

Original Article

Intravenous Drug Incompatibilities in the Intensive Care Unit of a Tertiary Care Hospital in India: Are they Preventable?

Shanmugam Sriram¹, S. Aishwarya², Akhila Moithu², Akshaya Sebastian², Ajith Kumar²

¹Department of Pharmacy Practice, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu, India

²Department of Pharmacy Practice, PharmD Intern, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu, India

ABSTRACT

Objective: The main aim of the study was to identify the physical and chemical incompatibilities among the drugs administered intravenously to patients admitted to the Intensive Care Unit (ICU) of a 1000 bedded hospital. The study also envisaged establishing pharmaceutical guidelines for the administration of incompatible medications. **Methods:** This prospective cross-sectional study was conducted from January to July 2018 in the ICU after getting approval from the Hospital Ethics Committee. A total of 104 medication charts were collected, and their data were analyzed. Compatibility of the selected drug with a second drug, when given together, was then analyzed using the Micromedex health-care series, Trissel's handbook of injectable drugs, and Manufacturer's product information. The pharmaceutical intervention was performed by preparing. The drug compatibility chart of selected drugs and the same was reported to the study department. **Findings:** Of 104 medication charts reviewed, 66 charts had incompatibility, accounting for 90 incompatibilities. Incompatibility between two intravenous (IV) bolus drugs constituted 68.8% with pantoprazole and ondansetron (85.4%) being the most frequent combination. Incompatibility between infusion-bolus was found to be 26.6%. Meropenem (infusion) and pantoprazole (bolus) constituted 16.6%. Incompatibility between two infusions in the same IV line was found to be 4.4%. A drug compatibility chart containing 19 selected drugs was prepared and submitted to the study department for their perusal. **Conclusion:** The current study showed that a significant number of drug incompatibilities occur in hospitalized critically ill patients in our tertiary care hospital. These incompatibilities could generally be prevented by adhering to proper medication administration techniques like flushing the line using compatible fluid or through a multi-lumen catheter or multiple IV access.

KEYWORDS: Critically ill patients, drug-related problems, intensive care unit, intravenous drug incompatibilities

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INTRODUCTION

The Intensive Care Unit (ICU) presents substantial patient safety challenges.^[1] In ICU, intravenous (IV) therapy is preferred over oral therapy. It is complex and error-prone hence requiring strategies to reduce the risk and complications.^[2] Infusion therapy is associated with a high risk of causing harm for patients. The administration of IV medications may be associated with undesirable effects, especially when administered in error.^[3] In a study by Tissot *et al.*, it is reported that

18.6% of the total medication errors (MEs) belong to the category physicochemical incompatibility.^[4]

Drug incompatibility results from the simultaneous dilution and/or administration of two or more drugs that interfere with the therapeutic efficacy of the medications and patient safety, visually evidenced by

Address for correspondence:

Prof. Shanmugam Sriram,
E-mail: visitram@yahoo.com

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change of solution color, precipitation, or turbidity.^[5] Physical reactions of drugs usually refer to either phase separation or precipitation due to a shift in the relation between ionization and nonionization and solubility. In chemical incompatibility, the medicine may undergo many chemical degradation pathways such as oxidation, reduction, hydrolysis, photolysis, or racemization. It can be perceived as turbidity, precipitation, and color changes. Therapeutic incompatibility may occur when two or more drugs are administered concurrently resulting in undesirable antagonistic or synergistic pharmacological activity.

These incompatibilities generally occurs between drugs and inappropriate diluents, two drugs: drug-drug incompatibility, when these are mixed in the same infusion line or the same IV container when these are administered one after the other within the same infusion line, drugs and adjuncts such as stabilizer and solvent and drugs and materials of IV containers like polyvinyl chloride.

Probable mechanisms for these incompatibilities may be due to medicines that precipitate on dilution, precipitation of medications due to pH change on mixing, ionic reactions forming insoluble substances, and denaturation of biological molecules.

