

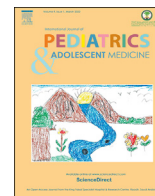
HOSTED BY



ELSEVIER

Contents lists available at ScienceDirect

## International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

Original article

## Urgent need to standardize labelling of acetaminophen-paediatric liquid drug products in Saudi Arabia

Nahar AlRuwaili <sup>a,\*</sup>, Faten Zaidan <sup>b</sup>, Areej AlFattani <sup>c</sup>, Saud Alenazi <sup>d</sup><sup>a</sup> Emergency Department, King Faisal Specialist Hospital & Research Center, Alfaisal University, Saudi Arabia<sup>b</sup> General Paediatric Department, KFSHRC, AlMaarefa University, Saudi Arabia<sup>c</sup> Biostatistician, King Faisal Specialist Hospital & Research Center, Saudi Arabia<sup>d</sup> Pediatric Emergency Medicine, Department of Emergency Medicine, Maternity & Children Hospital, Qassim, Saudi Arabia

## ARTICLE INFO

## Article history:

Received 25 February 2021

Received in revised form

12 July 2021

Accepted 19 September 2021

Available online 23 September 2021

## Keywords:

Acetaminophen

Supratherapeutic dose

Drug

Liver toxicity

## ABSTRACT

In this study, dosing instructions in package inserts of all 12 paediatric liquid acetaminophen products registered in pharmacies in the Kingdom of Saudi Arabia were analysed to determine the potential for administering a supratherapeutic dose of acetaminophen. Doses in millilitres were calculated as mg/kg for four age groups: three months old, one year old, six years old, and twelve years old, and based on the 3rd, 50th, and 75th weight percentiles of each age group.

Acetaminophen concentrations in the products varied, and only two products included Arabic language instructions. The dosing instructions in eight products included an age overlap. The most affected age group was the 1-year-old group, with 21 supratherapeutic doses across all 12 products. The least affected age group was the 12-year-old group, with 8 supratherapeutic doses in total.

The absence of strict supervision and monitoring of labels of paediatric liquid acetaminophen products increases the risk of liver toxicity in children. Therefore, we call for an immediate standardisation of all dosing instructions regarding the dose per weight and the inclusion of instructions in Arabic.

© 2022 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Acetaminophen drug has been overused in the treatment of pain and fever [1]. It exerts its action by centrally inhibiting the synthesis of prostaglandin E<sub>2</sub> by cyclooxygenase-1 and cyclooxygenase-2. Acetaminophen is metabolised to *N*-acetyl-4-benzoquinoneimine, which, if accumulated, leads to complications because of its toxicity [2]. The recommended single therapeutic dose of acetaminophen is 10–15 mg/kg to be taken every four to 6 h as required [3]. Literature reports have shown that even a single dose of 15 mg/kg can effectively lower an episodic fever [4,5].

Acetaminophen is available as an over-the-counter drug, on its own or in combination with medications of different therapeutic

classes such as sedatives, antihistamines, opioids, and decongestants. Ingestion of any form of acetaminophen will result in an overdose if used incorrectly [6]; even if the correct individual dose is administered, the total daily dose may exceed the therapeutic dose. A chronic intake of acetaminophen overdose is termed repeated supratherapeutic ingestion (RSTI), which is the toxic dose ingested over a period of greater than 8 h [7]. As defined by Dart et al., it is the total intake of at least 200 mg/kg acetaminophen over a single 24-h period, at least 150 mg/kg over a 24-h period in 48 h, or an intake at least 100 mg/kg acetaminophen over a 24-h period in 72 or more hours [8]. RSTI of acetaminophen has a considerable potential to result in hepatotoxicity [9,10]. In the United States, acute liver failure in paediatric patients per se has been found to be caused primarily by acetaminophen toxicity [1]. A prospective multi-centre study of 348 paediatric patients with acute liver failure, conducted by Squires Jr. et al. in 2006 [11], showed that most cases were a consequence of acetaminophen toxicity.

Patients who report to the hospital after more than 24 h following an acetaminophen overdose are suspected of having a hepatocellular injury [12], manifested by increased transaminase enzymes, a prolonged coagulation profile, and increased bilirubin levels [13].

