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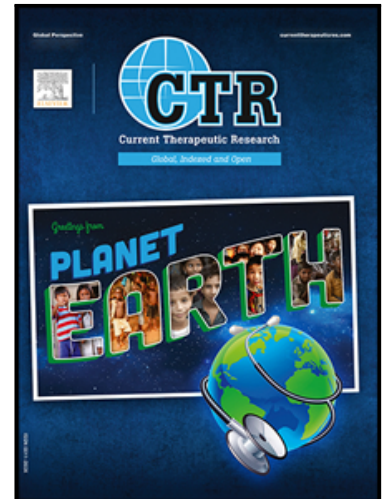


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Parental experience of potential adverse drug reactions related to their oral administration of antipyretic analgesics in children in Saudi Arabia

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Abstract:	<p>Background Oral antipyretic analgesics are commonly used medicines in children with the potential for adverse drug reactions (ADRs). The aim of this study was to explore parental experiences of potential ADRs related to their oral administration of antipyretic analgesics in children in the Kingdom of Saudi Arabia (KSA).</p> <p>Methods For this cross-sectional survey, a paper-based questionnaire, consent form and information sheet were handed out to 1000 parents who had administered an oral antipyretic analgesic to their children in the previous three months. Data were entered and analyzed using SPSS v.21.0 (IBM Corporation, Somers, NY, USA). Simple descriptive and inferential statistics were used. Management and ethical approvals had been gained.</p> <p>Results In March-April 2017, 661 parents agreed to participate giving a response rate of 66.1%. Of the surveyed sample, 208 parents had observed one or more potential ADRs (31.5%, n=208/661). Parents (n=208) most commonly reported potential ADRs (n=523) were: loss of appetite (23%, n=120/523), stomach ache (20.3%, n=106/523), abdominal colic (13%, n=68/523), and diarrhea (10.3%, n=54/523). Parents described severity of the ADRs as 'slight' (71.8%, n=342/476), 'annoying to the child...' (7.9%, n=85/476), 'significant and affecting daily tasks' (3.6%, n=17/476) and 'significant and led to the hospital' (6.7%, n=32/476). Fever was the top ranked reason for using antipyretic analgesics (41.0%, n=271/661), followed by toothache (25.0%, n=165/661) and tonsillitis/laryngitis (24.7%, n=163/661). 34.7% of parents (n=165/476) did not seek medical attention when a potential ADR occurred while 26.3% (n=125/476) of parents took their children to hospital clinics.</p> <p>Conclusions Although the majority of parentally reported (but not proven) ADRs were mild, a number of significant ADRs were reported. Future research should consider whether there is a role for physicians and pharmacists in educating parents in KSA, and perhaps more widely, about the optimal use of oral antipyretics and analgesics in children.</p>
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Parental experience of potential adverse drug reactions related to their oral administration of antipyretic analgesics in children in Saudi Arabia

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Authors' Contributions

Mansour Tobaiqy conceived the study and, together with KM, MR, AMA, AHA, MT and ZA designed the questionnaire and performed the study. The manuscript was written by all authors.

Parental experience of potential adverse drug reactions related to their oral administration of antipyretic analgesics in children in Saudi Arabia

Abstract

Background

Oral antipyretic analgesics are commonly used medicines in children with the potential for adverse drug reactions (ADRs). The aim of this study was to explore parental experiences of potential ADRs related to their oral administration of antipyretic analgesics in children in the Kingdom of Saudi Arabia (KSA).

Methods

For this cross-sectional survey, a paper-based questionnaire, consent form and information sheet were handed out to 1000 parents who had administered an oral antipyretic analgesic to their children in the previous three months. Data were entered and analyzed using SPSS v.21.0 (IBM Corporation, Somers, NY, USA). Simple descriptive and inferential statistics were used. Management and ethical approvals had been gained.

