. In later stages of the disease, a reduction in estimated glomerular filtration rate, e-GFR, for three months or more is sufficient for diagnosis) (Dtb, 2006).

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency: the administration of paracetamol at therapeutic doses does not induce hemolysis in patients with glucose-6-phosphate dehydrogenase enzyme deficiency. G6PD is an enzyme necessary for blood stability, and its deficiency can expose red blood cells to oxidative damage and hemolysis (hemolytic anemia). The cause-and-effect relationship between paracetamol and hemolytic anemia has not been confirmed, and cases of hemolytic anemia reported in association with paracetamol are most likely due to overdose (Beutler, 1991; Bartsocas, 1982; Pootrakul et al., 1983; Cottava et al., 1990).

Cholestyramine: it is recommended to take cholestyramine at least one hour after the administration of paracetamol. Cholestyramine can reduce the absorption of orally administered paracetamol.

Chloramphenicol: reduce chloramphenicol doses when co-administered with paracetamol.

Warfarin: in patients receiving warfarin therapy, administration of paracetamol doses equal to or greater than 2 g/day for multiple days requires more frequent monitoring of the INR index than usual (due to the pharmacological interaction, INR index may increase, leading to an increased risk of bleeding).

Aspartame: the presence of aspartame among excipients is a contraindication for administering the medicinal product to patients with phenylketonuria.

Sucrose: administer acetaminphen-based syrup formulations with caution to diabetic patients, as they may contain sucrose.

Sodium Metabisulfite: some pharmaceutical formulations may include sodium metabisulfite among excipients. This substance can trigger allergic reactions, including severe bronchoconstriction, in suscettible individuals and asthmatic patients.

Pregnancy: clinical studies in humans have not shown teratogenic or fetotoxic effects. Based on limited studies, the use of paracetamol during pregnancy has been associated with a reduced risk of miscarriage and preterm birth. The FDA has classified paracetamol as class B for drug use during pregnancy (class B includes drugs for which reproductive studies in animals have not shown a risk to the fetus and there are no controlled studies in pregnant women, or drugs for which animal studies have shown adverse effects [in addition to decreased fertility] that have not been confirmed in controlled studies in the first trimester, and for which there is no evidence of harm in later stages of pregnancy).

Breastfeeding: paracetamol is excreted in breast milk in clinically insignificant quantities. Based on available literature data, the use of paracetamol during breastfeeding is not contraindicated.

Interactions

Alcohol: the interaction between alcohol and paracetamol depends on the type of alcohol intoxication, whether acute or chronic. In the case of acute intoxication, alcohol inhibits the oxidative metabolism of paracetamol and exerts a protective effect against hepatic damage. The protective effect diminishes with the elimination of alcohol from the body and tends to attenuate, the longer the time gap between alcohol and paracetamol intake (protection is maximal when alcohol and paracetamol are consumed simultaneously). Unlike what is observed in cases of acute intoxication, chronic alcohol consumption causes a modest (approximately 2-fold) and brief increase in the CYP2E1 isoenzyme (the cytochrome P450 isoenzyme primarily involved in the oxidative metabolism of paracetamol in cases of acute alcohol intoxication), suggesting that other cytochrome P450 enzymes may be involved in chronic intoxication conditions. Ethanol is also metabolized by the CYP2E1 enzyme and acts as an inducer of this enzyme. Chronic ethanol intake leads to an increase in the levels of this enzyme. Based on available literature data, chronic alcohol consumption dose not appear to expose individuals to greater hepatotoxicity from paracetamol, whether in cases of overdose or therapeutic use of the drug. However, chronic alcoholics may be more vulnerable to toxic hepatic effects from paracetamol in the early days of alcohol cessation when CYP2E1 levels are elevated due to pharmacometabolic induction by ethanol and there is no competition, as a substrate for the enzyme, between ethanol and paracetamol. Based on available data, the administration of paracetamol at the maximum therapeutic dose during this period also does not seem to result in adverse effects on liver function tests. Although the possibility that chronic alcohol consumption increases the risk of paracetamol-induced liver toxicity (likely due to insufficient glutathione availability) cannot be excluded, there is insufficient evidence to confirm greater toxicity of this pharmacological interaction in chronic alcoholics compared to non-users or those who occasionally consume modest amounts of alcohol (Prescott, 2000; Gomez-Moreno et al., 2008).