\* Corresponding author. College of Medicine, Alfaisal University Consultant, Paediatric Emergency Medicine & Medical Toxicologist, Department of Emergency Medicine, King Faisal Specialist Hospital & Research Center, P.O. Box 3354 MBC 84, Riyadh, 11211, Saudi Arabia.

E-mail address: [Rewali@hotmail.com](mailto:Rewali@hotmail.com) (N. AlRuwaili).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

Caregivers typically depend on prescription guidelines when they administer medications. Variable methods for ensuring that the correct dose of over-the-counter medication have been used. A study conducted in Duke Medical Centre showed that the colour-coded method of labelling is more comprehensible than the traditional drug labels. Furthermore, using the weight of a child instead of the child's age, with clear differentiation between doses, was reported to increase the awareness of caregivers regarding the correct therapeutic dose in a home setting [14]. The primary objective of this study was to assess the dosing instructions that are included in the packages of all the paediatric liquid acetaminophen products available in the Saudi market.

## 2. Materials and method

### 2.1. Data collection and analysis

A total of 50 pharmacies that were registered with the Saudi Food and Drug Authority were surveyed for all paediatric acetaminophen-containing liquid products. A total of 12 products were collected and labelled with numbers 1 through 12, while the actual names of the products were kept confidential. To prevent the overlooking of occurrences of suprathreshold doses, the Saudi national chart growth for females [15] was used as the standard chart for weight and percentile measures for all ages. The weight percentiles for each age were grouped as follows: 3% (lowest), 50% (medium), and 97% (highest).

The ages that were most commonly mentioned in the dosing instructions of the package inserts across all products were divided into four groups: '3 months old', '1 year old', '6 years old', and '12 years old'.

The age classification was selected based on the common age categories that have been found in different paediatric liquid acetaminophen-containing products proposed by companies manufacturing and distributing the products across KSA.

The main problems with the age categories (rather than taking specific ages) were as follows:

- 1-Nonspecific for certain weight may include 10 kg child or 20 kg with wide range of doses that make older children dose might be given to younger kids.
- 2-Duplication of ages in different groups, which should be avoided.

For each age group, the required dose in millilitres was calculated, based on the desired dose in milligrams per body weight and the concentration of acetaminophen in the product. For example, product 1 contained 160 mg of acetaminophen in each 5 mL of the product (160 mg/5 mL). The package inserts instructed that a 5-year-old child receives 5 mL of the product. In our study, a 5-year-old child would be randomised to the 6-year-old group, and accordingly, the dose would be calculated according to the weight of a 6-year-old child. In our study, a suprathreshold dose was defined as a dose higher than 15 mg/kg.

The results are expressed as mean  $\pm$  standard deviation (SD) for continuous variables and as percentages for categorical variables. The variables were compared using a 2-sample *t*-test, the chi-square test, and Fisher's exact test.

### 2.2. Ethical considerations and data availability

The data required for this research were available prior to the start of the study and were obtained through routine clinical care.

Personal information of patients was kept strictly confidential. Each patient was assigned a study-specific patient number, and all

patient data were entered into a designated Excel data sheet without any patient identifiers.

The data collected for this study and generated by the analyses in this study were stored in the Paediatric Research Unit, KFSHRC, and accessed only by the principal Investigator and the assigned assistant clinical research coordinators.

A waiver of informed consent was obtained.

## 3. Results

Packages of 12 acetaminophen-containing products were analysed for an overlap of age and/or weight per dose, the use of weight to determine the dose, the dose, the concentration of acetaminophen, and the availability of Arabic instructions (Fig. 1).

In two of the products, acetaminophen was combined with another medication and an age overlap was found in eight of the twelve products. For example, according to the package insert of product 1, children who are 1–5 years old should receive 2.5 mL of the product, and children who are 5–12 years old should receive 5 mL of the product. In this example, the dose for a 5-year-old child can be either 2.5 mL or 5 mL, which is not only confusing but may also result in an incorrect dose being administered to that child. Only three products included dosing instructions based on weight and not on age; however, one of them was found to have a weight overlap. Arabic instructions were included with only two of the products. The package insert instructions for age-based dose are detailed in Table 1 and are highlighted in red colour.

