ISSN: 2474 - 9206

Review Article

Journal of Anesthesia & Pain Medicine

Paracetamol - the Drug with a "Safety Tag" But to what Extent?

Amit Sharma

Amit Sharma Chest Specialist, National Institute of Respiratory Diseases (NITRD), Autonomous Institute under the Ministry of Health and Family Welfare - Government of India, New Delhi, India

***Corresponding author**

Amit Sharma Chest Specialist, National Institute of Respiratory Diseases (NITRD), Autonomous Institute under the Ministry of Health and Family Welfare - Government of India, New Delhi, India

Submitted: 08 Nov 2021; **Accepted**: 12 Nov 2021; **Published**: 23 Nov 2021

citation: *Amit Sharma (2021) Paracetamol - the Drug with a "Safety Tag" But to what Extent? J Anesth Pain Med 6(2): 23 -24.*

Paracetamol (PCM) is one of the most commonly used drugs for relief of fever and pain. It is an over the counter (OTC) drug and is available without a prescription. The World Health Organization (WHO) Pain control step ladder places PCM as the first level in pain control and recommends a total dose of 4 g in 24 hours (1). There is a complacent sense of safety associated with the use of PCM which has increased over time because of increase in viral pandemics and epidemics such as Dengue, Chikungunya and now the Covid- 19 Pandemic caused by the novel coronavirus Sars-CoV_2.

This short review will attempt to focus on the apparent safety of higher doses of PCM in such conditions because of emerging evidence which is now casting doubts on such full-proof safety of a molecule which always had a narrow therapeutic index of safety. In fact, acute liver failure in adults is most commonly caused by PCM and one-fourth of acute pediatric liver failures are also attributed to PCM (2).

These figures are almost shocking because the safety protocols made by countries around the world emphasize on the specific use of PCM for control of fever and pain in viral fevers and 650 mg every 6 hrly is very commonly recommended. But the gap between salvation and doom is very less in this drug because of small difference of dose for efficacy and toxicity.

Not only there may be acute Liver failure due to damage to the hepatocytes by PCM and but also acute nephro-toxicity probably due to its Cyclooxygenase (COX) inhibitory action along with the presence of cytochrome P-450 isoenzymes in the kidney, damage by N-deacetylase and synthetase enzymes (3).

Some people have an increased genetic susceptibility for PCM toxicity due to an inherited deficiency of the enzyme, glutathione synthetase and in this special population even therapeutic doses of PCM may cause serious liver injury in a higher proportion of patients (4).

Most of the endemic viral infection such as Dengue, Chikungunya etc. usually causes high fever and severe arthralgias and myalgias. Since such viral infections especially Dengue may cause thrombocytopenia and in serious cases, bleeding, the Non-steroidal Anti-Inflammatory drugs (NSAID), especially Aspirin, may affect platelet function and thus increase the risk of bleeding (5). Hence the management protocol of such viral fevers usually discourages the use of Aspirin and other NSAIDs in such situations. PCM though a good anti-pyretic and a mild analgesic is not able to fully control or rather relieve the symptoms of the patients especially headache and body ache along with arthralgias.

The liver is frequently affected in viral hemorrhagic fevers such as yellow fever and dengue, bacterial illnesses such as Enteric Fever and Tuberculosis, parasitic diseases such as Malaria and fungal infections such as Histoplamosis and in all these diseases fever is usually the most prominent symptom (6). PCM use in higher doses may thus add to the toxic damage caused by these conditions on the liver.

There is also now a lot of documentary evidence emerging which points to the hepato-toxicity which is caused by the Sars-CoV2 virus, the causative agent of the Covid-19 pandemic which is currently threatening the entire human kind with a menace which is almost palpable (7). Fever is one of the main initial symptoms of Covid-19 infection and it can now be at least presumed if not proved that using PCM in the symptomatic control of fever would only compound the damage done by the etiological agent of Covid-19 to the liver.

PCM is absorbed through the alimentary tract and 90% of it reaches the Liver for metabolism. Glutathione depletion can take place if the quantity of PCM is high because Glutathione is an antioxidant and rapid depletion by PCM would lead to generation of free oxygen and nitrogen species which target the Liver cells and cause hepatocellular injury (8).

Alcohol abuse increases the risk of hepatotoxicity and nephrotoxicity at therapeutic doses of 4 g PCM per day and even at lower doses. A history of alcohol consumption in large amounts on a

chronic regular basis should be obtained from the patients as this patient cohort are at a much higher risk of liver and Kidney injury as explained above (9).