Results

In March-April 2017, 661 parents agreed to participate giving a response rate of 66.1%. Of the surveyed sample, 208 parents had observed one or more potential ADRs (31.5%, n=208/661). Parents (n=208) most commonly reported potential ADRs (n=523) were: loss of appetite (23%, n=120/523), stomach ache (20.3%, n=106/523), abdominal colic (13%, n=68/523), and diarrhea (10.3%, n=54/523). Parents described severity of the ADRs as 'slight' (71.8%, n=342/476), 'annoying to the child...' (7.9%, n=85/476), 'significant and affecting daily tasks' (3.6%, n=17/476) and 'significant and led to the hospital' (6.7%, n=32/476). Fever was the top ranked reason for using antipyretic analgesics (41.0%, n=271/661), followed by toothache (25.0%, n=165/661) and tonsillitis/laryngitis (24.7%, n=163/661). 34.7% of parents (n=165/476) did not seek medical attention when a potential ADR occurred while 26.3% (n=125/476) of parents took their children to hospital clinics.

Conclusions

Although the majority of parentally reported (but not proven) ADRs were mild, a number of significant ADRs were reported. Future research should consider whether there is a role for physicians and pharmacists in educating parents in KSA, and perhaps more widely, about the optimal use of oral antipyretics and analgesics in

children.

Keywords: antipyretic analgesics, adverse drug reactions, children, parents, survey

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Introduction

Oral antipyretic analgesics including acetaminophen (paracetamol) and the non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, are commonly used medicines in children, with established evidence of efficacy and effectiveness [1-4]. Both are classified in many countries, including the Kingdom of Saudi Arabia (KSA), as ‘over-the-counter’ (OTC) medicines with ease of availability and access to parents for oral administration to their children. Antipyretic analgesics are reported as being the most common OTC medicines purchased by the public in KSA and freely available on prescription from governmental hospitals or for a charge from private pharmacies. [5]. However, this ease of availability has led to cases of incorrect dose administration by parents with their children, resulting in potential adverse drug reactions (ADRs) [6]. ADR is defined by the Medicines and Healthcare products Regulatory Agency (MHRA) as ‘an unwanted or harmful reaction which occurs after administration of a drug or drugs’ [7].

Children are prone to issues of drug misuse and overdose of medicines [8, 9]. Described by Torissi et al. (2018) as a challenging to research population given that children are ‘very sensitive to the undesirable effects of the drugs due to their physiological differences’ [10]. ADRs account for between 4 and 6% of hospital admissions, with incorrect drug dosage constituting one of the leading causes for ADRs [7, 8]. Several studies reported ADRs in children when administered higher than recommended doses [1-6, 8-14]. These reactions included gastrointestinal, renal, and hepatic system ADRs. Several factors affect the exposure of children to antipyretic analgesics rendering children more vulnerable to potential ADRs [8-10]. A major determinant was parental misconceptions about the potentially harmful effects of fever on their children. Hence the perceived need to act quickly in reducing a raised temperature by administering oral antipyretic analgesics [6]. Furthermore, as children are a diverse group in terms of weight and age they experience variable responses to drugs resulting in potential ADRs [8-10]. Li et al. (2011) reported that the highest percentage of drug overdose cases seen in hospital emergency departments were in children under the age of five years old [15].

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Several factors contributed to the overdose and misuse of medicines which included parents' lack of knowledge and inexperience in how to correctly administer oral antipyretic analgesics [6, 15]. Miscalculation of the doses based on weight, individualized dosing and medication liquid formulation, can lead to greater risk of dosing errors in children [16, 17]. A study conducted to assess parental ability to correctly calculate the appropriate acetaminophen dose found that only 30 out of 100 parents were able to do so [18]. Inappropriate storage and disposal of medicines is another cause of misuse [19]. A large study comprising 1,641 households from 22 cities reported that 80% of Saudi homes had an average of at least two expired or unused medicines, with oral antipyretic analgesics constituting half of these medicines [20]. Recently, the Saudi Food and Drug Authority warned against overdosing children less than 12 years of age with paracetamol and there are ongoing concerns about the misuse of analgesics and other medicines by the public in KSA [21].