The extent and severity of the damage caused by incompatibility depend on the patient's condition and the type of drug administered. Significant consequences are multiorgan failure, severe liver dysfunction, toxic shock, local embolus, myocarditis, respiratory difficulties, systemic allergic reactions, local allergic reactions, thrombosis, thrombophlebitis, phlebitis, and local redness.^[6-12]

Recent studies showed or recommended the following preventive strategies for preventing the IV drug incompatibilities as helpful: the usage of multiple lumen catheter, use of in-line infusion filters,^[13,14] separate IV infusion by time and place, flushing the IV line with a fluid compatible to the drug administered,^[15] and the color-coding system for drug pH.^[16]

The main objective of this study was to identify and document the physical and chemical incompatibilities among the drugs administered intravenously to patients admitted to the ICU of a tertiary care hospital in India and to establish pharmaceutical guidelines for the administration of incompatible drugs.

METHODS

This cross-sectional study was conducted at a 1000-bedded, private tertiary care multi-specialty teaching hospital located at Coimbatore. The study was

conducted in the ICU of the hospital for a length of 6 months (January 2018–June 2018).

The study protocol was prepared and submitted to the Institutional Ethical Committee of the study hospital. The approval from the committee was obtained as a letter (SRH/EC.12-14/2017-18 dated 28th December 2017).

The inclusion criteria of our study were all inpatients of age 18 years and above, of either sex, getting admitted to the study site during the study, with length of stay equal to or longer than 24 h, prescriptions with 4 or more IV drugs and patients who were willing to participate were included in the study. We also excluded inpatients who were younger than 18 years, and who are not willing to participate in the study were excluded from the study.

Medication charts of 104 consecutive patients admitted in the ICU and treated with four or more IV drugs were analyzed. The patient baseline characteristics such as age, sex, the reason for hospitalization, comorbidities, laboratory investigations, diagnosis, and medication charts were obtained.

Compatibility of selected drugs with a second drug was analyzed using MICROMEDEX DRUG DATABASE which is available with the Department of Pharmacy Practice and TRISSEL'S HANDBOOK OF INJECTABLE DRUGS. A two-dimensional compatibility chart was then prepared to indicate the compatibility of a selected drug with a co-administered drug. Furthermore, the analysis of high alert medications, drug-drug interactions (DDI) was also analyzed.

RESULTS

The total number of patients included in the study and had fulfilled the inclusion criteria was 104 of which 72 (69.23%) were male and 32 (30.77%) were female. The result of gender categorization revealed that the overall study population was predominantly male population. The most dominant group was middle adulthood which accounts for 41.3% of the whole study population. The average age of the whole study population was found to be 58.03 ± 17.49 years.

The analysis showed that, out of 104 prescriptions, 66 prescriptions had incompatibility, summing to 90. IV incompatibility of continuous infusions and bolus doses when administered one after the other using the same line was 26.6% ($n = 24$) [Figure 1].

The analysis of drugs prescribed to the study population revealed that a minimum of 5 medicines and a

Table 1: Drug type frequency of intravenous incompatibilities between continuous infusion and bolus dose

Number	Continuous infusion	Bolus dose	Effect/result	n (%)
1	Meropenem	Pantoprazole	Precipitation	4 (16.6)
2	Clindamycin	Pantoprazole	Red precipitation	3 (12.5)
3	Piperacillin/tazobactam	Pantoprazole	Precipitation	3 (12.5)
4	Metronidazole	Pantoprazole	Reddish-brown discoloration and cloudy precipitation	3 (12.5)
5	Meropenem	Ondansetron	White precipitation	2 (8.3)
6	Amikacin	Pantoprazole	Precipitation	2 (8.3)
7	Ceftriaxone	Ondansetron	Haziness with micro precipitation	2 (8.3)
8	Glycopyrrolate	Pantoprazole	Orange discoloration	1 (4.1)
9	Fluconazole	Pantoprazole	Haziness and micro precipitation	1 (4.1)
10	Levofloxacin	Pantoprazole	Orangish-yellowish discoloration	1 (4.1)
11	Piperacillin/tazobactam	Midazolam	White haze	1 (4.1)
12	Thiamine	Furosemide	Haze/turbidity/particulate matter	1 (4.1)

Table 2: Drug type frequency of intravenous incompatibilities between continuous infusions at the same time

