Paracetamol : The Safest Analgesic for all Ages-A Systematic Review

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Abstract

Paracetamol (Acetaminophen)is a commonly used drug available over the counter to control mild to moderate pain and fever. It has potent analgesic and antipyretic action but rather weaker anti-inflammatory effectsas compared to other Non-steroidalanti-inflammatory drugs (NSAIDs).Aside from its well established antipyretic and analgesic properties,Paracetamol in the form of intravenous formulations has found more novel uses in recent years and more research is being carried out in this regard. Through this review article, we shall discuss the role and itsuse of paracetamol in general practice.

Introduction

Paracetamol is an active metabolite of phenacetin and was synthesized in 1878 by Morse and first used clinically by von Mering in 1887[4]. Due to apprehensions about itssafety, it had limited use till 1950s. Nowit is one of the most commonly used drug worldwide which is available over the counter without prescription and used in almost all age groups. It is on the WHO Model list of essential medicines, the most important medications needed in basic health system[6]. Paracetamol is also available in fixed-dose combinations containing narcotic and non-narcotic analgesics (including aspirin and other salicylates), barbiturates, caffeine, vascular headache remedies, sleep aids, toothache remedies, antihistamines, antitussives, decongestants, expectorants, cold and flu preparations, and sore throat treatments.[2]

Pharmacology

The principal therapeutic effects of NSAIDs derive from their ability to inhibit PG production. The first enzyme in the prostaglandin synthetic pathway is Cyclooxygenase (COX), also known as Prostaglandin – endoperoxide synthase[1,2,3]. This enzyme converts Archidonic acid to the unstable intermediates Prostaglandin - endoperoxide synthase 2 (PGG2) and ProstaglandinH2 (PGH2)and leads to the production of the prostanoids, ThromboxaneA2 (TXA2), and a variety of Prostaglandins[2,3]. There are two forms of Cyclooxygenase COX, COX-1 and COX-2. It acts by inhibiting COX – 1 and COX -2 in brain and possesses weak anti – inflammatory activity because it is ineffective in presence of peroxides generated at the site of inflammation. The exact mechanism of Paracetamol is still not completely understood.It is thought that number of central mechanisms, including prostaglandin synthesis, serotonergic opioid and nitric oxide (N0) and cannabinoid pathways are likely to be involved in combination or interrelated[3,4]. Paracetamol has excellent bioavailability. Peak plasma concentration reaches within 30-60 minutes with a plasma half-life of two to three hours. It is rapidly absorbed from Gastro intestinal tract[1]

(Figure 1 & Table 1)

Therapeutic Uses

Fever: Paracetamol is used for reducing fever in people of all ages. The WHO recommends that paracetamol be used to treat fever in children only if their temperature is greater than 38.5 degrees Celsius (101.3 degrees Fahrenheit).

Pain: Paracetamol is indicated for mild to moderate pain such asheadache, mild migraine, musculoskeletal pain, osteoarthritis,Dysmenorrhea. It is used for patients with gastric disorder, patients with bleeding disorder in which prolongation of bleeding time is not desirable.[1,2,3]

Post-operative Pain: It is used nowadays being used as preemptive intravenous preparation for acute post-operative pain and study done by Jebaraj B et al suggests reduction in consumption of opioids takes place after surgeries.[12]Paracetamol when combined with NSAIDs may be more effective for treating post-operative pain than either paracetamol alone or NSAIDs alone. Paracetamol is analgesic / antipyretic of choice for children with viral infections or chicken pox.[2]

Safe option for Pregnancy: Pregnant women can safely use paracetamol. In fact, it is considered as one of the safest fever reducer/pain reliever for pregnant women. The FDA has assigned paracetamol Pregnancy Category B which means that it may be safe for use during pregnancy.

Adverse effects: In therapeutic doses, it is quite safe and well tolerated. Acute Paracetamol toxicity can occur in children who at this age have lower glucuronide conjugation ability than adults in whom hepatic functions are compromised or in chronic alcoholics in whom there is cytochrome P-450 induction[2,3,4]. Normally, paracetamol is metabolized by glucuronide and sulfate conjugation (major pathway). However, N – acetyl-p-benzoquinoeimine is a highly toxic metabolite formed by cytochrome P – 450 enzymatic system (minor pathway). The little amount of the metabolite so formed from the therapeutic doses of paracetamol, normally gets detoxified by conjugation with glutathione.With toxic doses of paracetamol (>150 mg/kg or 10 g in adult) large amounts of this toxic metabolite are formed which cannot be handled and detoxified through glutathione conjugation. Instead, this metabolite forms covalent

bonding to hepatic and renal cellular proteins causing necrosis and cell death[3,4].

