The Suitability of The Precription of Non-Sterile Concoctions For Children at XXX Mother and Child Hospital Makassar : Compatibility and Stability Study

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Abstract: Medicines for pediatric patients are often not available so the doctor will prescribe a compound drug which usually consists of one or more drugs. This study aims to determine the potential for incompatibility and instability of drugs to non-sterile compound prescriptions in children at RSIA XXX in Makassar during January to April 2020. Samples were obtained based on a purposive technique with retrospective data which were then assessed for drug incompatibility and stability based on the official literature. Based on the sampling results obtained 150 prescription sheets consisting of 18 drugs. The results of literature studies on drugs have shown no potential for incompatibility, but there are 16 drugs of which have the potential to experience instability, either caused by humidity or exposure to light. The drugs are Ambroxol, Vitamin B Complex, Cefadroxil, Cefixime, Cetirizine, Chlorpheniramine Maleate, Codeine, Co-trimoxazole, Dexamethasone, Erythromycin, Methylprednisolone, Paracetamol, Prednisone, Salbutamol, a combination of Triprolidine HCl and Pseudoephedrine HCl and Vitamin C. Potentially unstable was affected by humidity as many as 7 drugs and exposure to light as many as 16 drugs while the potential for drug incompatibility was not found.

Keywords: incompatibility, stability, pediatric prescription

1. Introduction

Drug compounding is often thought of as the process of combining, mixing, or altering ingredients to make sterile or non-sterile drugs that are tailored to the patient's needs [1]. The preparation of a mixture in the form of powder as an alternative medicine for children has become a special concern in health services. Puyer compound preparations (pulveres) have several advantages and disadvantages when compared to other preparations. Some of the advantages include that the dose is easily adjusted to the child's weight appropriately, the medicine can be combined according to the patient's needs, is more practical, and the method of administration is easy, especially for small children who are not able to swallow tablets. Disadvantages include possible side effects, drug interactions and drug incompatibility and stability issues [2].

In the research, several articles showed that there were three active substances in one recipe which was the highest number of active substances prescribed from all selected sample blended recipes. And it is possible that the greater the number of active substances contained in the compound preparation, the greater the potential for incompatibility and drug interactions and of course this can also affect drug stability [3].

From the various research results that have been carried out by previous researchers, it becomes an input for pharmaceutical staff to be able to conduct assessments and analyzes of compound

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prescriptions in hospitals as a form of quality assurance of compounded preparations. Pharmacists must be able to understand every physical and chemical aspect of a drug, so that they can perform prescription screening properly, especially in estimating the occurrence of instability and incompatibility of a prescription preparation. Pharmacists must also have a good stock of knowledge to be able to provide the best solution if there are problems in the preparation of the compound. From this, the purpose of this study was to determine the potential for incompatibility and stability of drugs in non-sterile concoction prescriptions for children at XXX mother and child hospital in Makassar.

2. Methods

The method in this study is to look at the potential for drug incompatibility and stability in non-sterile children's concoctions using a retrospective method. The data taken were all non-sterile concoction recipes for pediatric patients at XXX mother and child hospital in Makassar for the period January 2020 - April 2020 using the purposive sampling method.

Data collection: All recipes for non-sterile concoctions for children were collected at XXX mother and child hospital in Makassar for the period January 2020 to April 2020 and then sorted out the recipes according to the inclusion and exclusion criteria used.

Data processing: Prescription data that had been obtained previously based on inclusion and exclusion criteria were then assessed for potential incompatibility and stability of the drug based on the official literature.

Data analysis: The data were then analyzed and studied according to the literature, then percentages were made and conclusions were drawn. The inclusion criteria in this study are: (1) Recipes for pediatric preparations, (2) Prescription for pediatric patients who receive >1 type of drug, (3) Pulveres dosage form. The exclusion criteria in this study were doctors' writings which were unreadable for researchers.

3. Result

This study discusses the assessment of children's non-sterile compound prescriptions in terms of drug incompatibility and stability based on the available literature. Prescriptions for children's non-sterile concoctions were collected from XXX mother and child hospital in Makassar, which was then reviewed for each drug in the prescription based on the literature regarding drug incompatibility and stability. Drug compounding is often thought of as a process of combining or altering ingredients to suit the needs of the patient.

