

Knowledge of Intravenous Preparation among Health Professionals and Assessment of the Sterile Product Label Information Coverage

by Erna Prasetya Ningrum

Submission date: 17-Dec-2024 10:52AM (UTC+0700)

Submission ID: 2415983939

File name: Erna_DIF_22_IJP_13_Juli.docx (106.61K)

Word count: 6084

Character count: 39257

Knowledge of Intravenous Preparation among Health Professionals and Assessment of the Sterile Product Label Information Coverage

Erna Prasetya Ningrum^{1,2}, Fita Rahmawati^{3*}, Marlyn Dian Laksitorini⁴, Endang Lukitaningsih⁵

1. Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
2. Department of Pharmacology & Clinical Pharmacy, Stifar Pharmacy Foundation, Semarang, Indonesia, 50192
3. Department of Pharmacology & Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
4. Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
5. Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281

Article Info

Submitted: xx-xx-xxxx

Revised: xx-xx-xxxx

Accepted: xx-xx-xxxx

*Corresponding author
Fita Rahmawati

Email:
rahmawati_f@ugm.ac.id

ABSTRACT

Individual knowledge of intravenous medicine (IVM) preparation is essential in patient safety. Comprehensive information on IV product preparation is indispensable within healthcare settings. Brochures constitute a primary resource for understanding the preparation of injectable medications. This research aims to investigate individual knowledge of IVM preparations and to assess the completeness of the information provided in package brochures regarding the IVM preparation processes. This research employed a cross-sectional design to investigate the subject matter. Questionnaires were utilized to identify the characteristics and individual knowledge of healthcare professionals involved in dispensing intravenous medicine (IVM). A number of 80 health professionals participated in the study. A checklist form was employed to evaluate the completeness of the information provided in 148 package brochures regarding IVM preparation. Subsequently, the data within the brochures were compared to the Regulation outlined by the Indonesian National Food and Drug Authority. The findings indicated that 79 respondents (98.75%) comprehended the reconstitution process, with 46 respondents (57.5%) undergoing aseptic dispensing training. Among the respondents, 48 (60%) primarily relied on brochures as their main information source, while 49 (61.25%) reported encountering details primarily concerning dose and solubility products. Among the 148 assessed brochures, storage methods were included in 146 (99%) brochures, reconstitution methods in 54 (36%) brochures, drug incompatibility in 28 (19%), stability of drugs in 12 (8%), and only 10 (7%) brochures provided a list of excipients. Enhancing individual knowledge regarding IVM preparation is crucial, necessitating support through comprehensive training initiatives. A significant proportion of medical personnel rely on brochures for information during IVM preparations, yet not all brochures comply with mandatory government regulations. The comprehensive inclusion of information within brochures is vital in preventing discrepancies and increasing the safety standards associated with administering intravenous preparations to patients.

Keywords: intravenous medication preparations, individual knowledge, package brochures

INTRODUCTION

The utilization of parenteral medications is widespread in hospitals, particularly within Intensive Care Units (ICUs). This prevalence stems from the recognized effectiveness of parenteral formulations specifically tailored for ICU use (Sohrevardi et al., 2017). Administering parenteral medications intravenously (IV) necessitates preparation before patient administration (Moraes et al., 2021). Errors in the preparation of IV medications are considered hazardous by the Institute for Safe Medication Practices (ISMP). Prior studies have delved into the utilization of IV preparations (da Silva C et al., 2021; Gaetani et al., 2017). In Coimbatore, India, 104 ICU patients received 24 incompatible IV medications, resulting in the presence of white haze and color changes in the solutions (Benlabed et al., 2019; Fernandez-Pena et al., 2021; S. Sriram et al., 2018). These accounts highlight the frequent occurrence of IV medication incompatibility incidents within healthcare services, presenting a significant concern warranting investigation within the global healthcare domain.

The extensive use of various intravenous (IV) preparations coupled with multiple phases in the preparation process underscores the necessity for complete information among healthcare professionals to mitigate potential side effects (Hani et al., 2019; Henkel et al., 2020; La Pietra et al., 2005; Maison, 2019; Tomczak et al., 2021). Adverse effects may arise from the incompatibility of preparations, a concern that can be mitigated through healthcare personnel's awareness of this issue, stemming from adequate training and access to literature on parenteral preparations (Gahart & Nazareno, 2014). A study conducted in a hospital in Karangany Regency, Central Java, involving 159 nurses, indicated that 83.08% of them possessed good knowledge regarding the

administration of intravenous preparations and 10.69% of nurses had undergone training in injectable drugs and aseptic techniques (Ahmad et al., 2016; Azni et al., 2021b; Neining et al., 2019; Pangestika, 2022; PERMENKES, 2014; Villiers, 2017). While the level of knowledge concerning aseptic technique training among medical personnel aligns with the findings in this research, there are discernible disparities concerning the completeness of requisite information, an aspect that prior studies have not addressed.

