Farmacia Hospitalaria 47 (2023) 16–19

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Original

Cross-sectional study of potential incompatibility of intravenous medications in a neonatal intensive care unit in Indonesia

Andika Dwi Mahendra[a,b,*], Suci Hanifah[b], Chynthia Pradiftha Sari[b]

[a] Department of Pharmacy, dr Soeradji Tirtonegoro General Hospital, Indonesian Islamic University, Klaten 57424, Indonesia
[b] Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Yogyakarta 55584, Indonesia

ARTICLE INFO

Article history:
Received 30 March 2022
Accepted 26 June 2022
Available online 25 January 2023

Keywords:
Administration, intravenous
Intensive Care Units
Neonatal
Drug incompatibility
Indonesia, hospitals

ABSTRACT

Objective: The purpose of this study is to determine the most common incompatible and unknown compatibility drug combinations and determine the compatibility of each pair of drugs used in hospitals based on reference books and journals.
Methods: This is a prospective cross sectional study. All babies who were admitted to the Neonatal Intensive Care Units from May 1 to July 31 2021 were sample of the study. Patients who did not receive at least two drug coadministrated concurrently and who stayed less than 24 hours were excluded. Only drug-drug combinations were considered and the other non-drug administrations (electrolyte solutions, parenteral nutritions, and blood products) were excluded. Compatibility data were obtained from literature and online search engines [micromedex NeoFax Essentials 2020, UCL Hospitals Injectable Medicines Administration Guide: Pharmacy Department, 3rd Edition, Trissel Handbook on injectable drugs 15th edition, and published journals].
Results: The most commonly prescribed drug combinations were ampicillin-gentamicin (31.72%), amikacin-ampicillin sulbactam (9.05%), amikacin-ampicillin sulbactam-aminophylline (3.08%). The most common drug incompatible combination was ampicillin - gentamicin (31.71%), for the most drug combinations whose compatibility unknown were amikacin-ampicillin sulbactam (9.05%).
Conclusion: The high prevalence of incompatible drugs and unknown compatibility was identified, so checking its compatibility can be carried out through a two-dimensional chart to minimize the incidence of incompatibilities.

Estudio transversal de incompatibilidad potencial de medicamentos intravenosos en una Unidad de Cuidados Intensivos Neonatales en Indonesia

Palabras clave:
administración intravenosa
Unidad de cuidados intensivos, neonatal
incompatibilidad de medicamentos
hospitales, Indonesia

RESUMEN

Objetivo: El propósito de este estudio es determinar las combinaciones de medicamentos incompatibles y de compatibilidad desconocida más comunes y determinar la compatibilidad de cada par de medicamentos utilizados en hospitales en base a libros de referencia y revistas.
Métodos: Se trata de un estudio transversal prospectivo. Todos los bebés que ingresaron en la Unidad de cuidados intensivos, neonatal del 1 de mayo al 31 de julio de 2021 fueron muestra del estudio. Se excluyeron los pacientes que no recibieron al menos dos medicamentos coadministrados y que permanecieron menos de 24 horas en la Unidad. Solo se consideraron las combinaciones fármaco-fármaco y se excluyeron de este estudio las demás administraciones no farmacológicas (soluciones electrolíticas, nutrición parenteral y hemoderivados). Los datos de compatibilidad se obtuvieron de la literatura y los motores de búsqueda en línea [micromedex NeoFax Essentials 2020, la Guía de administración de medicamentos inyectables de los Hopitales de la UCL [University College London], Departamento de Farmacia, 3ª edición, el Manual Trissel sobre medicamentos inyectables, 15.ª edición y revistas publicadas].
Resultados: Las combinaciones de fármacos más prescritas fueron ampicilina-gentamicina (31,72%), amikacina-ampicilina sulbactam (9,05%), amikacina-ampicilina sulbactam-aminofilina (3,08%). La combinación medicamentosa incompatible más común fue ampicilina - gentamicina (31,71%), la mayoría de combinaciones medicamentosas cuya compatibilidad se desconocía fue amikacina-ampicilina sulbactam (9,05%).

* Corresponding author.
E-mail address: andikadwimahendra@gmail.com (A.D. Mahendra).

https://doi.org/10.1016/j.farma.2022.11.007

Conclusiones: La alta prevalencia de fármacos incompatibles y de compatibilidad desconocida identificada, permite que la comprobación de su compatibilidad se pueda realizar a través de un gráfico bidimensional para minimizar la incidencia de incompatibilidades.

