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Potential for Incompatibility, Instability, and Prescription Drug Interactions in Pulveres Prescription Pediatric Patients at RSI (Islamic Hospital) Sultan Hadlirin, Jepara, Indonesia

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ABSTRACT

In Indonesia, there are still many doctors who prescribe compounded medicines for pediatrics, including pulveres. Compounding is an alternative for pediatrics who cannot swallow tablets, but compounding medicines is a concern because it can cause incompatibility and instability during storage and cause side effects, drug interactions. This study aimed to determine the potential for incompatibility, instability, and drug interactions on pediatric patient prescription sheets. This research is descriptive observational, and data collection is carried out retrospective, data taken from prescription sheets for pediatric patients at RSI Sultan Hadlirin Jepara. The total sample in this study was 247 prescriptions that met the inclusion criteria. The results of the study showed that the age classification of patients 0-5 years who received pulveres prescriptions was 175 (71.8%), while for those aged 6-11 years, it was 72 (29.1%). Based on the number of medications, 197 (80.1%) patients received 4-6 medications, while 50 (20.3%) pediatric patients received 2-3 medications. There is no potential for 0% incompatibility. There is the potential for instability in the pediatric prescription sheets. As many as 62 (25.1%) of the active drug substance preparations that experience instability include CTM, paracetamol, and vitamin B complex. There were 126 (51.0%) potential drug interactions based on the pharmacodynamic mechanism of action and 126 (51.0%) based on moderate severity in the salbutamol tablet preparation with pseudoephedrine. It can be concluded that on the prescription sheet, there is no potential for 0% incompatibility, there is a potential for instability of 62 (25.1%), and there is moderate interaction, and pharmacodynamic mechanisms were 126 (51.0%).

1. Introduction

Pediatrics is a series of growth and development from newborns through childhood to adulthood. Pediatric group from 2 to 11 years old. Pediatrics is a group of patients who are susceptible to disease because the immune system and physiological functions of organs are not yet fully developed. So selecting appropriate medicinal preparations in pediatrics becomes a problem in itself for health services, so doctors make pulveres prescriptions to resolve the issue. Pulveres preparation has advantages and disadvantages compared to other preparations. The advantages include the dosage being easily

adjusted to the child's exact weight. The medication can be combined according to the patient's needs, and it is more practical, the method of administration being easy, especially for young children who are not yet able to swallow tablets. Disadvantages include possible side effects of incompatibility, instability, and drug interactions.¹⁻⁵

Incompatibility is an event where drugs are not mixed physically or chemically, resulting in loss of potency, increased toxicity, or other side effects. There are examples of recipes for preparing pulveres preparations. Drugs that experience incompatibility are ambroxol, and vitamin C with cetirizine. Vitamin C

is incompatible with alkalis, heavy metal ions, especially copper and iron, oxidizing agents, methenamine, phenylephrine hydrochloride, pyrilamine maleate, salicylamide, sodium nitrite, sodium salicylate, theobromine salicylate, and picotamide. Instability is the inability of a pharmaceutical dosage form to maintain its physical, chemical, therapeutic, and microbial properties during storage and use by patients. Some drugs have the potential for instability, namely chlorpheniramine maleate, tremenza, and Vitamin B Complex, which are hygroscopic. Vitamin B Complex drugs contain the active substances vitamin B1 and vitamin B2, which are hygroscopic, and Ca pantothenate is slightly hygroscopic during the process of compounding and storing the drug.⁶⁻⁸

Patients who take two or more drugs simultaneously have the potential for drug interactions where the drug response can increase or decrease. Examples of drug interactions that often occur in pediatric inpatients include combinations of rifampicin with isoniazid, ibuprofen with dexamethasone, acetaminophen with isoniazid, gentamicin with cefotaxime, gentamicin with ceftriaxone and diazepam with dexamethasone.⁷⁻⁹ This study aimed to evaluate potential incompatibility, instability, and drug interactions in pulveres prescription pediatric patients at RSI (Islamic Hospital) Sultan Hadlirin, Jepara, Indonesia.