Laboratory test: paracetamol can interfere with uric acid testing (measured using the phosphotungstic acid method) and blood glucose testing (measured using the glucose oxidase-peroxidase method).

Oral anticoagulants: paracetamol can enhance their pharmacological action (Boeijinga et al., 1982).

Barbiturates: they increase the risk of paracetamol-induced hepatotoxicity (Pirotte, 1984).

Busulfan: paracetamol may inhibit its metabolism. Caution is advised within 72 hours of paracetamol administration.

Caffeine: based on laboratory in vitro data, caffeine appears to promote the formation of the hepatotoxic metabolite of paracetamol when both drugs are combined in high quantities. This interaction has been observed for caffeine doses

significantly higher than those normally consumed in the diet or in therapeutic combinations with paracetamol (Cameron et al., 2007).

Carbamazepine, cimetidine, phenobarbital, glutethimide, rifampicin: the co-administration with paracetamol requires caution because these drugs induce hepatic monooxygenases.

Chloramphenicol: paracetamol may reduce its pharmacological effect through

Cholestyramine: It can reduce the rate of paracetamol absorption.

Diazepam, ethinylestradiol: paracetamol may increase their toxicity (Mulley et al., 1978; Rogers et al., 1987).

Oral contraceptives: they may reduce paracetamol-induced analgesia due to increased metabolism of the latter (Miners et al., 1983).

Meperidine, propantheline, pentazocine: they may reduce the absorption of paracetamol.

Metoclopramide, domperidone: They may accelerate the absorption of paracetamol.

Probenecid: it may decrease clearance and increase the half-life of paracetamol (Kamali, 1993).

Propranolol: it appears to reduce the paracetamol clearance (through metabolic inhibition) (Baraka et al., 1989).

Sulfinpyrazone, tobacco: they may reduce the activity of paracetamol (Dordoni et al., 1973; Miners et al., 1984).

Tramadol: an additive analgesic effect has been observed when tramadol is used in combination with paracetamol compared to individual drug monotherapy (Filitz et al., 2008).

Warfarin: paracetamol may increase the anticoagulant activity of warfarin, especially with prolonged treatment, but the effect is not consistent. The mechanism of interaction is not known; it has been hypothesized that one of the paracetamol metabolites may inhibit the vitamin K epoxide reductase enzyme, responsible for the anticoagulant action of warfarin (Thijssen et al., 2004). The paracetamol-warfarin interaction exhibits high interindividual variability, and the same dose of paracetamol may significantly increase the INR index in one patient but not in another (possible genetic basis for response variability).

Zidovudine: granulocytopenia may occur when zidovudine is used in combination with paracetamol.

Side effects

In a study conducted by the Milan Poison Control Center (CAV), during the period of January-February 2007, it was revealed there were 203 consultations related to paracetamol exposure, either alone or in combination, (approximately 800 annually). Among these cases, 63% were reported in children under the age of 6, with approximately 89% attributed to accidental exposure. Within the group of children under 6, 46% of exposures resulted from therapeutic errors involving overdose. Consultations were primarly associated with paracetamol formulations, listed in descending order of occurrence: suppositories (53 total cases, 40 of which were due to overdose, with 38 occurring in children under 6), tablets/capsules/lozenges (62 cases), and syrup (33 cases). Adverse effects reported in the pediatric population included: hypotonia, hypo-reactivity, hepatic and renal damage (one report in a 4-year-old child who received paracetamol syrup at a dosage exceeding 150 mg/kg within 24 hours), hypothermia (a 3-year-old child treated with paracetamol suppositories at a dosage of 78 mg/kg in 24 hours plus ibuprofen), drowsiness, vomiting (exposure to paracetamol syrup at 42 mg/kg in a 5-year-old child and 154 mg/kg in a 2-year-old child), and cutaneous edema (an 8-year-old child treated with 500 mg paracetamol suppositories along with non-steroidal anti-inflammatory drugs) (BIF, 2007).

