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Clinically significant of drug-drug interactions among children: a review

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ABSTRACT

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. 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. This article's review explored previous research results from PubMed and Google Scholar as literature resources and PRISMA flow chart as protocol for article selection process. A total of 9 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 drug-drug interaction including midazolam-phenobarbital, cannabidiol-clobazam, Paxlovid-tacrolimus, inhaled fluticasone propionate-lopinavir/ritonavir, rifampicin-warfarin, clofazimine-moxifloxacin, benzatropine-haloperidol, and enalapril-spironolactone. In 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

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. 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. Review artikel ini mengeksplorasi hasil penelitian sebelumnya dari PubMed dan Google Scholar sebagai sumber literatur dan menggunakan diagram alur PRISMA sebagai protokol dalam proses pemilihan artikel. Sebanyak 9 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 obat-obat meliputi midazolam-phenobarbital, cannabidiol-clobazam, Paxlovid-tacrolimus, inhalasi fluticason propionate-

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lopinavir/ritonavir, rifampicin-warfarin, clofazimine-moxifloxacin, benzatropin-haloperidol, dan enalapril-spironolactone. Simpulan, 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.

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 sources of ADEs that may affect patient condition, worsening the children's development, and slower the stabilization process.[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 an 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 by 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, the 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.

MATERIAL AND METHODS

A literature review of drug-drug interaction among children was carried out using the sources of the primary literature websites, namely PubMed and Google Scholar. Specific terms including "drug interaction" and "children or pediatric" were chosen as search keywords based on the main article topic. All articles were assessed with inclusion and exclusion criteria. Inclusion criteria such as assessing the drug-drug interaction among children (≤18 y.o.), the research conducted among inpatient settings including general ward, emergency department, and intensive care unit, the content of the article is appropriate with keywords, published at the last of 10 years, and full paper accessed. In addition, the exclusion criteria consist of article review types and studies that do not address ADE related to drug interactions. We also used the PRISMA flowchart as a guideline for the article selection process (FIGURE 1).

RESULTS

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).