The age group that was impacted the most was the '1-year-old' group, which was associated with a total of 21 suprathreshold doses across all weight percentiles. The age group that was impacted the least was the '12-year-old' group, which was associated with only 8 suprathreshold doses across all weight percentiles. In addition, when we calculated the actual doses to determine whether they were suprathreshold, we noticed that there was the likelihood of subtherapeutic doses being administered, most prominently in the '12-year-old' group. A subtherapeutic dose was defined as any dose lower than 10 mg/kg.

The package inserts of all products were found to include instructions that would result in suprathreshold doses when the dose was calculated according to the weight percentile in each of the age groups. The highest number of suprathreshold doses, 11, was associated with two products. The suprathreshold doses are summarised for each product in Table 2.

## 4. Discussion

It not uncommon for parents to administer suprathreshold doses of acetaminophen to their children. Alomar et al., in 2011 [16], interviewed 200 caregivers in King Faisal Specialist Hospital and Research Centre regarding acetaminophen dosage. Thirty percent of the caregivers interviewed indicated that they have administered suprathreshold acetaminophen doses to sick children, and nine percent of the caregivers reported having administered suprathreshold doses repeatedly, potentially resulting in toxicity and liver injury. A similar study by Li et al. in 2000 [17,18], conducted in the Urban Academic Pediatric Emergency Department, showed that 50% of the surveyed caregivers administered suprathreshold doses of acetaminophen to children in their care. The children most affected were those younger than one year of age. A lower likelihood of inaccurate doses being administered to children was observed with caregivers who calculated the dose based on weight rather than on age.

This study showed that all analysed products included in their package insert dosing instructions that could have led to the administration of suprathreshold doses of acetaminophen,

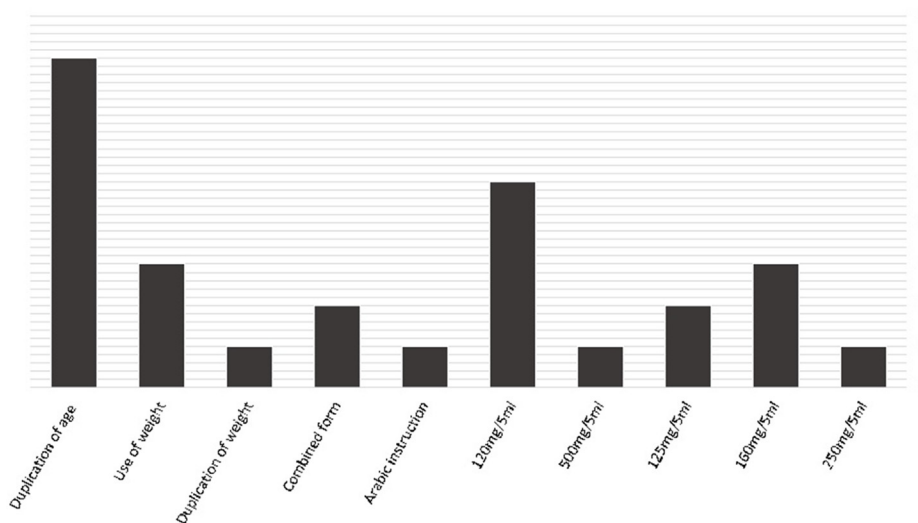


Fig. 1. Demographic data in all products.

Table 1

Total number of suprathereapeutic dose (STD) for every product per weight for every percentile per age (mg/kg).

	3 months of age			1 year of age			6 years of age			12 years of age		
	3rd %	50%	97%	3rd %	50%	97%	3rd %	50%	97%	3rd %	50%	97%
Product 1	26 <sup>a</sup>	21	17	32	25	20	15	12	9	n/a	n/a	n/a
Product 2	16	13	10	19	15	12	15	12	9	n/a	n/a	n/a
Product 3	n/a <sup>b</sup>	n/a	n/a	16	13	10	11	9	7	12	9	5
Product 4	27	22	17	32	25	20	30	24	18	16	12	7
Product 5	27	22	17	24	19	15	15	12	9	8	6	4
Product 6	13	11	8	16	13	10	n/a	n/a	n/a	n/a	n/a	n/a
Product 7	n/a	n/a	n/a	17	13	10	16	12	9	8	6	4
Product 8	n/a	n/a	n/a	n/a	n/a	n/a	8	6	5	8	6	4
Product 9	n/a	n/a	n/a	n/a	n/a	n/a	20	16	12	21	16	10
Product 10	35	29	23	43	34	27	40	32	24	21	16	10
Product 11	35	29	23	43	34	27	40	32	24	21	16	10
Product 12	55	37	36	50	40	31	31	25	18	17	12	8
<sup>c</sup>	7	6	6	10	6	5	6	5	4	5	3	0
<sup>d</sup>	19			21			15			8		