Optimal drug stability plays a pivotal role in mitigating the risks associated with administering intravenous preparations (Ahmad et al., 2016; Hecq et al., 2019; Sabins et al., 2019; Tomczak et al., 2021). Interventions by clinical pharmacists serve to minimize the potential for pharmacy-related complications (Frankenfeld et al., 2018; Kumar et al., 2020; Malfar et al., 2018; Marsilio et al., 2016; Nilsson et al., 2022; Stroppel et al., 2023). It is crucial to consider the knowledge healthcare professionals possess regarding intravenous preparations, as this knowledge is instrumental in reducing the likelihood of preparation incompatibility and potential toxicity effects (NHS, 2019; Royal Hospital For Women, 2011). The quality of intravenous (IV) preparations significantly relies on the suitability of the preparation, information which is typically found on the drug label (Dwijayanti et al., 2016). Dosage label information conformity with standard requirements is often referenced in drug registration documents (National Food Drug, 2017, 2022b, 2022a).

In Indonesia, studies focusing on medical personnel's knowledge of intravenous preparations and the completeness of information provided on drug labels remain relatively scarce. This research aims to investigate the knowledge among medical staff concerning the mixing of preparations and to evaluate the completeness of the information presented on labels or brochures

accompanying these preparations. The aim is to highlight the potential inclusion of important reconstitution information for intravenous preparations within mandatory drug registration regulations. This inclusion seeks to mitigate errors and prevent unwanted side effects associated with these preparations.

7 MATERIALS AND METHODS

Research design

This research was structured as a descriptive research utilizing a cross-sectional design. The research was conducted in two phases. Firstly, questionnaires were used to evaluate the characteristics and individual knowledge regarding the reconstitution of parenteral preparations among medical personnel. Secondly, it encompassed an assessment comparing the information provided on the intravenous (IV) product labels to the regulations stipulated by the National Food and Drug Authority. Questionnaires served as the tool to identify the characteristics and individual knowledge of medical personnel, while a checklist form was utilized to evaluate the completeness of the intravenous medication (IVM) package brochures. The research protocol received ethical clearance from the Health Research Ethics Committee of Sultan Agung Islamic Hospital Semarang (No. 119/KEPK-RSISA/VI/2023).

The research was conducted between June and July 2023. The initial stage involved distributing online questionnaires using convenient sampling to facilitate the participation of participants beyond the confines of Semarang City, Central Java, Indonesia. The subsequent phase took place at a private hospital located in Semarang.

The collection of "knowledge information" was carried out throughout Indonesia, so the scope is broad. Not only medical personnel working in the hospital where the research took place. For the collection of brochure data, only at Sultan Agung Hospital, Semarang, because there is further research on the use of preparations there.

Research population

The initial stage

The initial stage of the research focused on examining the characteristics of Indonesian medical personnel involved in dispensing intravenous (IV) parenteral solutions. This phase utilized a questionnaire administered through Google Forms, employing convenience sampling methods. Meanwhile, the subsequent stage involved the examination of brochures concerning

parenteral preparations used at a private hospital in Semarang City, Central Java, Indonesia, utilizing accidental sampling methods. The sample in the first stage comprised responses obtained from medical personnel engaged in the preparation of intravenous solutions. Medical personnel in this study involved hospital pharmacists, industrial pharmacists, nurses, and midwives. For the second stage, brochures pertaining to intravenous parenteral preparations utilized in the hospital, and medical personnel involved in their usage. The formula used to calculate the minimum sample of medical personnel questionnaires using parenteral preparations with Lemeslow is as follows:

$$n = \frac{Z^2 \times P(1 - P)}{d^2}$$
$$n = \frac{1,96^2 \times 0,3(1 - 0,3)}{0,1^2} = 80,67$$

Description:

n (sample size), Z (Z-Score on confidence) 95%=1,96, P (maximum estimate) 30%, d (error rate) 10%.

A total of 80 respondents participated in the first stage, selected based on specific inclusion criteria. These criteria encompassed healthcare professionals involved in preparing parenteral formulations within healthcare facilities, medical personnel engaged in the administrative registration of parenteral formulations, and professionals working within industries linked to manufacturing parenteral preparations. The exclusion criteria in this study were medical personnel in health care units who did not mix parenteral preparations.

The second stage

The formula used to assess the completeness of information within brochures (Malik & Chusni, 2018) was as follows:

$$n = \frac{N}{1 + (N \times e^2)}$$

Description:

n (sample size), N (population sample)

The second stage of the research employed Slovin's formula to determine the sample size. In the hospital where the research took place, there were 250 parenteral preparations available. Utilizing Slovin's formula with a margin of error set at 6%, the calculation yielded a sample size of 148 from these preparations.

Short Title

Furthermore, an exclusion criterion was applied to brochures regarding intravenous preparations bearing identical trade names and active substances from the same manufacturer.

Research Instrument

The questionnaire contains two sections. The initial section encompassed respondents' attributes such as length of employment, educational qualifications, job positions, and work locations. Subsequently, the questionnaire's second section focused on participants' understanding of IV preparation, including aspects such as participation in aseptic technique training, sources of drug information, requisite information during reconstitution, and identification of incompatibilities with parenteral preparations. Distributed via Google Forms, the questionnaire facilitated the collection of respondents' characteristic data and the depth of respondents' knowledge of IV mixing. The questionnaire has been used by Azni et al., 2021 and has been validated.