Introduction

Drug incompatibility is a condition in which an undesirable interaction occurs during the preparation or administration process[1]. Patients admitted to the Intensive Care Unit (ICU) will require several intravenous medications due to the patient's condition[2]. This condition will be more complicated when the patient is in Neonatal Intensive Care Unit (NICU) because the condition of patients who have fluid restriction, low infusion rate, and poor venous access[3,4]. This condition may increase the likelihood that the patient will receive concurrent intravenous medications[4]. In Indonesia, studies related to intravenous drug compatibility have only been carried out in the Pediatric Intensive Care Unit (PICU)[5] but never in the NICU. Based on above problems, this study aims to determine the most common incompatible and unknown compatibility drug combinations based on reference books and journals.

Materials and methods

We performed prospective cross-sectional study to see the drug combination given in one line (y-site) in the NICU of a tertiary hospital in Central Java (Indonesia). All babies who were admitted to the NICU from May 1 to July 31 2021 were sample. Patients who did not receive at least two drug coadministrated concurrently and who stayed less than 24 hours were excluded. The ethic statement from faculty of medicine, Muhammadiyah University of Surakarta was obtained for this study No. 3860/C.2/KEPK-FKUMS/XI/2021.

A drug combination is defined as a combination of two or more drugs administered concurrently. While pairs of drugs are defined as involving drugs obtained from drug combinations. It includes administration of drug by bolus, infusion, or syring. Only drug-drug combinations were considered and the other non-drug administrations (electrolyte solutions, parenteral nutritions, and blood products) were excluded. Compatibility data were obtained from literature and online search engines. The main source used is Micromedex NeoFax Essentials 2020, other supporting data such as UCL Hospitals Injectable Medicines Administration Guide: Pharmacy Department, 3rd Edition, Trissel Handbook on injectable drugs 15th edition, and published journal were used during this study. Drug compatibility was classified in three categories: compatible (C), incompatible (I), and No Information Available (NI).

Results

A total of 112 neonates was included to the study with 6,173 drug administrations and 1,558 drug combinations administered concurrently. The drug combinations consisted of 2 drugs co-administered as many as 1130 (72.53%), combination of 3 drugs in one line (314, 20.15%), 4 drug combinations (104, 6.68%), and 5 drug combinations (10, 0.64%). Clinical characteristics and demographics are displayed on Table 1.

A total of 1,558 drug combinations consisted of 244 drug combinations (15.66%) were compatible, 702 drug combinations (45.06%) were incompatible, and 612 drug combinations (39.28%) were classified as no information available. The most common drug classified incompatible, compatible, and unknown compatibility was shown on Table 1. While the drugs which often administered were ampicillin sulbactam (22.10%), ampicillin (12.98%), gentamicin (10.22%), aminophylline (9.20%), amikacin (8.44%), paracetamol (7.31%), meropenem (6.95%), cefotaxime (6.11%), metronidazole (4.60%) and ciprofloxacin (2.28%).

Discussion

There were 702 incompatibles drug combination in which more than 50% is contributed by ampicillin–gentamicin. This incompatibility is due to the inactivation of aminoglycosides by beta-lactam antibiotics. Gentamicin should be given 1 hour before the administration of ampicillin[6]. Ampicillin, furosemide, phenobarbital, phenytoin, and meropenem are drugs that have a high pH (> 7) and in theory will precipitate if they are in a solution with a low pH such as 5% glucose (pH 4-4.5)[5]. The solubility of the drug can be increased by the ionization process of a molecule. If the drug molecule acts as a proton acceptor (lowry-bronsted base), ionization may occur if the molecule is in a low pH solution usually as a hydrochloride or hydrogen sulfate salt. Conversely, if a molecule can lose a proton or hydrogen ion (a lowry-bronsted weak acid), ionization occurs if the molecule is present at a high pH[7]. Changes in concentration will affect the drug incompatibility. Drugs that are compatible at low concentrations will increase incompatibility at higher concentrations[1].

No international guidelines exist for handling incompatibility issues. Decision-supporting tools such as handbooks, two-dimensional incompatibility charts, online databases, and published research are available to assist in minimizing the incidence[8]. To reduce the occurrence of incompatibility, it can be done by making a list of frequently used drugs with theirs compatibility, so that health workers will quickly and easily check before administration[2]. Expertise in identifying incompatibility especially in the NICU is very important. Taking into account things such as optimal concentration, solvent's pH, container and also the characteristics of the drugs before administration is the main step to minimize drug incompatibility.