Number	Infusion-1	Infusion-2	Effect/result	n (%)
1	Paracetamol	Metronidazole	Turbidity	1 (25)
2	Meropenem	Acyclovir	Precipitation	1 (25)
3	Paracetamol	Acyclovir	Particulate formation	1 (25)
4	Meropenem	Calcium gluconate	Yellow color	1 (25)

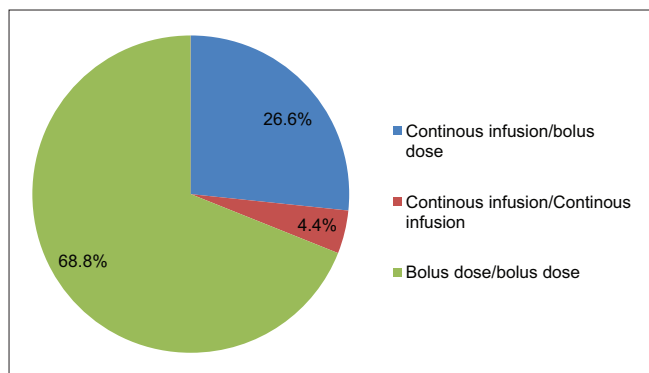


Figure 1: The frequency of IV drug incompatibilities by different types of infusion in the study patients (n = 104)

maximum of 24 drugs were found. The average number of medications prescribed was found to be 11.2 ± 3.8 . Our analysis showed that the average ratio of IV drugs per patient were 7.74 ± 2.84 . The majority of the study population has received antibiotics, anti-ulcer medications and anti-emetics.

Of 104 prescriptions analyzed, 42 prescriptions had DDIs. The results showed that there was a total of 65 DDIs of which 76.9% were major, and 16.9% were of moderate severity. Minor DDI constituted to 3.1% of the total DDI. One contraindicated pair was observed which is fluconazole and ondansetron combination which would result in QT interval prolongation.

Based on our observation and results, IV drug compatibility-alert card was prepared to enhance the rational use of IV medication and patient safety.

DISCUSSION

Errors in the administration of IV drugs are numerous, with IV drug incompatibility being a significant problem. The current study provides information about the incompatibility of IV drugs administered in patients admitted to ICU.

In the study by Machotka *et al.*, they have analyzed 50 medication charts within 12 months (January 2011–December 2011) comprising 54% females and 46% males, with a total of 318 IV drugs.^[17] In the present study, 104 medication charts were analyzed. The study revealed that the male population was predominant, with 69.25% and 30.77% females. The average age of the study population was found to be 69.38 ± 5.25 years.

Most of the patients were hospitalized in the ICU due to Nervous System disorders comprising of 35.5% followed by respiratory system disorders (20.1%). Poisoning (11.5%) and road traffic accidents (RTA) (7.68%) cases were also seen.

The study on incompatibilities in the adult ICU conducted by Marsilio *et al.* analyzed 100 medication charts and found 68% of incompatibility.^[18] In the present study, 63.4% of incompatibilities were found on analysis of 104 medication charts. Although a decreased prevalence of incompatibilities was found in the present study, this rate nevertheless remains high. This high rate of incompatibilities in the present study is correlated with multiple IV medications prescribed to critically ill patients.

Table 3: Drug type frequency of intravenous incompatibilities between bolus doses at the same time

Number	Bolus 1	Bolus 2	Effect	n (%)
1	Ondansetron	Pantoprazole	Turbid precipitation + yellow discoloration	53 (85.4)
2	Furosemide	Pantoprazole	Haze/turbidity/particulate matter	3 (4.8)
3	Ketorolac	Pantoprazole	Haze, microparticulates, yellow discoloration	3 (4.8)
4	Dexamethasone	Pantoprazole	Precipitation	2 (3.2)
5	Fentanyl	Pantoprazole	Haze and micro precipitation	1 (1.6)

Kahmann *et al.* found 15% of incompatible combinations from the analysis of 78 different medication regimes.^[19] The present study also analyzed 78 different IV drug regimes and found 26.9% of combinations tested exhibited drug incompatibility reactions. This difference in prevalence might be due to the diversity of morbidity profiles among the patients that might change the drug therapy regimen to be used. Most of the patients in the present study had comorbidities with either sustained hypertension (SHT) and diabetes mellitus or SHT alone of about 10.9%.

