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Addressing the Intravenous Therapeutic Incompatibilities in ICU: Evaluating It's Pharmacoeconomic Impact on Patient Care

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KEYWORDS

Drug interactions, Intensive Care Unit, Intravenous drugs, Therapeutic incompatibilities, Healthcare costs

ABSTRACT:

Introduction: Drug-drug interactions (DDIs) within the Intensive Care Unit (ICU) would have a major impact on patient outcomes, prolong hospital stays, and increase healthcare expenditures. This prospective observational study assesses the compatibility of intravenous (IV) drugs administered to ICU patients at Sudha Institute of Medical Science, Erode, focusing on the therapeutic incompatibilities along with their clinical and financial implications.

Methodology: This study was conducted from January to June 2023. It involved 75 ICU patients who were on more than two intravenous drugs and had more than 24 hours of ICU stay. Drug compatibility was assessed using references such as Lexicomp, Trissel's Handbook of Injectable Drugs, and manufacturer product information. The study analyzed drug interactions, their severity, and the impact on patient outcomes. IBM SPSS 29.0.1.0 was used for conducting statistical analyses that include descriptive statistics, ANOVA, and the Mann-Whitney U Test.

Results: The study found that therapeutic incompatibilities were present in several drug combinations, and the most common was Tramadol & Ondansetron at 16.67%. Patients with drug interactions had significantly longer stays in the ICU, and the average stay was between 4-7 days. The financial burden was substantial with the total cost of prolonged ICU stays amounting to ₹731,827, as compared to ₹69,163 for patients without drug interactions. Socioeconomic impact was most visible among patients from lower middle-class backgrounds (70.37%).

Conclusion: Therapeutic incompatibilities are a significant factor for extended ICU stays and increased health care costs, particularly among economically vulnerable patients. Appropriate medication management and adherence to strict protocols of drug administration are essential in reducing the incidence of drug interactions, improving clinical outcomes, and reducing financial burdens in critical care settings.

1. Introduction

Intravenous (IV) therapy is indispensable in intensive care units (ICUs), where critically ill patients often require the concurrent administration of multiple medications to manage complex medical conditions.[1] The precision and immediacy of IV therapy make it a cornerstone of modern critical care; however, it also brings significant challenges, particularly the risk of therapeutic incompatibilities.[2] These incompatibilities can arise when drugs or fluids interact unfavorably within a shared IV line, leading to consequences such as precipitation, chemical degradation, altered pharmacokinetics, and toxicity. Such events not only compromise the efficacy of the administered drugs but also pose serious risks to patient safety, including

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catheter blockages, delayed treatment, and adverse clinical outcomes. Addressing these issues is critical to ensuring high-quality patient care in ICU settings.[3]

Despite the availability of standard guidelines, such as those outlined in compatibility charts and resources like the Trissel Handbook, the incidence of IV therapeutic incompatibilities remains unacceptably high. In the retrospective analysis of 100 patients, 7.2% of drug pairs were incompatible, but procedural interventions with SOPs significantly reduced this rate.[4] Additionally, the high-pressure nature of ICUs often necessitates rapid decision-making, which can inadvertently lead to errors in drug preparation or administration. For example, a study by Maison O et al. (2018) highlighted that drug incompatibilities accounted for 12% and 17% of drug pairs infused in the ICU and HSU, respectively, and pharmacists can raise awareness and propose tools to reduce their incidence.[5]

Pharmacoeconomic considerations further underscore the importance of addressing IV therapeutic incompatibilities. The financial burden of managing complications—ranging from extended hospital stays and additional treatments to equipment replacement costs—places significant strain on healthcare systems.[6] In this context, evaluating the pharmacoeconomic impact of IV incompatibilities becomes essential to justify investments in preventative measures.[7] The present study aims to fill this critical research gap by systematically assessing the prevalence, causes, and outcomes of IV therapeutic incompatibilities in ICUs, with a particular focus on their economic and clinical implications. By identifying actionable insights and proposing evidence-based interventions, this research seeks to enhance the safety, efficiency, and cost-effectiveness of IV therapy in critical care settings, ultimately improving patient outcomes and optimizing resource utilization.

