Research Article

Analysis of Various Doses of Paracetamol in the Indian Market: A Need to Revisit

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ABSTRACT

Introduction: One of the most often used OTC antipyretic and analgesic is paracetamol or acetaminophen. Despite being a widely used medicine, the mechanism by which it reduces fever and pain remains unknown. Although paracetamol is available in a variety of formulations, there are no set guidelines for the various formulations of paracetamol alone or in combination.

Materials and Methods: In the Department of Pharmacology at Government Doon Medical College, the study was planned as an observational cross-sectional study. Data regarding different paracetamol dosages and dosages of paracetamol in fixed dose combinations (FDCs) with various ingredients were gathered and evaluated from the editions of Drug Today, Current Index of Medical Specialties (CIMS), Monthly Index of Medical Specialties (MIMS), and India 2021/2022.

Results: Analysing Drug Today, CIMS and MIMS, it was found, 810 formulations of paracetamol tablets are available in the Indian market, of which, 77 formulations contain only paracetamol, rest being fixed dose combinations (FDCs). Among all the available FDCs with paracetamol having 2or 3 drug formulation, among the 2 constituent FDCs group containing paracetamol, 47% drugs have paracetamol in 325 mg or less dose, whereas, 53% drugs are in clear violation of the notice by CDSCO, by containing more than 325 mg paracetamol.

Conclusion: In spite of widespread use there is ambiguity in paracetamol doses, as well as absence of data for few constituents in the FDCs. Thus, further research into paracetamol dosing, as well as strict regulation is the need of the hour for one of the most widely used drug.

Keywords: Paracetamol, acetaminophen, OTC, fixed dose combinations (FDCs).

INTRODUCTION

Paracetamol or acetaminophen is one of the most commonly used over the counter (OTC) antipyretic and analgesic. It is available in multiple drugs formulations such as oral tablets, syrups, injectable, suppositories, of which predominantly used is oral tablet for adults.

Despite being one of the commonly used medicine, the mechanism by which it reduces fever and pain is still debatable. Most commonly adopted theory is that, the paracetamol act through the cyclooxygenase (COX) pathway, similar to that of non-steroidal anti-inflammatory drugs (NSAIDs). It is due to the fact that, prostaglandins in human are ubiquitous in nature and are involved in pain, fever, inflammation etc. Other mechanisms may include inhibition of l-arginine nitric oxide pathway, central serotonergic mechanism or through cannabinoid receptors.[1]

What is known about this subject- One of the most widely used over-the-counter (OTC) analgesics and antipyretics is paracetamol, also known as acetaminophen. It is available in a variety of pharmacological forms, including oral tablets for adults and syrups, injectables, suppositories, and injectables. Paracetamol tablet is available in wide range of doses from 80 mg to 1000 mg, along with being available as fixed dose combinations (FDCs). As per the United Kingdom recommendation, 500-1000mg paracetamol per dose, with maximum up to 4 gm daily can be given for fever and pain reduction.

What this study adds- Although, paracetamol is available in a wide range of doses and combinations, there are no fixed guidelines available for the use of paracetamol in India. This study explores the need for regulatory guidelines for paracetamol usage in the Indian market.

Oral acetaminophen has 70-80% bioavailability. Peak plasma concentrations occur within 30–60 min, and the t1/2 in plasma is about 2 h. Some 90%–100% of drug may be recovered in the urine within the first day at therapeutic dosing, primarily after hepatic conjugation with glucuronic acid (~60%), sulfuric acid (~35%), or cysteine (~3%); small amounts of hydroxylated and deacetylated metabolites also have been detected. [2]

Paracetamol tablet is available in various doses such as 80mg,100mg,125mg, 170mg, 250mg, 300mg, 325 mg, 500 mg, 625 mg, 650 mg, 1000mg. As per Chong et al, people using paracetamol tablet without combination, almost 44% used 650 mg tablet instead of the other available doses. Amongst, 24.4% of consumers took two or more

tablets of paracetamol 650 mg per intake.[i] Intravenous dose of PCM is 15 mg/kg for less than 50 kg and 1 gm above 50 kg every 4-6 hours. [3-4]

Although paracetamol is available in various combinations, there are no fixed guidelines available for the various formulations of only paracetamol or in combination with other drugs. The present study was done to assess various formulations of tablet paracetamol and it's combinations present in Indian market.

