RESEARCH ARTICLE

AGE OF CHILDREN CONTRIBUTES TO POTENTIAL DRUG INTERACTION AT NINE PRIMARY HEALTH CARES

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ABSTRACT

Introduction: Adverse drug reaction including drug interaction should be prevented early in children's patients since children are vulnerable subjects due to their biological development process. Our study aimed to identify the potential drug interaction in children's patients from nine primary health cares (PHC) at Tangerang.

Methods: This study was done with an analytical cross-sectional approach at nine PHC. All children patients from age 1 to 18 years old were recruited for two weeks study. All prescriptions were analyzed and categorized for potential drug interactions.

Results: We identified 19 mild and moderate but not serious potential drug interactions from 791 prescriptions (2%). The most common mild potential drug interaction is paracetamol and domperidone as well as mefenamic acid and dexamethasone for moderate potential drug interaction. Number of drugs and gender did not significantly correlate to potential drug interactions, but age did (p=0.04).

Discussion: We identified that age correlated significantly to potential drug interactions. In brief, the older the patients, the higher the possibility for the drug interactions, thus physicians should be more aware in prescribing drugs to older children's patients.

Keywords: Prescriptions, physicians, children, drug interaction, adverse drug reaction

INTRODUCTION

Drug interaction is defined as the effects occurring from the combination of two or more drugs that influence each other.[1] The interaction may vary from synergistic or inhibitory or eliminating actions. If the combination of drugs will result in enhancing each other's action then it is called synergistic. Combination of drugs that will end in reducing each other's action is called inhibitory. The other type of drug interaction is elimination, in which, a combination of drugs will stop each other's action, resulting in the inactivation of both drugs.[2,3] It is a big challenge for every physician to decide whether drug interaction will give beneficial or detrimental effects on a patient's treatment.

Children are the most vulnerable group of patients due to their developing body system. Differences in body physiology compared to adults make drug dosing more complicated. Furthermore, changing dose due to age differences may result in higher possibility of drug interaction.[4] One study in West Mexico reported, 37 paediatric patients at the hospital presented moderate and major potential drug interactions screened by Micromedex 2.0 database. Age and number of drugs prescribed contributed to the presence of drug interaction.[5] Another study that involved 19.4 million prescriptions for infants in Taiwan hospitals found 3.53 % potential drug interactions. Furosemide interaction with digoxin as well as acetaminophen interaction with anti-cholinergic predominated the most interaction presented at the infants' prescription.[6] Higher potential drug interaction in children was reported by the US Children Hospital. In brief, among 54.549 children patients hospitalized at the Paediatric ICU, they found 75% potential drug interaction among total prescriptions and most of the potential drug interactions were categorized as moderate to serious. In this study, number of drugs, chronic disease and length of stay contributed to the presence of potential drug interactions.[7] Additionally, a cohort study in Swedish reported that there were 0.14% potential drug interaction classified as “should be avoided” and 1.3% classified as “need adjustment for safety reason” among 231.078 children prescriptions from hospital database.[8] Consistent data was reported from Seoul National University Hospital that 115 children's patient were reported to have 592 potential drug interactions from 258 drugs prescribed during the study. They identified that most potential drug interactions did not cause clinically adverse drug reaction, however, appropriate monitoring system should be implemented since adverse drug reaction from drug interaction could be very severe and life threatening.[9]

Although many research centres reported low prevalence rate of drug interactions, life-threatening interactions may develop related to children bodily physiology, thus anticipating and early detection for life-threatening interaction should be provided to favour the patients safety. Potential drug interaction data in children's prescription at primary health cares are still minimal. This study aimed to enhance the data of potential drug interactions at the primary health care to give an appropriate approach in choosing the proper drug regimens for children's safety.

METHODS

Study design

This study was done descriptively with cross-sectional approach. Correlation among factors were analyzed separately. In brief, all children patients' prescriptions data were withdrawn from drug alert system called CIDIA Database. CIDIA was registered under Ministry of Law and Human Rights of Indonesia Republic with the certificate number of EC00201978384. All studies were done through the CIDIA database for over two weeks.[10]

Sample of prescriptions

Total prescriptions from patients aged 1 to 18 years old were recruited and analyzed during the study regardless of the diagnosis of the disease from nine public health centers at Tangerang districts.

Statistical analysis

Descriptive data were shown as number and percentages. Correlation among factors was analyzed using the parametric chi-square test. Significant correlation was defined as probability value less than 0.05 ($p<0.05$).

ETHICAL CLEARANCE

This study was ethically approved by the Ethics Committee Faculty of Medicine Universitas Islam Negeri Syarif Hidayatullah with the registry number of B-005/F12/KEPK/TL.00/02/2021.

