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Off-Label Drug Use in Acute Respiration Infection Patient at Pangandarn Hospital, Pangandaran District, West Java - Indonesia

Nur Rahayuningsih, Muharam Priatna, Dewi Amalia Sulistiani

Department of Pharmacology, Bakti Tunas Husada University. Tasikmalaya, West Java, Indonesia

Abstract

Acute respiratory infections (ARIs) are infectious diseases of the upper or lower respiratory tract that cause a spectrum of illnesses from mild to severe infections. ARI is one of the leading causes of death in children in developing countries. The high incidence of ARI in children results in the use of off-label drugs. Off-label medicine is the use of drugs outside the provisions of the license relating to dose, age, route of administration, contraindications. This study aims to determine the use of off-label drugs in children with a diagnosis of ARI at Pandega Pangandaran Hospital, Pangandaran District, West Java - Indonesia. This study was an observational study with a cross sectional design and data collection was done retrospectively using Chi-square data analysis with a significance level of 0.05. Of the 84 patients who fit the inclusion criteria, there was an off-label drug use of 16.01% with the categories of off-label age (11.16%), off-label dose (4.37%), and off-label indication (0.48%) while in the category of route of administration and contraindications no off-label drug use was found. The most common type of off-label drug used was cetirizine antihistamine. Based on the results, pharmacist's supervision related to the risk of drug use is strongly recommended.

Keywords: Acute respiratory infection, pediatric, off-label drugs

Introduction

Acute respiratory infections (ARIs) are infectious diseases of the upper or lower respiratory tract that can produce mild to severe illness depending on the causative agent, host, or environmental variables. According to the World Health Organization, ARI is one of the top causes of morbidity and mortality from infectious diseases globally, with newborns, children, and the elderly bearing the greatest risk.[1]

One of the leading causes of death in children in developing countries is ARI, because they can cause respiratory failure and renal failure, especially in children.[2] According to the 2018 health profile data results, the prevalence of ARI in Indonesia was 20.54% of 1000 toddlers. West Java Province is among those with a high incidence of ARI, with a rate of 14.7%, which is greater than in other provinces.[3]

Off-label medication is the off-label use of drugs related to dose, age, route of administration, contraindications, and indications that are not mentioned in the product labeling approved by the Food and Drug Administration (FDA).[4] Off-label use of drugs may increase the risk of adverse drug events (ADEs) or unintended drug effects, which are medication-related side effects that occur in patients, such as adverse drug

Corresponding Author: Nur Rahayuningsih. Faculty of Pharmacy, Bakti Tunas Husada University, Tasikmalaya, West Java - Indonesia. Email: nur.rahayuridwan@gmail.com
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reactions (ADRs) and medication errors. Off-label use of medications in children may increase the likelihood of medication errors.[5] Knowing that pediatric patients have physiologically rudimentary organs and that differences in pharmacokinetic responses between pediatric patients and adults must be considered, off-label use of drugs involves a higher risk of unwanted side effects compared to on-label use of drugs.[6] Therefore, this study aimed to determine the use of off-label drugs in pediatric patients with ARI at Pandega Pangandaran Hospital, Ciamis, West Java Indonesia. This study was conducted in the hope of providing information regarding the use of off-label drugs and reducing the risk of drug use.

Methods

This is an observational study with a descriptive-quantitative research design and a cross-sectional approach, and the data was collected retrospectively at Pangaran Hospital, Pangandaran District, West Java - Indonesia from medical record data containing information on name, age, gender, and diagnosis. In addition, data collection was also sourced from drug prescriptions of patients diagnosed with ARIs aged 0-12 years from January to December 2022.

The sampling technique used in this study was purposive sampling. Informed consent is not required because this study uses a retrospective method for data collection. No medical interventions were performed during the study. All ethical considerations were followed and patient files were processed anonymously. The Ethics Committee of Bakti Tunas Husada Tasikmalaya University approved the research protocol.

We consulted literature such as the National Drug Information Center, the Indonesian Pediatric Association Health Sciences Specialty Formulary, the British National Formulary for Children (BNF), and the Drug Information Handbook (DIH) 21st edition to identify drug prescriptions. Data were analyzed using chi-square in SPSS Statistics version 26.

Research ethics clearance has been obtained from the Research Ethics Commission of the Health Research Ethics Commission of Bakti Tunas Husada University Tasikmalaya with No.015/E.01/KEPK-BTH/II/2023.