In the Italian National Pharmacovigilance Network, from January 2001 to March 2007, there were 29 reports of severe adverse reactions to paracetamol in pediatric patients (age <18 years), including 4 cases of Stevens-Johnson syndrome and 3 cases of Lyell's syndrome.

In the report of suspected adverse reactions in pediatric patients for the year 2008 in Italy, published by the Italian Medicines Agency (AIFA), paracetamol ranked 16th with 159 reports of adverse reactions. In the pediatric population specifically, paracetamol ranked 4th in the age group of 1-month to 2-year, with 12 reports, including 2 severe cases (amoxicillin/clavulanic acid combination ranked 1st with 23 reports); it ranked 6th in the age group of 2-11-year, with 12 reports, including 4 severe cases (amoxicillin/clavulanic acid combination ranked 1st with 52 reports); and it ranked 5th in the age group 12-17-year, with 9 reports, including 3 severe cases (amoxicillin/clavulanic acid combination ranked 1st with 26 reports) (BIF, 2009).

In the United States, each year, inappropriate use of paracetamol is responsible for 112,000 calls to poison control centers, 56,000 emergency room visits, 26,000 hospitalizations, and 450 overdose-related deaths (mostly due to accidental errors). According to the American Toxic Exposure Surveillance System, 23% of overdose cases in children under 6 years old are caused by administering adult dosages (Nourjah et al., 2006). The U.S. Food and Drug Administration (FDA) recommended starting in January 2014 to avoid prescribing combination drugs containing paracetamol in doses exceeding 325 mg as a precautionary measure to reduce accidental overdosage of the drug (Food and Drug Administration - FDA, 2014).

General: hypersensitivity reactions (cross-reactivity with salicylates), including urticaria, dyspnea, hypotension, angioedema, and skin eruptions.

Hypersensitivity reactions to paracetamol are generally rare and involve the skin and/or respiratory system, with less frequent occurrences of anaphylactic shock (Bousetta et al., 2005; Daghfous et al., 2005; Juliade et al:, 2000).

Genitourinary: papillary necrosis.

Hematological: thrombocytopenia, leukopenia, pancytopenia, neutropenia, agranulocytosis; (very rare) disseminated intravascular coagulation (DIC).

DIC is a systemic process that can lead to both thrombosis and bleeding and is characterized by uncontrolled thrombin production. In the Italian National Pharmacovigilance Network, for the year 2005, 3 cases of DIC during paracetamol treatment were reported (two in adult patients and one in a 19-month-old child). In the literature, cases of DIC are often related to hepatopathy resulting from paracetamol overdose, but there is no direct evidence of a correlation between paracetamol intake and the development of disseminated intravascular coagulation ("GIF Report 2005," 2006; Read et al., 1986; Thornton et al., 1990).

Liver/biliary: toxic hepatitis, particularly in cases of pre-existing liver dysfunction; (very rare) fulminant hepatitis.

Fulminant hepatitis has been reported in a child under 24 months of age treated for 4 days with 1 g/day of paracetamol (BIF, 2005). Malnutrition or fasting are predisposing factors for the development of paracetamol-induced hepatotoxicity, even at recommended dosages (up to 4 g/day in adults); hepatotoxicity has been found to be dose-dependent (a patient in a state of malnutrition exhibited liver toxicity after treatment with 4 g/day of paracetamol, but not after taking 2.6 g/day) (Kurtovic, Riordan, 2003).

Musculoskeletal: rhabdomyolysis**.**

Literature data on episodes of paracetamol-induced rhabdomyolysis are limited: two reports resulted from paracetamol use as an antipyretic at a dose of 1 g/day for 2 days followed by 4 g/day for another two days in combination with azithromycin (500 mg/day) in the first case, and after a 3-day therapy with dosages of 500 mg/day for two days and 2 g/day on the third day in the second case (Italian National Pharmacovigilance Network, 2008). Rhabdomyolysis due to hypersensitivity to paracetamol has also been reported in a 17-year-old patient treated with 400 mg orally, who had previously reported allergies to antibiotics and the same paracetamol (Moneret-Vautrin et al., 1999). Rhabdomyolysis has also occurred in cases of intentional toxic paracetamol ingestion (Nelson et al., 2007; Yang et al., 2001).