RESULTS

Characteristics of children patients

A total of 791 children's patients from nine PHC were recorded in the CIDIA Database. There was no predominance of gender in this study since male patients were 50% compared to 50% female patients (Table 1). However, children's patients aged 1 to 5 years old predominated the total patients (60%). The highest number of children's patients were coming from Paku Haji PHC (31%), then Cisoka PHC (16%). The lowest number of children's patients (3%) were coming from Rajeg PHC (Table 1).

Table 1. General characteristic of children patients of nine primary health care at Tangerang district

Characteristic	Pediatric patients (n = 791)	Percentage
Primary Health Cares		
Cisoka	124	16
Jambe	88	11
Kedaung Barat	29	4
Paku Haji	250	31
Pasar Kemis	87	11
Pasir Nangka	70	9
Rajeg	22	3
Sukawali	44	5
Tigaraksa	77	10
Gender		
Male	398	50
Female	393	50
Age		
Male		
1 – 5 years old	252	32
>5 years old	147	18
Female		
1 – 5 years old	220	28
>5 years old	172	22

Characteristics of potential drug interactions

From Table 2, we identified 19 (2%) potential drug interactions, 7 from male's patients and 12 from the females. We further categorized the drug interaction and found that there was no serious potential drug interaction. Potential drug interaction categorized as mild interaction predominated the type of drug interaction found in all prescriptions (84%). The rest of drug interactions were moderate type (Table 2).

Table 2. Characteristics of drug interaction in children patient at nine primary health care

Characteristics	Number of patients (n = 791)	Number of drug interactions (n = 19)	Percentages
Male	398	7	37
Female	393	12	63
Type of drug interaction			
Male (n=7)			
Mild		5	26
Moderate		2	11
Serious		0	0
Female (n=12)			
Mild		11	58
Moderate		1	5
Serious		0	0
Number of drugs			
1 drug	80	0	0
2 drugs	186	5	26
3 drugs	305	9	48
4 drugs	174	5	26
5 drugs	40	0	0
6 drugs	6	0	0

Further analysis from CIDIA had shown that the most common mild potential drug interaction was between paracetamol and domperidone and the most common moderate drug interaction was mefenamic acid and dexamethasone (Table 3). Interestingly, the number of drugs did not associate directly to the occurrence of potential drug interactions. There were 26% potential drug interactions identified in the patients who received 2 drugs. The potential drug interaction increased to 48% in the patients receiving 3 drugs, however, the potential drug interaction decreased to 26% in the patients receiving 4 drugs per prescription and decreased to 0% in the patients receiving 5 or 6 drugs in one prescription. Thus, in children, prescribing more drugs will not increase the risk of drug interaction.

Table 3. The most common potential drug interactions in children patient at nine primary health care

Type	Drug 1	Drug 2	Pharmacokinetic	Pharmacodynamic
Mild	Paracetamol	Domperidone	Domperidone increases the absorption of paracetamol	
Moderate	Mefenamic acid	Dexamethasone		Both drug increase toxicity of each other through pharmacodynamic synergism

Factors associated with drug interaction

As depicted in Table 2, the increasing number of drugs prescribed did not directly correlate with the occurrence of potential drug interaction in one prescription. Consistent with the descriptive data, in Table 4, we found that there was no significant correlation between the number of drugs prescribed and the potential drug interactions (p = 0.88). We further analyzed the role of gender and age in the occurrence of potential drug interaction and found that gender did not contribute to the drug interaction (p=0.28) but age did (p=0.04). In brief, the potential drug interaction was 2% in the 1 to 5 years old patients and doubled into 4% in the 6 to 18 years old patients. Thus, the older the patients the higher the potential drug interaction appeared (Table 4).

Table 4. Factors influencing potential drug interactions in children's patients at nine primary health care

Characteristics	Number of patients (n = 270)		Significances
	Interaction (+)	Interactions (-)	
Number of drugs			
1 – 3 drugs	14	557	P = 0.88
4 – 6 drugs	5	215	
Gender			
Male	7	391	P = 0.23
Female	12	381	
Age			
1 – 5 years old	7	465	P = 0.04
6 _ 18 years old	12	307	

DISCUSSION

The essential findings of our study at nine primary health cares at Tangerang are (1) there were 2% potential drug interactions found from 791 children's patient prescription; (2) most of the potential drug interactions were mild and moderate; (3) there was no correlation between the number of drugs and the presence of potential drug interaction and (4) age significantly contributed to potential drug interaction while number of drugs and gender did not.