Suprathereapeutic dose (STD) is defined any dose above 15 mg/kg.

<sup>a</sup> Doses of twelve products in millilitres were transformed into milligrams per weight in kilograms for each of the ages: 3 months, 1 year, 6 years, and 12 years for percentiles 3rd, 5th and 75th as per the Saudi Female Growth Chart for weight.

<sup>b</sup> n/a: not available; age not available in the package of the identified product.

<sup>c</sup> Total STD in all products for every age per percentile.

<sup>d</sup> Total STD in all products per age.

Table 2

Total number of suprathereapeutic doses per product for age.

	3 months	1 year	6 years	12 years	Total number of STD per product
Product 1	3*	3	0	n/a <sup>b</sup>	6
Product 2	1	1	0	n/a	2
Product 3	n/a	1	0	0	1
Product 4	0	1	n/a	n/a	1
Product 5	n/a	n/a	n/a	2	2
Product 6	n/a	n/a	0	0	0
Product 7	n/a	1	1	0	2
Product 8	n/a	n/a	2	2	4
Product 9	3	3	3	2	11
Product 10	3	3	3	1	10
Product 11	3	2	0	0	5
Product 12	3	3	3	1	10

<sup>a</sup> Total number of suprathereapeutic doses for every age per product.

<sup>b</sup> n/a: not available; age not available in the package of the identified product.

irrespective of the weight or the age of the child. Some of these instructions suggested higher doses than other instructions, with a potential to cause hepatic injury. In addition, instructions recommending the administration of doses within the subtherapeutic range could also lead to an increased risk of RSTI, if the caregiver did

not observe the desired therapeutic effect of the administered dose on pain or fever, and administered additional doses until relief was achieved, potentially resulting in the ingestion of a supra-therapeutic dose.

An overlap of a particular age between two age groups in the

dosing instructions is a common cause of confusion among caregivers and a potential cause of acetaminophen toxicity in children, who may receive higher doses than needed. It is especially important for the caregiver to understand that a child at a specific age could weigh different from another who is of the same age. In paediatrics, doses of medications are calculated according to either the child's weight or the surface area of the child's body. Accordingly, dosing instructions in the package insert should provide the dose per weight that is required to reach the most accurate actual dose, irrespective of the child's age. This method of calculation is also easy to use for caregivers. Instructions in the Kingdom of Saudi Arabia should generally be in Arabic, given that this is the local language, and including Arabic instructions should reduce the likelihood of the instructions being misunderstood. Moreover, acetaminophen concentrations should be standardised across all paediatric acetaminophen products. Caregivers and medical staff may not know what the concentration of acetaminophen in a particular product is, which presents another risk of supra-therapeutic dose administration. Some products may have a high concentration of acetaminophen, such as 500 mg/5 mL, while others may have a lower concentration of 125 mg/5 mL. Combination products of acetaminophen and another drug cause additional concerns due to the likelihood of incorrect calculation. Therefore, the use of combination products should be discouraged.

## 5. Conclusion

Acetaminophen has the potential to induce hepatotoxicity at supratherapeutic doses. This study showed that it is common for dosing instructions in package inserts of paediatric acetaminophen products to recommend doses that are supratherapeutic. These findings highlight an urgent need for a national standard for safe dosing instructions that will serve as a guide for parents for safe administration of acetaminophen to their children and ensure that liver injury is prevented.