Skin: skin rashes; (very rare) Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), acute generalized exanthematous pustulosis.

Severe skin reactions associated with paracetamol use have been observed in both pediatric and adult patients. Based on literature data reported by the U.S. regulatory agency for drug use, the Food and Drug Administration (FDA), paracetamol, when

administered as a single drug, has been linked to 3 cases of Stevens-Johnson syndrome, 17 cases of toxic epidermal necrolysis, and 6 cases of acute generalized exanthematous pustulosis. None of these cases resulted in fatalities, but all required hospitalization and resolved upon discontinuation of paracetamol. An additional search using the FDA Adverse Event Reporting System (FAERS) for adverse drug events from 1969 to 2012 there were 91 reported cases of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with the use of paracetamol-containing drugs, with 16 cases of acute generalized exanthematous pustulosis, resulting in 67 hospitalizations and 12 deaths. In most cases, the involved drugs contained only paracetamol; a small portion of events occurred with injectable paracetamol or fixed-dose combinations of paracetamol and opioids. Of the 91 cases of Stevens-Johnson syndrome, 6 were classified as probably associated with paracetamol, and the rest as possibly associated. Among the 16 cases of acute generalized exanthematous pustulosis, 1 case was classified as probably associated with acetaminohen, and the others as possibly associated. Of the seven probable cases, 6 resulted in hospitalization and one in death. Cutaneous symptoms occurred within a range of 24 hours to eight days after the initiation of paracetamol therapy (Food and Drug Administration, 2013).

Toxicity

Overdose: paracetamol exhibits a very low therapeutic index (the ratio between LD50 and ED50), which means that even slightly higher doses than therapeutic levels can lead to drug overdose poisoning. Overdosing occurs in adult patients with doses of 7.5-10 g, resulting in necrosis of hepatic and renal cells, while doses of 25 g can be potentially lethal. In children, doses equal to or exceeding 150 mg/kg are considered potentially hepatotoxic.

To assess the risk of developing liver damage, the plasma concentration of paracetamol should be measured 4 hours after ingestion. Paracetamol concentrations exceeding 300 mg/ml after 4 hours of ingestion or exceeding 45 mg/ml after 15 hours result in liver injury in 90% of severe cases, while concentrations lower than 120 mg/ml after 4 hours or 30 mg/ml after 12 hours lead to moderate liver damage.

Symptoms appear within 24 hours of poisoning and include nausea, vomiting, sedation, sweating, and abdominal pain. The latter may indicate the onset of liver damage, which typically occurs within 24-48 hours of intoxication and peaks within 72-96 hours. Other signs of hepatotoxicity include elevated transaminase levels, serum bilirubin concentration, and a prothrombin time exceeding 20 seconds. Liver failure, encephalopathy, coma, and death may ensue. Liver failure can be complicated by acidosis, cerebral edema, hemorrhage, hypoglycemia, hypotension, infection, and renal failure.

The risk of hepatotoxicity is higher in patients with a history of alcoholism or those taking medications that inhibit paracetamol metabolism, during fasting or low-protein diets (Whitcomb et al., 1994), and in cases of vitamin E deficiency. Renal insufficiency generally accompanies hepatic dysfunction but can also occur independently. Overdosing may also lead to cardiac dysfunction and pancreatitis.

Liver damage due to overdose is caused by a highly reactive paracetamol metabolite, N-acetyl-p-benzoquinoneimine. At therapeutic doses, the metabolite formed by hepatic and renal oxidases is eliminated through conjugation with glutathione and excreted as a conjugate with mercaptopurine and cysteine. At doses higher than therapeutic levels, the metabolite surpasses the availability of glutathione, which is completely depleted in an attempt to eliminate benzochinoneimine. The excess metabolite accumulates in the body and binds to the sulfhydryl groups of hepatic cells, impairing their functionality.

