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RESEARCH ARTICLE

Utilisation study of antipyretic drugs in paediatric patients

Arina Dery Puspitasari[1,3], Anita Nur Azizah[2], Wenny Putri Nilamsari[1], Robby Nurhariansyah[3], Ika Nursetyo Palupi[3]

[1] Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2] Bachelor Programme Study of Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[3] Universitas Airlangga Hospital, Surabaya, Indonesia

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Correspondence
Arina Dery Puspitasari
Department of Pharmacy Practice
Faculty of Pharmacy
Universitas Airlangga
Surabaya
Indonesia
arinadery@ff.unair.ac.id

Abstract

Background: Fevers are common in children with underlying diseases; thus, antipyretics are often used. There are no specific established guidelines for the use of antipyretics in children. **Objective:** This study aimed to determine the profile of antipyretics used by paediatric inpatients at Universitas Airlangga Hospital and to identify possible side effects and interactions associated with antipyretics use. **Method:** This study was observational and conducted from March to June 2023. Convenience sampling was used to collect data retrospectively from patients' medical records. The data were analysed descriptively. **Result:** A total of 87 paediatric patients met the inclusion criteria. All paediatric patients received intravenous metamizole as an antipyretic treatment (100.0%), with 3 x 8 - 20 mg/kgBW as needed (55.2%) being the most used dosage regimen. Metamizole as monotherapy was the most widely used pattern (80.5%), showing the shortest mean therapy duration. Paracetamol was only used in switching (11.5%) and alternating (8.1%) patterns. Abdominal pain was the most actual suspected side effect of metamizole (3.4%). No potential drug interactions associated with antipyretics were found. **Conclusion:** In general, intravenous metamizole effectively reduced fever in most paediatric patients hospitalised at Universitas Airlangga Hospital.

Introduction

Fever is a clinical manifestation of diseases, especially diseases caused by infections. Infection and fever in children can also result from non-infectious causes such as inflammation (Barbi *et al*., 2017). Although most fevers in children are self-limiting, an increase in body temperature above 39°C can have negative consequences; therefore, every child with a fever needs to be examined and given appropriate therapy (World Health Organisation, 2013).

The frequent occurrence of fever in children makes antipyretics one of the most common drugs given to children (Tasker *et al*., 2013). There are various antipyretics available to treat fever in children. Paracetamol is usually the drug of choice because it is associated with fewer adverse effects compared to ibuprofen (Tasker *et al*., 2013). Another antipyretic drug that is available to treat fever in children is metamizole (Zahn *et al*., 2021). The use of metamizole itself is still controversial and has been banned in several countries because of its potential to cause agranulocytosis (de Leeuw *et al*., 2017).

Studies regarding the effectiveness of paracetamol, ibuprofen, and metamizole as antipyretics have had varied results. In a meta-analysis by Kuo and colleagues in 2021, there was no significant difference regarding paracetamol's effectiveness compared to ibuprofen. Studies related to metamizole's effectiveness compared to other antipyretics in children are still very limited. Antipyretic drug use patterns during hospitalisation may vary, including alternating and combining antipyretics. However, the effectiveness of using antipyretics alternately or in combination has varied results, and there has been a lack of data on

safety regarding these practices (National Institute of Health and Care Excellence, 2013).

In selecting antipyretics, practitioners need to weigh the risks and benefits of each antipyretic, especially regarding their potential side effects and contraindications. Besides antipyretics, paediatric inpatients also receive other therapies as part of their treatment that might cause drug interactions. Specific guidelines regarding antipyretic use in children have also not been established, especially regarding the use of metamizole as an antipyretic. Due to the lack of information regarding the use of metamizole as an antipyretic in children and the complexity of therapies given in the hospital, this study aimed to determine the profile of antipyretics used on paediatric inpatients at Universitas Airlangga Hospital and identify possible side effects and interactions associated with antipyretic use.

