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Potential Incompatibility Problem of Intravenous Drugs' Administration Among Intensive Care Unit (ICU) patients in PKU Muhammadiyah Yogyakarta Hospital

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ABSTRACT

Drugs' administration among hospitalized patients in ICU commonly is given intravenously. Mixing the intravenous drugs may result in incompatibility problem that might affect the drugs' stability and bioavailability. The aim of the study was to investigate the potential incompatibility problem of intravenous mixing drugs' administration among ICU patients at PKU Muhammadiyah Yogyakarta Hospital. This study was a cross-sectional study in which design and data were obtained from ICU patients' medical records retrospectively with purposive sampling in order to observe the pattern of intravenous drug's combination. The potential incompatibility problem was analyzed using the Handbook on Injectable Drugs. There were 79 out of 119 medical records which fulfilled sample inclusion criteria taken in this study. Parenteral dosage form was commonly used rather than non-parenteral (62.06%) among ICUs' patients. The potential incompatibility pattern consisted of incompatibility of intravenous drugs, electrolyte solutions/parenteral nutrition in mixture form, and the electrolyte solutions/parenteral nutrition, which are administrated simultaneously. Potential incompatibility of intravenous dosage was found in 50 events out of 79 patients (0.63 events per patients), which consisted of 8 events (8.51%) in using of drugs administrated simultaneously, 10 events (19.23%) in using of electrolyte solutions/parenteral nutrition in mixture form, and 32 events (11.72%) in using of electrolyte solutions/parenteral nutritions administrated simultaneously. Common potential incompatibilities types were precipitation of drugs and drug adsorption to packaging materials.
Keywords: incompatibility; intravenous; intensive care unit

INTRODUCTION

Most ICU patients received medication parenterally and, in most cases, patients received more than one intravenous dosage form at the same time. Rapid drug response becomes a critical point in ICU patients[1]. The patient commonly administered two or more parenteral dosage forms mixed in the final container before administrated[2]. In Advent Hospital, Bandung, there were 7.78% of mixing parenteral dosage forms in 2015 whereas in RSUD Prof. Dr. Margono Soekarjo, Purwokerto, numbers of mixing parenteral dosage forms were 667 mixings in neurosurgery ward during February 2010 [3,4].

Mixing two or more parenteral dosage forms may result in incompatibility. Incompatibility that often happened was a physical incompatibility characterized by their appearance changes in the mixing drugs such as the formation of precipitation, haziness, discoloration, or crack of the emulsion[2]. This incompatibility can destabilize even reduce the bioavailability of active ingredients that influence the effectivity of drugs[5,6]. Precipitation that occurred could result in platelet aggregation if mixing drugs were administered to the patient[2].

A study related to intravenous drug incompatibility in ICU patients in Indonesia still limited. This study aimed to investigate the potential incompatibility problem of intravenous mixing drugs' administration among ICU patients in PKU Muhammadiyah Yogyakarta Hospital.

METHODOLOGY

The study was a cross-sectional study design. Data were obtained from PKU Muhammadiyah Hospital Yogyakarta ICU patients' medical record in 2015 retrospectively with a purposive sampling technique. Then data was observed to evaluate by the pattern of drug's combination. The potential incompatibility was analyzed using the Handbook on Injectable Drugs.

Subject of the study shorted according to the inclusion and exclusion criteria of the study. Inclusion criteria of the study including (1) Patients who received parenteral dosage form during admission in ICU (2) ICU patients who received two or more dosage intravenously at the same time (3) Patients who were hospitalized in the ICU in 2015. The exclusion criteria of this study were incomplete medical records which were not listed time of drug administration so that it was difficult to confirm if more than two drugs were administered at the same time. The population of the study was ICUs' patients of PKU Muhammadiyah Hospital Yogyakarta during the period January-December 2015 (total population of 234 patients). According to sample size calculation, at least 68 patients' medical record needs to be obtained that match to our inclusion criteria (confidence level=90%). In this study, 79 patients were analyzed.

Data collected then analyzed descriptively. Analysis based on patient characteristics such as demographic characteristics (age, gender) and patient illness characteristics (illness history, ICU admission diagnosis, discharge status from ICU), parenteral and non-parenteral dosage forms' usage percentage, intravenous dosage form's usage combination patterns, compatible, incompatible, and unknown intravenous dosage form's usage percentage.

RESULT AND DISCUSSION

In 2015, there were 234 patients who were hospitalized in PKU Muhammadiyah Hospital. Seventy nine patient medical records were included in this study out of 119 patient medical records that already obtained (40 patient medical records were excluded). Most of the patients were male (58.23%), age range >60 years old (50.63%) and had medical histories such as hypertension (25.63%) and Diabetes Mellitus (23.13%). Each patient had 2 medical histories on average. Most of the patients that administered in the ICU ward were diagnosed with cardiovascular disorders (36.745), infection (13.95%), and respiratory disorders (13,49%). Most of the patients' status after receiving treatment in ICU was "move to the other ward" (38.82%) and dead (32.94%).