Treatment for acute paracetamol poisoning: Treatment should be started early within 16 hours of paracetamol ingestion. Vomiting should be induced or gastric lavage done. Activated Charcoal should be given orally to prevent further absorption.The antidote of choice for paracetamol poisoning is N- acetylcysteine (IV) or methionine (orally).[2,3]

Administration in children: Paracetamol use should only be considered when the child has pain or they have temperature above 38.5 degree Celsius and should not be used to settle the child.The strength and formulation that is appropriate for the age of the child should be used. Adult preparations should not be used in children.Dosing instructions should be followed.The dose should be measured correctly with help of properly supplied tool.The dose should be given at appropriate intervals, it can be given every 4 to 6 hours but not given more than 4 times a day.The label of the medicines should be read properly and confusion should be avoided.

Discussion

Paracetamol is a very popular over the counter available safe analgesic and generally tolerated well within recommended doses. It has potent analgesic and antipyretic activity andmild anti- inflammatory activity. It shows very little gastrointestinal toxicity and can be prescribed to infants,children, pregnant /lactating women and elderly and whom aspirin is contraindicated. The platelet function is not affected and hence it does not increase bleeding time.A literature review by Macario et al suggests thatapart from its oral and rectal use, intravenous route is also being used nowadays[6].A study done by Sen H et al suggests that during intravenous regional anesthesia, when Paracetamol is added to the injected lidocaine, the overall quality of the block has been shown to improve[10].A study done by Yalcin et al suggests that when administered before induction of anesthesia, 1g IV paracetamol was found to be equally successful to ketamine in preventing remifentanil induced hyperalgesia[11]. Paracetamol used as IV for acute post-operative pain in adults has proved to be effective. Studies conducted by Jebaraj et al shows that IV paracetamol reduces post-operative opioid consumption, opioid related adverse effectsand extubation time after surgeries[12].

Conclusion

Paracetamol is relatively safe and most common drug used among all age groupsranging from children to adults including pregnant women within recommended dose to prevent toxicity. Improper self dosing is one of the biggest problem faced in giving paracetamol. The parentsneed to consult a pediatrician to know how to use paracetamol safely, including making sure the dose, formulation and strength and how administration is safe. The use of Paracetamol as IV infusion for post-operative pain and surgeries has proved to be effective. Therefore, paracetamol is currently a preferred analgesic for oral and maxillofacial surgeons.

References

References are available on request at editor@healtalkht.com

Fig.1 Mechanism of action of Paracetamol

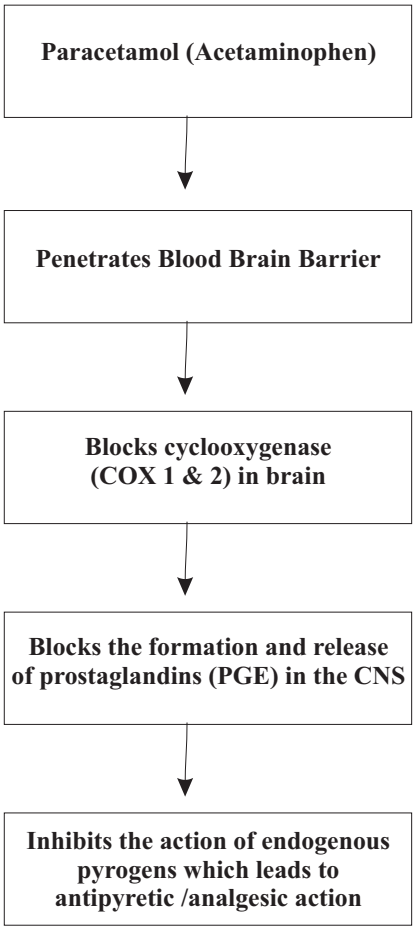

Table.1 Given below is Dosage of Paracetamol[5]

Oral	Adult	Children
Mild to Moderate pain and fever	325 – 650mg 4-6 hrly Max : 4 g daily	General dosing : 10-15 mg/kg/dose 3 to <6 months – 60mg 6 months to < 2 yr- 120mg 2 to < 4 yr – 180mg 4 to <6 yr – 240mg 6 to <8 yr – 240 or 250mg 8 to < 10 yr – 360 or 375mg 10 to < 12 yr – 480 or 500mg 12-16 yr – 480 or 750mg Given 4-6 hourly if necessary Max : 4 doses in 24 hr.
Intravenous	Adult	Children
	33-50 kg: 15mg/kg as a single dose, at least 4 hrly. Max : 60mg/kg (up to 3g) >50 kg: 1 g as single dose, atleast 4 hrly. Max : 4 g daily , infusion over 15 minutes	<10 kg: 7.5 mg/kg as a single dose, atleast 4 hrly. Max: 30 mg/kg daily. 10-33 kg: 15 mg/kg as single dose, atleast 6 hrly. Max : 60 mg/kg (upto 2 g) >33-50 kg: 15 mg/kg as a single dose atleast 4 hrly. Max : 60mg/kg (upto 3 g) Infusion over 15 minutes
Syrup	250mg/5ml	125mg/5ml
Rectal	0.5 –1 g 4-6 hrly Max : 4 g daily	3 months to<1 yr 60-125 mg ; 1 to <5 yr 125-250 mg 5-<12 yr 250-500 mg Given 4-6 hrly if necessary , upto 4 times daily