Methods

Design

This study used an observational descriptive design with a cross-sectional study type. It was conducted retrospectively between March and June 2023 using patient medical records at Universitas Airlangga Hospital. The inclusion criteria were paediatric patients with fever who had been diagnosed and received antipyretics during their hospitalisation at Universitas Airlangga Hospital. Convenience sampling was used as the sampling technique. Paediatric patients were categorised as having a fever when their body temperature reached 37.4°C or higher, measured from the axillae. The minimum sample size calculated using the Slovin formula was 82 samples.

Ethical approval

The Ethics Committee of Universitas Airlangga Hospital granted ethical approval (Number 023/KEP/2023).

Assessment

Data obtained from patient medical records were analysed to determine the profile of antipyretics. This included the clinical data, type of antipyretics, dosage regimentation, and route and administration time. Symptoms recorded in the patient's medical records were used to identify suspected side effects, while potential drug interactions were identified through antipyretics and other drugs administered to the paediatric patients. The results were then analysed descriptively using Micromedex and VigiAccess to define the side effects and drug interactions.

Results

Out of 114 paediatric patients, 27 were excluded from this study, consisting of 21 patients who received antipyretics for analgesic purposes, five who did not have their fever temperature recorded, and one who was discharged voluntarily. As a result, 87 paediatric patients met the inclusion criteria. Table I shows the characteristics of the paediatric patients. The paediatric patients were mostly male (54.0%), with preschoolers the largest age demographic (27.6%). Pneumonia was the most common diagnosis (26.4%).

Table I: Paediatric patients' characteristics (n = 87)

Characteristics	Number (%)
Gender	
Male	47 (54.0%)
Female	40 (46.0%)
Age	
Neonates (0-28 days)	0 (0.0%)
Infant (1-12 months)	9 (10.3%)
Toddler (1-3 years)	23 (26.4%)
Preschooler (3-6 years)	24 (27.6%)
School-age (6-12 years)	21 (24.1%)
Adolescent (12-18 years)	10 (11.5%)
Diagnosis*	
Respiratory	
Pneumonia	23 (26.4%)
Acute respiratory infection	10 (11.5%)
Bronchopneumonia	5 (5.7%)
Tonsillopharyngitis	5 (5.7%)
Pharyngitis	5 (5.7%)
Others	6 (6.9%)
Gastrointestinal	
Acute gastroenteritis	15 (17.2%)
Others	3 (3.4%)
Systemic	
Fever	9 (10.3%)
Dengue haemorrhagic fever	5 (5.7%)
Dengue fever	4 (4.6%)
Others	6 (6.9%)
Urinary tract	
Urinary tract infection	6 (6.9%)
Blood	
Leukocytosis	2 (2.3%)
Neurological	
Febrile convulsion	1 (1.1%)
Grand mal seizure	1 (1.1%)
Exanthem	
Measles	1 (1.1%)
Roseola	1 (1.1%)

*One patient could have more than one diagnosis.

Table II shows the profile of antipyretics used on paediatric patients. All paediatric patients with fevers (100.0%) received intravenous (IV) metamizole as their antipyretic. Both IV (9.2%) and oral (9.2%) were the most used administration routes of paracetamol. Metamizole at doses of 3 x 8 – 20 mg/kgBW as needed was the most widely used antipyretic dosing regimen (55.2%). All paracetamol IV doses given to paediatric patients (9.2%) were lower than the doses in previous literature.

Table II: Antipyretic profiles used by paediatric patients (n = 87)