Month	Recipe Sheet	Non Concoction Recipe	Total	Percentage
Januari 2020	22	105	127	22,92%
Februari 2020	46	113	159	28,70%
Maret 2020	66	120	186	33,57%
April 2020	16	66	82	14,80%
Total	150	404	554	100,00%

Table 1. Population in Children's Non-Sterile Concoction Recipes at XXX Mother and Child Hospital in Makassar Period January 2020 - April 2020

Based on Table 1 is data on the population that has been collected, the most monthly population data obtained is March 2020 with a percentage of 33.57% and the least is April 2020 with a percentage of 14.8%. Recipes in the form of concoction are 150 recipes while those in the form of non-concoction are 404 recipes so that the total population collected is

554 recipes. The population collected is in the form of prescriptions which are non-sterile prescriptions specifically for children.

Table 2. Samples for Children's Non-Sterile Concoction Recipes at XXX Mother and Child Hospital in Makassar Period January 2020 - April 2020

Month	Recipe Sheet	Percentage
Januari 2020	22	14,66 %
Februari 2020	46	30,66 %
Maret 2020	66	44,00 %
April 2020	16	10,66 %
Total	150	100,00 %

Based on Table 2 is a table regarding the number of samples obtained where the most collected monthly sample is March 2020 with a percentage of 44% and the least is April 2020 with a percentage of 10.66%. The total sample collected was 150 recipes. All samples obtained were included in the inclusion criteria and no samples were found that included in the exclusion criteria.

Table 3. Profile of Types of Drugs Concocted in Children's Prescriptions at XXX Mother and Child Hospital in Makassar Period January 2020 - April 2020

Medicine Name	Recipe Sheet	Percentage
Ambroxol HCl	101	22,64%
B kompleks	33	7,39%
Cefadroxil	43	9,64%
Cefixime	1	0,22%
Cetirizine	1	0,22%
Chlorpheniramine Maleat	8	1,79%
Codein	1	0,22%
Cotrimoksazole	4	0,89%
Dexamethasone	76	17,04%
Eritromisin	24	5,38%
Mebhidrolin Napadisilate	86	19,28%
Metilprednisolon	7	1,56%
Parasetamol	3	0,67%
Prednisone	2	0,44%
Salbutamol	7	1,56%
Triprolidin HCl + Pseudoefedrin HC	1 1	0,22%
Vitamin C	46	10,31%
Amoxicillin	2	0,44%
Total	446	100%

Based on Table 3, it is obtained prescription data that the types of drugs that are most often used in prescribing concoctions are Ambroxol HCl (22.9%), Mebhidrolin Napadisilat (19.28%) and Dexamethasone (17.04%).

	Therapy Classes	Amount	Perscentage
Sistem	Mukolitik	101	22,64%
Respirasi	Bronkodilator	7	1,56%
_	Antihistamin	95	21,3%
	Dekongestan	1	0,22%
Antiinfeksi	Antibakteri	74	16,59%
Analgesik	Anlagesik narkotika	1	0,22%
C	Analgesik non narkotika	3	0,67%
Endokrin	Kortikosteroid	85	19,05%
Vitamin dan	Mineral	79	17,71%
	Total	446	100%

Table 4. Profile of Drug Therapy Classes Formulated at XXX Mother and Child Hospital in Makassar Period January 2020 - April 2020

Based on Table 4, there are 5 therapeutic class data including: Respiratory System, Antiinfection, Analgesic, Endocrine, and Vitamins and Minerals. The therapy class that is most often used for the treatment of compound prescriptions is the Respiratory System therapy class.

Table 5. Prescribing Profiles of Non-Sterile Children's Prescriptions Based on Different Combinations of Prescription Drugs for the Period January 2020 - April 2020

Recipe Combination	No. Of Recipes
Eritromisin + Mebhidrolin Napadisilat + Ambroxol + Dexamethasone	13
Cetirizine + Ambroxol	1
Vitamin C + Ambroxol + Dexamethasone	10
Cefadroxil + Dexamethasone + Ambroxol + Mebhidrolin Napadisilat	20
Prednison + Cefadroxil	2
Ambroxol + Mebhidrolin Napadisilat	10
Kotrimoksazol + Dexamethasone	1
Cefadroxil + Mebhidrolin Napadisilat +Dexamethasone	1
Dexamethasone + Mebhidrolin Napadisilat	2
Chlorpheniramine Maleat + Dexamethasone	1
Eritromisin + Dexamethasone	1
Eritromisin + Mebhidrolin Napadisilat + Ambroxol	4
Cefadroxil + Mebhidrolin Napadisilat + Ambroxol + Metilprednisolon	3
Mebhidrolin Napadisilat + Dexamethasone + Ambroxol	8
Eritromisin + Mebhidrolin Napadisilat + Ambroxol + Dexamethasone + Salbutamol	3
Cefadroxil + Dexamethasone + Ambroxol	2
Cefadroxil + Dexamethasone	1
Cefadroxil + Mebhidrolin Napadisilat + Kodein +Metilprednisolon	1
Cefadroxil + Mebhidrolin Napadisilat + Ambroxol	9
Eritromisin + Metilprednisolon + Salbutamol +Mebhidrolin Napadisilat + Ambroxol	1
Eritromisin + Mebhidrolin Napadisilat + Dexamethasone	1
Vitamin C + Ambroxol + Dexamethasone +Chlorpheniramine Maleat	1
Parasetamol + Chlorpheniramine Maleat + Ambroxol + Kotrimoksazol +	1
Dexamethasone	1
B Kompleks + Ambroxol + Dexamethasone + Mebhidrolin Napadisilat	1
Kotrimoksazol + Dexamethasone + Ambroxol + Mebhidrolin Napadisilat	1
Metilprednisolon + Mebhidrolin Napadisilat + Ambroxol	2
Vitamin C + Chlorpheniramine Maleat	1
Cefadroxil + Ambroxol	2