The aim of this study was to explore parental experiences of potential adverse drug reactions related to their oral administration of antipyretic analgesics in children in Saudi Arabia.

Methods

Research Design

A cross-sectional survey using a paper-based questionnaire was handed out with an information sheet and consent form to the parents of children who had used an oral antipyretic analgesic, with or without a prescription, in the previous three months.

Setting and Recruitment Process

This study was conducted in March - April 2017 in pediatric outpatient clinics, pediatric emergency rooms and hospital waiting areas at four hospitals in Jeddah, KSA: the Maternity and Children's Hospital, the East Jeddah General Hospital, the King Abdul-Aziz Hospital and the Maternity and Children's Hospital Al-Aziziah. Parents were recruited by convenience sampling without any stratification. The researcher handing out the study materials offered assistance to any parents who needed help with completing the questionnaire.

Questionnaire

The questionnaire was based on a recent study of ADRs conducted by members of the research team [21, 22]. It included the following items: demographics (which parent filled in the questionnaire, age of child, gender, number of siblings, parents' levels of education), symptoms and frequency of any previously experienced ADRs, severity of each ADR, and if the child had previously suffered ADRs which parents believed were attributable to the use of antipyretic analgesics. The severity of the potential ADR was categorized by parent respondents as 'slight', or 'annoying to the child or an allergy but they were still able to perform their daily tasks', or 'significant and affecting daily tasks', or 'significant and led to the hospital', or lastly, 'fatal'. Other items collected in the questionnaire focused on parents' reasons for administering oral antipyretic analgesics, where parents would obtain these medicines, who parents would consult on use of these medicines, whether parents read the medicines information leaflet, under which circumstances parents would re-use remaining prescribed oral antipyretic analgesic medicines, and parents' experience of providing the right dose of antipyretic analgesics.

The questionnaire was tested for face and content validity by a panel of 10 academic and healthcare staff and then piloted with 12 parents. No changes were made to the questionnaire post-pilot, so these responses were included in the final dataset.

Completed questionnaires were collected by clinical staff and stored securely for research team collection.

Data Analysis

Questionnaire data were entered and analyzed using SPSS v.21.0 (IBM Corporation, Somers, NY, USA). Simple descriptive and inferential statistics were used in reporting the results.

Ethical approval

Management authorization had been gained from the Ministry of Health (M.O.H) Reference Number (892225) and ethical approval from the National Committee of Bio and Medical Ethics, Reference Number (872863).

Results

One-thousand information sheets, consent forms and questionnaires were handed out with 661 parents agreeing to participate in the survey, giving a response rate of 66.1%. Mothers accounted for 63.8% (n=422/661), and 27.8% (n=184/661) were fathers with the remainder (8.3%, n=55/661) not disclosed. Demographics and experience of administering antipyretic analgesics are reported in Table 1 with details of potential ADRs in Table 2. Parents' responses related more to sons (44.8%, n=296/661) than daughters (38.1%, n=252/661) with the remainder again not disclosed (17.1%, n=113/661). The children were aged below five years of age (29%, n=192/661), with 58.9% in the 5 years to under 10 years age group (n=389/661) while 12.1% of the children were 10 years or older (n=80/661). Most were from families of 2 to 5 children (57.5%, n=380/661). The majority of mothers (52.6%, n=348/661) and fathers 58.4% (n=386/661) had completed higher education. However, some mothers (15.1%, n=100/661) and fathers (3.8%, n=25/661) described themselves as 'illiterate'. Assistance was offered in completing the questionnaire.

