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Review: Clinical pharmacology, therapeutic applications and clinical presentation of paracetamol and ibuprofen

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Abstract

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) represent one of the main therapeutic classes of molecules contaminating the environment. The main objective of this review was to seek information about ibuprofen and paracetamol when used as an antipyretic and analgesia in humans. NSAIDs inhibit the synthesis and the release of prostaglandins from arachidonic acid, acting as non-selective inhibitors of cyclooxygenase enzymes, namely cyclooxygenase-1 and cyclooxygenase-2 isoforms. The therapeutic dose of paracetamol is 0.5-1 g in adults (maximum of 4 g/day) and 10-15 mg/kg every 4-6 hours in children. It is indicated for the symptomatic relief of fever, mild musculoskeletal pain, headache, migraine. The usual dose of ibuprofen is 400 to 800 mg three times a day. Ibuprofen is one of the most effective and widely used NSAIDs in the treatment of dental pain. Acute toxicity of NSAIDs occurs only at high, unrealistic concentrations, while sub-lethal effects arise also at low, environmentally relevant concentrations of all these drugs. Main outcome measures: adverse events requiring drug discontinuation; systemic reactions related to ibuprofen and paracetamol, clinical pharmacology with therapeutic applications, and analgesic effects of combinations with anti-inflammatory drugs and caffeine in non-cancer pain. Ibuprofen, paracetamol has gastrointestinal pharmacological profiles of renal symptoms, asthma, and adverse effects.

Keywords: Paracetamol, Ibuprofen, Pharmacology, drugs, therapeutic.

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1. Introduction

Paracetamol (acetaminophen) is a safe, effective, well-tolerated, and cheap analgesic and antipyretic drug with relatively few adverse effects when used at the recommended therapeutic dosage. It was first introduced in the year 1955 for its clinical application and since then, it is widely used almost throughout the world. In many countries, the drug is readily available over-the-counter without the need for a prescription. It's easy availability and no need for a prescription made it one of the commonest drugs used for suicidal or self-harm purposes. Its toxicity was noticed in the 1960s [1]. Since then the number of cases coming to the emergency department kept on increasing, especially in UK. It is also a frequent cause of poisoning in many other countries, including North America, Australia, and New Zealand and several other countries in Europe [2]. An increasing number of the cases brought the idea of legalization of the drug from over the counter policy to prescription-only status. Following legislation in 1998 to limit pack sizes, beneficial effects on paracetamol- related mortality and morbidity were reported in England. Although following legislations to limit pack sizes, morbidity, and mortality are reduced, however, strict measures are required to reduce breaches of sales guidelines [3]. The role of media and the internet should be more emphasized in awareness about hepatic failure due to paracetamol toxicity.
Ibuprofen is (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid. Ibuprofen was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. Gastric discomfort, nausea, and vomiting, though less than aspirin or indomethacin, are still the most common side effects[3]. Ibuprofen is the most commonly used and most frequently prescribed NSAID [4]. It is a non-selective inhibitor of cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclo-oxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever [5]. With this background we review the clinical features, pharmacology, management and preventive measures to reduce the load to intentional toxicity.

2. Clinical pharmacology

Paracetamol has excellent anti-pyretic activity, moderate analgesic, and almost no anti-inflammatory property. It acts by inhibiting prostaglandin synthesis by its action on a cyclo-oxygenase-3 enzyme, (an alternate splice product of cox-1 enzyme) [6]. The therapeutic dose of paracetamol is 0.5-1 g in adult (maximum of 4 g/day) and 10-15 mg/kg every 4-6 hours in children [7]. It is indicated for the symptomatic relief of fever, mild musculoskeletal pain, headache, migraine. The most common route of administration is the oral route (in the form of tablets, effervescent tablets & suspension); other routes are the rectal route as a suppository and in hospital settings, it can be given via intravenous infusion.