Drugs that were administrated to ICU patients were classified with parenteral and non-parenteral drugs. There were 62.06% of non-parenteral drugs' administration (commonly per oral) such as valsartan and isosorbide dinitrate in a total of 1890 drugs. Administration of parenteral drugs was common via intravenous and subcutaneous routes such as furosemide and ceftriaxone and was commonly used by medical personnel to treat patients who need intensive treatment especially ICU patients. Another study stated that most of the parenteral drugs' administration in internal diseases ward of Margono Soekarjo Hospital were caused by weak and unconscious patients' condition also to get rapid onset[7]. Other reasons for parenteral drugs' administration because drugs were often poorly absorbed via oral route or patients unable to receive drugs in other routes[1]. Most ICU patients in this study were diagnosed with cardiovascular disorders diseases such as angina which required rapid onset therapy.

Administration of intravenous dosage forms was dominated by two combinations of drugs pattern such as furosemide and nitroglycerin combination. This study also found that there was three combinations of intravenous drugs that administrated to the patient. Three drug combinations were levofloxacin, n-acetylcysteine, and tigecycline combination. This study found that there were 50 events of potential incompatibility in 79 patients at the administration of intravenous dosage form (0.63 events each patient). It showed the potential incompatibility didn't occur for each patient. Potential incompatibility pattern can be seen in Table I. Potential incompatibility pattern including incompatibility of intravenous drugs administrated simultaneously, electrolyte solutions/parenteral nutrition in mixture form, and electrolyte solutions/parenteral nutritions administrated simultaneously.

Table I. Incompatibility Form of Intravenous Drugs' Administration to ICU Patients of PKU Muhammadiyah Yogyakarta in 2015 based on Handbook on Injectable Drugs 15th Edition

	Potential Incompatibility Pattern	Incompatibility Form
Drug-drug incompatibility		
1	Dopamine Hydrochloride-Furosemid	Precipitation
2	Insulin-Norepinephrine	Precipitation
3	Levofloxacin-Nitroglycerin	Precipitation
4	Dobutamine Hydrochloride-Furosemid	Cloud forming
5	Morphine Sulfate-Sodium Bicarbonate	Physical incompatibility
6	Mannitol-Potassium Chloride	Precipitation
7	Mannitol-Pantoprazole	Precipitation
8	Sodium Bicarbonate-Norepinephrine	Increased pH solution
Drug-electrolyte solutions/parenteral nutritions incompatibility		
a.	**Drug-electrolyte solutions/parenteral nutritions in mixture form**	
1	Nitroglycerin + NaCl 0.9%	Packaging material adsorption
2	Sodium Phenytoin + NaCl 0.9%	Pengendapan
3	Atracurium Besylate + NaCl 0.9%	Packaging material adsorption
4	Imipenem-Sodium Cilastin + NaCl 0.9%	Degradation kinetics
5	Insulin + NaCl 0.9%	Packaging material adsorption
6	Isosorbide Dinitrate + NaCl 0,9%	Packaging material permeation
7	Meropenem + NaCl 0.9%	Degradation kinetics
b.	**Drug-electrolyte solutions/parenteral nutritions administrated simultaneously**	
1	Nitroglycerin -NaCl 0.9%	Packaging material adsorption
2	Isosorbide Dinitrate-NaCl 0.9%	Packaging material permeation
3	Amiodarone-NaCl 0.9%	Packaging material adsorption
4	Atracurium Besylate-Ringer's Lactate	Syringe material adsorption
5	Insulin-NaCl 0.9%	Packaging material adsorption
6	Amiodarone-D5%	Packaging material adsorption
7	Atracurium Besylate-D5%	Syringe material adsorption
8	Atracurium Besylate-NaCl 0.9%	Syringe material adsorption

Drug and drug incompatibility

There were 8.51% events of potential incompatibility, 37.23% events of compatibility, and 54.26% events of unknown compatibility out of 94 events of the intravenous drugs' administration simultaneously. Potential incompatibilities that may occur including precipitation, cloud forming, physical incompatibility, and increased pH of the solution. Furosemide and dopamine hydrochloride's simultaneously intravenous administration were incompatible at *y-site*. This incompatibility depends on dopamine hydrochloride's formulation tested. Dopamine which was supplied by Astra and DuPont would lead to pH adjustment with sodium hydroxide and/or hydrochloride. It would result in compatibility if it was administrated with furosemide. Dopamine's formulation which was supplied by Abbott and American Regent contained buffer and was incompatible with furosemide by forming white precipitate immediately.