Profile	Number (%)
Type of antipyretics*	
Metamizole	87 (100.0%)
Paracetamol	17 (9.5%)
Route of administration*	
Metamizole	
Intravenous	87 (100.0%)
Paracetamol	
Intravenous	8 (9.2%)
Oral	8 (9.2%)
Rectal	3 (3.4%)
Dosage regimentation*	
Metamizole IV	
Routine	
3 x 8–20 mg/kgBW	35 (40.2%)
4 x 8–20 mg/kgBW	1 (1.1%)
As needed	
3 x 8–20 mg/kgBW	48 (55.2%)
4 x 8–20 mg/kgBW	4 (4.6%)
8–20 mg/kgBW	3 (3.4%)
Paracetamol IV	
Routine	
3 x <15 mg/kgBW	1 (1.1%)
4 x <15 mg/kgBW	1 (1.1%)
As needed	
3 x <15 mg/kgBW	2 (2.3%)
4 x <15 mg/kgBW	2 (2.3%)
<15 mg/kgBW	2 (2.3%)
Oral paracetamol	
Routine	
3 x 10 – 15 mg/kgBW	1 (1.1%)
4x10–15 mg/kgBW	1 (1.1%)
4x<10 mg/kgBW	1 (1.1%)
As needed	
3x10–15 mg/kgBW	5 (5.7%)
Rectal paracetamol	
As needed	
125 mg	2 (2.3%)
250 mg	1 (1.1%)

*One patient could receive more than one antipyretic, route, or dosage.

Table III shows the mean duration of temperature reduction and antipyretic therapy. Metamizole IV administered as monotherapy was the most widely used pattern in paediatric patients (80.5%) and shows the shortest mean therapy duration compared to other patterns. Paracetamol was only used in switching (11.5%) and alternating (8.1%) patterns. Paediatric patients whose antipyretics were switched from rectal paracetamol to metamizole IV (2.3%) showed the shortest mean duration of temperature reduction compared to other patterns.

Table III: Mean duration of temperature reduction and antipyretics therapy (n=87)

Usage patterns	Number (%)	Mean duration	
		Temperature reduction	Antipyretic therapy
Monotherapy			
• Metamizole (IV)	70 (80.5%)	25.8 hours	33.5 hours
Switching			
• Metamizole (IV) → Paracetamol (IV)	4 (4.6%)	64 hours	64.6 hours
• Metamizole (IV) → Paracetamol (Oral)	3 (3.5%)	47.2 hours	60.0 hours
• Paracetamol (Rectal) → Metamizole (IV)	2 (2.3%)	22.9 hours	57.9 hours
• Paracetamol (Rectal) → Metamizole (IV) → Paracetamol (Oral)	1 (1.2%)	100.5 hours*	120.5 hours*
Alternating			
• Metamizole (IV) with paracetamol (IV)	3 (3.5%)	69.1 hours	133.6 hours
• Metamizole (IV) with paracetamol (Oral)	3 (3.5%)	23.2 hours	127.2 hours
• Metamizole (IV) with paracetamol (Oral and IV)	1 (1.2%)	28 hours*	28 hours*

*Cannot be averaged because n=1.

Table IV shows the suspected actual side effects of antipyretics. Abdominal pain was the most suspected actual side effect of metamizole (3.4%). No potential

drug interactions were found in the use of antipyretics with other drugs.

Table IV: Suspected actual side effects of antipyretics (n = 87)

Suspected side effects	Number (%)	Other used drugs	Diagnosis
Metamizole			
Vomiting	1 (1.1%)	Ceftriaxone	Pneumonia
Nausea	1 (1.1%)	-	Pneumonia
Abdominal pain	3 (3.4%)	Becom C, Curcumin	Tonsillitis (1), fever (1), dengue fever (1)
Paracetamol			
Vomiting	1 (1.1%)	Amikacyn, Ambroxol, Salbutamol, Alerfed	Pneumonia

Discussion

The incidence of fever in this study, which was more common in boys, could be attributed to genetic factors. Since males only have one X chromosome and females have two, males are known to have poorer innate immunity than females, considering several innate immunity-related genes are found in the X chromosome (Jaillon *et al*., 2017). Research conducted by Norcahyanti and colleagues in 2021 also discovered that boys were more likely to develop infections than girls. Children's age groups can indicate their stage of development. This includes the immune system related to the child's susceptibility to diseases with fever manifestations (Simon *et al*., 2020). In this study, fevers mostly occurred in pre-schoolers aged three-to-six-years, followed by toddlers aged one-to-three years. A child's immune system, which will reach full maturity at the age of seven to eight years, could cause a high prevalence of fever in toddlers and pre-schoolers (Kloc *et al*., 2020).