Following an oral dose, the drug is well absorbed from the gastrointestinal tract, reaching a peak plasma concentration within 30-60 minutes. The drug is metabolized in the liver, 80% of an administered dose (therapeutic dose), undergoes glucuronide conjugation and sulfate conjugation; the remaining drug undergoes hydroxylation to form a highly reactive oxidative product, N-Acetyl P Benzo-quinine (NAPQI), which in turn conjugates with glutathione, GSH to form mercapturic acid and is eliminated in urine [8]. Hepatic toxicity generally occurs when the glutathione stores fall to less than 30% of the normal [9]. The supply of hepatic GSH is limited and in case of an overdose of paracetamol, the amount of NAPQI formed is greater than the GSH available such that NAPQI is not conjugated and being an active product, it exerts hepato-toxic effects and causes renal tubular necrosis by reacting with the nucleophilic aspects of the cells. Paracetamol in the dose of 10-15 g can potentially lead to fatal hepatic-toxicity [10]. Severe hepatocellular damage and renal tubular necrosis can result from taking 150 mg/kg in a single dose [11]. The risk of hepatic cellular injury is increased by any condition that leads to an increase in the production of NAPQI (patients on some drugs like Rifampicin, Phenobarbitone, Phenytoin, Carbamazepine, etc.) or conditions with low GSH reserves such as fasting, malnutrition, alcoholic related or other types of liver diseases, HIV positive patients, cystic fibrosis and genetic variation. Ibuprofen is supplied as tablets with a potency of 200 to 800 mg. The usual dose is 400 to 800 mg three times a day [12]. It is almost insoluble in water having pKa of 5.3 [13]. It is well absorbed orally, peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half-life of 1.8 to 2 hours. The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism. The drug is more than 99% protein bound; extensively metabolized in the liver and little is excreted unchanged [14]. Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti-cogulants and oral hypoglycemic needs not be altered. More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds [15]. Old age has no significant effects on the elimination of ibuprofen. Renal impairment also has no effect on the kinetics of the drugs, rapid elimination still occur because of metabolism [16]. The administration of ibuprofen tablets either under fasting conditions or immediately before meals yield quiet similar serum concentrations-time profile. When it is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption [17].

3. Therapeutic Applications

Low dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over the counter medications [18]. It is widely used as an analgesic, an anti-inflammatory and an antipyretic agent. Racemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to

moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis, and soft tissue disorder. A number of other actions of NSAIDs can also be attributed to the inhibition of prostaglandins (PGs) or thromboxane synthesis, including alteration in platelet function (PGI2 and Thromboxane), prolongation of gestation and labor (PGE2, PGF2A), gastrointestinal mucosal damage (PGI2 and PGE2), fluid and electrolyte imbalance (renal PGs), premature closure of ductus arteriosus (PGE2) and bronchial asthma (PGs) [19].

The main therapeutic applications of ibuprofen are as follows:

3.1. Patent Ductus arterosus (PDA)

This is a frequent complication in premature infants. So far, intravenous indomethacin is the standard mode of medical therapy. However, because of the adverse effects of indomethacin, other PG inhibitors such as ibuprofen have been studied for the closure of ductus arteriosus, and results indicated that ibuprofen is as effective as indomethacin [20].

3.2. Rheumatoid and osteo-arthritis (RA and OA)

Ibuprofen is widely used in the management of numerous inflammatory, musculoskeletal, and rheumatic disorders because they are highly effective having minimal toxicities [21]. Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours. In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms of anti-inflammatory effects [22]. Higher doses, 1200 to 1600 mg per day have been compared with a number of NSAIDs and it has been found to be as effective and well tolerated. Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen. For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen are equally effective [23]. Roughly, 1% of rheumatoid arthritis (RA) patients receiving NSAIDs are prone to develop major GI bleeds. With ibuprofen, gastric toxicity has been observed in 10 - 32% of patients [24].