A checklist format was utilized to evaluate the completeness of the intravenous (IV) product brochure content in accordance with the Regulation of the National Food and Drug Authority. The checklist encompassed minimum requisite information mandated by the Regulation, comprising details on the medicine's name, dosage form, drug administration guidelines, drug composition, indications, posology, administration methods, contraindications, warnings and precautions, drug interactions, guidance on use during pregnancy and breastfeeding, side effects, excipient listing, packaging type and size, distribution authorization number, registrant name and address, manufacturer details, usage instructions, drug classification, specific warnings, and additional details recommended by the Regulation of the National Food and Drug Authority No. 24 of 2017. These supplementary aspects included information on the impact of the

medication on the ability to operate machinery, overdose precautions, mechanism of action, pharmacodynamics, pharmacokinetics, non-clinical safety data, drug incompatibility, storage guidelines, stability information, additional dosage forms and packaging, licensing industry particulars such as name and address, reconstitution methods, initial drug approval or re-registration details, and the date of product information modification.

Data analysis

The research questionnaire data underwent descriptive analysis and was presented in tabular format to identify the characteristics of healthcare personnel involved in utilizing parenteral preparations. Based on the Regulation of the National Food and Drug Authority, the assessment of IV product brochure completeness involved identifying the required information specified for inclusion in the label. Subsequently, the data were calculated as a percentage representing the extent of adherence to the guidelines stipulated by the Regulation of the National Food and Drug Authority.

RESULTS AND DISCUSSION

Social Demographic

The social demographic aspect of the research was divided into four questions, encompassing inquiries regarding occupation, length of work experience, workplace, and working department. The characteristics of respondents' working departments included pharmacists/pharmaceutical technical personnel working in hospital/clinic/primary healthcare center pharmacy installations, laboratories within the pharmaceutical industry, and research and development (R&D) roles. The medical ward category encompassed work units related to Maternal and Child Health, intensive care units, inpatient care, and outpatient services within the hospital.

Table I. Demographic profile of medical personnel utilizing parenteral preparations

No	Characteristic of respondents	Frequency N= 80	Percentage
1	Occupation		
	Physician	1	1.25
	Pharmacist	38	47.5
	Midwives	13	16.25

	Characteristic of respondents	Frequency N= 80	Percentage
	Nurse	14	17.5
	Pharmaceutical Technical Personnel	14	18
2	Length of work experience		
	≥ 5 years	57	71.25
	< 5 years	23	28.75
3	Workplace		
	Hospital	59	73.8
	Pharmaceutical industry	3	3.75
	Public health center	18	22.5
4	Working Department		
	Pharmacy department	43	53.75
	Medical ward	37	46.25

Table I. illustrates data from 80 respondents primarily involved in handling parenteral preparations, among whom 38 (47.5%) were identified as pharmacists. A significant majority of respondents reported having a work experience of ≥ 5 years, totaling 57 (71.25%) individuals. The predominant usage of parenteral preparations was observed within hospital settings, accounting for 59 (73.8%) instances, with the primary working department being a pharmacy depot for 43 (53.75%) respondents. The characteristics of respondents at the Karanganyar Regency Hospital, Central Java, the largest length of service was > 5 years, amounting to 74.21%, with the work location in the treatment room at 69.81% (Azni et al., 2021b).

The collected data suggests significant progress in ensuring the appropriateness of healthcare procedures among medical personnel. Notably, pharmacists emerge as the only medical professionals engaged in reconstituting intravenous preparations within hospital premises or community health centers. This exclusivity is attributed to pharmacists' intricate understanding of preparations' physical and chemical attributes, enabling them to minimize errors during the

mixing process. Physicians make specific preparation requests concerning the distribution of parenteral preparations to inpatient units, after which the preparations are mixed at the pharmaceutical depot and subsequently distributed accordingly (Kemenkes, 2016).

Medical Personnel's Knowledge of Reconstitution of Intravenous Preparations

The assessment of reconstitution knowledge within the questionnaire encompassed four fundamental questions: comprehension of reconstitution processes, participation in aseptic technique training, commonly utilized sources of information, and required information during reconstitution. Understanding reconstitution involved appropriately mixing intravenous preparations with other substances or suitable solvents. Analysis of the research data concerning medical personnel handling intravenous preparations revealed that some of these individuals lacked knowledge regarding the proper mixing of preparations. The distribution of knowledge about the reconstitution of parenteral preparations among medical personnel can be seen in Table II.

Short Title

Table II. Distribution of knowledge of the reconstitution of parenteral preparations among medical personnel

No	Variable	Frequency N=80	Percentage
1	Understanding of reconstituting parenteral preparations		
	Yes	79	98.75
	No	1	1.25
2	Previous participation in aseptic technique training		
	Yes	46	57.5
	No	34	42.5
3	Sources of information on reconstitution of parenteral preparations		
	Brochure	48	60
	Book	29	36.25
	Seminar	2	2.5
	Internet	1	1.25
4	Information required during reconstitution		
	Dose	49	61.25
	Solubility	18	22.5
	BUD (Beyond-use dates)	10	12.5
	Incompatibility	3	3.75
5	Encounter with incompatibility during reconstitution of parenteral preparations		
	Yes	47	58.75
	No	33	41.25