Drug interactions are defined as the effects occurring from the combination of two or more drugs that influence each other.[1] The interaction may vary from synergistic or inhibitory or eliminating actions. The biggest challenge for every physician is to decide whether drug interaction will give beneficial or detrimental effects on a patient's treatment.

Children are the most vulnerable group of patients due their developing body system. Differences in body physiology compared to the adults and age-dependent physiological changes in children make drug dosing is more complicated.[11] Furthermore, changing dose due to age differences may result in higher possibility of drug interaction.[4] Thus, regular evaluation of potential drug interaction in children patients are fully required since extrapolating adult drug interactions data will not resemble the real condition about drug interaction in children patient.[11] Different incidence of potential drug interactions in patient children worldwide were noted. As an example, one study in West Mexico reported, 37 paediatric patients at the hospital presented moderate and major potential drug interactions screened by Micromedex 2.0 database. Age and number of drugs prescribed contributed to the presence of drug interaction.[5] Another study that involved 19.4 million prescriptions for infants in Taiwan hospitals found 3.53% potential drug interaction. Furosemide interaction with digoxin as well as acetaminophen interaction with anti-cholinergic predominated the most interaction presented at the infants' prescription.[6] Higher potential drug interaction in children was reported by the US Children Hospital. In brief, among 54.549 children patients hospitalized at the Paediatric ICU, they found 75% potential drug interactions among total prescriptions and most of the potential drug interaction were categorized as moderate to serious. In this study, number of drugs, chronic disease and length of stay contributed to the presence of potential drug interactions.[7] Additionally, a cohort study in Swedish reported that there were 0.14% potential drug interaction classified as “should be avoided” and 1.3% classified as “need adjustment for safety reason” among 231.078 children prescriptions from hospital database.[8] Consistent data was reported from Seoul National University Hospital that 115 children's patient were reported to have 592 potential interaction from 258 drugs prescribed during the study. They identified that the most potential drug interactions did not cause clinically adverse reactions, however, an appropriate monitoring system should be implemented since adverse drug reactions from drug interaction could be very severe and life threatening.[9] Our study found that potential drug interaction presented 2%

at nine primary health care facilities at Tangerang. Differences among centres were recorded depending on the place of study (hospitals vs. primary care), type of place (ICU vs. inpatient ward) and type of patients (children vs. infant). Although many research centres reported low prevalence rate of drug interactions, life-threatening interactions may develop related to children physiology, thus anticipating and early detection for life-threatening interaction should be provided to favour the patients safety.

Interesting result from our study is age but not gender and number of drugs prescribed significantly contributing to the presence of drug potential interactions. Unlike previous studies that found the number of drugs prescribed significantly contributed to the presence of drug interactions, our study validated that increasing the number of drugs prescribed did not correlate to the incidence of potential drug interaction. We found that the highest rate of potential drug interactions were recorded at 2, 3 and 4 combinations of drugs but not the 5 or 6 or more combinations. Additionally, children at age 6 – 18 years old experienced more potential drug interactions compared to the younger children, 1 – 5 years old. We have not found a specific explanation due to this finding, however, our national drug formularies strictly regulate drugs for paediatric patients especially to children below 5 years old. In brief, only safe and validated drugs were allowed to be given to the 1 – 5 years old patient. Physicians may prescribe more drugs to older children since they were considered as 'near to adults' in body physiology. Additionally, when analysing potential drug interaction, patient-related factors can influence the magnitude of the interactions including paediatric age groups. Different age group may result in different dose, wider regiment of drugs in the formularies and more indication and combination.[11]

Regardless of the disease, we found that the most common potential drug interaction is paracetamol and domperidone in the mild category as well as mefenamic acid and dexamethasone in the moderate category. Even though, clinical implication of domperidone and paracetamol potential drug interaction may be minimal, in-vitro, domperidone was reported to significantly increase the plasma paracetamol concentrations thus may increase the toxicity of paracetamol in some cases.[13] Additionally, mefenamic acid and dexamethasone may decrease the activity of acid phosphatase in myocarditis.[14] Both drugs also have synergistic action in increasing gastrointestinal bleeding.[15]

CONCLUSION

Drug interaction may bring beneficial or detrimental effect in the treatment result. Children are one of vulnerable group of patients prone to have polypharmacy and adverse drug reaction due to their age-dependent bodily change. We identified 2% potential drug interaction in children's patient in nine primary health care at Tangerang. Subsequently, age contributed significantly to the presence of drug interaction. Briefly, older children aged 6 to 18 years old prone to have more drug interactions. Thus, our study validated age as one important factor for physician to prescribe drug and prevent potential drug interaction.

CONFLICT OF INTEREST

There is no conflict of interest declared.

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