3.3. Cystic fibrosis (CF)

High dose ibuprofen therapy has also been shown to be effective in decreasing inflammation, probably by decreasing polymorphonuclear cell influx into the lungs. The risk of developing GI side effects from high dose ibuprofen therapy is low in patients with CF [25].

3.4. Orthostatic hypotension

Ibuprofen is useful in the treatment of severe orthostatic hypotension as with other NSAIDs [26]. Toxic effects are unlikely at doses below 100 mg/kg but can be life-threatening or severe above 400 mg/kg. However, large doses do not indicate that the clinical course is likely to be lethal [27].

3.5. Dental pain

Ibuprofen is one of the most effective and widely used NSAIDs in the treatment of dental pain. Dental practitioners have relied on ibuprofen and other NSAIDs to manage acute and chronic orofacial pain [28]. A dose of 400 mg of ibuprofen provides an effective analgesic for the control of postoperative pain after third molar surgery [29]. A liquid gel preparation of ibuprofen 400mg provides faster relief and superior overall efficacy in post- surgical dental pain.

3.6. Dysmenorrhea, fever and headache

Non-prescription ibuprofen is useful for managing minor aches and pains, reducing fever, and relieving symptoms of dysmenorrhea. Dysmenorrhea is the most common menstrual complain [30]. Ibuprofen was superior to placebo for pain relief and menstrual fluid PGF2 alpha suppression. Cyclooxygenase inhibitors reduce the amount of menstrual prostanoids release, with a concomitant reduction in uterine hyper contractility [31]. Over-the-counter (OTC) ibuprofen preparations are mainly used for acute indications, such as fever or headaches, especially tension type headache [32]. It has been reported that the combined use of paracetamol and ibuprofen reduce fever very rapidly [33]. Fever almost invariably accompanies uncomplicated falciparum malaria. In a randomized double-‘blind’ study, a single dose of ibuprofen was compared with paracetamol for the treatment of fever >38·5 °C due to uncomplicated falciparum malaria. Ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4-5 hrs after dosing and thus should be considered as an antipyretic agent in the management of uncomplicated falciparum infections, providing there is no contraindication to its use [34]. Evers et al. in 2006, conducted a double blind study to investigate the efficacy of zolmitriptan and ibuprofen in the treatment of migraine in children and adolescents. Pain relief rates after two hours were 28% for placebo, 62% for zolmitriptan, and 69% for ibuprofen [35].

3.7. Prophylaxis of Alzheimer disease

The administration of NSAIDs, particularly ibuprofen markedly reduced neurodegeneration [36]. In some studies, ibuprofen showed superior results compared to placebo in the prophylaxis of Alzheimer’s disease, when given in low doses over a long time.

3.8. Parkinson’s disease (PD)

Inflammation and oxidative stress have been implicated as pathogenic mechanisms in PD. Epidemiologic evidence showed that regular use of NSAIDs, particularly non-aspirin COX inhibitors such as ibuprofen lower the risk of PD. It induced apoptosis significantly in early and late stages, suggesting that these anti-inflammatory agents might inhibit microbial proliferation [37].

3.9. Breast cancer

Harris et al. in 1999 conducted a study for the utilization of NSAIDs in breast cancer. The breast cancer rate was decreased by approximately 50% with regular ibuprofen intake and 40% with regular aspirin intake. Results suggested that specific NSAIDs may be effective chemo-preventive agents against breast cancer [38].

3.10. Acute pain

The results of some recent reviews and meta-analyses of the analgesic activity of paracetamol. Single doses of paracetamol show analgesic activity in a variety of acute pain syndromes; however, a common finding is that paracetamol is somewhat less effective than NSAIDs. Furthermore, paracetamol has, like the NSAIDs and selective COX-2 inhibitors, better analgesic activity in acute post-surgical pain than in the long-term pain of osteoarthritis. However, paracetamol is used extensively and increasingly given intravenously postoperatively as part of multi-modal analgesia regimens [38].