Results and Discussion

Data from a total of 84 pediatric patients were collected in this study. With a total of 206 prescriptions, there are 33 prescriptions (16.01%) are included in off-label drugs. Table 1 shows the demographic information for the study subjects. There were 50 males (59.52%) and 34 females (40.48%) among the participants. The largest number was 13.10% in patients aged 1 to 12 years, followed by 86.90% in patients aged 1 to 12 months. The common cold was the most common diagnosis in this study (59.5%).

According to Setyaningrum et al.'s report, there is an overwhelming prevalence of off-label medication use among pediatric demographics, with an incidence rate of incidence rate of 21%. Furthermore, off-label pharmaceutical usage has been reported to be especially widespread in pediatric patients in the early stages of development. As a result, it is critical to monitor the dangers associated with off-label pharmaceutical usage closely, particularly when given to children.[7] As can be seen from Table 2, the off-label drug's use of 16.01% with the categories of off-label age (11.16%), off-label dose (4.37%), and off-label indication (0.48%) while in the category of route of administration and contraindications no off-label drug use was found.

Table 1. Demographic Data of the Study Subjects

Characteristics	Frequency	Percentage (%)
Gender		
Male	50	59.52
Female	34	40.48
Age		
Neonates (0-28 days)	0	0
Infants (1-12 months)	11	13.10
Children (1 year-12 years)	73	86.90
Diagnoses		
Common cold	50	59.50
Asthma	27	32.10
Bronchopneumonia	4	4.80
Pneumonia	2	2.40
Bronchiolitis	1	1.20

Table 2. Distribution of Off-label Drug Use

Category	Frequency	Percentage (%)
Age	23	11.16
Dosage	9	4.37
Indication	1	0.48
Contraindication	0	0
Route of administration	0	0
Total	33	16.01

Off-label use of drugs in the age category is a drug that is used outside the permitted age range. There were 23 cases of use of off-label drugs in this study; the findings are similar to the study conducted by Tuloli in that the use of offline drugs is mostly given to children under the age of 12 years, especially in children under 2 years of age.[8]

Off-label drug prescribing is more common in pediatric patients because special formulations for children are still very limited, while clinical trials for licensed drugs are mostly conducted in children. Cetirizine is the most widely used off-label drug in the age category. The chi-square test analysis showed that there was no association between gender and off-label drug use in this age group, with a significance value of 0.161>0.05 (Table 3).

Cetirizine is not suggested for children under the age of two, according to the BNFC (British National Formulary Children) 2019–2020. According to Tan Rou et al.'s study, the use of antihistamine-containing drugs in children should be limited as there is a high risk of ADR in children.[9]

Cetirizine will cause restlessness, insomnia, and drowsiness if it is given to children under the age of 2 years. BNFC 2019-2020 also advises refusing to give salbutamol to children under 2 years old due to their later onset of action and higher rate of side effects. Oral bronchodilators are not recommended for use compared to inhaled counterparts. Hypokalemia, hypoglycemia, tachycardia, anxiety, and other consequences may occur with low-risk ingestion.[10]

The National Drug Information Center states that children above the age of 6 years should only use Symbicort®. The safety and efficacy of Symbicort® use in children younger than 6 years old is yet unknown. Budesonide and formoterol fumarate dihydrate, which are utilized in Symbicort®, are asthma controllers that require daily administration over an extended period to produce and preserve a controlled asthmatic state.

Triamcinolone can exhibit anti-inflammatory activity so that it can be used in asthma management. Triamcinolone cannot be used in children under 6 years old, according to the BNFC 2019-2020. Side effects of triamcinolone can cause headaches and visual disturbances.[11] Statistically, for children (aged 2–11 years), the rate of off-label prescribing is high, which is concerning as several studies have reported that off-label prescribing is a risk factor for adverse reactions.[12]

The off-label dosage category refers to drugs that are administered without following the dosage listed in the distribution license. In the data obtained, there were nine cases of off-label use of ambroxol. The official dose of ambroxol, according to PIONAS, is at the age of 2–6 years, 15 mg/2.5 mL given 2-3 times a day, and for ages 6–12 years, 15 mg/5 mL. In this study, the use of ambroxol at the age of 1 year and 4 months was given 15 mg/5 mL every three times a day, and at the age of 7 years, 15 mg/2.5 mL every three times a day. The side effects of ambroxol are nausea, vomiting, stomach discomfort, and dry mouth.[13]

Off-label drug use in pediatric patients is necessitated by the limited availability of medicines that are specifically marked for use in this population. Therefore, determining the appropriate dose for children sometimes involves extrapolation from adult dosing guidelines, which can result in underdoses and overdoses.[14] Which may result in underdoses and overdoses. Administration of insufficient or excessive doses of drugs insufficient or excessive poses a significant health risk for children.