The evaluation of aseptic technique training among health workers in the research focused on whether they had undergone training conducted by certified professionals with explicit and measurable guidelines, rather than merely participating in sessions led by fellow medical personnel lacking clear instructions. Table II. presents the distribution of medical personnel's knowledge regarding the reconstitution of parenteral preparations. A substantial majority of healthcare staff (91%) exhibited an understanding of reconstitution, with 79 individuals (98.75%) showcasing this comprehension. Furthermore, 46 individuals (57.5%) had participated in aseptic dispensing training. Only 46 individuals have aseptic dispensing training, because not all hospitals have provided or asked their medical staff for training and lack of information about the requirements of people who mix intravenous preparations. The primary information source utilized by medical staff for aseptic dispensing services was brochures, with 48 individuals (60%) relying on them. In addition, the essential

information sought for reconstitution comprised dosage (49 individuals, accounting for 61.25%) and solubility (18 individuals, constituting 22.5%). Furthermore, 34 (42.5%) respondents have not followed the training in our study. A previous study by Azni et al (2021) showed around 10 % of personnel had not received the training (Azni et al., 2021b).

In the research context, sources of information serve as essential tools to assess the solubility of intravenous preparations, ascertain drug stability during administration, and determine appropriate dissolution methods (Moraes et al., 2021). Within hospital settings, particularly in the Intensive Care Unit (ICU), infusion pumps are extensively used to maintain precise medication dosages administered to patients continuously. These preparations, often administered over extended periods ranging from one hour to more than four hours, necessitate healthcare personnel's awareness regarding the stability of the preparation post-mixing with other solutions for specific durations. Brochures

commonly serve as the primary choice for acquiring information about parenteral preparations in healthcare services. However, it is important to note that not all brochures encompass or provide comprehensive details about the medication. An emerging trend among clinical pharmacy practitioners is the utilization of Lexicomp. However, in Indonesia, particularly in Central Java province, there remains a scarcity of practitioners employing this application. This is primarily due to the substantial cost involved in using the application, mandatory registration, and the necessity for training before utilizing this tool for preparation-related purposes.

An example illustrating the insufficient information in brochures relates to product incompatibility. Incompatibilities among preparations are frequently encountered within hospital settings, involving intravenous preparations combined with solvents, thereby changing the solubility of the preparation. For example, a scenario involves the administration of a 100 mg/2 mL phenytoin preparation dissolved in 40 mL, administered at a slow pace due to the preparation's increased viscosity. The thickened consistency of the preparation poses a potential risk if administered over a brief duration.

The data obtained indicates that the level of knowledge of medical personnel in handling preparation mixing correlates with a reduced occurrence of incompatibilities concerning intravenous preparations. In addition, healthcare workers frequently rely on brochures as a primary information source during the mixing process. This aspect warrants considerable attention, as incomplete information within these resources may potentially increase the likelihood of medication administration errors or incidents of incompatibility.

Information Completeness in the Brochures in accordance with the Regulation of the National Food and Drug Authority

Table III. presents the results derived from the comparison of information contained in the brochures with the Regulation outlined by the Head of the Food and Drug Agency of the Republic of Indonesia concerning criteria and procedures for drug registration. The population data for evaluating the completeness of information within parenteral preparation brochures amounted to 250, from which a sample of 148 preparations was obtained. In addition, comprehensive information regarding the mixability aspect in the brochures was not necessarily available.

Table III. Compliance with the minimum required information in the package brochures in accordance with the Regulation of the National Food and Drug Authority

No	Characteristics	Frequency N=148	Percentage
1	Medicine name	148	100
2	Dosage form	148	100
3	Drug administration	33	22
4	Drug composition (name and strength of active substance)	148	100
5	Indication	148	100
6	Posology and method of administration	131	89
7	Contraindications	147	99
8	Warning-caution	146	99
9	Drug interactions	120	81
10	Pregnancy and breastfeeding	72	49
11	Side effects	145	98
12	Excipient list	10	7
13	Type and size of packaging	148	100
14	Distribution authorization number	148	100

Short Title

No	Characteristics	Frequency	Percentage
		N=148	
15	Name of registrant and/or drug owner in accordance with applicable regulations	0	0
16	Address of the registrant and/or drug owner in accordance with applicable regulations	0	0
17	Manufacturer name	148	100
18	Manufacturer address	143	87
19	Instructions for use	129	87
20	Drug class	0	0
21	Special warnings, for example:	146	99
	a. On medical prescription		
	b. Limited over-the-counter drug warning signs (P. No.1-P. No.6)		
	c. Warning box		
	d. Sourced/ in contact with swine		
	e. Alcohol content		

Table III presents the mandatory information stipulated by the Regulation of the National Food and Drug Authority No. 24 of 2017, which should be present in the package brochures. Out of the 148 (100%) brochures assessed, essential information such as drug names, dosage forms, drug composition (including the name and potency of active substances), indications, types and sizes of packaging, distribution permit numbers, and manufacturer names were universally included. However, information crucial for medication administration, pregnancy or breastfeeding, and an excipient list fell below the required threshold, registering a percentage below 50% in the brochures. Remarkably, the data indicated a complete absence (0%) of information regarding the registrant and/or drug owner's name, the registrant's address, and drug classification within these brochures. Furthermore, the preparation brochures exclusively listed injection preparations, and only 10 (7%) of all sampled brochures provided a list of excipients. In parenteral preparations, the inclusion of excipients holds significance concerning the compatibility of active substances. This information is crucial because the stability of the preparation depends on the formulation, including the selection of excipients (WHO, 1996).

