[IJPTher] Article Review Request

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Abraham Simatupang:

I believe that you would serve as an excellent reviewer of the manuscript, "A Review: Clinically Significant of Drug-Drug Interactions Among Children," which has been submitted to Indonesian Journal of Pharmacology and Therapy. The submission's abstract is inserted below, and I hope that you will consider undertaking this important task for us.

Please log into the journal web site by 2023-10-11 to indicate whether you will undertake the review or not, as well as to access the submission and to record your review and recommendation.

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"A Review: Clinically Significant of Drug-Drug Interactions Among Children"

Introduction: Drug-drug interactions among children are a getting along concern in health care settings, specifically intensive care units, as sources of adverse drug events that may affect patient condition. Children admitted to pediatric intensive care units are more prone to drug-drug interactions owing to the diseases and medications complexity. This condition could put the patient at high risk of harm, particularly with his critical condition, so need intense consideration from clinical practitioners to prevent adverse drug events caused by potential drug-drug interactions. **Objective:** This article's review attempts to explore the important drug-drug interactions among children, including explaining the drug combination, mechanism, and related adverse drug events to help health practitioners recognize it earlier before prescribing the medication. **Method:** This article's review explored previous research results from PubMed as literature resources and PRISMA flow chart as protocol for article selection process. **Result**: A total of 8 articles discussed comprehensively about the type of drug combinations, mechanism of drug-drug interactions, and associated adverse drug events with significant drug-drug interactions that commonly occurred in children's patient during the treatment. The interaction occurred including the combination of midazolam-phenobarbital, cannabidiol-clobazam, Paxlovid-tacrolimus, inhaled fluticasone propionate-lopinavir/ritonavir, rifampicin-warfarin, clofazimine-moxifloxacin, and benzatropine-haloperidol. **Conclusion**: Gaining a better understanding of drug-drug interactions among children will empower healthcare professionals to develop useful strategies to recognize, manage, and prevent various types of pharmacokinetic and pharmacodynamic interactions. Especially at different stages in terms of age, physiology, and complexity of the disease in children.

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Dear Reviewer
Thank you for completing the review of the manuscript for the Indonesian Journal of Pharmacology and Therapy. We appreciate your contribution to the quality of the work that we publish.

Regards,
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A[Farmako1] Review: Clinically Significant of Drug-Drug Interactions Among Children

ABSTRACT

Introduction: Drug-drug interactions among children are a getting along concern in health care settings, specifically intensive care units, as sources of adverse drug events that may affect patient condition. Children admitted to pediatric intensive care unit are more prone to drug-drug interactions owing to the diseases and medications complexity. This condition could put the patient at high risk of harm, particularly with his critical condition, so need intense considerations from clinical practitioners to prevent adverse drug events caused by potential drug-drug interactions. **Objective:** This article's review attempts to explore the important drug-drug interactions among children, including explaining the drug combination, mechanism, and related adverse drug events to help health practitioners recognize it earlier before prescribing the medication. **Method:** This article's review explored previous research results from PubMed as literature resources and PRISMA flow chart as protocol for article selection process. **Result**: A total of 8 articles discussed comprehensively about the type of drug combinations, mechanism of drug-drug interactions, and associated adverse drug events with significant drug-drug interactions that commonly occurred in children's patient during the treatment. The interaction occurred including the combination of midazolam-phenobarbital, cannabidiol-clobazam, Paxlovid-tacrolimus, inhaled fluticasone propionate-lopinavir/ritonavir, rifampicin-warfarin, clofazimine-moxifloxacin, and benzatropine-haloperidol. **Conclusion**: Gaining a better understanding of drug-drug interactions among children will empower healthcare professionals to develop useful strategies to recognize, manage, and prevent various types of pharmacokinetic and pharmacodynamic interactions. Especially at different stages in terms of age, physiology, and complexity of the disease in children.

