

Nurses' knowledge and management of incompatibility issues in intravenous pharmaceutical preparations

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Abstract

Administering multiple intravenous (IV) preparations through a single catheter line can lead to incompatibility issues, such as precipitation. Precipitation can be avoided with sufficient knowledge by nurses during the administration of IV preparations to patients. This research aims to assess nurses' knowledge and management of incompatibility issues in IV pharmaceutical preparations. This non-experimental research collected data through interviews with healthcare professionals (nurses). The research was conducted at Sultan Agung Islamic Hospital, Semarang. A total of 14 healthcare professionals (nurses) who reconstituted and administered IV pharmaceutical preparations to patients in the Intensive Care Unit (ICU) participated in the research. The results revealed that 13 nurses (92.9%) encountered incompatibility incidents with seven types of drugs. Five nurses (29.4%) reported incompatibility issues with cefoperazone. The most frequently observed incompatibility was color change, reported by seven nurses (53.8%), such as white spots appearing during phenytoin reconstitution and discoloration in IV pharmaceutical preparations of cefoperazone and ceftriaxone. The most common approach to addressing incompatibility was replacing the preparation, reported by six nurses (46.2%). The handling of incompatibility problems can differ between nurses. Therefore, training is needed on the material of incompatibility of sterile preparations, to obtain the appropriate standard operating procedure (SOP) for handling incompatibility of IV pharmaceutical preparations.

Keywords: incompatibility, IV preparation, nurses' knowledge, questionnaire

1. INTRODUCTION

Intravenous (IV) preparations are widely used in hospitals, particularly in Intensive Care Units (ICUs) (Dwijayanti et al., 2016; Rickard et al., 2015). The simultaneous use of multiple IV drugs often results in drug incompatibility (Caecilia et al., 2023; Hanifah et al., 2018; Syahbarni et al., 2021). Physical drug incompatibility can be observed through phenomena such as precipitation in the intravenous line (Hanifah, 2019). Reconstitution of IV

preparations that can form precipitants, one of which is phenytoin in a solvent. Precipitation in IV mixtures can lead to a reduction in drug concentration, phlebitis, and potentially harmful effects on patients' organs (Simoes et al., 2022).

A study conducted at a military hospital in Germany reported IV drug incompatibility in 61.4% of 104 patients (Wagner et al., 2023). Such incompatibilities can be prevented through adequate knowledge of IV drug mixing by healthcare professionals responsible for reconstitution (Borgonovo et al., 2023). Knowledge of incompatibility can also aid in the development of protocols to prevent these issues (Ribeiro et al., 2022). This is because the worst impact of an incompatibility that is not handled properly can cause technical problems or fatal death (Hanifah, 2019). The assessment of IV drug incompatibility influences healthcare professionals' decisions and how they resolve these issues. Based on this background, the present research aims to assess nurses' knowledge and management of IV drug incompatibility incidents in hospitals.

2. RESEARCH METHODS

This prospective non-experimental research collected data through interviews with healthcare professionals who reconstitute and administer IV pharmaceutical preparations in the ICU. The research was conducted at Sultan Agung Islamic Hospital, Central Java, Indonesia, and received ethical clearance from the Sultan Agung Islamic Hospital Research Ethics Committee (No. 119/KEPK-RSISA/VI/2023).

Research Subjects

The research population comprised all healthcare professionals at the hospital where the research was conducted. Purposive sampling was used to select participants. The inclusion criteria included nurses working in the ICU of Sultan Agung Islamic Hospital, Central Java, who reconstituted and administered IV pharmaceutical preparations to patients. Nurses unwilling to participate in the interviews were excluded from the research. The population in the study was 17 respondents, 3 respondents were excluded because they were unwilling to be interviewed. A total of 14 nurses participated as respondents.

Research Materials

This research employed a questionnaire consisting of six open-ended questions. The interview questions covered whether the respondents had encountered incompatibility, the types of preparations where incompatibility was observed, the types of incompatibility

identified, the steps taken to resolve the incompatibility, whether IV pharmaceutical preparation incompatibility occurred across different batch numbers, and whether there were differences in compatibility across different dosages.