The package brochure is mandated to encompass information regarding drug effects, which holds paramount importance, given that 3-16% of inpatients encounter drug-related side

effects (Oyebode, 2013). Research findings indicate that respondents predominantly utilize brochures as their primary information source, surpassing other media for increasing their knowledge base (Al Bardaweel & Dashash, 2018). Pharmaceutical preparations failing to meet safety, efficacy, quality, and labeling standards and aligning with legal, scientific, and technological advancements within the medical domain are subject to withdrawal and disposal (National Food Drug, 2017). Standards and requisites for drug and medicinal substance quality involve adherence to the Indonesian pharmacopeia, analytical methodologies, and various other standardized quality prerequisites as outlined in the regulations by the Head of the National Food Drug Authority (National Food Drug, 2022b).

The information in the brochures regarding the compatibility of intravenous preparations appears to be limited. Our research findings revealed that details on reconstitution methods were present in 54 (36%) instances, immiscibility was mentioned in 28 (19%) cases, and only 10 (7%) brochures included an excipient list. Assessing compliance with the mandatory minimum information required in package brochures according to the Regulation of the National Food and Drug Authority revealed a concerning trend. Notably, not all preparations currently available in the market encompass the required minimum information. Out of the 21 characteristic data points assessed, only 7 were

included by drug manufacturers at a 100% rate. Alarming, for 3 data points, no manufacturer provided any information. Such inadequacies have the potential to increase the occurrence of undesirable events during the use of these preparations.

Optional Data Recommended By the National Food and Drug Authority

Table IV. illustrates optional information outlined in the brochures according to the Regulation of the National Food and Drug Authority. Our findings revealed that the most frequently included details were instructions on drug storage, present in 146 (99%) instances, followed by drug mechanism of action, which

accounted for 128 (86%) brochures. Contrastingly, certain optional information was noticeably absent from the brochures. For instance, the address of the licensor's industry was entirely omitted. Moreover, the drug license for medicinal preparations solely mentioned the name of the licensor's industry in a mere 6 (4%) instances. Elements of optional data that fell short of the 50% inclusion threshold encompassed information on effects on the ability to operate machinery, pharmacodynamics, pharmacokinetics, non-clinical safety data, immiscibility, stability, packaging forms, and other registered preparations, name of the licensing industry, method of reconstitution, date of registration, and the date of modification made to product information

Table IV. Optional information recommended by the Regulation of the National Food and Drug Authority

No	Characteristics	Frequency N=148	Percentage
1	Effect on the ability to drive and operate machinery	36	24
2	Overdose and medication	85	57
3	a. How the drug works	128	86
	b. Pharmacodynamics	32	22
	c. Pharmacokinetics	43	29
4	Non-clinical safety data	8	5
5	Drug incompatibility	28	19
6	Storage procedure	146	99
7	Stability and duration of use after reconstitution or container opening	12	8
8	Dosage forms and packaging specifications	48	32
9	Name of the licensing industry	6	4
10	Licensing industry address	0	0
11	Reconstitution procedure	54	36
12	First-time drug approval/ re-registration	7	5
13	of product information modification	4	3

The current research highlights a significant gap in the provision of complete information by pharmaceutical preparation manufacturers, particularly concerning vital details essential for medical personnel engaged in the reconstitution of intravenous preparations (Azni et al., 2021b, 2021a). Specifically, data such as stability, incompatibilities, and the potential effects of drug utilization on drivers, alongside administration-related registration dates, were found to be lacking. This is because optional

information is recommended by the Regulation of the National Food and Drug Authority.

Analysis revealed that only 8% of pharmaceutical preparations encompassed information on drug stability, both post-reconstitution and after the container had been opened. This requires particular attention as intravenous preparations are often utilized over prolonged periods, especially those intended for administration via injection pumps. Moreover, the issue of drug stability becomes crucial in instances where a single package is used multiple times or

Short Title

divided. Despite nearly all intravenous preparations (99%) including information on storage methods, it is crucial to acknowledge that drug damage can result from various factors beyond storage conditions, such as interactions with other medications. For instance, a study has investigated diphenhydramine HCl preparations' chemical and physical stability in normal saline and 5% dextrose injections stored under refrigeration (2 °C-8 °C) for 14 days (Sabins et al., 2019).

Health practitioners require essential information regarding the reconstitution of

intravenous drugs during service, as many preparations necessitate dilution in appropriate solvents. It is crucial to note that not all solvents are suitable for every intravenous drug preparation. Some intravenous preparations are combined with specific solvents that could potentially lead to precipitation. This phenomenon arises due to a chemical reaction between the drug and solvent, posing a significant risk if administered to a patient, potentially causing blockages within blood vessels.