2. Methods

This study is a descriptive observational research. This study uses secondary data from prescription copies of pediatric patients at RSI (Islamic Hospital) Sultan Hadlirin, Jepara, Indonesia. A total of 247 recipes were used as research samples in this study, where the recipes used as samples met the inclusion criteria. The inclusion criteria in this study were prescription sheets for pediatric patients aged 0-11 years, prescription sheets containing compounded medicines in the form of powder preparations, prescription sheets containing more than two types of medicine, and complete prescription sheets. This

research was conducted at the Sultan Hadlirin Islamic Hospital Jepara, and an ethical review was carried out at the Bioethics Commission for Medical or Health Research, Faculty of Medicine, Universitas Muhammadiyah, Purwokerto with Registration Number: KEPK/UMP/133/III/2023.

Data analysis was carried out using the SPSS program version 21. Data processing was carried out using univariate analysis, namely analyzing the quality of variables at a time, by using a frequency distribution test. The frequency distribution test is in the form of a table. The frequency distribution test only shows the value for each variable, which is expressed as a number and percentage of the total cases. In this study, univariate frequency test analysis was used to determine the classification of patient age, drug use, potential incompatibility, instability, and drug interactions. The research results were presented in percentage form.

3. Results and Discussion

Table 1 shows that the age classification of patients who received pulveres prescriptions was 175 (71.8%) aged 0-5 years, while for those aged 6-11 years, there were 72 (29.1%). This is because pediatric patients at the age of infants or neonates have more critical clinical conditions due to differences in physiological function, so they are more susceptible to the administration of several drugs. so pediatric patients are given pulveres prescriptions at doses according to their needs. In another study, it was shown that pediatric patients aged 0-5 years (56%) received more prescriptions compared to pediatric patients aged 6-11 years (46%). Other research also shows that pediatric inpatients aged <2 years are 119, while those aged >2 years are 81. This is because patients at the age of babies or neonates are susceptible to disease.^{10,11}

Table 1 shows that 197 (80.1%) patients received 4-6 drugs, while 50 (20.3%) pediatric patients received 2-3 drugs. In another study, it was shown that 56% of prescription sheets received >2 drugs. In another study, prescription sheets for >2 drugs were 9.12%.

This was adjusted to the symptoms of the disease experienced by the patient so that patients were given >2 drugs for the indicated indication. In another study, prescription sheets received 4-6 drugs, as many as 44.78%, and in other research, results were found to be 3.5% on prescription sheets. This is

because the type of medication given is based on the clinical conditions of different patients, thus influencing the amount of medication given by the doctor.^{12,13}

Table 1. Classification of prescription sheets based on the number and age of patients at RSI Sultan Hadlirin Jepara.

Classification	Total N = 247	Percentage (%)
Patient age		
0 – 5 years	175	71,8
6 – 11 years	72	29,1
Number of drugs		
2-3	50	20,3
4-6	197	80,1

Table 2 shows the names of drugs prescribed by doctors for pediatric patients. It can be concluded that 67 (27.1%) drug prescriptions consist of a combination of drugs (Erdosteine+Salbutamol+Crofed+Dexamethasone) and 35 (14.1%) combinations medication (Erdosteine+Salbutamol+Dexamethasone). Erdosteine functions for the symptomatic treatment of chronic bronchitis, which has the effect of stabilizing mucus secretion and thinning phlegm, making it easier for patients to expel phlegm. Salbutamol functions as a fast-acting β_2 adrenergic, which functions as a bronchodilator that can improve the airway so that symptoms of shortness of breath can be reduced. Crofed contains (Pseudoephedrine HCl and triprolidine HCl) which is used to treat symptoms of nasal congestion in cases of flu or colds. Pseudoephedrine HCl is a decongestant drug. Dexamethasone is a glucocorticoid drug that is used for its anti-inflammatory and analgesic effects. This combination drug can be used to treat the symptoms of ARI. Acute respiratory infection (ARI) is an acute infectious disease that attacks one or more parts of the respiratory tract from the nose to the lung sacs (alveoli) including the adnexal tissue such as the sinuses or

cavities around the nose (para nasal sinuses), the middle ear cavity, and pleura.^{14,15}

