Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Acetaminophen overdose in the Intensive care Unit: A "fervent" prayer over defervescence!

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BASED ON ARTICLE

Roumeliotis N, Pullenayegum E, Taddio A, Rochon P, Parshuram C. **Liver enzymes after short-term acetaminophen error in critically ill children: a cohort study**. Eur J Pediatr. 2022 Aug; 181(8):2943-2951. doi: 10.1007/s00431-022-04502-y.

SUMMARY

The authors evaluated drug-associated hepatic injury following enteral administration of acetaminophen overdosing error (AOE) in intensive care unit (ICU). They defined AOE as daily acetaminophen exceeding a dosing by > 10% the upper limit of maximum recommended dose for weight and age (> 82.5 mg/kg/day or > 4400 mg/day). In this retrospective study children (< 18 years of age) admitted to the pediatric and cardiac intensive care unit at SickKids, Toronto January, 2008 to January, 2018 who received enteral acetaminophen were included. They included 147,485 doses of acetaminophen over 65,564 patient-days. In general, the patients received a median of 2 doses of acetaminophen per day (IQR 1–5), with the median dose being 12.37 mg/kg (IQR 11.0–13.7). AOE occurred 1 in every 9.5 patient-days on acetaminophen. On 119 patient days, AOE was both above 4400 mg and above 82.5 mg/kg. In patients with AOE, the median time from admission to first daily overdose error was 23.7 h (IQR 99.1 to 29.1, N=3348), suggesting the majority of dosing errors occurred on the first ICU day. There were 3446 patient-days where an AOE was >100 mg/kg/day, occurring in 1118 admissions. Daily AOE were more frequent in infants, cardiac patients, mechanically ventilated patients, and patients with higher severity of illness. The number of medications received in complex patients had been shown to be a risk factor for medication and dosing error. They did not find any significant difference in the mean measured aspartate or alanine transaminase (AST or ALT) levels taken in the 24 to 96 h post error, compared to those without error. Mean AST or ALT were also similar with a sensitivity analysis using a larger daily AOE and when evaluating sub-populations such as cardiac patients and less severely ill patients (as per PRISM III score). On the contrary, AST or ALT decreased significantly over the course of ICU admission ($p < 0.0001$) as a part of natural history of the illness. With every advancing ICU day, ALT and AST significantly decreased (0.27 per day for ALT, 0.6 for AST, $p<0.0001$) but gamma glutamyl transpeptidase (GGT) significantly increased by 1.34 per day ($p<00,001$). Increasing patient severity of illness was significantly associated with worse liver enzymes; with every increase in PRISM III score associated with an average increase in ALT by 4.95, AST by 10, and GGT by 2 ($p<0.0001$). Cardiac ICU patients had significantly lower liver enzymes on average than pediatric ICU patients

(26.6 units lower for ALT, 6.5 units lower for AST, and 22 units lower for GGT). A sensitivity analysis using > 100 mg/kg/day as the upper daily acetaminophen error cut-off did not reveal any subsequent significant increase in liver enzymes in the 24 to 96-h post-error window, compared to measurements taken outside the window. Authors concluded that the AOE occurs frequently in ICU settings. Despite the vigilance, they did not find any associated increase in liver enzymes following AOE [1]

COMMENTARY

Pain and fever in the ICU are often worrisome issues leading to heated debates and discussions between doctors and caregivers as to what should be our threshold for prescribing acetaminophen. To avoid hepatotoxicity, it is felt that children and their mothers should rather "tolerate" some amount of pain and fever than overdosing, often misconceived as apathy. After a forced or inadvertent overdose, the conscientious pediatrician loses sleep with guilt and fear that hepatotoxicity may ensue. Residents and nurses are frequently reprimanded for errors. To make matters worse, anecdotal reports of an unrelated liver failure, or litigations hover like dark clouds around the ever-so-worried and cautious physician. The dilemma of achieving rapid defervescence or analgesia versus overdosing of acetaminophen is not an easy one. Should I cross the recommended threshold dose? Can I dare a 3-4 hourly prescription? Will I have a narrow escape?

In this light, Roumeliotis et al attempted to put this debate to rest. It is not logical to expect a randomised controlled study on overdosage of acetaminophen. No ethical committee in the world would consciously permit the same in children. Hence, one can only make sense of the same only through retrospective yet robust analysis. This was a large cohort with a modest follow-up. The authors were careful to only include patients with enteral (not parenteral) delivery of acetaminophen. The authors showed that even in the best of ICUs in developed countries, frequent prescription errors do occur. This was a remarkable transparency, least expected. Presumably, those with high PRISM-III scores had more frequent AOE. The window of error was assessed within 24 to 96 hours of AOE, the crescendo of expected liver injury. One can always argue that liver enzymes are not the ideal markers to assess real liver damage but is there a better alternative? N-acetyl-p-benzoquinone imine (NAPQI), is a toxic by-product of acetaminophen detoxified in the liver. In research studies, high levels of NAPQI after acetaminophen over-ingestion signifies poor liver functions [2]. Despite efforts, NAPQI is not readily available in all hospitals, more so in India. Hence for all practical purposes, liver enzymes continue to be the most practical bedside assessment.

The authors found that after adjusting statistical confounders, there was no difference in the liver enzyme elevation in those with AOE versus those without. ALT and AST decreased with advancing ICU stay. This is likely explained by improving organ dysfunction post-recovery (whether infectious, surgical, or traumatic). GGT increased with advancing ICU stay which may be explained by prolonged fasting in PICU or cholestasis associated with medications or parenteral nutrition. However, one cannot help but notice an element of bias or error which is expected in retrospective analyses. It is possible that liver enzymes do not reflect mild hepatic injuries and indicate only when dysfunction has progressed. Also those with already compromised liver functions may not have been preferentially selected to receive higher or loading doses of acetaminophen, thereby muting the real drug toxicity.

In a pun-intended humour, so far we believed Temple et al with "fervent prayers" that acetaminophen prescription should only be bound to 60-90 mg/kg/day [3,4]. Does this study break that barrier and push the boundaries? The authors documented that doses as high as >4 g/day do not cause much harm.

What does this study mean for India? For a start, we must come clean, acknowledge and document our AOEs. Pooled studies from India may reveal a higher prevalence of AOE than developed countries. This may change the conventional pharmacoepidemiology and safety profile of acetaminophen. Conversely, acetaminophen is reported to be an etiology in 21% of acute liver failure in Indian children [5]. Over-reporting of AOEs in critically ill patients is possible as it may often be difficult to tease out inherent systemic issues complicating the liver injury. Pediatricians should still be aware that acetaminophen syrups/ drops come in various concentrations and mistakes are likely in busy health care setups. The antidote N-acetyl cysteine has limitations and is not always dependable. It should be cautioned that this study does not give us the freedom for indiscriminate use of the drug nor empower us with overconfidence. This study comes only as a breather to relieve us from the panic of inadvertent overdosing of acetaminophen.

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