3.11. Treatment of chronic pain, low back pain, osteoarthritis

Chronic pain is a major and common problem with significant associated disability and health care burden. Paracetamol provides pain relief in chronic osteoarthritic pain although the effect size is small. As in the treatment of acute pain, the NSAIDs provide better pain relief but the effect size of NSAIDs is still small. Like NSAIDs, paracetamol may decrease the synovitis of osteoarthritis, although, as determined by serial X-rays, treatment with paracetamol still resulted in a slight deterioration of knee osteoarthritic manifestations in many patients after treatment for 2 years [39].

There are, however, some important limitations in many clinical trials. The short duration, often only up to 6 weeks, is a clear limitation for a drug that may be used for very long periods but continued clinical trial of an inactive placebo is unethical. Despite its lower efficacy than NSAIDs, paracetamol is widely recommended as the preferred initial analgesic in osteoarthritis and low back pain because of its superior tolerance [40]. In terms of cost-benefit, paracetamol is favored over both the non-selective NSAIDs and the selective COX-2 inhibitors even when these drugs are used with proton pump inhibitors to reduce their adverse gastrointestinal effects. This is because the better control of the symptoms by both classes of NSAIDs is outweighed by the cost of treatment of their adverse effects [41]. The NSAIDs are of course considered if the response to paracetamol is inadequate.

3.12. Cancer pain

Paracetamol is widely administered with opioids for the treatment of pain due to cancer. It is listed as an essential drug for hospice use [42]. The WHO Pain Relief Ladder lists prompt oral administration of drugs in the following order: non-opioids such as NSAIDs or paracetamol; then combination products

for moderate pain containing opioids such as codeine, hydrocodone or oxycodone; then, as necessary, strong opioids such as morphine or transdermal fentanyl, as necessary until the patient is pain-free. This three-step approach is inexpensive and stated to be 70–90 % effective. In Europe and Australia, paracetamol is routinely prescribed at step 1 and continued at steps 2 and 3, whereas in North America paracetamol is often confined to steps 1 and 2. Patients with severe cancer pain should be treated immediately with opioids. A variety of other drugs and treatments, including corticosteroids, anti-depressants, the epidural dosage of analgesics, and neurological techniques may be useful depending upon cancer and its treatment [43].

4. Analgesic effects of combinations with NSAIDs, opioids and caffeine in non-cancer pain

4.1. Paracetamol plus NSAIDs

Generally, the combination of NSAIDs and paracetamol provides greater analgesia than paracetamol alone for acute pain after orthopedic, gynecological, and dental surgery. The contrast between the combination and NSAIDs alone is less clear although 64 %of studies show that the combination has greater acute analgesic activity than NSAIDs alone. More recently, greater activity has been noted for combinations of paracetamol (1,000 mg) and ibuprofen (400 mg) than that produced by combinations of paracetamol (1,000 mg) or ibuprofen (400 mg) with codeine 30 mg [44]. In experimental animals, the combination of paracetamol and an NSAID produces synergistic effects (Miranda et al. 2006, 2008) or additive actions in tests of anti-nociceptive activity. There have been few studies on the efficacy of the combination of paracetamol and an NSAID in the treatment of osteoarthritis. However, a recent large-scale trial showed that the combination of paracetamol (3 g daily) and ibuprofen (1.2 g daily) generally produced a slightly greater effect than the same dose of paracetamol alone, but there was no significant contrast with ibuprofen alone [45].

Although paracetamol does not suppress the inflammation of rheumatoid arthritis, combinations with NSAIDs show greater analgesic and anti-rheumatic activity than the NSAIDs alone [46]. The combination of indomethacin and paracetamol is of particular note as indomethacin (50 mg daily) and paracetamol (4 g daily) have very similar efficacy to a much larger dose of indomethacin (150 mg daily) alone. Further clinical trials of this type (i.e. a small dose of a NSAID and a full dose of paracetamol versus a larger dose of an NSAID alone) should be conducted. Alternating dosage of paracetamol and ibuprofen has been used as an antipyretic treatment in children but is only used if the child does not respond to one drug alone [47].