Pneumonia, followed by acute gastroenteritis, was this study's most frequent diagnosis among paediatric patients. Infectious agents are the root cause of both diseases. Patients with acute bacterial gastroenteritis and pneumococcal pneumonia often have high fevers (El-Radhi *et al*., 2018). In this study, pneumonia and acute gastroenteritis paediatric patients had average highest body temperatures of 38.5^{o}C and 38.7^{o}C, respectively.

Metamizole was the main antipyretic utilised in this study. The high use of metamizole in children could be attributed to its effectiveness in lowering body temperature, wide therapeutic index, minimal contraindications, and lower cost (Zahn *et al*., 2021). Metamizole also has more analgesic potency than paracetamol (Ince *et al*., 2015). This makes metamizole administration more advantageous because it also helps to relieve discomfort during fever. In this study, paracetamol was only given to patients with exceptional needs, such as those whose temperatures did not stabilise after receiving metamizole several times.

No studies have stated the optimal time to switch from metamizole to paracetamol. However, in this study, patients' antipyretics were mostly switched from metamizole to paracetamol from the second to the fourth day of treatment. The most frequent antipyretic administration route in this study was intravenous, which can be attributed to paediatric palatability. The intravenous route has several benefits over the oral route, including faster onset and higher bioavailability.

The most widely used antipyretic dosage regimen in this study was intravenous metamizole 3x8–20 mg/kgBW as needed, and this is in agreement with previous literature. The literature stated that metamizole should be given at doses of 8–16 mg/kgBW for children up to 14 years old and in a single dose of 500–1000 mg for children 15 years old and older or weighing over 53 kg.

In this study, all intravenous paracetamol doses given to paediatric patients were below the doses in previous literature. Meanwhile, the oral and rectal paracetamol doses were already in agreement with the literature, except for one patient who received oral paracetamol below the advised dose (El-Radhi *et al*., 2018). The rectal route was preferably utilised only when the PO route was impractical, or there was no availability for IV administration. Patients' clinical conditions and the rounding off from calculations are the factors that influence clinicians in determining the dose given to paediatric patients.

In this study, paediatric patients received antipyretics in one of three ways: monotherapy, switching, or alternating. Patients who received metamizole monotherapy had the shortest mean therapy duration compared to other patterns. Administration of a single antipyretic is recommended unless the child still feels uncomfortable after receiving one type of antipyretic (National Institute of Health and Care Excellence, 2013). Patients whose antipyretics were switched from rectal paracetamol to intravenous metamizole achieved the shortest mean duration of temperature reduction. In this case, paracetamol was only administered once in the emergency room and was switched to intravenous metamizole because they had not reached a stable, normal temperature.

Suspected actual side effects were analysed based on the patients' reported symptoms that were not apparent when they were admitted to the hospital and only appeared after the administration of therapy. During the routine visits, the medical staff entered the patients' daily symptoms in their medical records, along with the medications taken. The records to determine the suspected actual side effects were also reviewed.

Even though in this study, abdominal pain was thought to be the most common suspected actual side effect of metamizole, reports of abdominal pain as a side effect of metamizole were lower compared to other NSAIDs such as ibuprofen, namely 421 versus 4,140 reports (World Health Organisations, 2023). This demonstrated that metamizole has fewer risks to the gastrointestinal system than other NSAIDs like ibuprofen. According to the World Health Organisation (2023), all medications other than ceftriaxone that paediatric patients took in this study had fewer reports of causing the suspected actual side effects than the antipyretics. No potential drug interactions were found in this study.

Limitations

Body temperature measurements were observed using the data taken during every eight-hour shift. Not to mention that the diagnosis that wasn't specific might affect the overall results, as different diseases might have different severity and different patterns of fever. Further studies need to be conducted prospectively to determine the rate of temperature reduction with more specific diagnoses and obtain more detailed data.

Conclusion

In general, the use of intravenous metamizole was effective in reducing fever experienced by most paediatric patients hospitalised at Universitas Airlangga Hospital.

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