ABSTRAK

Pendahuluan: Interaksi obat-obat pada anak-anak merupakan suatu hal yang menjadi perhatian di fasilitas pelayanan kesehatan, khususnya unit perawatan intensif, sebagai sumber terjadinya efek samping obat yang dapat mempengaruhi kondisi pasien. Anak-anak yang dirawat di unit perawatan intensif lebih rentan terhadap interaksi obat-obat karena kompleksitas penyakit dan pengobatannya. Kondisi ini dapat menempatkan pasien pada risiko bahaya yang tinggi, terutama dalam kondisi kritis, sehingga memerlukan pertimbangan dari praktisi klinis untuk mencegah efek samping akibat interaksi obat-obat potensial. **Tujuan**: Ulasan artikel ini bertujuan untuk mengeksplorasi interaksi obat-obat yang penting pada anak-anak, termasuk menjelaskan kombinasi obat, mekanisme, dan efek samping obat terkait untuk membantu praktisi kesehatan mengenalinya lebih awal sebelum meresepkan obat. **Metode:** Review artikel ini mengeksplorasi hasil penelitian sebelumnya dari PubMed sebagai sumber literatur dan menggunakan diagram alur PRISMA sebagai protokol dalam proses pemilihan artikel. **Hasil**: Sebanyak 8 artikel membahas secara komprehensif mengenai jenis kombinasi obat, mekanisme interaksi obat-obat, dan hubungan efek samping obat dengan interaksi obat-obat signifikan yang umum terjadi pada pasien anak selama pengobatan. Interaksi yang terjadi antara lain kombinasi midazolam-phenobarbital, cannabidiol-clobazam, Paxlovid-tacrolimus, inhalasi fluticasone propionate-lopinavir/ritonavir, rifampicin-warfarin, clofazimine-moxifloxacin, dan benzatropine-haloperidol. **Kesimpulan:** Pemahaman yang lebih baik mengenai interaksi obat-obat yang terjadi di kalangan anak-anak akan memperkuat profesional kesehatan untuk mengembangkan strategi yang berguna untuk mengenali, mengelola, dan mencegah berbagai jenis interaksi farmakokinetik dan farmakodinamik. Terutama pada tahapan yang berbeda dalam hal usia, fisiologi, dan kompleksitas penyakit pada anak.

Keywords: adverse drug event, children, critically ill, drug-drug interaction, pharmacokinetics.