Administering substances capable of restoring cellular glutathione stores, such as acetylcysteine and methionine, allows for the removal of excess metabolite and serves as effective antidotes in cases of paracetamol poisoning.

The treatment of overdose includes: 1) gastric lavage if paracetamol was ingested within the previous 4 hours; 2) administration of activated charcoal and colestyramine within 1 hour of antipyretic ingestion; 3) glucose infusions (for hypoglycemia control); 4) plasma transfusions or coagulation factor administration (for hypoprothrombinemia control); 5) parenteral fluid administration in case of vomiting; 6) administration of thiol compounds such as acetylcysteine and

methionine (antidotes). Antidote administration should continue if plasma paracetamol concentrations indicate a high risk of hepatotoxicity and should be discontinued if the risk is low.

In patients with a history of alcoholism or those taking pharmacometabolic inducers (carbamazepine, phenytoin, barbiturates), the antidote is also administered when the plasma concentration of paracetamol is at 50% of the reference level.

Acetylcysteine should be administered as soon as possible, within the first 8 hours of paracetamol ingestion. Acetylcysteine may cause skin rashes, angioedema, bronchospasm, and hypotension (Mant et al., 1984).

The dosage of acetylcysteine in adult patients is 150 mg/kg IV infusion over 15 minutes, followed by two infusions lasting 4 and 16 hours (50 mg/kg in 500 ml of glucose solution for the first infusion and 100 mg/kg in 1000 ml of glucose solution for the second). The total dose is 300 mg/kg over 20 hours. Alternatively, 140 mg/kg can be administered orally, followed by 17 doses of 710 mg/kg every 4 hours (total dose: 1330 mg/kg over 72 hours) (Meridith, Vale, 1986).

Methionine enhances hepatic glutathione synthesis and is more effective when administered orally rather than parenterally, although nausea and vomiting can reduce absorption and efficacy. The adult dosage is as follows: 2.5 g orally followed by three doses of 2.5 g every 4 hours (total dose: 10 g in 12 hours).

Reproductive Toxicity: paracetamol does not appear to possess teratogenic effects. Its administration during pregnancy has been associated with a reduced risk of miscarriage and preterm birth (small clinical studies). In a study evaluating prenatal paracetamol exposure, women exposed to the drug during the third month of pregnancy exhibited a preterm birth risk of 1.14 (95% CI 1.03-1.26), with this risk increasing in women with pre-eclampsia (HR 1.55, 95% CI 1.16-2.07) but not in those without pre-eclampsia (HR 1.08, 95% CI 0.97-1.20). Smoking and coffee consumption did not modify the effect of paracetamol. The study did not find any associations between paracetamol use and the risk of preterm complications, spontaneous abortions, stillbirths, low birth weight, or growth defects relative to gestational age (Rebordosa et al., 2009).

LD50: after oral administration: 338 mg/kg (mouse). After intraperitoneal administration: 500 mg/kg (mouse).

Pharmacology

Paracetamol (also known as acetaminophen) is a drug with analgesic and antipyretic properties; it lacks anti-inflammatory activity (selective inhibition of prostaglandin synthesis). Chemically, it is a para-aminophenol derivative.

Paracetamol has been used in medicine as an antipyretic since 1893.

It is administered orally or rectally to reduce pain and fever. It represents a valid alternative to salicylates or other NSAIDs when the latter are contraindicated, such as in cases of asthma, peptic ulcer, or patients under 12 years old (as salicylate administration in children under 12 salicylates can lead to Reye's syndrome).

The lack of anti-inflammatory activity at therapeutic doses is due to the selective inhibition of prostaglandin synthesis.

The analgesic action of paracetamol is attributed to: 1) inhibition of cyclooxygenase in peripheral nerve endings, blocking the onset of painful impulses; 2) reduction of neuronal interconnections of nociceptive stimuli, interfering with spinal cord-cortex transmission; 3) activation of descending serotoninergic pathways modulating primary nociceptive afferents. Paracetamol is effective as an analgesic in pain conditions without an inflammatory component, such as migraine, headache, dysmenorrhea, and osteoarticular pain. When administered parenterally, the drug is used for post-operative pain management and fever control in intensive care.