Frequency of potential ADRs, severity and causality: Of the surveyed sample, 208 parents had observed one or more potential ADRs (31.5%, n=208/661). The most commonly reported potential ADRs (n=523) were: loss of appetite (23%, n=120/523), stomach ache (20.3%, n=106/523), abdominal colic (13%, n=68/523), diarrhea (10.3%, n=54/523), bloody stool (7.6%, n=40/523) and anxiety (5.4%, n=28/523). Less frequent potential ADRs were rash (5.4%, n=28/523) and weight loss (5.2%, n=27/523), feeling of isolation (5.0%, n=26/523), anemia (3.6%, n=19/523) and fatigue (1.3%, n=7/523). Regarding the severity of the potential ADRs, 71.8% (n=342/476) were perceived by parents as 'slight', 17.9% (n=85/476) perceived the

1 ADRs as 'annoying to the child or an allergy but they were still able to perform their
2 daily tasks' or 'significant and affecting daily life tasks' (3.6%, n=17/476) when
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4 describing the potential ADR and 6.7% (n=32/476) perceived them as 'significant and
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6 led to the hospital'; none reported experiencing a fatal potential ADR. Respondents
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8 were either certain that the antipyretic analgesic had caused the adverse reaction
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10 (33.9%, n=224/661) or disagreed (28%, n=185/661) or were uncertain (38.1%,
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12 n=252/661). Only 40.4% of parents (n=84/208) were able to name the medication
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14 they believed had caused the potential ADR with acetaminophen (paracetamol) and or
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16 ibuprofen, carrying different brand names and concentrations.
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24 ***Reasons to use antipyretic analgesics:*** Fever was the top ranked reason for using
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26 antipyretic analgesics (41.0%, n=271/661), followed by toothache (25.0%,
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28 n=165/661) and tonsillitis/laryngitis (24.7%, n=163/661).
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34 ***Parents' knowledge of the correct dose of antipyretic analgesics:*** 71% (n=467/661)
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36 of all the respondents believed they were experienced in giving the right dose of
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38 medicines. However, 19.3% (n=128/661) stated they were not and 10.0% (n=66/661)
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40 indicated 'maybe'.
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46 ***Consultation on use and purchasing of antipyretic analgesics:*** 64.7% of parents
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48 (n=427/661) consulted a doctor prior to using oral antipyretic analgesics, 19.8%
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50 consulted a pharmacist (n=131/661) while 12.6% consulted family members
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52 (n=83/661) and very few asked friends (1.8%, n=12/661) or searched on the Internet
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54 (1.2%, n=8/661). Most parents (80.2%, n=530/661) read the enclosed medication
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56 leaflet, however, 19.8% did not (n=131/661). Parents most commonly obtained oral
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1 antipyretic analgesics through a physician's prescription (72.3%, n=478/661) and
2 26.5% purchased these medicines without a prescription (n=175/661). Very few
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4 bought directly from supermarkets (1.1%, n=7/661) or online (0.2%, n=1/661).
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10 ***Re-use of previously prescribed antipyretic analgesics for their child for another***
11 ***illness without medical consultation:*** 57.7% of parents (n=381/661) stated that they
12 would re-use an oral antipyretic analgesic previously prescribed for their child for
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14 another illness without medical consultation. The remainder would not re-use the
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16 medication (31.6%, n=209/661) or did not respond to this question (10.7%,
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19 n=71/661).
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27 ***Parents' response following a potential ADR affecting their children:*** 34.7% of
28 parents (n=165/476) stated that they did not seek medical attention when a potential
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30 ADR occurred while 26.3% of parents (n=125/476) took their children to hospital.
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32 The remainder either stopped giving the medicine (16.6%, n=79/476) or would take
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34 their child to the hospital emergency room (7.4%, n=35/476). When parents were
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36 asked whether they thought that the medication they gave to their children caused the
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38 potential ADR, responses were 'yes' (33.9%, n=224/661), 'no' (28%, n=185/661) and
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42 'uncertain' (38.1%, n=252/661).
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Discussion