Table V. Optional information on the compatibility of intravenous preparations in the package brochures in accordance with the Regulation of the National Food and Drug Authority

No	Characteristics	Frequency	Percentage
1	Excipient List	10	7
2	Drug incompatibility	28	19
3	Storage procedure	146	99
4	Stability and duration of use after reconstitution or container opening	12	8
5	Reconstitution procedure	54	36

In our study, an evaluation of the information present in the brochures regarding the compatibility of intravenous preparations, as outlined in the Regulation of the National Food and Drug Authority No. 24 of 2017, revealed several significant aspects: 1) Storage methods were mentioned in 146 (99%) instances, a critical detail influencing physicochemical properties due to polymorphism; 2) Reconstitution methods were specified in 54 (36%) cases, a crucial factor in intravenous administration; 3) Drug incompatibility was addressed in 28 (19%) brochures; and 4) Drug stability was addressed in 12 (8%) instances. Of the 5 aspects, only the storage aspect was almost fulfilled in 148 brochures, while the other points were not, because improper storage will accelerate the deterioration of the drug or make it unstable.

Notably, potential incompatibilities, such as alkaline pH-induced interactions, have been observed in studies involving medications like phenytoin (32%) and sodium bicarbonate (8%) (Gaetani et al., 2017; Garcia et al., 2021; Gersonde et al., 2017; Hecq et al., 2019; Henkel et al., 2020; Kamin et al., 2014).

The research data emphasizes information essential for health practitioners in hospital

settings, encompassing aspects like excipient lists, non-mixing instructions, storage protocols, stability guidelines, and reconstitution methods for intravenous preparations. However, there is a noticeable lack of necessary information required for the reconstitution of intravenous preparations in the available brochures. This is particularly concerning as previous studies indicate that many practitioners and health workers predominantly rely on brochures as their primary reference during reconstitution. Consequently, the information required by medical personnel in hospital settings remains significantly limited, especially concerning the adequacy of the drug administration's suitability based on the available preparation brochures or brochures.

LIMITATIONS OF THE RESEARCH

The limitations in this research include the number of respondents that may not fully represent all healthcare professionals in Indonesia, despite the online distribution of questionnaires. The second limitation is that the number of brochures analyzed may not fully represent all intravenous (IV) preparations used in Indonesia,

specifically, as they were sourced from only one hospital in Semarang.

CONCLUSION

A portion of healthcare professionals involved in preparing parenteral preparations have yet to undergo aseptic dispensing training, highlighting the continued need to enhance knowledge regarding mixing parenteral preparations among healthcare workers. Pharmaceutical manufacturers should supplement information in IV preparation brochures regarding excipient lists, non-mixing instructions, storage procedures, stability, and reconstitution methods to guide medical personnel. This is essential as many healthcare workers in hospitals rely on brochures as their primary source of information for mixing IV preparations.

ACKNOWLEDGMENTS

10 We extend our gratitude to the Indonesia Endowment Funds for Education (LPDP) and the Center for Higher Education Funding (BPPT) for their generous support in funding this research. In addition, our sincere appreciation goes to the private hospital in Semarang, Central Java, Indonesia, for providing the brochures for intravenous preparations. Our heartfelt thanks also go to all the medical personnel who actively participated in the questionnaire survey, contributing significantly to the success of this study.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- Ahmad, I., Ali, L. ., & Ahmed, S. (2016). *Stability of drugs and drug products*. (First). Higher Education Commission - Pakistan Disclaimer:
- Al Bardaweel, S., & Dashash, M. (2018). E-learning or educational leaflet: Does it make a difference in oral health promotion? A clustered randomized trial. *BMC Oral Health*, *18*(1), 1–8. <https://doi.org/10.1186/s12903-018-0540-4>
- Azni, M., Rahmawati, F., & Wiedyaningsih, C. (2021a). *Faktor risiko sediaan intravena yang berhubungan dengan kejadian flebitis Di RSUD Kabupaten Karangnyar*. Universitas Gadjah Mada.
- Azni, M., Rahmawati, F., & Wiedyaningsih, C. (2021b). 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>
- Benlabed, M., Perez, M., Gaudy, R., Genay, S., Lannoy, D., Barthélémy, C., Odou, P., Lebuffe, G., & Décaudin, B. (2019). Clinical implications of intravenous drug incompatibilities in critically ill patients. In *Anaesthesia Critical Care and Pain Medicine* (Vol. 38, Issue 2, pp. 173–180). Elsevier Masson SAS. <https://doi.org/10.1016/j.accpm.2018.04.003>
- da Silva C, M., Camerini, F., de Mendonça H, D., Marins, A., & Fassarella, C. S. (2021). Analysis of drug incompatibilities in a cardiac intensive unit: a cross-sectional study. *Enfermeria Global*, *20*(2), 95–108. <https://doi.org/10.6018/eglobal.438931>
- 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>
- Fernandez-Pena, A., Katsumiti, A., De Basagoiti, A., Castaño, M., Ros, G., Sautua, S., De Miguel, M., & Campino, A. (2021). Drug compatibility in neonatal intensive care units: gaps in knowledge and discordances. *European Journal of Pediatrics*, *180*(7), 2305–2313. <https://doi.org/10.1007/s00431-021-04028-9>
- Frankenfeld, C., Mittal, S., Melendez, Y., Mendez-Vigo, L., Lamp, K. C., Keller, K. N., & Bertolami, S. R. (2018). Daptomycin: A comparison of two intravenous formulations. *Drug Design, Development and Therapy*, *12*, 1953–1958. <https://doi.org/10.2147/DDDT.S167010>
- Gaetani, M., Frndova, H., Seto, W., & Parshuram, C. (2017). Concurrent intravenous drug administration to critically ill children: Evaluation of frequency and compatibility. *Journal of Critical Care*, *41*, 198–203. <https://doi.org/10.1016/j.jcrc.2017.05.027>
- Gahart, B. L., & Nazareno, A. R. (2014). *Intravenous medications* (Deborah L. Vogel (ed.); THIRTIETH). Deborah L. Vogel.
- Garcia, J. H., Crespo, J. C. L., Handa, A. Y., Padilha, K.