Data Analysis

The responses from the questionnaires were analyzed, grouped, and the percentage of similar responses was calculated. The results were presented in tables and interpreted to summarize healthcare professionals' knowledge and management of IV drug incompatibility in the ICU.

3. RESULTS AND DISCUSSION

Respondents' social demographics

Medical personnel questionnaire regarding incompatibility of IV drug mixtures adapted from Hanifah, 2019. The population in the study was 17 respondents, 3 respondents were excluded because they were unwilling to be interviewed. A total of 14 nurses participated as respondents. The general characteristics of the nurses, including gender and years of experience at Sultan Agung Islamic Hospital, Central Java, are presented in Table 1.

Table 1. Demographic characteristics of nurse respondents

Years of Experience	Sex	
	Male	Female
<5 years		1
5-10 years	1	4
>11 years	1	7

This study produced data obtained in accordance with ethical permission from the Research Ethics Committee of Sultan Agung Islamic Hospital (Number 119/KEPK-RSISA/VI/2023) that of the 14 respondents, 12 (86%) were female, with the majority (75%, n=8) having 11-15 years of work experience. Most of the respondents in this research were female nurses. This aligns with the findings of Azni et al., 2021, which indicate that nurses' knowledge is influenced by various factors, including years of work experience. However, a study conducted by Lovia et al. (2019) at Dr. M. Djamil Hospital in Padang involving 14 healthcare professionals (nurses) found that work experience alone is not the sole determinant of knowledge, as some respondents with fewer years of service exhibited superior knowledge and experience (Lovia et al., 2019).

Nurses' knowledge and management of intravenous (IV) incompatibility

Based on interviews with 14 respondents, one nurse reported no experience of drug incompatibility at work, thus rendering further questions inapplicable for that respondent. The responses on IV drug incompatibility are summarized in Table 2.

Table 2: Healthcare professionals' responses regarding iv drug incompatibility

No	Interview Questions	Answers	No. of Respondents	Percentage
1	During your time working at the hospital, have you encountered IV drug incompatibility?	Yes	13	92.9
		No	1	7.1
2	If yes, which drugs were involved?	Ceftriaxone	1	5.9
		Cefoperazone	4	23.5
		Mannitol	5	29.4
		Meropenem	2	11.8
		Antibiotics	1	5.9
		Ceftriaxone	3	17.6
3	What type of incompatibility occurred?	Cefixime	1	5.9
		Crystal formation	3	23.1
		Color change	7	53.8
		Partial dissolution	1	7.7
4	How did you address the issue?	Precipitation	2	15.4
		Administered via bolus	1	7.7
		Administered without resolution	4	30.8
5	Did you observe any differences in incompatibility with the same IV drug but different batch numbers?	Replaced with new preparation	6	46.2
		Added solvent	2	15.4
		Did not observe batch numbers	5	38.5
6	Have you encountered differences in incompatibility with the same IV drug but different dosages?	Observed differences	4	30.8
				30.8
		No differences observed	4	30.8
6	Have you encountered differences in incompatibility with the same IV drug but different dosages?	Yes	4	30.8
		No	9	69.2

The research results showed that 92.9% (n=13) of respondents encountered incompatibility issues. Five nurses (29.4%) reported incompatibility with cefoperazone, which caused a color change from white to cloudy yellow. The most frequently observed incompatibility was a color change, as reported by 53.8% (n=7) of respondents. The most common action taken to resolve incompatibility was to replace the IV preparation, reported by 46.2% (n=6) of respondents. Eight respondents (61.6%) observed whether incompatibility also occurred with different batch numbers. Moreover, 69.2% (n=9) of respondents did not encounter differences in incompatibility due to varying dosages. They indicated that IV drug incompatibility was not influenced by dosage, although dosage is related to the drug's pH, which can affect the formation of precipitates.

