

Acute pain management: acetaminophen and ibuprofen are often under-dosed

Gregorio P. Milani^{1,2} · Franca Benini³ · Laura Dell’Era² · Davide Silvagni⁴ · Alberto F. Podestà⁵ · Rossella Letizia Mancusi⁶ · Emilio F. Fossali² · on behalf of the PIERRE GROUP STUDY

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Abstract Most children with pain are managed by either acetaminophen or ibuprofen. However, no study has so far investigated if children are prescribed adequate doses of acetaminophen or ibuprofen in emergency department. Aim of this retrospective study was to investigate the prevalence of under-dosage of these drugs in children presenting with pain in emergency department. Children initially prescribed with acetaminophen or ibuprofen for pain management were included. The χ^2 automatic interaction detection method was used considering the percentage variation from the minimum of the appropriate dose as dependent variable while prescribed drug, age, gender, body weight, type of hospital (pediatric or general), and availability of internal

guidelines on pediatric pain management in the emergency department as independent variables. Data on 1471 children managed for pain were available. Under-dosage was prescribed in 893 subjects (61%), of whom 577 were prescribed acetaminophen and 316 ibuprofen. The use of acetaminophen suppositories, body weight <12 kg or >40 kg, and the use of oral ibuprofen identified clusters of children associated with under-dosage prescription.

Conclusion: Prescription of acetaminophen and ibuprofen was frequently under-dosed. The use of suppositories, lower and higher body weight, and the use of ibuprofen were associated with under-dosage. Under-dosing may reflect prescription of anti-pyretic doses.

Gregorio P. Milani and Franca Benini equally contributed to the work

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✉ Gregorio P. Milani
milani.gregoriop@gmail.com

Franca Benini
franca.benini@sanita.padova.it

Laura Dell’Era
lauradellera@ymail.com

Davide Silvagni
davide.silvagni@ospedaleuniverona.it

Alberto F. Podestà
podesta.alberto@sancarlo.mi.it

Rossella Letizia Mancusi
rossella.Letizia.Mancusi@uniroma2.it

Emilio F. Fossali
emilio.fossali@unimi.it

- ¹ Pediatric Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico and Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
- ² Pediatric Emergency Department, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Via della Commenda 9, 20122 Milan, Italy
- ³ Pediatric Pain and Palliative Care Service, Department of Women’s and Children’s Health, University Hospital, Padua, Italy
- ⁴ Azienda Ospedaliera Universitaria Integrata, Verona, Italy
- ⁵ Dipartimento Materno Infantile, ASST Santi Paolo e Carlo, Ospedale San Carlo Borromeo, Milan, Italy
- ⁶ CREA Sanità, University of Tor Vergata, Rome, Italy

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What is Known:

- Pain is frequent in children presented to emergency department.
- International recommendations on pain management are often not implemented.

What is New:

- Acetaminophen and ibuprofen were frequently underdosed in children prescribed for pain in the Italian emergency departments.
- Under-dosage may be related to the habit of using acetaminophen and ibuprofen in the recommended range for fever treatment.

Keywords Paracetamol · Pain treatment · Oligoanalgesia · Barriers · Dose errors · Fever

Introduction

In emergency medicine, acute pain management includes non-pharmacological and especially pharmacological strategies [4, 8]. Recommended drug management for acute to moderate pain is based on acetaminophen or ibuprofen [7]. Several data demonstrate that pain is often not treated [5, 11], but no study has so far investigated if children are prescribed adequate doses of acetaminophen or ibuprofen. Aim of this study was to investigate the prevalence of under-dosage of acetaminophen and ibuprofen for pediatric pain management in emergency department.

Methods

Four Italian pediatric hospitals and 18 general hospitals with a separate pediatric emergency room were invited to participate in a retrospective survey on pain management among children with acute pain.

Subjects ≥ 4 weeks and < 14 years of age with acute pain initially prescribed with acetaminophen or ibuprofen were eligible. Exclusion criteria were: simultaneous (i.e., < 10 min apart) prescription of both acetaminophen and ibuprofen, chronic management with opioids and pre-existing chronic liver or kidney disease. Patients without information on body weight, dosage, and prescribed route of administration of acetaminophen or ibuprofen were also excluded.

Following doses were considered appropriate [12]: for oral acetaminophen 15–20 mg/kg body weight (1000 mg in children ≥ 50 kg body weight), for rectal acetaminophen 30–40 mg/kg body weight, for intravenous acetaminophen 7.5 mg/kg body weight (15 mg/kg in children ≥ 10 kg), and

for oral ibuprofen 10 mg/kg body weight (400 mg in children ≥ 40 kg body weight).

Data on type of hospital (pediatric or general) and availability of internal guidelines on pediatric pain management were also collected. For each prescription, the percentage variation from the minimum of the appropriate dose was calculated. Wilcoxon test was used to compare these variations among children receiving oral, intravenous, rectal acetaminophen and oral ibuprofen. Furthermore, the possible factors triggering under-dosage of either acetaminophen or ibuprofen were addressed using the χ^2 automatic interaction detection method. This approach involves the construction of a decision tree that splits the sample into progressively smaller subsets based on which factor is most strongly related to the outcome at each split. For this purpose, the percentage variation from the minimum of the appropriate dose was considered as dependent variable while prescribed drug, age, gender, body weight, type of hospital (pediatric or general), and availability of internal guidelines on pediatric pain management in the emergency department were considered as independent variants. Statistical significance was assigned at $P < 0.05$. The study protocol was approved by the ethics committees of the participating centers and was conducted in accordance with the 1964 Helsinki declaration and its later amendments.