Lower doses may compromise the effectiveness of treatment, but administration of excessive doses of a drug may increase the risk of toxicity.[15] According to the findings of the chi-square test analysis, there is no correlation between gender and the use of off-label drugs in the dosage category, with a significance value of 0.149 > 0.05 (Table 4).

Off-label usage of a drug occurs when it is used outside of the indications specified on the drug's brochure or when it isn't released in compliance with the BPOM distribution permit. The drug that was prescribed with an off-label indication in this study was zinc, which is an official indication.[9]

Zinc is a drug to treat diarrhea in children, but in this study, it was given in chidlren with ARI. In general, zinc is used to help speed up the healing of children's diarrhea. But according to Rerksuppaphol's research, zinc can reduce inflammation, decrease airway obstruction, and reduce chest tightness, a high respiratory rate, and hypoxia.[16]

Table 3. Profile of Off-label Drug Use: Age Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Cetirizine HCl	Children under the age two years are not recommended	Given to children aged 4 months, 11 months, and 1 year	**6**	**8**	0,161
Salbutamol	Children under the age two years are not recommended	Given to children aged 8 months and 1 year	**0**	**4**	
Symbicort®	Not suggested for children under the age of six	Given to 4-year-olds and 5-year-olds	**0**	**3**	
Triamcinolone	Not suggested for children under the age of six	Given to 4-year-olds and 5-year-olds	**0**	**2**	
Total			**6**	**17**	

Table 4. Profile of Off-label Drug Use: Dose Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Ambroxol	15mg/5ml 2-3 times daily	15mg/2,5 ml 3 times daily	**6**	**3**	0,149
Total			**6**	**3**	

Table 5. Profile of Off-label Drug Use: Indication Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Zinc	Relieves the symptoms of diarrhea in children	Used for patients with ARI	**1**	**0**	1000
Total			**1**	**0**	

Side effects of zinc should be monitored as they may cause temporary abdominal discomfort.[17] Based on the chi-square test analysis results, with a significance value of 1000 > 0.05, there is no relationship between gender and off-label drug use in the indication category (Table 5). Of-label use of drugs in children is common globally, as well as in Indonesia. The term "off-label" refers to the unapproved use of approved medications, and it may seem like a nearly simple concept. Prescribing and dispensing medications with pre-existing off-label regimens remains a problem today, primarily due to unmet clinical demands. Off-label techniques are necessary in some treatment domains. Thus, the physicians face challenges with this practice.[18]

Since the right to information and informed consent are components of the patient's rights, parental informed consent is a crucial component of the off-label process in pediatrics. From a liability standpoint, it is preferable to obtain informed permission.[19] The informed consent of the patient was mandated in many European nations (including the UK, France, Italy, the Netherlands, and Sweden) in addition to the off-label use.[20]

The limitation of the research is that there was not any further conversation with the doctors; accordingly, the reasons for using off-label medications are unknown. The other drawback is that this investigation was limited to respiratory medications rather than all drugs. It's challenging to compare the results of this study with those of others due to limited research location. However, it's crucial to acknowledge the uniqueness of this study and recognize the valuable insights it can provide to the research community.

Conclusion

It can be concluded that there is still off-label use of drugs on pediatric patients with a diagnosis of ARI at Pandega Pangandaran Hospital, West Java - Indonesia in the period 2022. The categories are off-label age 23 cases (11.16%), off-label dose 9 cases (4.37%) and off-label indication 1 case (0.48%). Based on the results of this study, it is known that the use of off-label drugs in children is still quite high, so supervision related to the risk of drug use needs to be carried out by pharmacists.