Phenytoin contains not less than 98.0% and not more than 102.0% $C_{15}H_{12}N_2O_2$, calculated based on the dry substance. According to its description, phenytoin is a white, odorless powder that melts at approximately 295°C. Phenytoin is practically insoluble in water, soluble in hot ethanol, and sparingly soluble in cold ethanol, chloroform, and ether. The description of phenytoin in salt form (phenytoin sodium) includes a white, odorless, slightly hygroscopic powder that gradually absorbs carbon dioxide from the air. Phenytoin sodium's solubility includes being easily soluble in water, with the solution usually being slightly cloudy due to partial hydrolysis and absorption of carbon dioxide, soluble in ethanol, and practically insoluble in ether and chloroform. Phenytoin sodium injection is a sterile solution of phenytoin sodium with propylene glycol and ethanol in water for injection, containing phenytoin sodium $C_{15}H_{11}N_2NaO_2$, not less than 95.0% and not more than 105.0% of the amount stated on the label. A warning for phenytoin injection preparations: do not use if the solution is cloudy or sediment has formed. The pH of phenytoin preparations is between 10-12.3 (Depkes RI, 1995). In research, phenytoin preparations, after reconstitution with normal saline, became cloudy or formed crystals, indicating incompatibility in IV pharmaceutical preparations.

Mannitol injection is a sterile or supersaturated solution of mannitol in water for injection. If crystallization occurs, warming or heating in an autoclave is necessary before use. Mannitol injection contains not less than 95.0% and not more than 105.0% $C_6H_{14}O_6$ of the amount stated on the label. The pH of mannitol injection is between 4.0-7.0 (Depkes RI, 1995). Research found crystallization occurred after reconstitution of IV mannitol preparations, which is a concern since the initial mannitol injection preparation is in solution form.

Ceftriaxone injection contains ceftriaxone sodium equivalent to not less than 776 µg ceftriaxone $C_{18}H_{18}N_8O_7S_3$ per mg, calculated as the anhydrous substance, and equivalent to not less than 90.0% and not more than 115.0% ceftriaxone $C_{18}H_{18}N_8O_7S_3$ of the amount stated on the label (Depkes RI, 2013). Research findings revealed a color change in ceftriaxone injection from white to dark yellow.

Cefoperazone sodium contains the equivalent of not less than 870 µg and not more than 1015 µg cefoperazone ($C_{25}H_{26}N_9NaO_8S_2$) per mg, calculated as the anhydrous substance. The description of cefoperazone includes a crystalline powder, white to pale yellow in color. Cefoperazone is easily soluble in water and methanol, sparingly soluble in absolute ethanol, and insoluble in acetone, ethyl acetate, and ether (Depkes RI, 2013). In research, after reconstitution, the color of cefoperazone injection changed from white or pale yellow to cloudy yellow.

Cefixime contains not less than 950 µg and not more than 1030 µg $C_{16}H_{15}N_5O_7S_2$ per mg, calculated as the anhydrous substance. Cefixime is described as a crystalline powder, white to light yellow in color. Cefixime is easily soluble in methanol; soluble in propylene glycol; sparingly soluble in ethanol, acetone, and glycerin; very slightly soluble in 70% sorbitol solution and octanol; practically insoluble in ether, ethyl acetate, hexane, and water. Cefixime has a pH between 2.6-4.1 (Depkes RI, 2013).

Meropenem for Injection is a sterile dry mixture of meropenem and sodium carbonate, containing meropenem $C_{17}H_{25}N_3O_5S$, not less than 90.0% and not more than 120.0% of the amount stated on the label. The pH of meropenem injection is between 7.3-8.3. Meropenem is described as a colorless to white crystalline substance. Meropenem is soluble in dimethylformamide and in 5% dibasic potassium phosphate solution; slightly soluble in water and 5% monobasic potassium phosphate solution; very slightly soluble in ethanol; practically insoluble in acetone and ether (Depkes RI, 2013).