Vitamin C + B Kompleks	28
Salbutamol + Dexamethasone + Mebhidrolin Napadisilat + Ambroxol	1
Chlorpheniramine Maleat + Ambroxol + Dexamethasone	1
Kotrimoksazol + Ambroxol + Mebhidrolin Napadisilat	1
Eritromisin + Mebhidrolin Napadisilat	1
Salbutamol + Ambroxol	1
Cefixime + Ambroxol + Salbutamol + Triprolidin HCl + Pseudoefedrin HCl	1
Parasetamol + Dexamethasone + Ambroxol + Vitamin C + B Kompleks	1
Parasetamol + Dexamethasone	1
Vitamin C + Dexamethasone	1
Vitamin C + Amoksisilin	1
Vitamin C + Chlorpheniramine Maleat + B Kompleks + Ambroxol	1
Vitamin C + Chlorpheniramine Maleat + Dexamethasone + Amoxicilin	1
Vitamin C + Ambroxol + Dexamethasone + B Kompleks	1
Cefadroxil + Mebhidrolin Napadisilat	2
Chlorpheniramine Maleat + Dexamethasone + Ambroxol + Amoxicilin	1
B Kompleks + Mebhidrolin Napadisilat	1
B Kompleks + Cefadroxil	1

Based on Table 5 above, data is obtained for the number of types of combinations of non-sterile children's concoction recipes, namely as many as 46 prescription sheets, of which there are 2 to 5 medicinal ingredients in the recipe.

Table 6. Non-sterile concoction recipes for children that are potentially unstable due to hygroscopic period January 2020 - April 2020

Medicine Name	Amount	Percentage
B Kompleks (B1, B5, B12)	33	22,00%
Eritromisin	24	16,00%
Parasetamol	3	2,00%
Vitamin C	46	30,66%
Salbutamol	7	4,66%
Cetirizine	1	0,66%
Cefixime	1	0,66%

Based on the data in table 6 that there are 7 drugs that are hygroscopic, including B complex (B1, B5, B12), Erythromycin, Paracetamol, Salbutamol (sulfate), Cefixime, Cetirizine (HCl) and Vitamin C.

Table 7. Non-sterile Children's Concoction Recipes Potentially Unstable Due to Photolysis Properties in Combination Drugs January 2020 - April 2020

Medicine Name	Amount	Percentage
Ambroxol HCl	101	67,33%
B Kompleks	33	22,00%
Cefadroxil	43	28,66%
Cefixime	1	0,66%
Cetirizine	1	0,66%
Chlorpheniramine Maleat	8	5,33%
Kodein	1	0,66%
Kotrimoksazol	4	2,66%
Dexamethasone	76	50,66%

Eritromisin	24	16,00%
Metilprednisolon	7	4,66%
Parasetamol	3	2,00%
Prednison	2	1,33%
Salbutamol	7	4,66%
Triprolidin HCl + Pseudoefedrin HCl	1	0,66%
Vitamin C	46	30,66%

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Based on Table 7 shows that there are 16 types of drugs that have the potential to experience instability due to light exposure according to the literature.

4. Discussion

This study discusses the assessment of children's non-sterile compound prescriptions in terms of drug incompatibility and stability based on the available literature. Prescriptions for children's non-sterile concoctions were collected XXX Mother and Child Hospital in Makassar which was then reviewed for each drug in the prescription based on the literature regarding drug incompatibility and stability. Drug compounding is often thought of as a process of combining or altering ingredients to suit the needs of the patient. Incompatibility is an event that a drug is not mixed physically or chemically and results in loss of potency, increased toxicity or other side effects. Drug incompatibility can occur before the drug reaches the patient resulting from physicochemical reactions between several drugs, between drugs and solvents or with the equipment used [2].