4.2. Paracetamol plus opioids

The addition of paracetamol to opioids can increase efficacy and provide an ‘opioid-sparing’ effect. Thus, intravenous paracetamol often lowers the required opioid dosage in acute pain but the adverse

effects of opioid treatment may not be decreased [48]. Systematic reviews examining paracetamol combined with various opioids for acute postoperative pain have shown increased efficacy when combined with codeine and oxycodone.

Combinations of paracetamol and codeine are used widely but the use of codeine in these preparations has received particular criticism. Codeine is a prodrug, its metabolism to morphine being responsible for its analgesic efficacy. Ultrafast metabolism to morphine by some patients may lead to greater relief of pain but an increased likelihood of adverse effects. Conversely, codeine is not converted to morphine in about 8 % of patients with a variant cytochrome P450 2D6, the result being a greatly reduced effect [48].

4.3. Paracetamol plus caffeine

The clinical analgesic activity of single doses of paracetamol is increased to a small, but statistically significant extent, by caffeine [49]. The mechanism may be the increased rate of absorption of paracetamol after dosage with caffeine. Conflicting interactions between caffeine have been reported in the mouse with caffeine both producing both lesser analgesia and a greater depression of the synthesis of nitric oxide ($NO^{\cdot}$) in the spinal cord [50]. One group has reported that PG synthesis is inhibited by caffeine alone (Fiebich et al. 2000) but confirmation of this observation is required. In recent years, a considerable number of papers have claimed that caffeine potentiates the hepatotoxicity of paracetamol.

4.4. Ibuprofen-Drug Interactions

Ibuprofen has established drug interactions with NSAIDs which are both pharmacokinetic or pharmacodynamics in origin [51]. The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, oral hypoglycemics, high dose methotrexate, antihypertensives, and angiotensin converting enzyme inhibitors, ß-blockers, and diuretics. Anticipation and care full monitoring can often prevent serious events when these drugs are used concomitantly [52]. Many overdose experiences have been reported in medical literature. The maximum daily dose for ibuprofen is 3200 mg. Ibuprofen may cause serious toxicity when overdosed, mainly in children on ingestion of 400 mg/kg or more. The symptoms of high doses include seizures, apnea, and hypertension, as well as renal and hepatic dysfunction. Ibuprofen has been implicated in elevating the risks of myocardial infarction, particularly among those chronically using high doses [53]. Desmopressin and NSAIDs should not be used in combination in patients with bleeding disorders. Coadministration of thiopurines and various NSAIDs (ketoprofen and ibuprofen) may lead to drug Interactions [54]. It has been observed that caffeine improves the antinociceptive efficacy of some non-steroidal anti-inflammatory drugs (NSAIDs) in several experimental models; however, these effects have been questioned in humans. Caffeine is able to potentiate the antinociceptive effect of ibuprofen. This effect was greater than the maximum produced by morphine in the experimental conditions. Caffeine also enhances the effectiveness of most analgesics,

including ibuprofen. A comparison of the cumulative response scores revealed a trend toward a greater response to ibuprofen-caffeine treatment of headaches [55].

4.5. Food-Drug Interaction

The absorption of ibuprofen and oxycodone, when given as a combination tablet, was affected by the concomitant ingestion of food. Food intake before the administration of a single dose of the combination did not affect ibuprofen absorption but marginally increased the extent, but not the rate, of oxycodone absorption [56]. The effect of food on the plasma concentration-time profile of sustained release dosage forms of ibuprofen has been investigated after an overnight fast or along with a heavy vegetarian breakfast. The formulation exhibited multiple peaks on the plasma concentration-time curve. Although the food did not affect the bioavailability of ibuprofen, there was a statistically significant increase in the mean concentration. Results indicated that while qualitative changes in the plasma concentration versus time curves are primarily influenced by the nature of the formulation and the type of meal, bioavailability is influenced by the absorption characteristics of the drug as well [57].