Acute respiratory infection (ARI) is a disease that often occurs in children. The period of coughs and colds in toddlers in Indonesia is estimated to be 3 – 6 times per year. Acute respiratory infections (ARI) are also one of the main causes of patient visits to health facilities. As many as 40% - 60% of medical visits at health centers and 15% - 30% of medical visits in hospital outpatient and inpatient departments are caused by ARI. Management of respiratory infections will be successful if the diagnosis of the disease is established more deeply so that treatment can be given before the disease develops further. In pharmacological therapy, the drugs most often used and the main choice are bronchodilators. The use of other drugs, such as corticosteroids, antibiotics, and anti-inflammatories, is given in certain conditions. Bronchodilators are given alone or in combination with the three types of bronchodilators and are adjusted according to the classification of the severity of the disease. Bronchodilators which have a working mechanism to widen the respiratory tract, are safe to give to patients under five.^{16,17}

Table 2. Composition of active substances in pulveres at RSI Sultan Hadlirin Jepara.

No.	Drug name	Total (247)	Percentage (%)
1	Cetirizine+Methylprednisolon+Erdostein+Salbutamol	3	1,21
2	Amoxicillin+Crofed+Dexamethasone	4	1,61
3	Amoxicillin+Cetirizine+Dexamethasone	5	2,02
4	Amoxicillin+Crofed+Erdostein+Dexamethasone+Salbutamol+Paracetamol	5	2,02
5	Amoxicillin+CTM+Dexamethasone+Vit B Complex	5	2,02
6	Cefadroxil+Ambroxol+Crofed+Dexamethasone+Paracetamol	5	2,02
7	Cefadroxil+CTM+GG+Prednison	5	2,02
8	Cetirizine+Erdostein+Salbutamol+Crofed+Dexamethasone	5	2,02
9	Cefadroxil+Ambroxol+Crofed+Dexamethasone	5	2,02
10	Cetirizine+Erdostein+Salbutamol+Dexamethasone	5	2,02
11	Cetirizine+Methylprednisolon+Salbutamol+Vit C	5	2,02
12	Cefadroxil+Erdostein+Salbutamol+Crofed+Dexamethasone+Vit C	6	2,42
13	Amoxicillin+Erdostein+Salbutamol+Crofed+Dexamethasone	6	2,42
14	Amoxicillin+Erdostein+Dexamethasone+Salbutamol	8	3,23
15	Cefadroxil+Crofed+Salbutamol+Dexamethasone+Erdostein	8	3,23
16	Crofed+Salbutamol+Dexamethasone+Vit C	8	3,23
17	Cefadroxil+Ambroxol+Crofed+Dexamethasone+Parasetamol	10	4,04
18	Cefadroxil+Ambroxol+CTM+Dexamethasone	10	4,04
19	Amoxicillin+CTM+GG+Dexamethasone+Vit C	10	4,04
20	Amoxicillin+CTM+Ambroxol+Dexamethasone	12	4,85
21	Cefadroxil+Ambroxol+Crofed+Dexamethasone+Salbutamol	15	6,07
22	Erdostein+Salbutamol+Dexamethasone	35	14,1
23	Erdostein+Salbutamol+Crofed+Dexamethasone	67	27,1

In Table 3, there was no potential or occurrence of 0% incompatibility found on the pulveres prescription sheet. This is because all the preparation formulas were mixed homogeneously when compounded by the researcher. This research is different from other research where there is an incompatibility of 3.4%, namely that there are film-coated tablet preparations that are not suitable for dispensing because they can cause incompatibility. Instability events were carried out by observing the prepared pulveres preparations, observations were carried out for 3 days. For days 1 and 2, the pulveres preparation did not change. On the 3rd day, there were several pulveres preparations that experienced instability, namely that the powder preparations looked wet and there were tablet granules separating from the pulveres. The instability of a drug can occur in the compounding process, namely during the crushing, mixing, and repackaging process. In this process, the active drug substance is, of course, exposed to air, exposed to light, and exposed to humidity. This observation was carried out at a room temperature of 26°C, and there were several

recipe sheets that experienced instability, namely 62 (25%). In this study, there were several tablets that experienced instability, including CTM and vitamin B complex tablets.¹⁶⁻¹⁸