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2 This research study investigated parental experience of potential adverse drug
3 reactions related to their oral administration of antipyretic analgesics in children in
4 Saudi Arabia. The results show that some parents experienced their child suffering
5 one or more potential ADRs, a small proportion of which were sufficiently severe the
6 concerned parents took their child to hospital. Given that one in five parents admitted
7 not reading the enclosed information leaflet, it can be concluded that they were either
8 unsure or did not have the experience to provide the correct dose of oral antipyretic
9 analgesic. Together with more than half of the parents re-using medications
10 prescribed for a possibly different condition, it is incumbent on pharmacists to
11 counsel thoroughly using short, clear, non-technical messages.
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29 Parents reported common and less common ADRs associated with their child's
30 antipyretic analgesic medicines use. Most were mild and commonly recognized in
31 clinical trials and post-marketing surveillance studies [3, 4]. The most common
32 potential ADRs reported by parents in this study were loss of appetite, stomach ache
33 and abdominal colic. Less frequent potential ADRs were rash, weight loss and
34 anemia. Even though rashes were reported in this study, nonetheless they are
35 considered in the literature as rare potential ADRs in response to NSAIDs [23]. Of
36 great concern were the two-hundred sixty-eight (n=51.2%) cases of gastrointestinal
37 tract (GIT) ADRs with complications including rectal bleeding and anemia reported
38 in this study (Table 2). GIT adverse effects, including peptic ulcer, bleeding and
39 perforation are known to be associated with the use of NSAIDs occurring due to
40 mucosal prostaglandin depletion and are considered as rare ADRs [24]. A population-
41 based survey conducted in France to describe upper gastrointestinal bleeding (UGIB)
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1 reported in 177 children, aged between 2 months and 16 years, revealed that 83
2 children were prescribed at least one NSAID in the seven days preceding the
3 admission and one-third of the UGIB were deemed attributable to use of ibuprofen or
4 aspirin at analgesic or antipyretic dose [25].
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11 Other determinants such as parental level of education clearly had an effect on the
12 administration of oral antipyretic analgesics. Surprisingly in this study, parents with a
13 high level of education, such as college or university degree, still did not read the
14 medication leaflet and often consulted family members rather than medical
15 professionals prior to administering the antipyretic analgesics. It would be expected
16 that level of literacy would play an important role in understanding drug related
17 instructions. However, parents could still be confused and miscalculate doses [26-28].
18
19 We suggest providing education and clear instructions to parents, as well as
20 healthcare professionals, on the appropriate use of oral antipyretic analgesics in
21 children. Fever is one of the most commonly consulted pediatric symptoms but there
22 is a lack of consensus in the guidance available to parents on the optimal way to
23 manage it [29-33]. Thus, appropriate counseling of the parents on fever, and the
24 proper use of oral antipyretic analgesics to manage it, should be encouraged.
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46 The majority of parents (58%) re-used medications previously prescribed for their
47 child for another illness without medical consultation. This has been shown to be a
48 major contributing factor for ADRs [34, 35]. Although we cannot be certain of any
49 link between reported ADRs and the medicines under investigation, it is clear that the
50 children's parents have made such a link to oral antipyretic analgesics. Educating the
51 public on the importance of correctly disposing of unused medicines, as well as
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1 consulting physicians prior to the re-use of any medicines, is crucial [31]. Schemes to
2 dispose of unused medication have been successfully carried out in some countries
3 [34, 35]. Previous studies found similar results about parental lack of knowledge
4 regarding ADRs associated with medicines [36-38].
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11 It is important for a physician to describe in appropriately measured language the
12 correct use of antipyretic analgesics to parents whether or not they have previously
13 been counselled on using similar medication. Additionally, there is a major role to be
14 played by pharmacists, as they can provide appropriate advice on the management of
15 fever and pain. Although ibuprofen and acetaminophen are generally regarded as well
16 tolerated and effective when used appropriately for the management of fever and pain
17 in children, they should be used cautiously in order to minimize the risk of ADRs [34-
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34 A limitation of this study is the possibility of recall bias in parents' experience of oral
35 antipyretic analgesics with their children which could affect the results. Also, it
36 should be noted that some questionnaires were filled in by parents in outpatient clinics
37 attending because of concerns about their child's health which could again have
38 influenced their answers. With some parents identifying as 'illiterate' the
39 administration of the survey by a researcher rather than self-completion may have
40 introduced some inconsistency. A further limitation was not asking specifically
41 whether the child was admitted to hospital as a consequence of any potential ADRs.
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56 **Conclusions**

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58 Not unexpectedly, parental experiences of potential ADRs related to their oral
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administration of antipyretic analgesics to their children in Saudi Arabia were varied.