5. Warnings

The use of OTC products containing aspirin, acetaminophens, ibuprofen, naproxen, or ketoprofen may increase the risk of hepatotoxicity and gastrointestinal hemorrhage in individuals who consume three or more alcoholic drinks daily [58].

Tamburini et al. have reported an atypical presentation of meningitis due to Neisseria meningitides in a patient who received large doses of ibuprofen. Anti-inflammatory therapy such as NSAIDs could reduce CSF inflammation and modify the clinical outcome in patients with bacterial meningitis. However, the use of NSAIDs is not recommended in bacterial meningitis due to a lack of studies [59].

Ibuprofen may exacerbate severe asthma. With this perception, ibuprofen was administered for postoperative pain management to a 17-year-old boy with allergic rhinitis and previous severe asthma (at a time when well controlled), who then had a severe asthma exacerbation. In addition, it has been reported that gastrointestinal tract anatomical abnormalities or dysmotility may be contraindications for therapy with high-dose ibuprofen in patients with cystic fibrosis [60].

Various studies in human and animal models have shown that paracetamol overdose may lead to renal dysfunction [61]. Overall, renal insufficiency occurs in approximately 1-2% of patients with paracetamol overdose[16]. Effects on the kidney are seen more in children and adolescents as compared to adults. The mechanism of paracetamol toxicity is not well understood in the kidney. Possible mechanisms, based on human and animal data, show the role of cytochrome P-450 pathway, as well as prostaglandin synthetize, and Deacetylate enzymes. The renal damage is usually in the form of acute tubular necrosis both clinically and histologically. Light microscopy shows normal glomeruli and vessels with tubular

epithelial cell necrosis [62]. Tubular swelling with loss of the tubular brush border and distortion of the mitochondrial organization are often seen on electron microscopy.

6. Clinical Presentation of Paracetamol

The clinical signs usually do not become apparent for the first 24-48 hours after an acute overdose of paracetamol. Liver failure may occur between 2-7 days following the ingestion. The clinical course of paracetamol toxicity is generally divided into 4 phases [63].

6.1. Phase 1 (0-24 hrs)

The patient is usually asymptomatic or may present with features like anorexia, nausea, vomiting, and malaise. The Liver Function Tests show a mild increase in the serum transaminase level (begins to rise approximately 12 hours after acute ingestion).

6.2. Phase 2 (18-72 hrs)

The patient usually experiences nausea, vomiting, abdominal pain (right upper quadrant). On examination, tenderness is present on the right upper quadrant; tachycardia and hypotension are usually present. The serum transaminase level continues to rise.

6.3. Phase 3 (72-96 hrs) Hapatic phase

This is the most critical phase. The patient is severely ill. Jaundice, coagulopathy with bleeding tendencies, hypoglycemia, hepatic flap, and hepatic encephalopathy occur because of hepatic necrosis and dysfunction. Metabolic acidosis with acute renal failure (due to hepatorenal syndrome) may develop. Death usually occurs because of multi-organ failure.

6.4. Phase 4 (4 days-3 weeks) Recovery phase

Patients who survive the critical illness of phase 3, are more likely to improve with resolution of the symptoms and organ failure.

6.5. Investigation of Paracetamol

The investigations include the timed serum paracetamol concentration, liver function tests (including prothrombin time or international normalized ratio), and kidney function tests. These tests are needed to assess risk and monitor progress. The plasma concentration of paracetamol has predictive value, if it lies above a semi-logarithmic graph which is obtained by joining the points between 1.32 mmol/L at 4 hours after ingestion to 0.33 mmol/L at 12 hours, then the prognosis is poor and serious hepatic damage is likely to occur [64].