INTRODUCTION

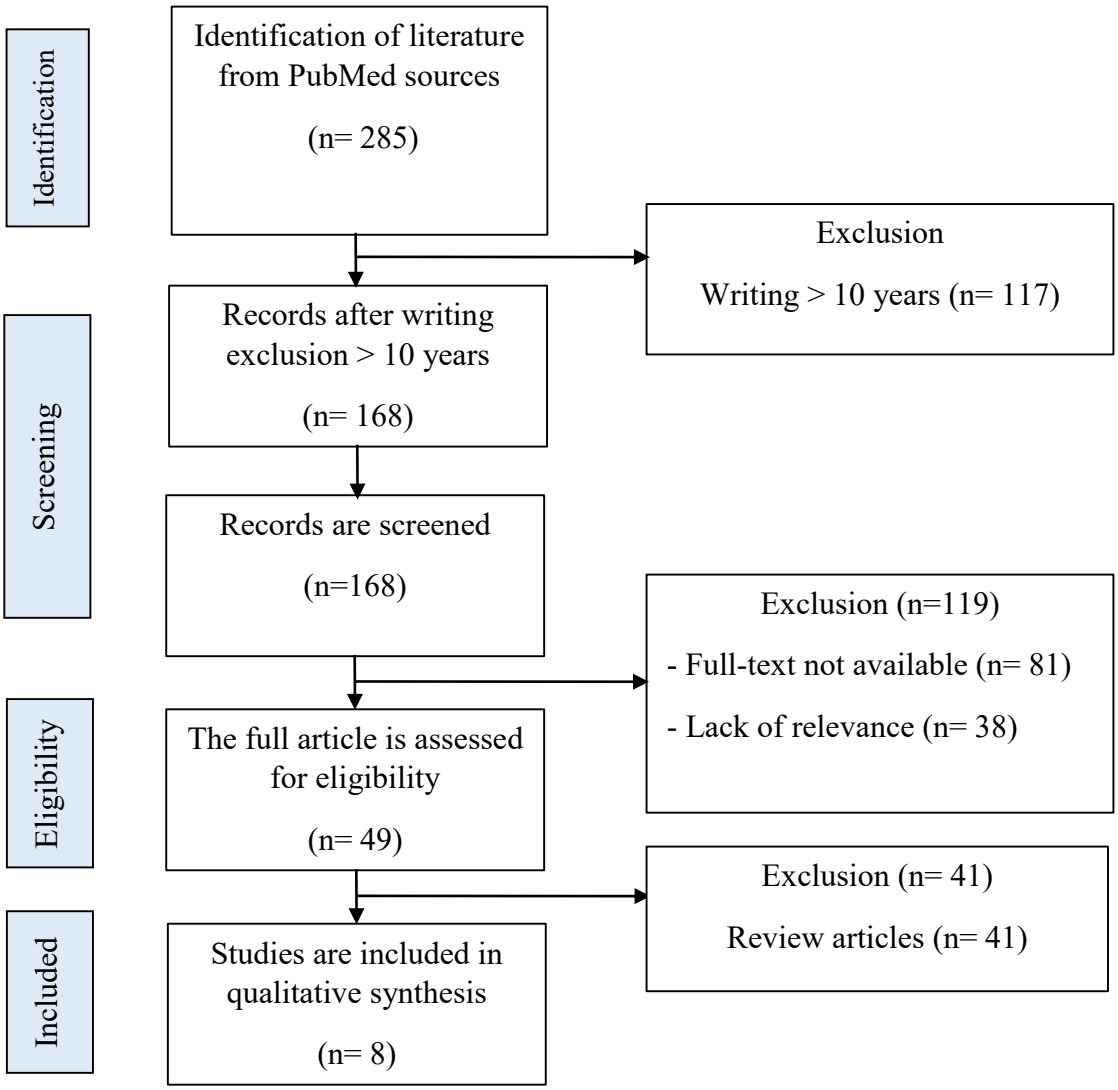
Recently, WHO initiated The Global Safety Challenge which highlights the medication without harm that would be addressed to achieve medication safety among patients around the world (1). This agenda is closely related to diminishing the incidence of drug-related problems that influence the result of Adverse Drug Events (ADEs) (2,3). Drug-drug interactions (DDIs) are a getting along concern in health care settings, specifically intensive care units (ICU) that handle critically ill conditions. Commonly, DDIs could be as sources of ADEs that may affect patient condition, worsening the children development, and slower the stabilization proses (4,5).

Children admitted to pediatric ICU (PICU) are more prone to DDIs owing to the diseases and medications complexity (6). Studies from several countries estimated about 58% of ICU patients are susceptible to a potential DDI (pDDI) with clinically significant drug interaction exposure occurring in 38% of patients. Moreover, this condition also implied to increase 9.83 days of length of stay among PICU patients (7–9). Moreover, ADEs related to DDIs in critically ill patients are becoming a serious concern including hypokalemia, QT-prolongation, seizures, and tachycardia (10). This condition could put the patient at high risk of harm, particularly with his critical condition, so need intense considerations from clinical practitioners to prevent ADEs caused by pDDI (11). Since it would be unattainable for most doctors to recall all types of pDDI among pediatric patients, enhancing the expertise of clinicians in terms of clinically significant DDIs could improve patient safety through diminish the risk of serious ADEs. Applying DDI analyzing software and assigning clinical pharmacists to detect and avoid DDIs have refined patient safety in wider clinical settings (7,12). However, physician still needs more knowledge about DDIs as a form of early consideration when prescribing patients beyond their own experiences (11).

Previous studies regarding pDDI among critically-ill patients dominantly focused on frequency, type, mechanisms, onset, severity, management, and clinical manifestation resulting from actual DDIs among adult, but important drug types involved in DDIs among pediatric patients have not yet been comprehensively documented (3,4,12–14). This article's review attempts to explore the important DDIs among children, including explaining the drug combination, mechanism, and related ADEs to help health practitioners recognize it earlier before prescribing the medication.