Table 3: Data on color changes in IV drug preparations after the reconstitution

IV Drug Preparation	Color Change
Phenytoin	Crystal formation
Ceftriaxone	Change in color to dark cloudy yellow
Cefoperazone	Change in color to dark cloudy yellow
Mannitol	Crystallization
Meropenem	Color change from yellow to milky white
Antibiotics	Color becoming dark yellow
Cefixime	Color change

Based on interviews, seven drugs were frequently reported to experience incompatibility: phenytoin, ceftriaxone, cefoperazone, mannitol, meropenem, ceftriaxone, and cefixime. Respondents noted incompatibility in IV mixtures involving cefoperazone and normal saline, where the mixture became significantly darker after reconstitution.

A 2009 study across 113 ICU units in 27 countries in 5 continents found that antimicrobials accounted for a large proportion of administration errors, with 179 cases documented (Valentin et al., 2009). Similarly, in this research, several nurses identified antibiotics as drugs that often exhibited incompatibility.

The color changes observed before and after reconstitution led many respondents to manage the issue by replacing the drug preparation. However, not all respondents took this approach; some continued administering the incompatible preparation without intervention. This occurred because some respondents considered IV incompatibility a common and somewhat routine event. Consideration of IV drug replacement can come from the same or different manufacturer with the same active substance or content. This is because incompatibility can occur due to the influence of the excipient of the carrier material or the stability of the preparation during storage. So that the replacement of the preparation can affect the incompatibility that occurs.

The presence of pharmacists in ICU wards has been shown to reduce the occurrence of drug incompatibility (Preslaski et al., 2013). In developed countries, nurses frequently seek pharmacists' advice to resolve incompatibility issues (Marsilio et al., 2016; Moraes et al., 2021). Moreover, pharmacist involvement in hospital wards can help prevent drug incompatibilities (Leape, 2009).

4. CONCLUSION

The survey results suggest that respondents lack sufficient knowledge about IV drug incompatibility. Responses to incompatibility vary, even for the same drugs. Therefore, there is a need for a comprehensive research on dispensing sterile preparations to all healthcare professionals, which can lead to the development of appropriate protocols for managing IV drug incompatibilities.

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6. REFERENCES

- Azni, M., Rahmawati, F., & Wiedyaningsih, C. (2021). Pengetahuan perawat mengenai faktor risiko sediaan intravena yang berkaitan dengan kejadian Flebitis. *Jurnal Sains Farmasi & Klinis*, 8(2), 174. <https://doi.org/10.25077/jsfk.8.2.174-181.2021>
- Borgonovo, F., Quici, M., Gidaro, A., Giustivi, D., Cattaneo, D., Gervasoni, C., Calloni, M., Martini, E., La Cava, L., Antinori, S., Cogliati, C., Gori, A., & Foschi, A. (2023). Physicochemical characteristics of antimicrobials and practical recommendations for intravenous administration: a systematic review. *Antibiotics*, 12(8). <https://doi.org/10.3390/antibiotics12081338>
- Caecilia, M., Munisih, S., & Mishanah. (2023). *Profil inkompatibilitas sediaan obat intravena pada pasien intensive care unit di RS ' X ' Semarang periode Januari – Juni tahun 2022*. 12(2), 60–64.
- Depkes RI. (1995). Farmakope Indonesia edisi IV. In *Departemen Kesehatan Republik Indonesia*.
- Depkes RI. (2013). *Farmakope Indonesia EDISI V* (V). Kementrian kesehatan RI.
- Dwijayanti, S., Irawati, S., & Setiawan, E. (2016). Profile of intravenous admixture compatibility in the intensive care unit (ICU) patients. *Indonesian Journal of Clinical Pharmacy*, 5(2), 84–97. <https://doi.org/10.15416/ijcp.2016.5.2.84>
- Hanifah, S. (2019). Pengetahuan dan persepsi tenaga kesehatan tentang inkompatibilitas intravena: studi kasus di satu unit perawatan intensif. *Kongres XX & Pertemuan Ilmiah Tahunan Ikatan Apoteker Indonesia, August*, 978–979.
- Hanifah, S., Ball, P., & Kennedy, R. (2018). Medication incompatibility in intravenous lines in a paediatric intensive care unit (PICU) of Indonesian hospital. *Critical Care and Shock*, 21(3), 118–127.
- Leape, L. L. (2009). Errors in medicine. *Clinica Chimica Acta*, 404(1), 2–5. <https://doi.org/10.1016/j.cca.2009.03.020>
- Lovia, S., Oktavia, Y., Almasdy, D., & Amelin, F. (2019). Studi Kualitatif Pengetahuan Perawat tentang Adverse Drug Reaction (ADR) di Bangsal Rawat. *Jurnal Sains Farmasi & Klinis*, 2407–7062, 95–103.
- Marsilio, N. R., Da Silva, D., & Bueno, D. (2016). Drug incompatibilities in the adult