Stability is defined as the capacity of a drug substance or drug product to remain within established specifications that maintain its identity, strength, quality and purity throughout the retest period or expiration date. Stability is an important factor of the quality, safety, and efficacy of a drug product. The drug product, which does not have sufficient stability, may result in changes in physical (such as hardness, dissolution rate, phase separation, etc.) as well as chemical characteristics (formation of high risk decomposers). The chemical stability of the drug is very important because it becomes less effective when it is degraded. Also the decomposition of drugs can produce toxic byproducts that are harmful to the patient [4]. A drug can be said to be stable if its levels do not decrease in storage. As for when the drug changes color, smell, and shape and there is microbial contamination, it can be concluded that the drug is unstable [5]. Studies on the incompatibility and stability of drugs in prescription formulations have not been widely carried out or researched, it is known that the physiology of children is still in its infancy so that it is a concern for adults to pay attention to the use of drugs in pediatric patients.

Based on Table 1 is data on the population that has been collected, the most monthly population data obtained is March 2020 with a percentage of 33.57% and the least is April 2020 with a percentage of 14.8%. Recipes in the form of concoction are 150 recipes while those in the form of non-concoction are 404 recipes so that the total population collected is 554 recipes. The population collected is in the form of prescriptions which are non-sterile prescriptions specifically for children. While table 2 is a table regarding the number of samples obtained where the most collected monthly sample is March 2020 with a percentage of 44% and the least is April 2020 with a percentage of 10.66%. The total sample collected was 150 recipes. All samples obtained were included in the inclusion criteria and no samples were found that included in the exclusion criteria. In table 3, it is obtained prescription data that the types of drugs that are most often used in prescribing concoctions are Ambroxol HCl (22.9%), Mebhidrolin Napadisilat (19.28%) and Dexamethasone (17.04%). In table 4, there are 5 therapeutic class data including: Respiratory System, Anti-infection, Analgesic,

Endocrine, and Vitamins and Minerals. The therapy class that is most often used for the treatment of compound prescriptions is the Respiratory System therapy class.

Based on Table 5 above, data is obtained for the number of types of combinations of non-sterile children's concoction recipes, namely as many as 46 prescription sheets, of which there are 2 to 5 medicinal ingredients in the recipe. The most commonly prescribed types of combinations include:

1. Cefadroxil + Mebhidroline Napadisyl + Ambroxol + Dexamethasone

2. B Complex + Vitamin C

3. Mebhidrolin Napadisilate + Ambroxol

Based on the data in table 6 that there are 7 drugs that are hygroscopic, including B complex (B1, B5, B12), Erythromycin, Paracetamol, Salbutamol (sulfate), Cefixime, Cetirizine (HCl) and Vitamin C. According to the data that has been collected, it is obtained The results show that the B Complex which consists of various types of B vitamins is hygroscopic, namely B1, B5 and B12. According to Martindale 36th based on the European Pharmacopoeia that Erythromycin has slightly hygroscopic properties. Paracetamol absorbs an insignificant amount of moisture at 25°C, at relative humidity up to 90%. Percentage of potential instability based on hygroscopic properties including, B Complex (B1, B5, B12) (22.66%), Erythromycin (16.66%), Paracetamol (2%), Salbutamol (sulfate), cefixime (0.66%), cetirizine (HCl) (4.66%) and Vitamin C (30.66%). In the 1st, 11th, 12th, 21st, and 33rd combinations containing Erythromycin where according to Martindale 36th, Erythromycin is slightly hygroscopic so it has the potential to become wet. The second combination contains Cetirizine (HCl) which has hygroscopic properties and has the potential to experience instability. In the 3rd, 22nd, 27th, 38th, 39th, and 41st combinations, one of the prescribed drugs, namely Vitamin C, is hygroscopic so it has the potential to experience instability. And the 30th and 34th combinations have the potential to experience instability because they contain the hygroscopic drug Salbutamol (Sulfate). The 15th and 20th combinations experienced potential instability because this type of combination contains Erythromycin which is slightly hygroscopic and Salbutamol (sulfate) is hygroscopic. The 23rd and 37th combinations contain a hygroscopic drug, namely Paracetamol. In the 24th, 45th and 46th combinations, the prescribed medicinal ingredients have hygroscopic properties, namely B complex (B1, B5, and B12 which have hygroscopic properties). The 29th, 40th and 42nd combinations experienced potential instability because they contain multivitamin drugs including Vitamin C and B Complex (which are hygroscopic are B1, B5, and B12). The 35th combination has the potential for instability because it contains hygroscopic drugs, namely Cefixime, Salbutamol (sulfate). The 36th combination has the potential for instability because it contains hygroscopic medicinal ingredients including Paracetamol, Vitamin C and B Complex (B1, B5 and B12). While in the 4th, 5th, 6th, 7th, 8th, 9th, 10th, 13th, 14th, 16th, 17th, 18th combinations, 19th, 25th, 26th, 28th, 31st, 32nd, and 44th have no potential for instability.