The limitation of this study is that the study was conducted in single hospital only. So that the incidence of intravenous incompatibility is only described in that one place. In addition, the period of the study was only carried out within three months. Therefore, further research can be carried out in multi center studies so it can describe the incidence rate and compatibility profile in NICU in Indonesia.

Table 1
Demographics and clinical characteristics.

Characteristics of the population	Value
Number of patients	112
Gender ratio (Male/Female)	56/56
Gestational age (weeks) (mean ± sd)	35 ± 3.63
Length of stay (mean ± sd)	9 ± 14.54
Number of intravenous drugs	23
The most frequent coadministered drug, n (%)	
Ampicillin-gentamicin (I)	494 (31.71%)
Amikacin- ampicillin sulbactam (NI)	141 (9.05%)
Amikacin-ampicillin sulbactam-aminophylline (NI)	48 (3.08%)
Amikacin- cefotaxime (C)	45 (2.89%)

sd: standart deviation, n: number of drug combinations, I: incompatible, C: compatible, NI: no information available

Table 2
Two-dimentional compatibility chart.

	amikacin	aminophylline	ampicillin sulbactam	ampicillin	cefepime	cefotaxime	ceftazidime	ceftriaxone	ciprofloxacin	dexamethasone	fentanyl	fluconazole	furosemide	gentamicin	heparin	meropenem	metronidazole	omeprazole	paracetamol	phenobarbital	piperacillin tazobactam	phytomenadione	vancomycin
amikacin		C	NI	I	C	C	C	C	NI	C	C	C	C	NI	I	NI	C	NI	NI	C	I	C	C
aminophylline	C		NI	C	I	NI	C	I	I	C	C	C	C	NI	C	C	NI	NI	NI	C	C	NI	C
ampicillin sulbactam	NI	NI		NI	I	NI	C	NI	I	C	C	NI	NI	NI	C	NI	C	NI	NI	C	C	NI	NI
ampicillin	I	C	NI		C	NI	NI	NI	NI	C	C	I	C	I	C	NI	C	NI	NI	C	C	NI	C
cefepime	C	I	NI	C		NI	NI	NI	NI	C	C	I	C	C	C	NI	C	NI	NI	C	C	NI	I
cefotaxime	C	NI	NI	NI	NI		NI	NI	NI	C	C	I	C	C	C	NI	C	NI	NI	C	C	NI	I
ceftazidime	C	C	NI	NI	C	NI		NI	NI	C	C	I	C	C	C	NI	C	NI	NI	C	C	NI	I
ceftriaxone	C	I	NI	I	C	NI	NI		NI	C	C	I	C	C	C	NI	C	NI	NI	C	C	NI	I
ciprofloxacin	NI	I	NI	NI	NI	NI	NI	NI		NI	NI	C	I	C	C	NI	C	NI	NI	C	C	NI	NI
dexamethasone	C	C	NI	NI	C	NI	NI	NI	NI		C	C	C	NI	C	NI	NI	NI	NI	C	C	NI	I
fentanyl	C	C	NI	NI	C	NI	I	C	NI	C		C	I	C	C	NI	C	NI	NI	C	C	NI	I
fluconazole	C	C	NI	I	C	NI	I	C	C	C	C		I	C	C	NI	C	NI	NI	C	C	NI	C
furosemide	C	C	NI	C	C	NI	C	C	I	C	C	I		I	C	C	NI	NI	NI	C	C	NI	NI
gentamicin	NI	NI	NI	I	C	NI	NI	NI	NI	NI	NI	C	I		C*	C	NI	NI	NI	C	C	NI	NI
heparin	I	C	NI	C	C	NI	C	C	NI	C	C	C	C	C*		C	C	NI	C	C	C	C	C*
meropenem	NI	C	NI	NI	NI	C	NI	NI	NI	C	NI	C	NI	C	C		I	NI	NI	C	NI	NI	C
metronidazole	C	NI	C	C	C	C	C	C	I	C	C	C	NI	C	C	I		NI	NI	NI	C	NI	NI
omeprazole	NI	NI	NI	NI	NI	NI	NI	NI	NI	C	C	NI	NI	NI	NI	NI	NI		NI	I	NI	NI	NI
paracetamol	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI		NI	NI	NI	NI
phenobarbital	C	C	NI	C	NI	NI	NI	NI	I	C	NI	I	NI	NI	C	NI	NI	I	NI		NI	NI	I
piperacillin tazobactam	I	C	NI	NI	C	NI	NI	NI	I	C	NI	C	NI	NI	C	NI	C	NI	NI	NI		NI	I
phytomenadione	C	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	C*	NI	NI	NI	NI	I	NI		NI
vancomycin	C	C	NI	C	I	I	I	I	NI	I	NI	C	NI	NI	C*	C	NI	NI	NI	I	I	NI	