In this study, the frequency of intravenous incompatibilities between continuous infusion and bolus dose (26.6%) is depicted in Table 1 and the frequency of intravenous incompatibilities between continuous infusions at the same time (4.4%) is tabulated in Table 2 and the incompatibilities occurred between two bolus drugs (68.8%) is shown in Table 3. Among these, incompatibility between pantoprazole and ondansetron (58.8%) was commonly observed. Moraes *et al.* (2011)^[20] found that the most common drug incompatibility occurred between piperacillin-tazobactam and midazolam. In another study conducted by Marsilio *et al.*,^[18] midazolam and cefepime were the most common drug incompatible pair. This between-studies difference might be due to the less prevalence of the incompatible pair piperacillin-tazobactam and midazolam (1.1%). Unlike the studies mentioned above, cefepime was not available in the drug regimes analyzed, consequently the difference in the results.

Pantoprazole was the most common drug involved in incompatibilities in the present study, followed by ondansetron and meropenem. The high frequencies of these drugs in incompatibilities might be relative because they are widely used in the ICU and are therefore present in numerous prescriptions.

In this study, pantoprazole was widely used for treating drug-induced gastrointestinal disturbances accounting for 9.3% of total IV medications administered. As this medication is available as a powder for solution, reconstitution must be done with D5W, Normal Saline or Ringer Lactate normal saline or ringer lactate (NS, or RL). The manufacture recommends the administration of pantoprazole through a dedicated line and avoids co-administration with other IV solutions.^[21]

Acute nature of patients in ICU necessitates the use of antibiotics frequently, and sometimes multiple antibiotic therapies need to be initiated.^[22] Nearly, 20%–40% of patients are documented to receive antimicrobial agents during hospitalization to treat and prevent nosocomial infections.^[23] In the present study, 24.5% of total IV medications were antibiotics with meropenem (5.2%), Piperacillin-Tazobactam (4.8%), and linezolid (3.2%) the frequently prescribed and the one to be involved in incompatibility.

Some medications are prone to show a higher risk of ME. These high-risk drugs can cause devastating consequences when misused.^[24] According to Tynnismaa *et al.*, the most common human rights defenders (HRDs) were oxycodone (5%), enoxaparin (3%), and noradrenaline (3%).^[25] In the present study, of 24 different HRDs observed, enoxaparin (20.7%) occurred the most, followed by insulin (12.2%) and amikacin (10%). As these medications are at heightened risk for ME, their safe use in clinical practice must be ensured.

In the study by Rodrigues *et al.* conducted in ICU, observed 67% major and 74% moderate interactions in the prescriptions analyzed. They identified the interaction between dipyron, and enoxaparin (35.8%) was the most prevalent.^[26] In our study, we noticed, 76.9% major and 16.9% moderate DDIs. Most of the significant drug interactions occurred with ondansetron comprising 38%. One contraindicated pair was observed between fluconazole and ondansetron resulting in QT interval prolongation, requiring electrocardiogram monitoring, though its clinical occurrence was not found in our study. The number of potential DDIs has a positive correlation with the number of prescribed drugs. Conceding the potential for higher risk of DDIs in ICU is essential in enhancing patient safety.

There were some limitations in our study, such as the analysis of incompatibilities involves the combination of only two drugs, unavailability of specific medication in the databases, inability to observe the clinical implication for patients. Although a pharmaceutical intervention in the form of the drug-incompatibility chart was developed, the adherence of health-care professionals to it was not evaluated.