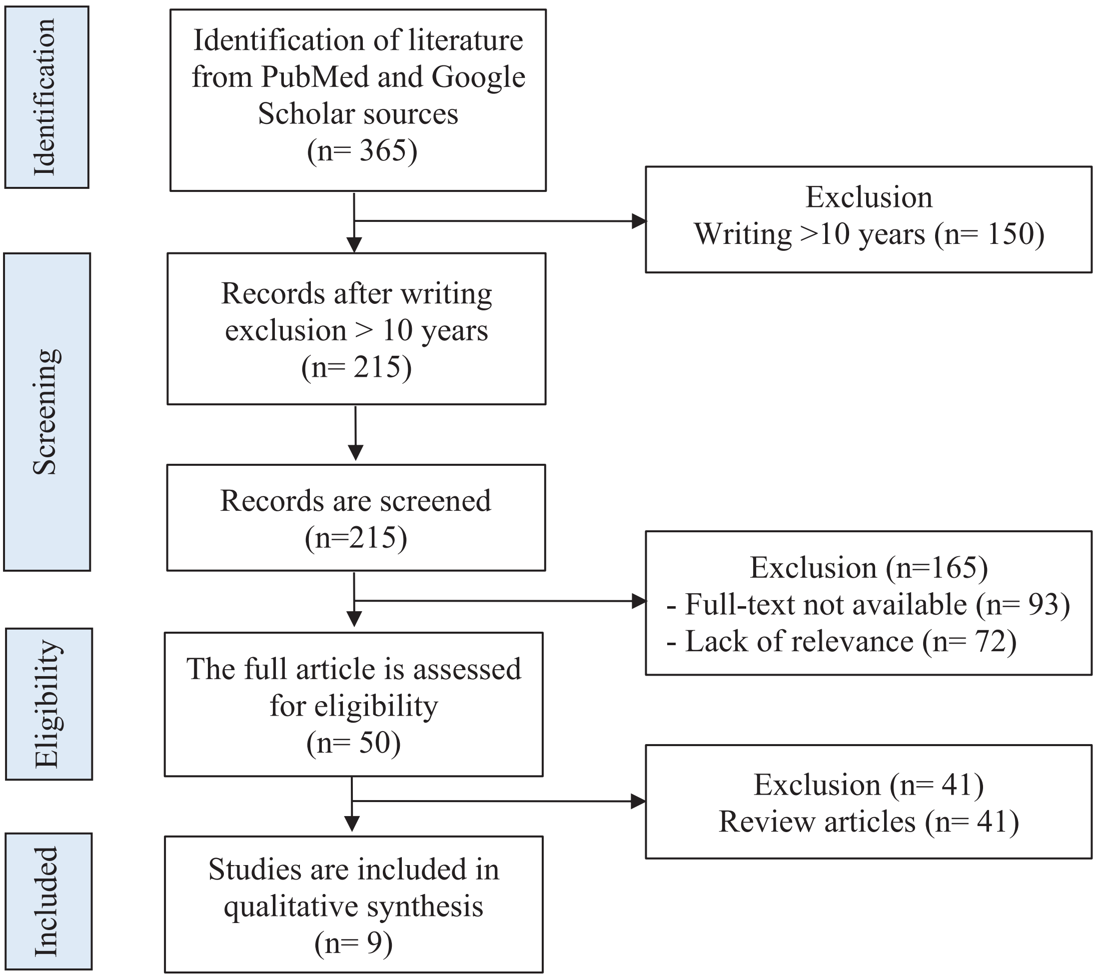

FIGURE 1. Search terms and publication selection process (PRISMA Flowchart)

TABLE 1. Types of drug-drug interaction and related adverse drug events among childre

References	Methods	Main drug use combination	Patient, population, and problem	Outcome target	Interaction mechanism	ADEs
Favie *et al.*[15]	Study design: PharmaCool prospective observational multi-centre study Sample number: 12 patients Study setting: NICU in the Netherlands and Belgium	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 hr after birth that raising midazolam clearance	Hypotension and cerebral hypoperfusion
Wheless *et al.*[16]	Study design: Open-label trial Sample number: 63 patients Study setting: Hospital ward in USA	Cannabidiol - Clobazam	Treatment-resistant epilepsy among pediatric patients (aged 1 to ≤17 yr)	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]	Study design: Case report Sample number: One patient Study setting: A hospital ward in New Haven, CT USA	Paxlovid (nirmatrelvir/ ritonavir) - Tacrolimus	A 14 y.o. 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.

TABLE 1. Cont.

References	Methods	Main drug use combination	Patient, population, and problem	Outcome target	Interaction mechanism	ADEs
Castro-Moraga et al.[18]	Study design: Case report Sample number: One patient Study setting: Hospital ward in Chile	Inhaled fluticasone propionate - Lopinavir/ ritonavir	A 5 y.o. 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]	Study design: Case report Sample number: One patient Study setting: Hospital in Japan	Rifampicin - Warfarin	A 4 y.o. 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 achieve INR therapeutic target that influence thromboembolism condition. This interaction cause 52.0% decrease in the anticoagulant index.
Poon *et al.*[20]	Study design: Case report Sample number: One patient Study setting: Texas Children's Hospital	Rifampicin - Warfarin	A 20 mo.o. 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.	Ineffectively of warfarin treatment by elevated 300% dose requirement of warfarin

TABLE 1. Cont.

References	Methods	Main drug use combination	Patient, population, and problem	Outcome target	Interaction mechanism	ADEs
Ali *et al.*[21]	Study design: Prospective observational study Sample number: 88 patients Study setting: Hospital in Cape Town, South Africa	Clofazimine - Moxifloxacin	A total of 88 participants with median age was 3.9 yr (between 0.5 – 15.7 yr) 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 *et al*[22]	Study design: Case report Sample number: One patient Study setting: Pediatric intensive unit in USA	Benzatropine - Haloperidol	A 17 y.o. 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.
Choi *et al.*[23]	Study design: Retrospective observational study Sample number: 159 patients Study setting: PICU at the Seoul National University	Enalapril – Spironolactone	A total of 159 patients aged <19 yr who were admitted in PICU at the Seoul National University between August 2019 and February 2020	Improve patient condition during stay in PICU	Pharmacodynamics: Synergistically increase the potassium level	Cause hyperkalemia