Low Back Pain

Paracetamol is frequently used in the treatment of acute low back pain, and some guidelines (European, USA) list it as a first-line therapy (Siot Guidelines, 2011; van Tulder et al., 2006; Chou et al., 2007). However, some literature data do not support the use of the paracetamol for acute back pain. Treatment guidelines for back pain, funded by the Ministry of Health and involving various Italian scientific societies, have classified paracetamol as an "intervention of undetermined utility" in the treatment of low back pain based on evidence of its effectiveness (Diagnostic-therapeutic pathways for patients with back pain, 2006). Using various databases (Medline, Embase, and CINAHL), some researchers selected randomized clinical trials comparing paracetamol to "no treatment," placebo, or "other treatment." The selection identified 7 clinical trials involving a total of 676 patients. The small-sized clinical trials (only one had more than 25 patients per group) and judged to have low methodological quality did not show statistically significant efficacy of paracetamol in the treatment of low back pain (Davies et al., 2008). A similar result was observed in a more recent, large-scale, randomized, double-blind, multicenter clinical trial that recruited over 1600 patients with acute low back pain, treated for up to 4 weeks with paracetamol three times a day (3990 mg/day), paracetamol “as needed” (maximum daily dose of 4 g), or placebo. The primary clinical outcome of the study was the time required for the recovery from lower back pain, defined as a reduction in pain score to 0 or 1 (on a 0-10 pain rating scale) maintained for one week. At the end of the study, no differences were observed among the three treatment groups in terms of

recovery time (17 days vs. 17 days vs. 16 days, respectively, for daily use of paracetamol, "as-needed" paracetamol, and placebo) and side effects (18.5% vs. 18.7% vs. 18.5%, respectively) (Williams et al., 2014). According to some researchers who participated in the trial, the lack of analgesic efficacy of acetaminphen in the treatment of low back pain may be due to the fact that back pain may follow different mechanisms than other painful conditions for which paracetamol has been effective as an analgesic, such as toothache and postoperative pain.

Osteoarthritis

Paracetamol is indicated for the analgesic treatment of osteoarthritis of the hip and knee joints and is recommended, along with nonsteroidal anti-inflammatory drugs (NSAIDs), by the EULAR 2003 and 2005 guidelines and the NICE guidelines updated in 2014 (Jordan et al., 2003; Zhang et al., 2005; NICE guidelines, 2014). However, a meta-analysis of data from 74 different clinical studies highlighted that paracetamol, at doses of 2 or 3 g/day, does not have superior analgesic effect to a placebo substance. In contrast, diclofenac, etoricoxib, or rofecoxib were found to be better than paracetamol in terms of pain relief (da Costa et al., 2016).

Paracetamol vs. Ibuprofen

Fever is an increase in body temperature caused by a rise in the reference value at the thermoregulatory hypothalamic center. It differs from hyperthermia because hyperthermia entails uncontrolled elevation of body temperature without altering the status of the hypothalamic thermoregulatory center. Hyperthermia results from excessive heat production and/or the body's inability to dissipate the generated heat. While hyperthermia can cause a significant and sudden increase in body temperature, fever appears to be physiologically regulated and generally does not exceed 41°C. Fever represents a homeostatic mechanism of the body in response to the immune response to pathogens.

Body temperature varies throughout the day with fluctuations of 0.5°C. Fever is defined as a temperature equal to or higher than 37.5°C when measured in the axilla, or higher than 38°C, exceeding the normal daily fluctuation for an individual.