METHODOLOGY

Study Type

The study is a Prospective Observational Study, which is designed to observe and analyze the compatibility of intravenous (IV) drugs prescribed to patients in the Intensive Care Unit (ICU) of Sudha Institute of Medical Science, Erode. The prospective nature of the study allows for the collection of data over a defined period, enabling researchers to track the drug interactions and therapeutic outcomes in real-time.

Study Period

The study was conducted from January to June 2023, allowing for a comprehensive collection of data over a six-month period. This timeframe ensures sufficient observations of drug compatibility in ICU settings, providing valuable insights into the practices and challenges faced by healthcare providers.

Study Site

The study was carried out at the Sudha Institute of Medical Science, Erode, which has a well-established ICU where patients receive critical care. The hospital setting was chosen due to its diverse patient population and its ability to provide a range of intravenous drugs for study. Approval from the Institutional Review Board of the hospital was obtained before proceeding with the study.

Study Method

The methodology of this prospective study involved data collection from ICU patients who were prescribed intravenous drugs. After receiving approval from the hospital's ethical committee, a specialized data collection form was developed to capture relevant patient and drug details. The form ensured systematic documentation of intravenous medications used and their therapeutic compatibility.

To assess the compatibility of the drugs, references such as Lexicomp, the manufacturer’s product information, and Trissel's Handbook of Injectable Drugs were consulted. These references helped determine the safe combination and administration of intravenous drugs to prevent potential drug-drug interactions or incompatibilities in the ICU setting.

Study Population

Sample Size Calculation

The sample size was determined using the formula:

$$n = \frac{t^2 \cdot p \cdot (1-p)}{m^2}$$

Where:

- t=10.827 (constant based on confidence level)

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- p=0.0175 (prevalence or proportion of incompatibility)
- m=0.052 (margin of error)

Therefore, the study aimed to include 75 ICU patients in the final analysis. This sample size was deemed adequate to provide statistically significant results on drug incompatibility in ICU prescriptions.

Study Criteria

Inclusion Criteria

The study included patients who met the following criteria:

- Prescriptions containing more than two intravenous drugs.
- Patients with an ICU stay of longer than 24 hours. This criterion ensured that only those who were critically ill and receiving continuous drug treatment were included, providing relevant data for assessing drug compatibility.

Exclusion Criteria

The following were excluded from the study:

- Drugs not available in the database used to assess incompatibility. If a drug's details were unavailable, it could not be included in the compatibility analysis, leading to its exclusion from the study.

Ethical Considerations

The study was approved by the Institutional Review Board of Sudha Institute of Medical Science. The ethical approval registration number is ECR/948/Inst/TN2018/RR-22, and the specific study approval number is SH/IEC/Approval-033/April 2023. Ethical considerations ensured that all data was collected with patient consent, and patient confidentiality was maintained throughout the research process.

Statistical Analysis

The collected data were analyzed using IBM SPSS 29.0.1.0 (171), a statistical software tool designed for social sciences research. The statistical methods used for analysis included:

- Descriptive Statistics: To summarize the basic features of the data.
- ANOVA (Two-Way Analysis of Variance): To assess the impact of two independent variables on the compatibility of intravenous drugs.
- Mann-Whitney U Test: To compare differences between two independent groups when the data are not normally distributed.

RESULTS:

Sociodemographic Characteristics of Study Participants

The study included 75 participants, with a slightly higher proportion of males (53.34%, n=40) compared to females (46.67%, n=35). Age-wise, the majority of participants were aged between 42 and 62 years (45.34%, n=34), followed by those aged over 63 years (32%, n=24). The younger age groups comprised 5.34% (n=4) in the 0-20 years category and 17.34% (n=13) in the 21-41 years category. In terms of lifestyle habits, 30.67% (n=23) of the participants reported smoking, and 21.34% (n=16) were alcohol users, with no participants reporting drug abuse. The average height of the participants was 158.7 cm ± 6.3 cm, while the average weight was 67 kg ± 9.7 kg. The average income was found to be 51,786.67 INR ± 13,091.