Simultaneous administration of insulin and norepinephrine at *y-site* immediately formed white precipitation after both drugs were mixed at the concentration of insulin and norepinephrine sequentially were 0.0064 mg/mL and 1 unit/mL. White precipitation formed can't be explained further because there were limited kinds of literature reviewing both drugs' mixing at the y-site[8].

Administration of dobutamine hydrochloride and furosemide simultaneously also potentially incompatible at the y-site. A study showed that both drugs resulted in incompatibility at the y-site administration formed white precipitation immediately after both drugs were mixed in y-site's tube. Mixing of both drugs would result in physical compatibility in 3 hours, but acetylcysteine of both drugs resulted in precipitation in 1 hour in another test[8]. Dobutamine is an acidic drug and furosemide had an alkaline property. When both drugs were mixed, it might affect on pH of the solution resulting in physical incompatibility. It will happen because of Furosemide in its acid forms poorly solubility in aqueous solution[9].

The addition of sodium bicarbonate at a concentration of 80 mEq/L into norepine-phrine at the concentration of 2 mg/L in the D5W solution resulted in incompatibility. Another study addition of sodium bicarbonate at a concentration of 2.4 mEq/L into norepinephrine at the concentration of 8 mg/L in D5W solution resulted in the inactivation of norepinephrine. The addition of some additives like sodium bicarbonate must be considered because it will result in the final pH of the mixture, increased being more than 6 because norepinephrine had the nature of alkali labile. Some admixture dosage forms should be administrated immediately after drug preparation has done to ensure full potency of the drug or both drugs can be administered separately in order to prevent incompatibility problem[8].

Drug and electrolyte solutions/ parenteral nutritions incompatibility

Drug and electrolyte solutions/parenteral nutrition in mixture form

There were 19.23% events of potential incompatibility problems, 69.23% events of compatibility, and 11.54% events of unknown compatibility out of 94 events of the mixing of drug and electrolyte solutions/parenteral nutrition. Potential incompatibilities that may be occurred at those events were packaging adsorption and permeation, precipitation, and kinetic degradation.

Mixing of nitroglycerin and natrium chloride 0.9% at the concentration of drug 200 mg/L, there was no drug concentration decrease after 52 hours at 29ºC in a light exposure glass bottle. Drug concentration decreased by about 14% when the solution was stored at 6ºC. If nitroglycerin was packaged in polyvinyl chloride bag, it resulted in 38% of drug concentration decrease in 48 hours at 4ºC and about 68% of drug dose decrease at 25ºC[8]. The stability problem of nitroglycerin could be caused by nitroglycerin's evaporation and adsorption to plastic bag[10].

Mixing of sodium phenytoin into natrium chloride 0.9% caused forming a crystalline form of phenytoin in 20 to 30 minutes at concentrations 1 to 10 g/L of sodium phenytoin in NaCl 0.9% and visible crystals in 6 to 9 hours[8]. Phenytoin as a free acid or sodium salt had a poor absorption and/or uncertainty in various dosage forms. This was because phenytoin had low solubility and dissolution rate[8].

Drug-electrolyte solutions/ parenteral nutritions administrated simultaneously

There were 11.72% events of potential incompatibility, 43,59% events of compatibility, and 44.69% events of unknown compatibility out of 273 events of the intravenous drugs' administration simultaneously. The researcher can't be sure whether those drug and electrolyte solutions/parenteral nutrition were mixed in y-site junction or in syringe, however the potential incompatibility is still observed. Most of potential incompatibilities are packaging adsorption and permeation also adsorption materials of syringe.

There would be compatibility and potential incompatibility in mixing of amiodarone hydrochloride into NaCl 0.9%. At the concentration 1.8 g/L of amiodarone hydrochloride in NaCl 0.9% physically drug was compatible with some or no lossing of amiodarone in 24 hours at 24ºC under

fluorescence light. In another study at the concentration 0.6 g/L of amiodarone hydrochloride in NaCl 0.9% physically drug was incompatible in 24 hours at room temperature. This incompatibility caused by adsorption of drug to polyvynil chloride infusion bags[8].

Mixing of atracurium becylate into ringer's lactate would increase degradation's rate of atracurium. Another study found 10-12% of atracurium lossed in 24 hours at 30ºC in mixing of atracurium becylate into Ringer's Lactate. Losing of atracurium becylate could resulted by potential adsorption of drug to materials of syringe[8].

CONCLUSION

Potential incompatibility in administration of intravenous dosage form to ICU patients has to be assessed with more complete literature in further study. Prevent and management when incompatibility was detected need to be studied. Prospective study is necessary, so we can observe the actual administration of those intravenous drugs. Further study is also necessary to observe the clinical effect to patients, result by the incompatibility. Medical records must be filled completely. Pharmacists in hospital have important role and responsibility of patients' monitoring also circumspection of intravenous dosage forms' administration to prevent the incompatibility events and decrease the potential incompatibility especially for ICU patients.

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