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 9 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, 8 different types of drug combinations among children that caused clinically significant DDIs were studied in the 9 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.[9,24,25]

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.[24] 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.[23]

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.[23,26]

Midazolam – phenobarbital

Pharmacokinetics drug interaction between midazolam and phenobarbital affects the metabolism phase. Phenobarbital is an inducer of CYP3A4 enzyme while midazolam is categorized as its substrate that will result in high clearance of midazolam so the exposure will be decreasing and may reduce the efficacy of midazolam. As sedation and/or anti-epileptic drug among neonate patients with hypoxic-ischaemic encephalopathy, phenobarbital co-medication significantly diminished midazolam clearance among neonates.[15] Phenobarbital persists as the first-line treatment for newborn seizures and midazolam as second-line therapy when phenobarbital monotherapy is ineffective.[27] Pre-clinical evidence demonstrates that phenobarbital may have synergistic neuroprotective properties when used with therapeutic hypothermia, which is currently regarded as a standard treatment for term neonates with moderate to severe encephalopathy.[27] Long-term exposure to phenobarbital is related to the hypotension effect and leads to a number of chronic issues with oxygen flow reduction that can cause organ hypoperfusion, including brain hypoperfusion. In addition, midazolam also influences hypotension episodes among 64% of newborn patients.[28] Moreover, concomitant use of both of the drugs, midazolam, and phenobarbital, among neonates may lead to sedation and respiratory depression due to additive CNS depression from these drugs. Although there are several risks from these drugs, controlling newborn seizures is critical to lowering the risk of neurological impairments, so these drug combinations are still needed.[15,27] Midazolam should be titrated to the desired effect and a 50% lower midazolam maintenance dose regimen could be appropriate to avoid overexposure during the initial days after birth.[15]

Cannabidiol – clobazam

Drug interaction between cannabidiol-clobazam with pharmacokinetics mechanism among children was studied in a clinical study that included 13 participants with recurrent epilepsy (ages 4 to 19 yr; mean age 11 yr) who were given CLB and CBD concomitantly. Co-administration of cannabidiol and clobazam significantly raises the active metabolite level of clobazam, N-desmethylclobazam.[29] Cannabidiol is a potent enzyme inhibitor of CYP 2C19 and CYP 3A4 which take a role to promote the N-desmethylclobazam metabolism.[30] The effect of this inhibition inevitably contributes to the accumulation of N-desmethyl clobazam, which has been demonstrated around 20 – 100% as potent as clobazam.[31] Adverse drug reaction due to DDIs between cannabidiol-clobazam has been reported affect to 77% of participants (10 participants) including drowsiness, ataxia, irritability, restless sleep, urinary retention, tremor, and loss of appetite.[29] These negative effects were experienced by participants who took a high dose of clobazam and the adverse drug reaction resolved with a dose adjustment of clobazam, reducing the clobazam dose regimen.[29]

Paxlovid (nirmatrelvir/ritonavir) – tacrolimus

According to the mechanism of action of ritonavir, paxlovid (nirmatrelvir/ritonavir) has the potential for drug interactions with immunosuppression, such as tacrolimus, everolimus, and cyclosporin. Ritonavir is a potent and irreversible inhibitor of the CYP3A enzyme.[32] Ritonavir suppression may be highest 2-3 d after exposure and last 3-4 d following withdrawal.[33] Due to the ritonavir mechanism action, it will increase levels of medications metabolized by the P450 CYP3A enzyme and mainly raise levels of tacrolimus, everolimus, and cyclosporin.[33,34] Common side effects resulting from these DDIs includes diarrhea. Moreover, other types of side effects from these DDIs have been reported from a case study among A 13 y.o. female with presentation of vomiting, headache, and malaise after restarting the tacrolimus treatment 12 hr prior to paxlovid treatment completion. This effect is caused by the toxic level of tacrolimus due to the DDIs with Paxlovid.[35] Discontinuation of tacrolimus should be decided to resolve the symptom and can be repeated after the normal level of tacrolimus with 48 hr washout period.[34,35]