Short Title

- G., & Secoli, S. R. (2021). In(compatibility) of intravenous drugs in critical units: adult cohort. *Revista Brasileira de Enfermagem*, 74(2), e20200501. <https://doi.org/10.1590/0034-7167-2020-0501>
- Gersonde, F., Eisend, S., Haake, N., & Kunze, T. (2017). Physicochemical compatibility and emulsion stability of propofol with commonly used analgesics and sedatives in an intensive care unit. *European Journal of Hospital Pharmacy*, 24(5), 293–303. <https://doi.org/10.1136/ejhpharm-2016-001038>
- Hani, C., Vonbach, P., Fonzo-Christe, C., Russmann, S., Cannizzaro, V., & Niedrig, D. F. (2019). Evaluation of incompatible coadministration of continuous intravenous infusions in a pediatric/neonatal intensive care unit. *Journal of Pediatric Pharmacology and Therapeutics*, 24(6), 479–488. <https://doi.org/10.5863/1551-6776-24.6.479>
- Hecq, J.-D., Krämer, I., & Vigneron, J. (2019). European Databases on Stability and Compatibility of Injectable Medicinal Products in Europe. *Pharmaceutical Technology in Hospital Pharmacy*, 4(3-4), 113–117. <https://doi.org/10.1515/pthp-2019-0012>
- Henkel, E., Vella, R., Behan, K., Austin, D., Kruger, P., & Fenning, A. (2020). The effect of concentration, reconstitution solution and pH on the stability of a remifentanyl hydrochloride and propofol admixture for simultaneous co-infusion. *BMC Anesthesiology*, 20(1), 1–12. <https://doi.org/10.1186/s12871-020-01194-5>
- Kamin, W., Erdnüss, F., & Krämer, I. (2014). Inhalation solutions - which ones may be mixed? Physico-chemical compatibility of drug solutions in nebulizers - update 2013. *Journal of Cystic Fibrosis*, 13(3), 243–250. <https://doi.org/10.1016/j.jcf.2013.09.006>
- Kemenkes. (2016). *Peraturan menteri kesehatan Republik Indonesia no 72 tahun 2016 tentang standar pelayanan kefarmasian di rumah sakit*. 1–63. <file:///Users/andreataquez/Downloads/gui-a-plan-de-mejora-institucional.pdf><http://salud.tabasco.gob.mx/content/revista>http://www.revisitaalad.com/pdfs/Guias_ALAD_11_Nov_2013.pdf<http://dx.doi.org/10.15446/revfacmed.v66n3.60060><http://www.cenetec.med.v66n3.60060>
- Kumar, A., Singh, P., & Nanda, A. (2020). Hot stage microscopy and its applications in pharmaceutical characterization. *Applied Microscopy*, 50(1). <https://doi.org/10.1186/s42649-020-00032-9>
- La Pietra, L., Calligaris, L., Molendini, L., Quattrin, R., & Brusaferrò, S. (2005). Medical errors and clinical risk management: state of the art. *Acta Otorhinolaryngologica Italica: Organo Ufficiale Della Società Italiana Di Otorinolaringologia e Chirurgia Cervico-Facciale*, 25(6), 339–346.
- Maison, O. (2019). Drug incompatibilities in intravenous therapy: evaluation and proposition of preventive tools in intensive care and hematology units. *European Journal of Clinical Pharmacology*, 75, 179–187.
- Malfará, M., Pernassi, M., Aragon, D., & Carlotti, A. (2018). Impact of the clinical pharmacist interventions on prevention of pharmacotherapy related problems in the paediatric intensive care unit. *International Journal of Clinical Pharmacy*, 40(3), 513–519. <https://doi.org/10.1007/s11096-018-0632-x>
- 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., MEDEIROS, F. S., & 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>
- National Food Drug. (2017). Peraturan kepala badan pengawas obat dan makanan Republik Indonesia nomor 24 tahun 2017 tentang kriteria dan tata laksana registrasi obat. *Bpom Ri*, 1–261.
- National Food Drug. (2022a). Peraturan badan pengawas obat dan makanan no. 14 tahun 2022 tentang penarikan dan pemusnahan obat yang tidak memenuhi standar dan/atau persyaratan keamann, khasiat, mutu, dan