- intensive care unit of a university hospital. *Revista Brasileira de Terapia Intensiva*, 28(2), 147–153. <https://doi.org/10.5935/0103-507X.20160029>
- Moraes, K. D., Gomes, I. V., Lima, O. P., Reis, R. L., Souza, M. N., Freire, N. D., Barros, J. F., S., M. F., & Nunes, D. M. (2021). Analysis of drug compatibility in Y in intravenous therapy: preparation of a preventive tool for a university hospital in Petrolina – PE. *Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde*, 12(1), 521. <https://doi.org/10.30968/rbfhss.2021.121.0521>
- Preslaski, C. R., Lat, I., MacLaren, R., & Poston, J. (2013). Pharmacist contributions as members of the multidisciplinary ICU team. *Chest*, 144(5), 1687–1695. <https://doi.org/10.1378/chest.12-1615>
- Ribeiro, G. da S. R., Campos, J. F., & da Silva, R. C. (2022). What do we know about flushing for intravenous catheter maintenance in hospitalized adults? *Revista Brasileira de Enfermagem*, 75(5), 1–11. <https://doi.org/10.1590/0034-7167-2021-0418>
- Rickard, C. M., Marsh, N., Webster, J., Playford, E. G., McGrail, M. R., Larsen, E., Keogh, S., McMillan, D., Whitty, J. A., Choudhury, M. A., Dunster, K. R., Reynolds, H., Marshall, A., Crilly, J., Young, J., Thom, O., Gowardman, J., Corley, A., & Fraser, J. F. (2015). Securing all intravenous devices effectively in hospitalised patients-the save trial: Study protocol for a multicentre randomised controlled trial. *BMJ Open*, 5(9), 1–7. <https://doi.org/10.1136/bmjopen-2015-008689>
- Simoes, A. M. N., Vendramim, P., & Pedreira, M. L. G. (2022). Risk factors for peripheral intravenous catheter-related phlebitis in adult patients*. *Revista Da Escola de Enfermagem*, 56, 1–9. <https://doi.org/10.1590/1980-220X-REEUSP-2021-0398EN>
- Syahbarni, S., Nanny Setiawati, M. C., & Ningrum, E. P. (2021). Gambaran kompatibilitas sediaan obat intravena dengan sediaan lain pada pasien di ICU. *Media Kesehatan Politeknik Kesehatan Makassar*, 16(1), 83. <https://doi.org/10.32382/medkes.v16i1.1796>
- Valentin, A., Capuzzo, M., Guidet, B., Moreno, R., Metnitz, B., Bauer, P., & Metnitz, P. (2009). Errors in administration of parenteral drugs in intensive care units: multinational prospective study. *BMJ (Online)*, 338(7700), 928–931. <https://doi.org/10.1136/bmj.b814>
- Wagner, L. A. F., Neining, M. P., Hensen, J., Zube, O., & Bertsche, T. (2023). Avoiding incompatible drug pairs in central-venous catheters of patients receiving critical care: an algorithm-based analysis and a staff survey. *European Journal of Clinical Pharmacology*, 79(8), 1081–1089. <https://doi.org/10.1007/s00228-023-03509-0>