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Submission date: 12-Jun-2020 12:59PM (UTC+0700)

Submission ID: 1342389144

File name: Potential Drug-drug Analysis in Children Out-patients with Bronchopneumonia Medication Prescriptions.docx (161.39K)

Word count: 1659

Character count: 9766

Borneo Journal of Pharmacy
Vol 3 Issue 2 May 2020
Page 52 – 56

http://journal.umpalangkaraya.ac.id/index.php/bjop/article/view/1316
DOI: https://doi.org/10.33084/bjop.v3i2.1316
e-ISSN: 2621-4814

Potential Drug-drug Interactions Analysis in Children Out-patients with Bronchopneumonia Medication Prescriptions

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Keywords:
Drug Interactions
Bronchopneumonia
Children
Outpatients

Abstract

Drug-drug interactions (DDIs) is defined as the alteration of efficacy and toxicity of some drugs in the presence of other drugs. In the treatments of bronchopneumonia in outpatient settings, there is a lack of documentation of DDIs. This study was aimed to observe the potential DDIs on the prescriptions of children with bronchopneumonia. An observational and cross-sectional study was conducted on outpatient children with bronchopneumonia prescriptions during 2017. Potential for DDI was identified by online drug interaction checkers. The potential DDI then classified based on its severity (minor, moderate, and major) and mechanism (pharmacokinetic and pharmacodynamic). Among 86 prescriptions analyzed, potential DDIs observed at 48.84% of it. Of that, there were 67 potential DDIs where 72.34% of it were categorized as moderate. The majority of potential DDIs was pharmacodynamic interaction (76.12%) with the most frequently involved drug pair was Ephedrine-Salbutamol (29,85%). Children outpatients with bronchopneumonia are at risk of potential DDIs, especially to minor and moderate potential DDIs. Prescriptions screening for potential DDIs followed by monitoring of therapeutical effects and associated adverse drug events will optimize patient safety.

Received: March 20th 2020
Accepted: May 7th 2020
Published: May 19th 2020

INTRODUCTION

Drug-drug interactions (DDIs) is defined as the change of efficacy and toxicity of some drugs in the presence of other drugs (Shetty *et al.*, 2018). The alterations occure both in pharmacokinetics (absorbtion, distribution, metabolism, and excretion) and pharmacodynamics (sinergism, antagonism, and competition in receptors) phase (Kulkarni *et al.*, 2013; Palleria *et al.*, 2013). In the clinical settings, DDIs is the main source of adverse drug event (Somogyi-Vegh *et al.*, 2019). A recent meta-analysis of several studies reports that DDIs has contributed to 1.1-5% of hospitalization and 0.25-25% of the adverse drug reaction related to hospitalization (Dechanont *et al.*, 2014; Ismail *et al.*, 2018). In outpatient settings, there is a lack documentation of DDIs and its prevalence is reported lower than in hospitalized patients because they are usually prescribed less drug combination (Vaidhun & Sathish, 2011). However, if they are prescribed with polypharmacy the potential of DDIs occurence will also rise.

Bronchopneumonia is one of life-threatning pneumonia manifestation commonly occur in children under 5 y.o. As the treatment of pneumonia, causative management using antibiotics and symptomatic drugs like antitusive, expecorant, antihistamine, analgesic-antipyretic used in bronchopneumonia management (Harris *et al.*, 2011; Chang *et al.*, 2014). Hence, high combination drugs potentially prescribed to the children with

bronchopnaumonia and its leading to the occurence of DDIs. The DDIs identification in bronchopneumonia prescriptions will optimize the outcome therapy and prevent the incidence of adverse drug reactions (Noor *et al*., 2019). This study was aimed to observe the potential DDIs on the prescriptions of children with bronchopneumonia.

MATERIALS AND METHODS

An observational and cross-sectional study was conducted on outpatient children with bronchopneumonia prescriptions during 2017 at a Hospital in Bangkalan, Madura Island, Indonesia. Study began after obtaining permition from the hospital. The Inclusion criteria were prescriptions of outpatient children age 0-14 y.o. diagnosed with bronchopneumonia without any infection comorbidities. Prescriptions contained one or two drugs with different route of administration were excluded. Potential for DDIs were identified by online drug interaction checkers from www.drugs.com. The drugs that not available in the database were than identified by www.drugbank.ca. The prescriptions contained drugs that not listed in that two online applications were also excluded. The potential DDIs then classified based on its severity (minor, moderate, and major) and mechanism (pharmacokinetic and pharmacodinamic). The management suggestion from the online applications also included.