The chemical nature of CTM is sensitive to light and hygroscopic, so the active substance is unstable and could potentially cause instability when compounded. The chemical properties of paracetamol are sensitive to light and the chemical properties of Vit B Complex are very labile to oxidation and hygroscopic. Drugs that experience incompatibility include Pseudoephedrine and vitamin B Complex (B1, B2, B6, B12, nicotinamide, and Ca Pantothenate), which, when mixed, cause instability. It was also stated in other research that there are several drugs that have the potential to cause instability, namely chlorpheniramin maleat, tremenza, and vitamin B complex are hygroscopic. Vitamin B complex drugs contain the active substances Vitamin B1 and Vitamin B2, which is hygroscopic, and Ca pantothenate is slightly hygroscopic during the process of compounding and storing the drug. When

compounding paracetamol, it has unstable properties such as hydrolysis, oxidation, photolysis, and degradation of drug compounds. So, when

compounding paracetamol, it is not stable in storage.¹⁷⁻¹⁹

Table 3. Incompatibility and instability of the pulveres prescription sheet at RSI Sultan Hadlirin Jepara.

Type of occurrence	Total N = 247	Percentage (%)
Incompatibility		
incompatibility occurs	0	0
Instability		
Instability occurs	62	25,1
Instability does not occur	185	75,2

Table 4. Classification of patient drug interactions at RSI Sultan Hadlirin Jepara.

Drug interaction mechanisms	Total N = 247	Percentage (%)
Pharmacodynamics	121	49,2
Pharmacokinetics	0	0
No potential for interaction	126	51,8
Severity of Drug Interactions	Total N = 247	Percentage (%)
Minor	0	0
Moderate	121	49,2
Major	0	0
No potential for interaction	126	51,8

In Table 4, the incidence of drug interactions based on pharmacodynamic mechanisms was 121 (49.2%). Examples of prescription sheets that experience pharmacodynamic interactions are Crofed tablet preparations (Triprolidine HCl & Pseudoephedrine HCl) and salbutamol, which have the risk of increasing blood pressure and heart rate, which causes a decrease in the sedation effect, so their use must be monitored and used carefully. Immediately stop using pseudoephedrine if cold symptoms have subsided. This is similar to other studies where there were 4 cases of pharmacodynamic interactions (2.2%), and in other studies, the results of pharmacodynamic interactions were 18 interactions (54.55%), namely the interaction of the drug salbutamol with drugs containing pseudoephedrine and triprolidine. namely that both can increase sympathetic (adrenergic) effects, including increased blood pressure and heart rate.^{17,18}

Moderate interaction is an interaction that can cause a decrease in the patient's clinical status. In this study, this β_2 agonist drug was the most potent bronchodilator available and was a powerful bronchodilator for asthma attacks. The mechanism of action of β_2 agonist drugs is through stimulation of β_2 receptors in the bronchi, causing activation of adenylylase. This enzyme converts ATP (Adenosinetriphosphate) into CAMP (cyclic-adenosine-monophosphate) with the release of energy, which is used for processes in cells. Increasing CAMP levels in cells produces a bronchodilation effect. In other research, there are several ways to overcome pseudoephedrine and salbutamol drug interactions, including avoiding drug combinations that have a high risk of drug interactions, adjusting the drug dose given to patients for two or more interacting drugs, giving a break of 2 hours before or 4 hours after Drugs that trigger interactions are given if they interact during the

absorption phase. In this study, the severity of drug interactions was not found in the pulveres prescription sheet.^{19,20}

4. Conclusion

There is no potential for incompatibility on the pulveres prescription sheet for pediatric patients. There is potential for instability in the pediatric prescription sheet. As many as 62 (25.1%) formula preparations that experience instability include CTM, paracetamol, and vitamin B complex. There is a potential for drug interactions based on the pharmacodynamic mechanism of action and based on the level of severity moderate as many as 125 (51.0%).

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