In the treatment of febrile conditions in pediatric patients, paracetamol has shown similar efficacy to ibuprofen. In a systematic review that considered 11 clinical studies (total children: 1982), it was not possible to draw conclusions because the clinical trials were small and the drugs were administered at varynig dosages (Goldman et al., 2004). In a subsequent systematic review, only randomized double-blind controlled clinical trials were evaluated (out of the 10 studies considered, 8 were also part of the previous systematic review, involving a total of 1078 children). The meta-analysis showed that ibuprofen (5-10 mg/kg) was slightly more effective than paracetamol (10-15 mg/day) (one additional child out of every 7 treated with ibuprofen had reduced fever at 4 and 6 hours compared to paracetamol) (Perrot et al., 2004). It was observed that the administration of paracetamol at doses of 12.5-

15 mg/kg/dose induced a temperature reduction similar to that observed with ibuprofen at a dose of 7.5-10 mg/kg/dose (respectively -1.6°C vs. -1.8°C).

The combination of paracetamol with ibuprofen or the alternating use of the two drugs did not result in evident clinical benefits that wold justifying their routine use. In the case of combination therapy, even if one of the parameters examined in clinical studies - reduction in body temperature one hour after drug administration or reduction in the duration of the febrile period - was more favorable with the combination of paracetamol and ibuprofen compared to the drug monotherapy, this "advantage" did not translate into significant clinical benefit (Lal et al., 2000; Erlewyn-Lajeunesse et al., 2006; Hay et al., 2008).

In one of the two clinical studies that evaluated alternating use of paracetamol and ibuprofen, a reduction in body temperature of 1°C was reported in a greater number of pediatric patients over the three days of alternating treatment compared to individual drugs ($p<0.001$) (Sarrell et al., 2006). In the other study, the percentage of children with a normal body temperature after 6 hours (primary endpoint) was higher in the group treated with ibuprofen and paracetamol after 4 hours than in the group treated with ibuprofen and placebo after 4 hours (83.3% vs. 57.6%) (Nabulsi et al., 2006).

The combination of the two drugs, paracetamol and ibuprofen, has been shown to be more effective than individual drugs in the treatment of acute postoperative pain in adults and adolescents (dental surgery) (Atkinson et al., 2015; Derry et al., 2013; Sniezek et al., 2011; Mehlisch et al., 2010). In children undergoing tonsillectomy, the combination of the two drugs was not superior in terms of analgesia compared to the use of single drugs (Merry et al., 2013).

Paracetamol plus tramadol

The combination of paracetamol with tramadol has been found to have an additive analgesic effect. The therapeutic combination is equivalent to the paracetamol/hydrocodone combination in reducing dental extraction pain after 4 and 8 hours (650/75 mg of paracetamol/tramadol equivalent to 650/10 mg of paracetamol/hydrocodone) (Frickie et al., 2002). In the treatment of postoperative pain in abdominal and orthopedic surgery, the combination of paracetamol plus tramadol (average dose of 1300 mg/day of paracetamol plus 150 mg/day of tramadol for 6 days) is comparable to paracetamol plus codeine (average dose of 1290 mg/day of paracetamol plus 129 mg/day of codeine) (Smith et al., 2004).

The therapeutic combination of paracetamol/tramadol has shown effective analgesic effects, superior to placebo, in the treatment of chronic recurrent pain: moderate back pain, hip or knee osteoarthritis, rheumatoid arthritis treated with DMARDs, and pain inadequately controlled with NSAIDs (Ruoff et al., 2003; Peloso et al., 2004; Silverfield et al., 2002; Lee et al., 2006).

In the treatment of low back pain, the administration of paracetamol plus tramadol (average daily dose of 1462.5 mg/168.75 mg) did not show any differences compared to monotherapy with tramadol (average daily dose of 225 mg) in reducing

pain symptoms. After 10 days, more than 80% of patients in each treatment group achieved satisfactory pain control (Perrot et al., 2006).

Considering the tolerability profile of the paracetamol/tramadol combination, the most common adverse effects (incidence >/= 10%) were headache, dizziness, and drowsiness. In comparative studies, the combination with tramadol was associated with a lower incidence of constipation and vomiting compared to the combination of paracetamol with codeine but with a higher frequency of headaches. The administration of paracetamol/tramadol (325/37.5 mg) showed less impact on reaction times to visual stimuli and less drowsiness compared to the combination of paracetamol/codeine (500/30 mg) (drowsiness: 4% vs. 50%) (Pickering et al., 2005).