## Authorship statement

Nahar AlRuwaili, Conception and design of study, acquisition of data, analysis and/or interpretation of data, Drafting the manuscript, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published, Faten Zaidan, analysis and/or interpretation of data, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published, Areej Alfattani, analysis and/or interpretation of data, Approval of the version of the manuscript to be published, Saud Alenazi, Conception and design of study, acquisition of data, Drafting the manuscript, Approval of the version of the manuscript to be published.

## Ethical considerations

The following other ethical considerations were taken.

- 1 All data needed for research already exist and were obtained through routine clinical care.
- 2 All data will be stored in Paediatric Research Unit, accessed only by the Principal Investigator and the assigned Assistant Clinical Research Coordinators.
- 3 The entire patient's information will be kept strictly confidential. Each patient will be given a study number, and all patient data will be entered into the designated data sheet (EXCEL) without any patient's identifiers.

- 4 Waiver of informed consent is submitted with justification.
- 5 The Declaration of Helsinki and GCP guidelines will be followed.

## Declaration of competing 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.

## Acknowledgements

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgements and have given us their written permission to be named. If we have not included an Acknowledgements, then that indicates that we have not received substantial contributions from non-authors.

## Visual abstract

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpam.2021.09.001>.

## References

- [1] Perkins JD. Acetaminophen sets records in the United States: number 1 analgesic and number 1 cause of acute liver failure. *Liver Transplant* 2006 Apr;12(4):682–6.
- [2] Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Therapeut* 2005 Jan 1;12(1):46–55.
- [3] Wallace C, Dargan P, Jones A. Paracetamol overdose: an evidence based flowchart to guide management. *Emerg Med J: Eng Manag J* 2002 May;19(3):202.
- [4] Sullivan JE, Farrar HC. Section on clinical pharmacology and therapeutics; committee on drugs. Fever and antipyretic use in children. *Pediatrics* 2011 Mar 1;127(3):580–7.
- [5] Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. *Clin Therapeut* 2013 Sep 1;35(9):1361–75.
- [6] Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol* 2002 Jan 1;40(1):3–20.
- [7] Bond GR, Caravati EM, Dart RC, Heard K, Hoffman RS, Rumack BH, et al. Guidelines for the management of acetaminophen overdose 2015; 2015.
- [8] Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006 Jan 1;44(1):1–8.
- [9] Henretig FM, Selbst SM, Forrest C, Kearney TK, Orel H, Werner S, et al. Repeated acetaminophen overdosing: causing hepatotoxicity in children clinical reports and literature review. *Clin Pediatr* 1989;28(11):525–8.
- [10] Heard K, Bui A, Mlynarchek SL, Green JL, Bond GR, Clark RF, et al. Toxicity from repeated doses of acetaminophen in children: assessment of causality and dose in reported cases. *Am J Therapeut* 2014;21(3):174–83.
- [11] Squires Jr RH, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006;148(5):652–8.
- [12] Alander SW, Dowd MD, Bratton SL, Kearns GL. Pediatric acetaminophen overdose: risk factors associated with hepatocellular injury. *Arch Pediatr Adolesc Med* 2000 Apr 1;154(4):346–50.
- [13] Miles FK, Kamath R, Dorney SF, Gaskin KJ, O'Loughlin EV. Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999 Nov;171(9):472–5.
- [14] Frush KS, Luo X, Hutchinson P, Higgins JN. Evaluation of a method to reduce over-the-counter medication dosing error. *Arch Pediatr Adolesc Med* 2004 Jul 1;158(7):620–4.
- [15] El Mouzan MI, Al Herbish AS, Al Salloum AA, Foster PJ, Al Omar AA, Qurachi MM, et al. Pattern of sex differences in growth of Saudi children and adolescents. *Gend Med* 2010 Feb 1;7(1):47–54.
- [16] Alomar M, Alenazi F, Alruwaili N. Accuracy of acetaminophen dosing in children by caregivers in Saudi Arabia. *Ann Saudi Med* 2011 Sep;31(5):513–7.
- [17] Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. *Pediatr Emerg Care* 2000 Dec 1;16(6):394–7.
- [18] Yoon E, Babar A, Choudhary M, Kutner M, Pysopoulos N. Acetaminophen-induced hepatotoxicity: a comprehensive update. *J Clin Transl Hepatol* 2016 Jun 28;4(2):131.