MATERIALS AND METHODS

The study was designed and conducted as an observational cross- sectional study in the Department of Pharmacology, Government Doon Medical college. The study was carried out in 2022.

Data about various doses of paracetamol and dose of paracetamol in fixed dose combinations (FDCs) along with different constituents was collected and analysed from Drug Today, Current Index Of Medical Specialities (CIMS), Monthly Index Of Medical Specialities (MIMS), India 2021/2022 editions.

Aim of the study is to analyse the variable doses of paracetamol and other fixed dose combinations of paracetamol available in the market.

Descriptive analysis of data was done with the help of SPSS 21 and MS Excel.

RESULTS

Analysing Drug Today, CIMS and MIMS, it was found, 810 formulations of paracetamol tablets are available in the Indian market, of which, 77 formulations contain only paracetamol, rest being fixed dose combinations (FDCs). Among these, highest dose is 1000mg and lowest is of 80 mg. The available formulations of paracetamol tablets without combination are of 650mg (34), 500mg (31), 1000mg (3), 625mg (3), 125mg (2), 550mg (1), 250mg (1), 170mg (1), 125mg (1) and 80mg (1).

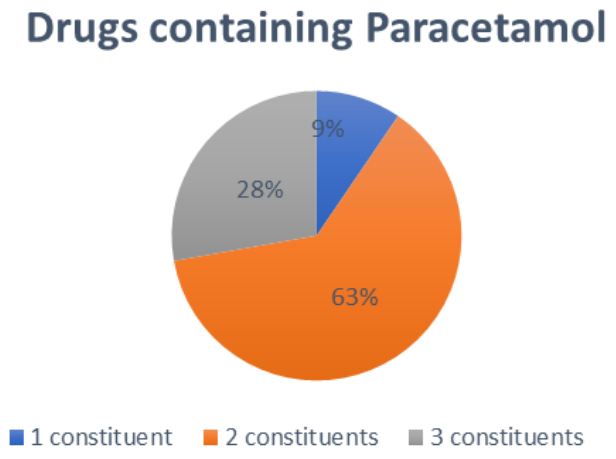

Figure 1: Drugs containing paracetamol (single constituents and FDCs)

There are 733 drugs available in combination with paracetamol, either as two drugs or as three drugs combination. 63% of the paracetamol combinations have 2 constituents in FDC and 28% of the drugs have 3 constituents in FDC. This has been depicted in the Fig 1.

Among the various FDCs, the dose of paracetamol most commonly present are 500mg (305) and 325mg (375). It was followed by 650mg (18) formulation.

Within the 2 constituent FDCs group, maximum number of combinations with paracetamol are found with aceclofenac (408), followed by combinations with nimesulide (200) bringing the combinations of paracetamol with NSAIDs to 89.3%. The different formulations of paracetamol with 2 drug FDCs with are depicted in Fig 2.