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Conflict of Interest

None declared

Reference

1. World Health organization. Pusat Pengobatan Infeksi Saluran Pernapasan Akut Berat [Internet]. 2020 [cited 2022 Oct 30]. *Available from: https://www.who.int/*
2. Lazamidarmi D, Sitorus RJ, Listiono H. Faktor-Faktor yang Berhubungan dengan Kejadian ISPA pada Balita. *Jurnal Ilmiah Universitas Batanghari Jambi*. 2021 Feb 8;21(1):299.
3. Badan Penelitian dan Pengembangan Kesehatan. *Laporan Nasional Riskesdas 2018*. Kementerian Kesehatan Republik Indonesia
4. Tefera YG, Gebresillassie BM, Mekuria AB, Abebe TB, Erku DA, Seid N, Beshir HB. Off-label drug use in hospitalized children: a prospective observational study at Gondar University Referral Hospital, Northwestern Ethiopia. *Pharmacology Research & Perspective*, 2017, 5(2),

e00304.
5. Anggraini D, Putra ON, Faizah AK. Peresepan Obat "Off-label" Pada Anak Dengan Penyakit Infeksi Saluran Pernapasan Akut. *Jurnal Ilmu Kefarmasian*. 2021;2(1).
6. O'Hara K. Paediatric pharmacokinetics and drug doses. *Australian Prescriber.* 2016;39(6):208–10.
7. Setyaningrum N, Gredynadita V, Gartina S. Penggunaan Obat Off-Label pada Anak di Apotek Kota Yogyakarta. *Jurnal Sains Farmasi & Klinis*. 2017 Dec 15;4(1):30.
8. Tuloli TS, Rasdianah N, Datau M. Gambaran Penggunaan Obat Off-Label Pada Pasien Pediatrik Rawat Inap Di Rumah Sakit. *Indonesian Journal of Pharmaceutical Education*. 2022 Jul 29;2(2):130–42.
9. Lazzerini M, Wanzira H. *Oral zinc for treating diarrhoea in children*. Vol. 2016, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd
10. Syafitri N, Faisal M, Indriyanti N. Kajian Penggunaan Obat Off-Label Pada Penyakit ISPA Pasien Pediatri di RSUD Majene. *Proceeding of Mulawarman Pharmaceuticals Conferences*. 2021 Dec 31;14:96–105.
11. Lin J, Zhou X, Wang C, Liu C, Cai S, Huang M. *Symbicort® Maintenance and Reliever Therapy (SMART) and the evolution of asthma management within the GINA guidelines*. Vol. 12, Expert Review of Respiratory Medicine. Taylor and Francis Ltd.; 2018. p. 191–202.
12. Tukayo BLA, Sunderland B, Parsons R, Czarniak P. High prevalence of off-label and unlicensed paediatric prescribing in a hospital in Indonesia during the period Aug.—Oct. 2014. Vol. 15, *PLoS ONE.* Public Library of Science; 2020.
13. Vervloet M, Puigmarti CM, Damen N, Marchange S, Langedijk J, Lisman J, et al. *Study on off-Label Use of Medicinal Products in European Union, European Union*. 2017.
14. Katy Sutcliffe, Gillian Stokes, Alison O'Mara, Jenny Caird, Kate Hinds, Mukdarut Bangpan, et al. Paediatric medication error : a systematic review of the extent and nature of the problem in the UK and international interventions to address it. *Social Science Research Unit, UCL Institute of Education.* 2014. 1–164 p.
15. Knopf H, Wolf IK, Sarganas G, Zhuang W, Rascher W, Neubert A. Off-label medicine use in children and adolescents: Results of a population-based study in Germany. *BMC Public Health*. 2013;13(1).
16. Rerksuppaphol S, Lakkana R. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. *Pediatric Reports* 2019;11(7954).
17. Paediatric Formulary Committee. *British National Formulary for Children 2019-2020*. 2019; Available from: https://nhathuocngocanh.com/
18. Rusz CM, Ősz BE, Jîtcă G, Miklos A, Bătrînu MG, Imre S. Off-label medication: From a simple concept to complex practical aspects. Vol. 18, *International Journal of Environmental Research and Public Health.* MDPI; 2021.
19. Aagaard L, Kristensen K. Off-label and unlicensed prescribing in Europe: implications for patients' informed consent and liability. Vol. 40, *International Journal of Clinical Pharmacy.* Springer Netherlands; 2018. p. 509–12.
20. Jaroszyński J, Mela A, Furtak-Niczyporuk M, Poniatowski ŁA, Dąbrowski J, Czajka-Bełz A, et al. Off-label use of medicinal products ñ legal rules and practices. *Acta Poloniae Pharmaceutica - Drug Research*. 2019;76(4):621–8.