The problem of moisture in a drug is a problem that must be considered because we know that moisture produces water and water is a growth medium for microbes so that it can trigger microbial growth, reduce drug performance, and most importantly damage the active ingredients. If a prescription consists of more than 1 medicinal ingredient, and one of them is hygroscopic, it will cause moisture and affect other medicinal ingredients. Hygroscopicity is the ability of a material to absorb or absorb moisture from the surrounding environment. The hygroscopicity of pharmaceutical solids is often evaluated due to the fact that the moisture taken up can affect the physical and chemical stability of pharmaceutical products [6]. Physical drug stability in question is when a drug can maintain

a physical form that can be seen using vision and chemical stability where a drug can maintain the integrity of the drug's chemical content with the time limit stated on the label which is influenced by the method and place of storage. Physical stability is affected by heat, light, and humidity which can speed up chemical reactions. Any change in physical appearance such as color fading or blurring can cause the patient or consumer to lose confidence in the product. As for the chemical stability caused by damage to the drug, it has been classified into incompatibility, oxidation, reduction, hydrolysis, and others [7].

Based on table 7 shows that there are 16 types of drugs that have the potential to experience instability due to light exposure according to the literature. Light exposure to Vitamin C can cause the oxidation process of Vitamin C to be accelerated. Vitamin B Complex (B1, B2, B3, B5, B6, B7, B9, B12), for B1, B2 and B3 and B12 must be protected from light and for B1 and B2 stored at 15-30°C. B6 has photosensitive properties and will degrade slowly when exposed to light, storage temperature range 15-30°C. Salbutamol is stored at a temperature of 2-30°C. In the dry state, pure paracetamol is stable up to 45°C. cetirizine can be exposed to temperatures ranging from 15-30°C. Codeine can be stored at temperatures up to 40°C. Amoxicillin at 20°C or lower. Chlorpheniramine maleate should generally be stored at less than 40°C, preferably at 15-30°C. In the activity of making powdered medicine, the medicine is first removed from the product container, then crushed or ground with mortar and pestle. The main thing that needs to be considered is that the drug must be mixed evenly or homogeneously, pay attention to the humidity and temperature in the room, as well as exposure to light at the place where the mixing process is carried out. If this is done correctly, it can help reduce the occurrence of instability in powdered drugs.

Then regarding the incompatibility, the data has been collected using several literatures. This data is used to assess whether the drug in the prescription formulation is incompatible with other drugs in the recipe. It was found that 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 pisotamide. Codeine is incompatible with bromide, iodide, alkalis, most precipitating alkaloids, ammonium chloride, valerates, and salts of copper, iron and tin. Chlorpheniramine maleate has been reported to be incompatible with calcium chloride, kanamycin sulfate, tartaric acid noradrenaline, sodium pentobarbital, and meglumine adipiodone. Pseudoephedrine and vitamin B comp which when mixed cause incompatibility. There is an interaction between Pseudoephedrine with vit. B1 and B2, where at the time of grinding Pseudoephedrine binds water from the air so that the mixture of vitamins B1 and B2 is not mixed. Vit. B1 and B2 become immiscible when in solution or in a wet state. B2 is incompatible with tetracycline, erythromycin, and streptomycin. B3 is incompatible with oxidizing agents, and incompatible with strong alkalis and acids. While other drugs were not found any incompatibility based on the literature used. From this, it can be concluded that there is no potential for drug incompatibility with prescription sheets obtained from XXX Mother and Child Hospital in Makassar for the period January 2020 to April 2020.

5. Conclusion

Based on the results of research at XXX Mother and Child Hospital in Makassar for the period January 2020 to April 2020 obtained 150 prescription sheets with 18 types of drugs from 5 therapeutic classes and based on incompatibility and stability studies, it can be concluded that those that are potentially unstable are affected by humidity as many as 7 drugs and exposure to light as many as 16 drugs. while the potential for drug incompatibility was not found.

Conflicting Interest

All authors declare no conflict of interest.

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