Incompatibilities are an issue of concern, especially in patients admitted to the ICU because of the large

Table 4: Drug-drug compatibility chart

Drug-Drug compatibility chart	Acetaminophen	Acyclovir	Amikacin	Ca gluconate	Ceftriaxone	Clindamycin	Dexamethasone	Fentanyl	Fluconazole	Furosemide
Acetaminophen	-	I	NT	NT	C	C	C	C	NT	NT
Acyclovir	C	-	C	C	C	C	C	C	C	C
Amikacin	C	C	-	C	C	C	C	C	C	C
Calcium Gluconate	NT	C	C	-	I	C	CV	C	CV	C
Ceftriaxone	C	C	C	I	-	I	C	C	CV	C
Clindamycin	C	C	C	C	I	-	C	C	CV	C
Dexamethasone	C	C	C	CV	C	C	-	C	C	C
Fentanyl	C	C	C	C	C	C	C	-	C	C
Fluconazole	NT	C	C	CV	CV	CV	C	C	-	CV
Furosemide	NT	C	C	C	C	C	C	C	C	C
Glycopyrrolate	NT	C	C	CV	C	C	C	C	C	C
Ketorolac	C	I	C	CV	C	C	C	C	C	C
Levofloxacin	NT	I	C	C	C	C	C	C	C	I
Meropenem	NT	CV	NT	CV	NT	NT	C	NT	C	C
Metronidazole	I	I	C	C	C	C	C	C	C	C
Midazolam	C	I	C	C	C	CV	I	C	C	CV
Ondansetron	C	I	C	C	CV	C	C	C	C	I
Pantoprazole	NT	CV	CV	CV	C	CV	I	I	I	CV
Piper/tazo	C	I	C	C	NT	C	C	C	C	C
Thiamine	NT	NT	C	C	C	C	C	C	NT	I
Drug-Drug compatibility chart	Glycopyrrolate	Ketorolac	Levofloxacin	Meropenem	Metronidazole	Midazolam	Ondansetron	Pantoprazole	Piper/tazo	Thiamine
Acetaminophen	C	C	NT	NT	I	C	C	NT	C	NT
Acyclovir	C	I	I	CV	C	I	I	CV	I	NT
Amikacin	C	C	C	NT	C	C	C	CV	C	C
Calcium Gluconate	C	CV	C	CV	C	C	C	CV	C	C
Ceftriaxone	C	C	C	NT	C	C	C	C	NT	C
Clindamycin	C	C	C	NT	C	I	C	C	C	C
Dexamethasone	C	C	C	C	C	C	C	I	I	C
Fentanyl	C	C	C	NT	C	C	C	I	I	C
Fluconazole	C	C	C	C	C	C	C	I	I	C
Furosemide	I	C	I	C	C	CV	I	CV	CV	NT
Glycopyrrolate	-	C	NT	NT	C	C	C	I	I	C
Ketorolac	C	-	I	NT	C	I	C	I	I	NT
Levofloxacin	NT	I	-	NT	C	C	C	I	I	NT
Meropenem	NT	NT	NT	-	NT	NT	CV	I	NT	NT
Metronidazole	C	C	C	C	-	C	C	I	I	NT
Midazolam	C	I	C	NT	C	-	C	CV	I	NT
Ondansetron	C	C	C	CV	C	C	-	I	I	NT
Pantoprazole	I	I	I	I	I	CV	I	I	I	NT
Piper/tazo	I	C	I	NT	C	I	C	CV	-	NT
Thiamine	C	NT	NT	NT	NT	NT	NT	NT	NT	-

NT=Not tested, CV=Caution variable, C=Compatible, I=Incompatible

number of parenteral drug applications. As there is a limited number of independent IV lines and the need for constant drug concentration, assessing their physicochemical compatibility is necessary to avoid negative consequences such as therapeutic failure, micro-embolisms, or even toxicity.

This study substantiated that a significant number of drug incompatibilities occur in ICU, clinical pharmacists have a crucial role in the detection and elimination of drug incompatibilities and other DRPs. The current study showed that a significant number of drug incompatibilities occur in hospitalized critically ill patients whom we studied. These incompatibilities could generally be prevented by adhering to proper medication administration techniques like flushing the line using compatible fluid, through a multi-lumen catheter, through multiple IV access, using in-line infusion filters, a spacing of medication or color-coding system. Pharmaceutical intervention by clinical pharmacists, in the form of drug compatibility chart [Table 4] for the common incompatible pair of drugs that was prepared and submitted, will enable the Physicians in the ICUs to be alert during the administration of such drugs.

AUTHORS' CONTRIBUTION

Authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and participated in drafting and revising.

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Conflicts of interest

There are no conflicts of interest.

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