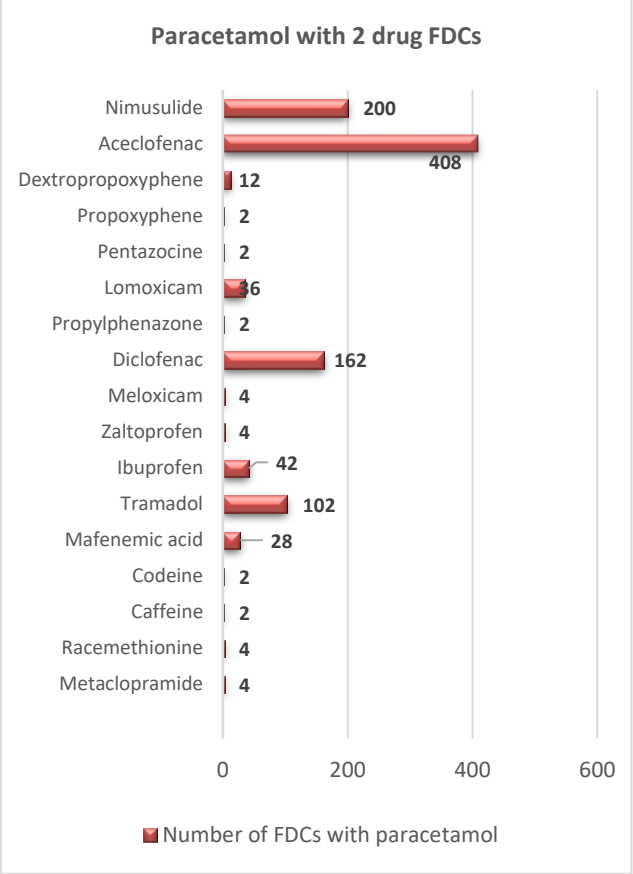

Figure 2: Different formulations of paracetamol in 2 drug FDCs

In the 3 constituent FDC with paracetamol group, it was seen that majority of the drugs are a combination of paracetamol and a nonsteroidal anti-inflammatory drug (NSAID) with a third constituent. Among these FDCs, the leading NSAIDs are Aceclofenac (298) and Diclofenac (100), followed by Ibuprofen (24) and Nimusulide (16). Serratiopeptidase is the most common third constituent in the 3 drug FDCs with paracetamol and NSAID, others being caffeine, menthol etc.

The following Fig 3. shows the different combinations of drugs in 3 constituent FDCs with paracetamol.

Among all the available FDCs with paracetamol having 2 or 3 drug formulation, 402 drugs contain paracetamol 325mg

or less, whereas, 336 drugs contain paracetamol more than 325mg as shown in Fig 4.