RESULTS AND DISCUSSION

During the period of study, a total of 158 prescriptions met the inklusions criteria. Of that, 72 prescriptions were excluded due to varoous reasons; 9 prescriptions only contained of one drugs, 3 prescriptions contained of two drugs with different route; 10 prescriptions consisted of probiotics; and 50 remaining contained of herbal medicine like succus liquiritae and echinaceae extract that not available in the the two online-application used. The remaining 86 prescriptions were analyzed for the potential DDIs. The prevalence of potential DDIs based on gender, age, and number of drug prescribed showed in patients characteistics as presented in **Table I.**

Table I. Patients characteristics

Characteristics	N (%)		Total (%)
	Potential DDIs	No Potential DDIS	
Gender			
Female	19 (22.09)	24 (27.91)	43 (50.00)
Male	23 (26.74)	20 (23.26)	43 (50.00)
Total	**42 (48.84)**	**44 (51.16)**	**86 (100.00)**
Age (years)			
<1	13 (15.12)	2 (2.33)	15 (17.44)
1-5	21 (24.42)	35 (40.70)	56 (65.12)
6-10	5 (5.81)	7 (8.14)	12 (13.95)
11-14	3 (3.49)	0 (0.00)	3 (3.49)
Total	**42 (48.84)**	**44 (51.16)**	**86 (100.00)**
Number of drug prescribed			
<5	30 (34.88)	10 (11.63)	40 (46.51)
5-10	7 (8.14)	21 (24.42)	28 (32.56)
>10	5 (5.81)	13 (15.12)	18 (20.93)
Total	**42 (48.84)**	**44 (51.16)**	**86 (100.00)**

Generally, the prevalence of potential DDIs is linear to the number of drug prescribed as Loya *et al.* (2009) reported that 46.2% dan 72.3% of polypharmacy had at least one potential DDIs. However, in this study the majority potential DDIs observed in the prescriptions contained less than five drugs. This discrepancy might be due to the prescribing culture and formulary used in the hospital. Out of the 42 potential DDIs found, most of them had moderate (80.95%) and minor (73.80%) severity that is sufficiently to warn us to have a monitoring for the potential dangerous, as shown in **Figure 1.**

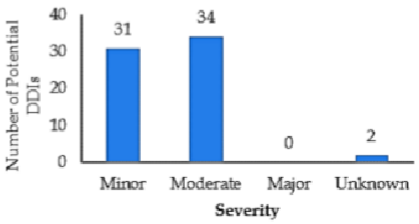

Figure 1. Severity of Potential DDIs

The prevalence of potential DDIs, its manifestations, and suggested management predominantly occur in the pharmacodynamic phase, as presented in **Table II**. The higher number of pharmacodynamics DDIs are probably due to the drug combinations prescribed is purposed to enhance the efficacy (Patel *et al*, 2014). The pair of ephedrine+salbutamol was counted 29.85% of pharmacodynamics DDIs and potentially harm to patients as it has moderate severity. The manifestation is similar to pseudoephedrine+salbutamol which was observed 4.48% of pharmacodynamics DDIs in this study. The administration of beta-2 agonists together with other adrenergic agents may result in the increase of cardiovascular side effects including escalation of pulse rate and systolic or diastolic blood pressure as well as ECG changes such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. These effects may be more common when the drugs are administered systemically or when recommended dosages are exceeded (Khalilian *et al.*, 2016). A meta-analysis by Salpeter *et al.* (2004) reported that beta-2 agonist use in patients with obstructive airway disease increases the risk for cardiovascular adverse events from three days to one year. The manifestation occure were an increase in heart rate and potassium concentrations depletion. Therefore, the oral concomitant use of ephedrine+salbutamol in children with bronchopneumonia must be counted for its benefit and risk. Use salbutamol in local route like inhaler will minimize the risk of cardiovascular event.

Another pharmacodynamic DDIs that need to be considered was from the pair of dexamethasone+teophyline. The co-administration of theophylline and corticosteroids theoretically may potentiate the risk of hypokalemia due to additive potassium-lowering effects. Theophylline inhibits adenosine receptors and blocks phosphodiesterase causing rised cyclic adenosine monophosphate resulting in increased levels of adrenergic activation and catecholamine release at larger dose (Barnes, 2010). Elevated catecholamine concentrations will lead to adverse effects such as metabolic acidosis, hyperglycemia, cardiac arrhythmias, and hypokalemia (Kardalas *et al.*, 2018). Additionally, corticosteroids conduce sodium retention through the increase of sodium tubular absorption and potassium excretion. Sodium retention and potassium loss may result in hypokalemic alkalosis in patients receiving glucocorticoids (Nasralla *et al.*, 2010). Consequently, if the benefits outweight the drawbacks, the use of dexamethasone and theophylline in children with bronchopneumonia should be followed by monitoring in potassium levels and the cardiovascular events (Zec *et al.*, 2016).