Another theoretical presumption as mentioned above is that NSAIDs should be avoided in viral hemorrhagic fevers as they interfere in platelet function and may cause bleeding, especially Aspirin. However, as mentioned, this disadvantage of NSAIDs in theory has not proven to translate in reality to any extent. A very large meta-analysis by Pierce CA et al. almost refutes the apprehension of Ibuprofen, a moderately strong NSAID being associated with more side effects as compared to PCM (10). In fact, detailed review of existing literature in this study showed increased efficacy of Ibuprofen on both analgesia and pyrexia as compared to PCM and also demonstrated equal safety profile for both the drugs.

Another NSAID which has shown good efficacy and safety in pyrexia and analgesia is Nimesulide (NMS). Though hepato-toxicity with the use of NMS has been a very contentious and controversial issue, it has several unique properties which other NSAIDs lack which include a reduced risk of nephrotoxicity and low Gastro-intestinal side effects due to its selective COX-2 inhibitory action (11). There is also a study which has demonstrated the similar efficacy and tolerability of NMS as compared to PCM in elderly patients (12). NMS has been blamed for serious hepato-toxicity but it is usually associated with chronic use. In viral fevers, which are usually self-limiting and fever is only seen later in complicated cases due to superinfections or some other causes. Moreover, the European Medical Agency (EMA) has allowed the use of NMS in patients above 12 years of age for not more than 15 days at doses not exceeding 200 mg per day because of its positive benefit/risk ratio. Hence PCM can be substituted by NMS or Ibuprofen if there is not complete resolution of fever and bodyache which are promptly relieved by NMS. This gives a great relief to the patient who may have crippling myalgias and arthralgias. Obviously, such use should be an exception and not a rule.

Conclusion

To conclude, PCM is a relatively safe drug for management of fever and pain but at higher therapeutic doses, it may be lead to both liver and kidney injury owing to the multiple factors outlined in the above review. There is no doubt that PCM should be the first choice of symptomatic management of Pyrexia and Pain in viral fevers, but when PCM fails to totally control these two distressing symptoms for patients with viral infections, then instead of escalating the dose of PCM, alternatives such as Ibuprofen and NMS may be tried for short term use in their recommended doses. It cannot be overemphasized that the use of high doses of PCM may be discouraged by health care providers owing to their acute damaging actions on the liver and kidney. Medical Regulatory agencies of the world such as WHO, CDC etc. may also reconsider or at least review the recommendations of high dose PCM for control of Viral fevers.

References

1. Ventafridda V, Saita L, Ripamonti C, De Conno F (1985) WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React 7: 93-96.
2. James L, Sullivan JE, Roberts D (2011) The proper use of acetaminophen. Paediatr Child Health 16: 544-547.
3. Mazer M, Perrone J (2008) Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J Med Toxicol 4: 2-6.
4. Larrey D, Pageaux GP (1997) Genetic predisposition to drug-induced hepatotoxicity. J Hepatol 26: 12-21.
5. Schrör K (1997) Aspirin and platelets: the antiplatelet action of aspirin and its role in thrombosis treatment and prophylaxis. Semin Thromb Hemost 23: 349-356.
6. Talwani R, Gilliam BL, Howell C (2011) Infectious diseases and the liver. Clin Liver Dis 15: 111-130.
7. Bongiovanni M, Zago T (2021) Acute hepatitis caused by asymptomatic COVID-19 infection. J Infect 82: 25-26.
8. James LP, McCullough SS, Lamps LW, Hinson JA (2003) Effect of N-acetylcysteine on acetaminophen toxicity in mice: Relationship to reactive nitrogen and cytokine formation. Toxicol Sci 75: 458-467.
9. Lieber CS, Lasker JM, Alderman J, Leo MA (1987) The microsomal ethanol oxidizing system and its interaction with other drugs, carcinogens, and vitamins. Ann NY Acad Sci 492: 11-24.
10. Pierce CA, Voss B (2010) Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother 44: 489-506.
11. Bennett A, Villa G (2000) Nimesulide: an NSAID that preferentially inhibits COX-2, and has various unique pharmacological activities. Expert Opin Pharmacother 1: 277-286.
12. Cunietti E, Monti M, Viganò A, D'Aprile E, Saligari A, Scafuro E, Scaricabarozzi I. A comparison of nimesulide vs paracetamol in the treatment of pyrexia in the elderly. Drugs. 1993;46 Suppl 1:124-6. doi: 10.2165/00003495-199300461-00026. PMID: 7506150