- label. *Bpom*, 1–16.
- National Food Drug. (2022b). Peraturan badan pengawas obat dan makanan nomor 23 tahun 2022 tentang standar dan/atau persyaratan mutu obat dan bahan obat. *Bpom Ri*, 11, 1–16.
- Neininger, M. P., Buchholz, P., Frontini, R., Kiess, W., Siekmeyer, W., Bertsche, A., Siekmeyer, M., & Bertsche, T. (2019). Incompatible intravenous drug combinations and respective physician and nurse knowledge: A study in routine paediatric intensive care. *European Journal of Hospital Pharmacy*, 26(4), 214–217. <https://doi.org/10.1136/ejhpharm-2017-001248>
- NHS. (2019). *Policy for the safe management and administration of intravenous medicines*. April, 1–42.
- Nilsson, N., Storesund, I., Tho, I., & Nezvalova-Henriksen, K. (2022). Co-administration of drugs with parenteral nutrition in the neonatal intensive care unit—physical compatibility between three components. *European Journal of Pediatrics*, 181(7), 2685–2693. <https://doi.org/10.1007/s00431-022-04466-z>
- Oyebode, F. (2013). Clinical errors and medical negligence. *Medical Principles and Practice*, 22(4), 323–333. <https://doi.org/10.1159/000346296>
- Pangestika, R. W. (2022). Hubungan usia, pendidikan, dan lama bekerja dengan pengetahuan tenaga kesehatan tentang inkompatibilitas sediaan intravena. *Media Farmasi*, 18(1), 36. <https://doi.org/10.32382/mf.v18i1.2693>
- PERMENKES. (2014). *Standar pelayanan kefarmasian di apotek. PMK no 35*. <https://ejournal.bioscientifica.com/view/journals/eje/171/6/727.xml>
- Royal Hospital For Women. (2011). *Administration of intravenous medication by nursing staff* (Issue July). <https://doi.org/10.1002/14651858.CD001000.pub3>. Couser
- S. Sriram, Aishwarya, S., Kumar, A. A., Moithu, A., & Sebastian, A. (2018). Intravenous drug incompatibility in intensive care units - A comprehensive review. *Innovations in Pharmaceuticals and Pharmacotherapy*, 6(3), 55–60. www.innpharmacotherapy.com
- Sabins, D., Diep, T., McCartan, P., Patel, S., & Zhao, F. (2019). Stability and Compatibility of Diphenhydramine Hydrochloride in Intravenous Admixtures: A New Look at an Old Drug. *Hospital Pharmacy*, 54(5), 330–334. <https://doi.org/10.1177/0018578718802586>
- Sohrevardi, S. M., Jarahzadeh, M. H., Mirzaei, E., Mirjalili, M., Tafti, A. D., & Heydari, B. (2017). Medication errors in patients with enteral feeding tubes in the intensive care unit. In *Journal of Research in Pharmacy Practice* (Vol. 6, Issue 2). https://doi.org/10.4103/jrpp.jrpp_17_9
- Stroppel, L., Schultz-Fademrecht, T., Cebulla, M., Blech, M., Marhöfer, R. J., Selzer, P. M., & Garidel, P. (2023). Antimicrobial preservatives for protein and peptide formulations: an overview. *Pharmaceutics*, 15(2), 1–53. <https://doi.org/10.3390/pharmaceutics15020563>
- Tomczak, S., Gostyńska, A., Nadolna, M., Reiser, K., Orlando, M., Jelińska, A., & Stawny, M. (2021). Stability and compatibility aspects of drugs: The case of selected cephalosporins. *Antibiotics*, 10(5), 1–16. <https://doi.org/10.3390/antibiotics10050549>
- Villiers, M. M. De. (2017). *Compatibility and stability of drug products and preparations*. January 2009, 672–702. <https://www.researchgate.net/publication/318380441%0ACompatibility>
- WHO. (1996). Annex 5: Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. *World Health Organization Technical Report Series*, 863, 65–80.

Knowledge of Intravenous Preparation among Health Professionals and Assessment of the Sterile Product Label Information Coverage

ORIGINALITY REPORT

7%

SIMILARITY INDEX

5%

INTERNET SOURCES

3%

PUBLICATIONS

3%

STUDENT PAPERS

PRIMARY SOURCES

1	international.fda.moph.go.th Internet Source	2%
2	journal.ugm.ac.id Internet Source	1%
3	Hanie Kusuma Wardani, Wahyu Kusuma Wardani. "Food Safety and Halal Certification Seminar Towards Mandatory Halal Food in October 2024", Journal of Community Engagement in Health, 2024 Publication	1%
4	jurnal.ugm.ac.id Internet Source	1%
5	Submitted to Universitas Sebelas Maret Student Paper	<1%
6	jsfk.ffarmasi.unand.ac.id Internet Source	<1%
7	Ade Gafar Abdullah, Isma Widiaty, Cep Ubad Abdullah. "Medical Technology and	<1%

Environmental Health", CRC Press, 2020

Publication

8	Submitted to Padjadjaran University Student Paper	<1 %
9	submission.als-journal.com Internet Source	<1 %
10	pmc.ncbi.nlm.nih.gov Internet Source	<1 %
11	ebin.pub Internet Source	<1 %

Exclude quotes On

Exclude matches < 15 words

Exclude bibliography On