7. Treatment of Paracetamol

The aim of the management of paracetamol toxicity focuses on the prevention of hepatotoxicity by an appropriate line of treatment which is achieved by limiting the absorption of the drug and by decreasing the toxic impact of NAPQI through replenishment of glutathione store. The general principle for limiting the drug absorption applies only if the patient is seen within the first hour of the acute ingestion of paracetamol. Gastric lavage with small amounts of tap water at ambient temperature followed by drinking the activated charcoal solution immediately after the removal of the tube decreases the absorption of paracetamol by 50-90%. The combination treatment comprising gastric lavage followed by activated charcoal may be replaced by charcoal alone, even in patients presenting with larger overdoses who arrive within 1 h of drug ingestion [65].

Specific treatment is carried out with **N-**Acetyl Cysteine (NAC). The treatment of paracetamol toxicity with NAC is originated in the UK in the year 1970. The World Health Organization Model List of Essential Medicines and Model Formulary of 2006 lists Acetyl Cysteine (NAC) as an antidote for use in the treatment of paracetamol overdose. NAC is best given within the first 8 hours following an acute overdose for maximum hepatoprotective effects. A study published in 1988 found that NAC is uniformly effective if given within eight hours of a single overdose, but subsequently its efficacy falls. A controlled trial provided evidence that NAC can improve outcomes even in patients with encephalopathy, so those who present more than eight hours after an overdose are still treated with this antidote [48].

The Medicines and Healthcare products Regulatory Agency (MHRA) has simplified the guidelines on the management of paracetamol overdose in 2012. All patients who have a timed plasma paracetamol level plotted on or above the line drawn between 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive NAC regardless of any risk factors they may have for hepatotoxicity. The treatment is continued until the patient is clinically stable and the liver transaminase level has fallen to less than 1000 IU/L along with normalization of the clotting screen or till the patient receives a liver transplantation [49].

NAC can be administered by oral and intravenous routes. The intravenous route is preferred in the presence of fulminant hepatic failure or if there is intolerance to oral therapy such as the patient is vomiting. Otherwise, the oral route of administration remains the stay of treatment. NAC oral dosing schedule is as a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours, to be continued for 72 hours. If vomiting occurs within 1 hour of ingestion of the drug, the dose has to be repeated. NAC intravenous dosage schedule is a total dose of 300 mg/kg approximately over 20 hours is given in aphasic regimen via intravenous infusion as 150 mg/kg in 200 ml of 5% glucose over 15 minutes, 50 mg/kg in 500 ml of 5% glucose over 4 hours and 100 mg/kg in 1000 ml of 5% glucose over 16 hours [50].

Intravenous NAC is associated with a higher incidence of adverse effects such as rashes, pruritus

(decreased by giving anti-histaminic like Chlorpheniramine), nausea, vomiting, hyponatremia, and anaphylactoid reaction. The anaphylactoid reaction is mediated by histamine and depends on the blood level of NAC. In the event of the development of an anaphylactoid reaction, the NAC therapy has to be discontinued and treatment with adrenaline, corticosteroid, and anti-histaminic has to be started immediately along with other supportive measures [51].

Other modalities of treatment of paracetamol toxicity include fluid replacement, symptomatic treatment of vomiting with drugs like metopimazine, vitamin K injection 10 mg intravenously for bleeding diathesis, correction of acidosis with sodium bicarbonate and liver transplantation in cases of fulminant hepatic failure.

Conclusion

Ibuprofen is suitable for self-medication with regards to its relatively wide spectrum of indication, good tolerance and safety. Overall, it has been rated as the safest conventional NSAID by the spontaneous adverse drug reaction reporting system in the United Kingdom.

Paracetamol is a familiar drug with widespread prescription and non-prescription use and there is little doubt that paracetamol will continue to be a useful analgesic in acute and chronic settings, both alone and in combination with NSAIDs and opioids. It has a remarkable safety record and minimal interactions with other drugs. Hepatotoxicity at excessive doses is a clear problem but the evidence for toxicity at doses up to 4 g/day is questionable. Paracetamol has a superior side-effect profile to other analgesics. The debate regarding the balance between recognizing the efficacy and regulation to limit adverse effects of paracetamol continues.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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