Although the majority of parentally reported (but not proven) ADRs were mild, a significant number of severe ADRs were reported. Future research should consider whether there is a role for physicians and pharmacists in educating parents in KSA, and perhaps more widely, about the optimal use of oral antipyretics and analgesics in children.

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Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Table 1. Demographics of participants and experience of administering oral antipyretic analgesic in children

Demographics n=661	Number of parents n (%)
Mothers education	
Illiterate	100 (15.1%)
Primary	4 (0.6%)
Intermediate	8 (1.2%)
Secondary	193 (29.2%)
University	348 (52.6%)
Higher Studies	8 (1.2%)
Fathers education	
Illiterate	25 (3.8%)
Primary	10 (1.5%)
Intermediate	19 (2.9%)
Secondary	212 (32.1%)
University	386 (58.4%)
Higher Studies	9 (1.4%)
Age of child attending paediatric outpatient clinic	
< 5 years	192 (29.0%)
5 and < 10 years	38 (58.9%)
>= 10 years	80 (12.1%)
Do you have experience of providing the correct dose of antipyretic analgesic?	
Yes	467 (70.7%)
No	128 (19.3%)
Maybe	66 (10.0%)
Who did you consult before using the antipyretic analgesic?	
Family	83 (12.6%)
Physician	427 (64.6%)
Pharmacist	131 (19.8%)
Friend	12 (1.8%)
Internet	8 (1.2%)
Did you read the enclosed leaflet attached to the antipyretic analgesic?	
Yes	530 (80.2%)
No	131 (19.8%)
How did you obtain the antipyretic analgesic?	
Physician's prescription	478 (72.3%)
Without prescription	175 (26.5%)
The supermarket	7 (1.1%)
From the internet	1 (0.2%)
Would you reuse an antipyretic analgesic previously prescribed to your child for another illness without medical consultation?	
Yes	381 (57.7%)
No	209 (31.6%)
Maybe	71 (10.7%)
Reasons for using antipyretic analgesic for your child?	
Fever	271 (41.0%)

Toothache	165 (25.0%)
Tonsillitis and laryngitis	163 (24.7%)
Earache	46 (7.0%)
After traumas, burns or rashes	6 (0.9%)
After trauma or bruises	3 (0.5%)
Other	7 (1.1%)

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Table 2. Parents' experience of ADR following administration of oral antipyretic analgesic in children

ADRs observed by parents in their children (n=523)*	
Appetite loss	120 (22.9%)
Stomach ache	106 (20.3%)
Abdominal Colic	68 (13.0%)
Diarrhea	54 (10.3%)
Blood in stool	40 (7.6%)
Anxiety	28 (5.4%)
Rash	28 (5.4%)
Weight loss	27 (5.2%)
Isolation	26 (5.0%)
Anemia	19 (3.6%)
Fatigue	7 (1.3%)
Severity of the ADRs affecting the children (n=476)*	
Slight	342 (71.8%)
Annoying to the child or an allergy but they were still able to perform their daily tasks	85 (17.9%)
Significant and affecting daily life tasks	17 (3.6%)
Significant and led to the hospital	32 (6.7%)
Fatal	0 (0.0%)
Do you think that the antipyretic analgesic used caused these adverse effects? (n=661)*	
Yes	224 (33.9%)
No	185 (28.0%)
Uncertain	252 (38.1%)
What was your decision when an ADR occurred with your child? (n=476)*	
I didn't do anything	165 (34.7%)
I went to the hospital clinic	125 (26.3%)
I went to the ER	35 (7.4%)
I stopped the medication	79 (16.6%)
I consulted a pharmacist	11 (2.3%)
I consulted a physician	48 (10.1%)
The physician changed the medication	2 (0.4%)
The physician lowered the dose	8 (1.7%)
Other	3 (0.6%)

***not all parents observed an ADR;
some parents observed multiple ADRs**