Paracetamol and asthma

Some epidemiological studies suggest an increased risk of asthma in pediatric and adult patients exposed to paracetamol, but this data requires further in-depth studies. Analysis of cross-sectional studies (13), cohort studies (4), and case-control studies (2), involving more than 425,000 patients, indicated an aggregated odds ratio (OR) for asthma of 1.63 (95% CI 1.46-1.77) in patients using paracetamol. The risk of asthma in children who had taken paracetamol in the year before asthma diagnosis and within the first year of life corresponded to OR value of 1.60 (95% CI: 1.48-1.74) and 1.47 (95% CI: 1.36-1.56), respectively. In one study, the odds ratio indicated a significant correlation between asthma and paracetamol (OR of 3.23, 95% CI: 2.9-3.6). The relative risk of asthma and wheezing in case of prenatal exposure to paracetamol was expressed as an OR of 1.28 (95% CI: 1.16-1.41) for asthma and 1.50 (95% CI: 1.10-2.05) for wheezing (Etminan et al., 2009).

Pharmacokinetics

After oral administration, paracetamol is rapidly absorbed in the gastrointestinal tract. Rectal absorption is approximately half of oral absorption.

Oral absorption is faster when the drug is administered in effervescent pharmaceutical forms: both the time to peak plasma concentration (27 vs. 45 minutes with effervescent and non-effervescent tablets, respectively) and the AUC 0-3 hours (223.8 vs. 198.2 micromoles•h/L) are higher, while the peak plasma concentration does not show significant differences (143 vs. 131 micromoles/L). Fifteen minutes after administration, 85% of patients who received paracetamol effervescent tablets had reached a plasma concentration equal to or greater than 70 micromoles/L (therapeutic range: 70-230 micromoles/L), compared to 10% of those who took non-effervescent tablets. After 30 minutes, the percentages in the two patient groups were 95% and 45%, respectively (Rygnestad et al., 2000).

Paracetamol undergoes first-pass hepatic metabolism.

Oral bioavailability: 70% and 90% after administration of 0.5 and 1-2 g, respectively.

Time to peak plasma concentration: 30-60 minutes.

Serum protein binding: proportional to drug plasma level. For values less than 60 mg/L, paracetamol does not appear to bind to plasma proteins; for toxic concentrations (up to 280 mg/L), serum protein binding is 20-50%. 10-20% of circulating paracetamol binds to red blood cells.

Apparent volume of distribution: 0.9 L/kg.

Paracetamol is widely distributed in the body's tissues, it permeates the placenta, and is secreted in breast milk.

It is metabolized in the liver and conjugated with glucuronic acid, sulfate, and cysteine. In cases of overdose, the proportion of the drug excreted as glucuronide increases (60-75% vs. 55%). About 10% is converted to N-acetyl-benzoquinoneimine by cytochrome P450-dependent hepatic oxidases; this metabolite is inactivated by glutathione and excreted in the urine as cysteine and mercapturic acid. In cases of high doses (greater than 150 mg/kg in a single administration or greter than 90 mg/kg in 24 hours for repeated administrations), the detoxification system becomes saturated, leading to increased levels of the metabolite, which, free, covalently bind to hepatocyte proteins, causing necrosis. Acute liver failure can result in pericarditis, subendocardial hemorrhages, and myocardial necrosis. Kidney damage can also occur.

Distribution half-life: 15 minutes (oral administration); 3-19 minutes (intravenous administration).

Elimination half-life: 1-3 hours; it increases in neonates, in case of overdose, and in cases of hepatic and renal insufficiency.

paracetamol is excreted in urine as either unchanged drug (less than 5% of the dose) or conjugated with glucuronic acid (60% of the dose), sulfate (35% of the dose), and cysteine (3% of the dose). Small amounts of hydroxylated and deacetylated derivatives have also been identified.

In case of renal insufficiency or dialysis, the plasma concentration of paracetamol and its conjugated derivatives increases (Prescott et al., 1989; Martin et al., 1993).

Classification

Chemical formula

$C_8H_9NO_2$

Molecular weight

151.17

Atc code

A03DB04

N02BE01

R01BA

R05DA20

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