Results

A total of 17 centers (including the four children's hospitals) accepted to participate (12 with and 5 without internal pain management guidelines). Data of 1471 children managed for acute pain between January 1, 2013 and October 31, 2014, were available. Among them, the prescribed dose was appropriate ($N = 518$) or even slightly (by $\leq 10\%$) excessive ($N = 60$) in 578 (39%) and insufficient in the remaining 893 (61%) cases. Among the latter, 577 children (333 males and 244 females) with a median age of 6.0 (interquartile range 2.0–10.5) years were prescribed acetaminophen, while 316 children (189 males and 127 females) with a median age of 5.8 (interquartile range 2.0–10.0) years were prescribed ibuprofen.

The percentage variation from the minimum of the appropriate dose (Table 1) was on average equal for oral and intravenous acetaminophen (20%) and significantly higher for rectal acetaminophen (47%, $P < 0.001$) and oral ibuprofen (30%, $P < 0.05$).

The χ^2 automatic interaction detection analysis identified the following terminal nodes: (1) rectal prescription of acetaminophen ($N = 130$, mean variation from the minimum appropriate dose 15%), (2) body weight < 12 kg ($N = 121$, mean variation from the minimum appropriate dose 14%) and > 40 kg ($N = 160$, mean variation from the minimum appropriate dose 18%), and

Table 1 Percentage variation from the minimum of the appropriate dose in 893 children (522 males and 371 females) prescribed with oral, rectal, or intravenous acetaminophen, respectively oral ibuprofen. Data are given as absolute values or median and interquartile range

	Number of patients	Variation from the minimum of appropriate dose (%)
Acetaminophen		
Oral	414	20 [20–27]
Intravenous	33	20 [7–33]
Rectal	130	47 [37–54]**
Ibuprofen, oral	316	30 [20–40]*

* $P < 0.05$, ** $P < 0.001$

(3) use of oral ibuprofen ($N = 196$, mean variation from the minimum appropriate dose 22%). The remaining variables (age, gender, type of hospital, and availability of internal guidelines) did not identify any terminal node.

Discussion

The results of this study point out that >60% of children with acute pain presented to an emergency department are prescribed an under-dose of acetaminophen or ibuprofen. Under-dosing occurs especially in patients prescribed with rectal acetaminophen, in patients with a body weight <12 kg or >40 kg and in patients prescribed with oral ibuprofen. Finally, under-prescription was similar in general and pediatric centers with and without internal guidelines for pain management.

Dose errors are common in pediatric pharmacotherapy [3]. In this study, under-dosing occurred significantly more often in children prescribed with rectal acetaminophen and oral ibuprofen. The lack of available adequate formulations likely accounts for under-dosing of the former. Furthermore, concerns about toxicity of non-steroidal anti-inflammatory agents probably underlay under-dosing of oral ibuprofen [10]. Patients weighing <12 kg or >40 kg were also prescribed under-dosage of acetaminophen and ibuprofen (a similar tendency was observed for children prescribed with antimicrobials and opioids) [9]. The similar prevalence of dose errors in both pediatric and general centers with and without internal guidelines for acute pain management confirms that physicians often do not adhere to guidelines based on review of evidence-based medicine [1]. Poor awareness or familiarity with guidelines account at least in part for this observation [2]. Furthermore, acetaminophen and ibuprofen are, in addition to pain, usually prescribed for fever management [6]. Currently recommended dosing regimens are lower by 30% or more when treating fever as compared to pain [6]. Hence, we speculate that the prescription of insufficient doses of these drugs for acute pain management may reflect, in many cases, prescription of anti-pyretic doses.

One limitation of the study is that it only considered weight-based regimens, while in some circumstances (e.g., excessive body mass index) other methods for dose scaling might be more appropriate. Furthermore, the findings are limited to the prescribing stage and do not consider potential errors during dispensing of drugs.

In conclusion, this study shows that >60% of children presented to Italian emergency departments with acute pain are prescribed an insufficient dose of acetaminophen or ibuprofen. Defining clinical practice guidelines on acute pain management is only one step in the process of developing evidence-based care for children. An appropriate next step is to devise effective methods for their implementation emphasizing that recommended doses of acetaminophen and ibuprofen are different when managing fever or pain.

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Authors' contributions All authors contributed in the study design and data interpretation, were accountable for all aspects of the work and approved the final manuscript as submitted. Dr. Milani coordinated the study. Dr. Benini, Dr. Dell'Era, Dr. Silvagni, Dr. Mancusi, and Dr. Fossali wrote the initial draft. Dr. Fossali supervised the study. Dr. Mancusi performed the statistical analysis. Dr. Podestà gave significant scientific inputs in his area of expertise.

Compliance with ethical standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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