METHOD

A literature review of drug-drug interaction among children was carried out using the source of the primary literature website, namely PubMed. Specific terms including "drug interaction" and "children or pediatric" was chosen as search keywords based on main article topic. All articles were assessing with inclusion and exclusion criteria. Inclusion criteria such as appropriate with keywords, published at the last of 10 years, and full paper accessed. In addition, the exclusion criteria consist article review types. We also used PRISMA flowchart as a guideline for article selection process (Picture 1).



Picture 1. Search terms and publication selection process (PRISMA Flowchart)

RESULT

All the main articles used to discuss the type of drug combinations, mechanism of DDIs, and associated ADEs with significant DDIs that commonly occurred in children's patient during the treatment (Table 1).

Table 1. The outcome of the use of Metformin vs Sulfonilurea with other antidiabetic drugs for pregnant women

References	Drug use combination	Patient, population, and problem	Outcome target	Interaction mechanism	ADEs
Favie *et al*[15]	Midazolam - Phenobarbital	Neonates with hypoxic-ischaemic encephalophaty treated with therapeutic hypothermia	Phenobarbital is an anti-epileptic drug to reduces neuronal excitability while midazolam as seizure control and gives adequate sedation	Pharmacokinetics. Phenobarbital increases CYP3A production in the early 24 hours after birth that raising midazolam clearance	Hypotension and cerebral hypoperfusion
Wheless *et al*[16]	Cannabidiol - Clobazam	Treatment-resistant epilepsy among pediatric patients (aged 1 to ≤ 17 years)	Cannabidiol regulate neuronal hyperexcitability and diminish the number of seizures. Clobazam is an adjunctive treatment for treat seizures among patients with Dravet syndrome.	Bidirectional interaction with pharmacokinetics mechanism. Cannabidiol alters the metabolism of clobazam in the pediatric population resulting in increased clobazam active metabolite concentration. There was elevated exposure both of cannabidiol and clobazam in plasma	Diarrhea, somnolence, apnea, skin rash, and psychomotor hyperactivity.

Young *et al*[17]	Paxlovid (nirmatrelvir/ritonavir) - Tacrolimus	A 14-year-old female with a kidney transplant	Tacrolimus aims to suppress immune system and nirmatrelvir/ritonavir used as COVID-19 treatment.	Pharmacokinetics: Ritonavir exhibits inhibition of P-glycoprotein and a strong inhibition of CYP3A4 enzyme which is involved in tacrolimus absorption and metabolism resulting in elevated tacrolimus levels within systemic circulation.	Significantly elevated tacrolimus level in serum until reached supratherapeutic level followed with QTc prolongation on ECG examination.
Castro-Moraga *et al*[18]	Inhaled fluticasone propionate - Lopinavir/ritonavir	A 5-year-old male with HIV infection	Lopinavir/ritonavir for the treatment of HIV infection to achieve virological and immunological control. Fluticasone propionate is a medication for treating rhinitis allergy.	Pharmacokinetics: Administration of an antriretroviral agent (lopinavir/ritonavir) significantly elevates the systemic absorption of fluticasone propionate due to fluticasone metabolism inhibition through the CYP3A4 pathway.	Cushing syndrome with laboratory abnormality, including dyslipidemia and mild insulin resistance.
Mito *et al*[19]	Rifampicin - Warfarin	A 4-year-old child with congenital heart disease and undergoing warfarin medication	Rifampicin as antibiotic for infective endocarditis treatment and warfarin as anticoagulant among patient with congenital heart disease.	Pharmacokinetics: Rifampicin regulates pregnane X receptor (PXR) activation that mediates CYP3A expression that reduce anticoagulant index.	Failure to ~~achive~~achieve INR therapeutic target that influence thromboembolism condition. This interaction cause 52.0% decrease in the anticoagulant index.