In the pharmacokinetics phase, the most common DDIs observed was ephedrine+vitamin C. Acidic urine increases the urinal elimination of ephedrine. However, the severity is minor and the clinical significance is unknown.

Table II. Prevalence of potential DDIs

Drug pairs	N (%)/ severity	Potential Manifestasion	Management
Pharmacokinetics DDIs			
Ephedrine-Vitamin C	9 (13.43) / Minor	The effect of ephedrine may be decreased	Considering for drug subtitution
Phenytoin-Dexamethasone	2 (2.99) / Moderate	The effect of dexamethasone may be decreased	Considering for drug subtitution
Phenytoin-Paracetamol	2 (2.99) / Moderate	The potential hepatotoxicity of paracetamol may be increased and its pharmacological effects may be decreased	Monitoring on liver function
Total		13 (19.40)	
Pharmacodynamics DDIs			
Chlorphenyramine-Domperidone	1 (1.49) / Unknown	The effect on cardiovascular may be increased	Monitoring of the presence of arrhythmia
Chlorphenyramine-Codein	1 (1.49) / Moderate	The effect on CNS may be increased	Monitoring on respiration function
Dexamethasone + Salbutamol	9 (13.43) / Minor	The effect on cardiovascular may be increased	Monitoring of the presence of arrhythmia
Dexamethasone +	4 (5.97) /	The effect on	Monitoring

Teophyline	Moderate	cardiovascular may be increased	for altered efficacy and safety of theophylline and altered serum potassium
Ephedrine + Salbutamol	20 (29.85) / Moderate	The effect on cardiovascular may be increased	Monitoring for blood pressure and heart rate
Ephedrine - Teophylin	1 (1.49) / Minor	The potential side effects like nausea, vommiting, tachycardia and insomnia may be increased	Monitoring of the presence of side effects
Methylprednisolon + Salbutamol	9 (13.43) / Minor	The hypokalemia risk and the effect on cardiovascular may be increased	Monitoring for serum potassium level and the presence of arrhythmia
Prednison-Salbutamol	1 (1.49) / Minor	The hypokalemia risk and the effect on cardiovascular may be increased	Monitoring for serum potassium level and the presence of arrhythmia
Pseudoephedrine-Salbutamol	3 (4.48) / Moderate	The effect on cardiovascular may be increased	Monitoring for blood pressure and heart rate
Salbutamol-Teophyline	1 (1.49) / Moderate	The hypokalemia risk and the effect on cardiovascular may be increased	Monitoring for serum potassium level and the presence of arrhythmia
Cetirizin- Sodium Valproate	1 (1.49) / Moderate	The effect on CNS may be increased	Monitoring for cognitif function
Total		53 (76.12)	
Unknown mechanism DDIs			
Dexamethasone-Ephedrine	2 (2,99) / Minor	The effect of dexamethasone may be decreased	Considering for drug subtitution
Domperidone-Paracetamol	1 (1,49) / Unknown	The serum level of domperidone may be increased	Considering for drug subtitution
Total		3 (4.48)	
Total		67 (100.00)	

Apart from the result above, this study has several limitations. As this study showed the potential for DDIs in the prescriptions, the actual occurr of DDIs in the patients could not be determined because the study was a single point cross-sectional and out-patient based. Moreover, herbal medicine and probiotics-contained prescriptions could not be determined for the DDIs. Therefore, future studies on potential and actual occurrence DDIs in outpatient children with bronchopneumonia in future still need to be conducted.

CONCLUSION

A considerable prevalence of potential DDIs has been observed in children outpatients with bronchopneumonia (48.84%) where moderate potential DDIs were the most common. Moreover, the use of probiotics and herbal medicine in bronchopneumonia treatments still need to be considered related unknown potential DDIs. Prescriptions screening for potential DDIs followed by monitoring of therapeutical effects and associated adverse drug events will optimize patient safety.

ACKNOWLEDGMENT

We would like to express our deep sense of gratitude to the Hospital for their permition and support during data collection. We would also thank to Akademi Farmasi Surabaya for the financial support during this study.

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