Conclusion

Based on the explanation above, there are 1,558 drug combinations consisting of 244 compatible drug combinations, 702 incompatible drug combinations, and 612 drug combinations classified as unknown. The most incompatible and no information available are combination of ampicillin-gentamicin (31.71%) and amikacin- ampicillin sulbactam (9.05%), respectively. The first step in reducing and minimizing the incidence was by seeing at a glance the compatibility between drugs using a two-dimensional chart (Table 2).

Declaration of authorship

1. The study concept and design, or the data collection, or the data analysis and interpretation: ADM, SH, CPS
2. Writing the article or critical review with significant intellectual contributions: ADM, SH, CPS
3. Approval of the final version for publication: ADM, SH, CPS

Funding

This work was funded by Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia.

Ethical approval

The research has been conducted in accordance to the ethical standards of the Declaration of Helsinki. The ethical statement was obtained from faculty of medicine, Muhammadiyah University of Surakarta No. 3860/C.2/KEPK-FKUMS/XI/2021.

Contribution to scientific literature

This is the first study to describe potential incompatibility of intravenous medication in a Neonatal Intensive Care Unit in Indonesia. Several studies in Indonesia describe potential incompatibility in Intensive Care Unit or Pediatric Intensive Care Unit but not in Neonatal Intensive Care Unit. Therefore, this study can serve as a reference in future Neonatal Intensive Care Unit studies with updated intravenous medication compatibility based on the latest references.

Conflict of interests

The authors declare that no conflicts of interest.

Acknowledgements

The authors would like to thank Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia (Grant IDs: 076/Kajur.Farm/70/Jur.Farm/VI/2021) for financially supporting.

References

1. Abdelkader A, Fathi HA, Hamad MA, Elsabahy M. Nanomedicine: a new paradigm to overcome drug incompatibilities. J Pharm Pharmacol. 2020;72(10):1289–305. doi: 10.1111/jphp.13292.
2. Castells Lao G, Rodríguez Reyes M, Roura Turet J, Prat Dot M, Soy Muner D, López Cabezas C. Compatibility of drugs administered as Y-site infusion in intensive care units: A systematic review. Med Int. 2020;44(2):80–7. doi: 10.1016/j.medine.2018.08.008.
3. Giorgi I, Guignard B, Fonzo-Christe C, Bonnabry P. Evaluation of tools to prevent drug incompatibilities in paediatric and neonatal intensive care units. Pharm World Sci. 2010;32(4):520–9. doi: 10.1007/s11096-010-9403-z.
4. Leopoldino RW, Costa HT, Costa TX, Martins RR, Oliveira AG. Potential drug incompatibilities in the neonatal intensive care unit: a network analysis approach. BMC Pharmacol Toxicol. 2018;19(1):83. doi: 10.1186/s40360-018-0265-7.
5. Hanifah S, Ball P, Kennedy R. Medication incompatibility in intravenous lines in a Paediatric Intensive Care Unit (PICU) of Indonesian hospital. Crit Care Shock. 2018;21(3):114–23.
6. Pacifici GM. Clinical pharmacology of ampicillin in neonates and infants: effects and pharmacokinetics. Int J Pediatr. 2017;5(12):6383–410. doi: 10.22038/ijp.2017.26942.2320.
7. Murney P. To mix or not to mix – compatibilities of parenteral drug solutions. Aust Prescr. 2008;31(4):98–101. doi: 10.18773/austprescr.2008.057.
8. Hanifah S, Ball PA, Kennedy RA. Management of Y-Site Incompatibility of Intravenous Medication: A Scoping Review. Indonesian Journal of Pharmacy. 2022;33(3):353–65. doi: 10.22146/ijp.2262. https://journal.ugm.ac.id/v3/IJP/article/view/2262.