Poon *et al*[20]	Rifampicin - Warfarin	A 20-month-old female with atrioventricular valve regurgitation and subsequent heart failure with a history of unsuccessful atrioventricular valve repair and undergoing a replacement with a 21-mm St Jude mechanical valve. Her laboratory result showed a positive culture for methicillin-resistant *Staphylococcus aureus* with MRSA artificial valve endocarditis diagnosis.	Rifampicin as antibiotic for endocarditis treatment and warfarin as anticoagulant for maintain INR value between 2.5 – 3.5.	Pharmacokinetics: Rifampicin induce an activation of CYP3A4 that modulate the alteration of warfarin metabolism.	~~Ineffectivity~~Ineffectively of warfarin treatment by elevated 300% dose requirement of warfarin
Ali *et al*[21]	Clofazimine - Moxifloxacin	A total of 88 participants with median age was 3.9 years (between 0.5 – 15.7 years) that undergoing treatment for rifampicin-resistant tuberculosis with one or more QT interval-prolonging agent.	Clofazimine and moxifloxacin are antimycobacterials agent for rifampicin-resistant tuberculosis.	Pharmacodynamics: Both clofazimine and moxifloxacin induce QTc prolongation.	Contribute to QTc prolongation with the highest ΔQTcF value being 20.0 ms that equivalent to a 3.5-fold increase on it.
Nkansah-Amankra and Sudhanthar [22]	Benzatropine - Haloperidol	A 17-year-old male with a medical history of mild cerebral palsy, autism spectrum disorder, and bipolar disorder with aggression	Haloperidol to treat his mental health conditions and benzatropine as a prophylaxis agent for dystonic movement resulting from haloperidol consumption .	Pharmacodynamics: Synergistic anticholinergic effect from both haloperidol and benzatropin.	Cause chronic urinary retention problem, specifically lead a obstructive uropathy contributed to acute kidney injury phase.

DISCUSSION

Pharmacotherapy attempts to attain particular therapeutic outcomes, raise patients' quality of life, as well as minimize medication dangers as well. However, inappropriate use of medication combination is frequent and predisposing pediatric patients, a vulnerable population, to ADE. The 8 studies included reported clinically significant of DDI affected therapeutic outcome and contributed to medication risk in the pediatric patients.

While recognizing ADEs owing to DDIs are an important part of pharmaceutical and healthcare practice, a comprehensive description of actual DDIs among pediatrics that clinically significance occurred commonly in healthcare settings has not been detailed yet. In this review, 7 different types of drug combinations among children that caused clinically significant DDIs were studied in the 8 studies with different specific population characteristics, resulting in difficulties in comparing the types and impact levels of DDIs. In addition, most DDI descriptions that refer to its occurrence and mechanism in the adult population. Hence, health practitioners rely on existing data generated in adults to manage DDIs among children population despite significant differences between the population, including maturation of metabolism and renal elimination mechanism, receptor sensitivity, and variable weight-adjusted dose of interacting drug pairs (9,23,24).

Regardless of the difference between adults and children in DDI impact and mechanism, case reports and descriptions of DDIs among adults can be used as references to manage DDI cases in children while taking into account the crucial differences and considering possible mechanisms that occurred (23). This consideration is important to avoid the possibility of potential ADE. Therefore, the case of DDIs among children that have been previously studied would also be highlighted as a consideration for providing the optimum regimen therapy for the patient, primarily to prevent the worsening of conditions in pediatric patients with critical illness (25).

All of the drug interaction pairs in this study has been fairly documented that generated from adult population studies. Based on Lexicomp drug interaction checker, the drug combination of inhaled fluticasone-lopinavir/ritonavir and rifampicin-warfarin are types of DDIs with major (class D) severity levels while the other combination with moderate (class C) severity level means less harmful but still need tight monitoring. The severity classification described each action to manage the DDI, such as avoid drug combination for class X, consider therapy modification for class D, and monitor therapy for class C (25,26).