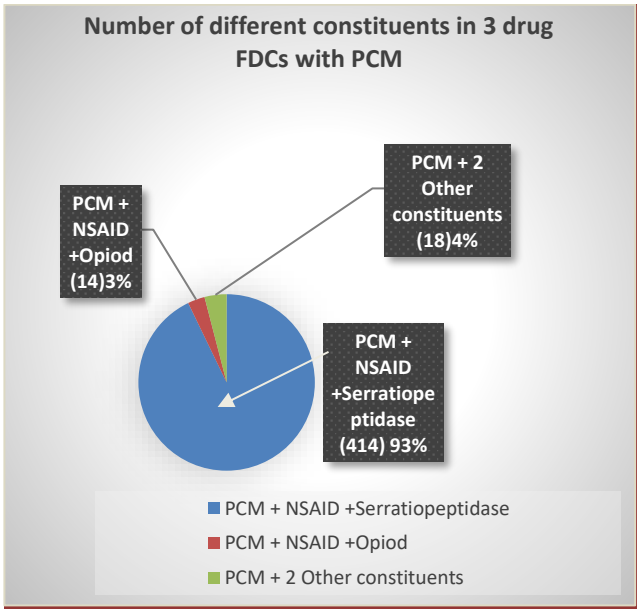

Figure 3: Different formulations of paracetamol in 3 drug FDCs

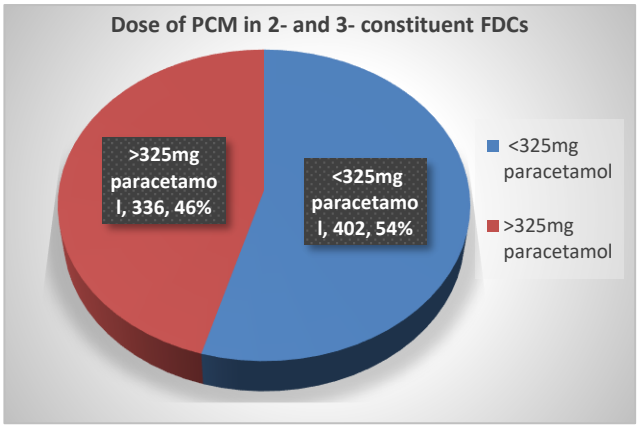

Figure 4: Different formulations of paracetamol in 3 drug FDCs

DISCUSSION

Acetaminophen or paracetamol is one of the commonly used over the counter (OTC) medicine for headache, fever and pain. Chong et al found that almost in 70% cases of headache and fever, patients used acetaminophen.[5] As per the United Kingdom recommendation, 500-1000mg paracetamol per dose, with maximum up to 4 gm daily can be given for fever and pain reduction.[6] Likewise, as per the Australian department of health the dose of paracetamol is similar to UK guidelines. But there are no Indian guidelines for paracetamol use. Although according to 2009 FDA advisory panel maximum dose per day of oral paracetamol is 2600 mg and maximum single dose is 650 mg for fever.[7]

Intravenous dose of PCM is 15 mg/kg for less than 50 kg and 1 gm above 50 kg every 4-6 hours. Considering this, a standard Indian male weighing 60kg will get 4-6 gram paracetamol per day IV, whereas, 2600 mg is the maximum oral dose of paracetamol per day as per FDA recommendation. According to Forrest et al, the bioavailability of oral paracetamol is 70-90 %. Thus, the dose of paracetamol reaching the blood appears to be far lower when given orally, as compared to intravenous infusion.[8] Based on data, the IV paracetamol dose should be lower than the oral paracetamol dose, regardless its ubiquitous distribution.

Paracetamol toxicity is one of the most common causes of poisoning worldwide. While paracetamol is described as relatively nontoxic when administered in therapeutic doses, it is known to cause toxicity when taken in a single or repeated high dose, chronic subtherapeutic doses, or after chronic ingestion.[9] Based on this data, as per letter no. F. No. 18-6/2011-DC, Central Drugs Standards Control Organisation (CDSCO) directed the manufacturers of prescription combination products containing paracetamol, to limit the amount of acetaminophen to no more than 325mg in each tablet or capsule. Higher dose combination paracetamol FDCs were suggested to be phased out during the following 3 years.[10]

In present study, among the 2 constituent FDCs group containing paracetamol, 47% drugs have paracetamol in 325 mg or less dose, whereas, 53% drugs are in clear violation of the notice by CDSCO, by containing more than 325 mg paracetamol. Similarly, in the 3 constituent FDCs group containing paracetamol, there are 30% drugs available in the market that have more than 325 mg paracetamol.

Among the 3 constituent FDCs group containing paracetamol, Serratiopeptidase is the most common third constituent with paracetamol and NSAID, others being caffeine, menthol etc. On research for any worldwide evidence, it came to light , based on letter no. F. No. 04-146/2007-DC, this combination is not authorised by CDSCO, and is under pending investigation.[11]

According to research, in the combination of caffeine with paracetamol and NSAID, caffeine is present in subtherapeutic range in the majority of FDCs on the market, for which a risk-benefit evaluation cannot be established.

The multiple combinations of paracetamol with different drugs such as, caffeine and serratiopeptidase, are marketed as wonder drugs and are being extensively used, thus escalating the risk of hepatotoxicity.

Although, paracetamol is available in a wide range of doses and combinations, there are no fixed guidelines available for the use of paracetamol in India.

CONCLUSION

We found no fixed guidelines are being followed for paracetamol usage, which is available over the range of 80mg to 1000mg in the market. There is lack of evidence of their comparative efficacy and safety with the availability of variable doses. In spite of widespread use there is ambiguity in paracetamol doses, as well as absence

of data for few constituents in the FDCs. Thus, further research into paracetamol dosing, as well as strict regulation is the need of the hour for one of the most widely used drug.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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