Inhaled fluticasone propionate – 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 y.o. 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 mo usage.[18] A study by Castro-Moraga et al. among a 5 y.o. 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.[36,37] 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.[18,37]

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.[38] In addition, both congenital heart disease and valve replacement are predisposing factors to infective endocarditis complication.[39] Children with congenital heart disease are projected to be 15 – 140 higher than the general population to acquire infective endocarditis.[40] In these studies, Rifampicin is a drug of choice as infective endocarditis antibiotics with gram positive bacterial coverage.[41] 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.[25] 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.[42] 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.[43] 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.

Clofazimine – moxifloxacin

Both of clofazimine and moxifloxacin are QT-prolonging agents. The combination between these drugs has a potential DDIs due to the synergistic effect of QTc prolongation with pharmacodynamics mechanism. Study among South African children with TB shown co-administration of clofazimine over moxifloxacin increase maximum drug effect of QTc prolongation over than 3 fold from 8.8 ms to 28.4 ms.[44] When these medicines are combined, keep an eye out for QTc interval prolongation and cardiac arrhythmias (including torsades de pointes) through ECG assessment, especially among patient with additional risk factors, such as female sex, bradycardia, hypokalemia, hypomagnesemia, cardiac disease, and higher drug concentrations, are more prone to have these potentially fatal toxicities.[21]

Benzatropine – haloperidol

Typically, benztropine should be avoided for children under the age of three, infants, or neonates due to their sensitivity to anticholinergic agents.[45] The combination of benzatropine and haloperidol is used to manage psychiatric disorders due to its benefits including diminishing the side effects of each drug and raising treatment effectiveness for certain psychiatric disorders compared with monotherapy.[46] Nevertheless, the combination of these drugs should be avoided as a routine regimen, especially for pediatric patients, due to their sensitivity and risk of potential DDIs. Concomitant use of these drugs should be limited to patients with extrapyramidal symptoms. Both haloperidol and benzatropine are equipped with anticholinergic effects that may enhance the risk of adverse effects of anticholinergic agents, such as tardive dyskinesias, urinary retention, dry mouth, and dry eyes.[47] Despite that, there is a limited report of actual DDIs for these drug combinations among the children population.

Enalapril – spironolactone

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor that is prescribed in pediatrics for the management of hypertension, heart failure, and chronic kidney diseases. In children, the most common adverse reactions reported with the use of enalapril are hypotension (0-19%), impaired renal function (0-29%), and hyperkalemia (0-13%).[48] In the pediatric population, spironolactone has been widely administered to treat heart failure attributed to congenital heart disease and to relieve pulmonary congestion in newborns with chronic lung disorders.[49]

Hence, the co-administration between enalapril and spironolactone is common among pediatrics with heart failure even in the presence of potential DDIs. The study revealed that interactions of enalapril – spironolactone were detected in over than half of the patients (58.9%) in the pediatric cardiology and thoracic surgery unit.[23] Concomitant administration of this drug may lead to severe hyperkalemia which life-threatening condition. Both enalapril and spironolactone synergistically affect the blockage of aldosterone production which implies potassium retention which causes hyperkalemia.[50,51] The systematic review study showed that the combination of spironolactone and ACEi medication elevated mean blood potassium levels by 0.19 mEq/L (95% CI, 0.12-0.26 mEq/L).[52] Hence, a single-center retrospective study among PICU population found hyperkalemia is a probable adverse drug reaction from an enalapril-spironolactone combination experienced in 9.1% of pediatric participants and suggested discontinuing the spironolactone medication to diminish potassium level.[23] Children should be avoided from prolonged hyperkalemia condition to prevent tachycardia that may lead to cardiac arrest.[53]

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 during their treatment in hospital, both in general inpatient ward and in the intensive care unit. 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. However, in clinical practice it still requires further study mainly larger randomized control trial and considering the patient's clinical condition because this research is still limited to case report results, observational, and non-randomized research.

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