Inhaled Fluticasone – Lopinavir/Ritonavir

Drug interaction between inhaled fluticasone-lopinavir/ritonavir with pharmacokinetics mechanism among children was discussed in a study from Chile that occurred in a 5-year-old male with stage N1 HIV infection transmitted vertically followed by rhinitis allergy symptoms (congestion, a runny nose, and snoring during nighttime). Co-administration of inhaled fluticasone during the regular treatment of antiretroviral agents, specifically lopinavir/ritonavir, is not recommended, and need to consider an alternative drug to replace inhaled fluticasone as a rhinitis allergy treatment. Lopinavir-ritonavir, a protease, that would significantly increase the systemic absorption of inhaled fluticasone, as well as lopinavir/ritonavir is a strong inhibitor of CYP3A4 that has an important role in fluticasone metabolism would be elevated fluticasone plasma concentration resulting in steroid accumulation that leads adrenal suppression and Cushing's syndrome with an average onset of 2.1 months usage (18). A study by Castro-Moraga et al. among a 5 year old male revealed that using inhaled fluticasone and lopinavir/ritonavir concomitantly caused Cushing's syndrome followed by dyslipidemia and mild insulin resistance (18). Insulin resistance at the post-receptor stage is predominantly induced by the

overproduction of glucocorticoids, which characterizes Cushing's syndrome and hinders glucose tolerance. Furthermore, corticosteroid accumulation would influence an excessive cortisol level that associated with risk of dyslipidemia among Cushing's syndrome patients (27,28). Considering an alternative agent to fluticasone propionate is highly recommended to ensure the patient's safety aspect, in particular the pediatric population. Inhaled beclomethasone as a corticosteroid with low lipophilicity and shorter-acting agent suggested to be used concomitantly with lopinavir-ritonavir when needed mainly due to no interaction detected on it (18,28).

Rifampicin - Warfarin

Moreover, DDI in the combination of rifampicin-warfarin among children with congenital heart disease has been studied in 2 studies, in Japan and Texas (19,20). Warfarin as vitamin K antagonists is the most lifelong anticoagulation prescribed for patient who have undergone mechanical valve replacement or have congenital heart disease with heart blood flow disturbance to prevent thromboembolism event (29). In addition, both congenital heart disease and valve replacement are predisposing factors to infective endocarditis complication (30). Children with congenital heart disease are projected to be 15 – 140 higher than the general population to acquire infective endocarditis (31). In these studies, Rifampicin is a drug of choice as infective endocarditis antibiotics with gram positive bacterial coverage (32). Moreover, the concomitant use of rifampicin-warfarin is common among pediatric patients with valve replacement and infective endocarditis even though the interaction between. Co-administration of rifampicin during regular treatment with warfarin, in particular among children, need careful consideration since the previous report from Texas showed these combinations elevate warfarin dose requirement

dramatically compared with usage among adult, with an increase of 300% dose requirement. The interaction due to the rifampicin induce an activation of CYP3A4 that modulate the alteration of warfarin metabolism, specifically raise warfarin metabolism resulting in raise the dose requirement (20).

The difference in DDI impact could come from disease severity, biochemical profile, and physiologic factors, including enzyme maturity between children and adults. These characteristics will affect the drug's bioavailability (24). Besides that, warfarin dosing for children is also challenging due to a multitude of factors affecting the pharmacokinetics profile, including age and the maturation function of CYP2C9 (33). The pharmacokinetics factor influences the anticoagulant response to warfarin, such as drug interactions that affect its absorption or metabolic clearance. Specifically, the anticoagulant effect is impeded by rifampicin which elevates hepatic clearance of warfarin (34). However, the physician should realize that a more aggressive approach to dose titration is needed when encountering DDIs of rifampicin-warfarin, especially in pediatric patients in the intensive care unit.

Physicians should consider all of the possible DDIs listings in pediatric patients prioritizing based on severity level of DDIs. The clinical significance of DDIs with pharmacokinetics mechanism can be avoided with dose titration or adjusting the administration intervals. In addition, some cases needed further action by stopping the drug combination and replacing the drug with the alternative one (18–20). Moreover, when drugs interact with the pharmacodynamics mechanism, stopping the drug combination used is a possible action to hinder DDIs. Furthermore, the treatment plan action not only based on DDIs event, the physicians also should consider thoroughly the patients' condition by weighing the risk and benefit ratio.

CONCLUSION

This review seeks to critically assess current knowledge besides to identify comprehensively the DDIs in children. By gaining a better understanding of this topic, this information will empower healthcare professionals to develop useful strategies to recognize, manage, and prevent various types of pharmacokinetic and pharmacodynamic interactions. Especially at different stages in terms of age, physiology, and complexity of the disease in children.

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