Occupational Status of Study Participants

The occupational status of the participants differed; however, most were involved in manual or trade-based professions. The highest numbers comprised farm laborers (10.66%, n=8) and network marketing associates (9.33%, n=7). Other professions held included those in the dying and cotton industry (8%, n=6) as well as handloom weavers (8%, n=6). Additional professional workers were painters (6.67%, n=5). There were 5.33% (n=4) participants who identified their occupations as conductors, tea masters, and tailors. There were a number of other occupations also reported, such as social workers, plumbers, electricians, mechanics, watchmen, and students, which made up 4% (n=3) of the total sample. The professions with more specialized fields included engineers, bankers, IT people, and business people, making up 2.67% (n=2) of the total sample. A few participants were engaged in diverse professions like journalism, teaching, or law enforcement, categorized as "Others" (5.32%, n=4).

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Medical Conditions of Patients Admitted to ICU

The reasons for admission into the ICU varied widely. The most common was coronary artery disease, with 16% (n=12) of the patients, followed by stroke at 13.33% (n=10). Other conditions of importance were acute appendicitis, 9.33%, n=7, and chronic obstructive pulmonary disease, 6.67%, n=5. Some of the other serious health conditions included acute inferior wall myocardial infarction, gangrenous cholecystitis, and urinary tract infections that accounted for 4% (n=3) of the patients. Other conditions, including chronic liver disease, hernia, reactive airway disease, and subacute intestinal obstruction, each represented 2.67% (n=2) of the patients. In addition, other isolated conditions included acute hydrocephalus, severe anemia, fibroid uterus, and TB, each reported among 1.33% (n=1) of the participants. Such conditions as pneumonia, seizure disorder, otogenic meningitis, among others, were similarly documented, with a 1.33% report among the participants. The fact that there are many such conditions shows that the study involved patients with different levels of complexity admitted to ICU.

Parenteral Medications Frequently Prescribed to ICU Patients

In the ICU, several parenteral medications were frequently prescribed to the study participants. The most commonly prescribed drug was pantoprazole, administered to 12.68% (n=52) of the patients, followed by ondansetron at 10.49% (n=43). Heparin (5.12%, n=21), paracetamol (4.88%, n=20), and ceftriaxone (3.66%, n=15) were also frequently prescribed. Other commonly used medications included furosemide and tramadol (2.93%, n=12 each), metronidazole, atropine, and cefixime (2.68%, n=11 each). Additionally, antibiotics like piperacillin & tazobactam (2.44%, n=10), and various corticosteroids, such as hydrocortisone (2.20%, n=9) and enoxaparin (2.20%, n=9), were frequently prescribed. A range of other medications were also used, including diclofenac (1.95%, n=8), amoxicillin clavulanic acid, and levetiracetam (1.71%, n=7 each). There were also cases of more specialized treatments, such as meropenem, ranitidine, and esomeprazole (1.46%, n=6 each). Other drugs like torsemide, dexamethasone, and vitamin K appeared less frequently. Overall, the total number of parenteral prescriptions in this study was 410.

Therapeutic Incompatibilities Identified in ICU Orders

The study identified several therapeutic incompatibilities in the orders of ICU patients. The most common was the paracetamol and ondansetron combination, which occurred in 14.7% (n=17) of patients, with a reduced analgesic effect of acetaminophen caused by the antiemetic effect of ondansetron. Tramadol and ondansetron were also responsible for a considerable 7.82% (n=9) cases in which enhanced serotonergic effect of serotonergic drugs were reported. The most frequently reported interaction was between paracetamol and tramadol. In 4.34% (n=5), the absorption of paracetamol was reduced due to paracetamol and tramadol. Combinations like furosemide and hydrocortisone (2.60%, n=3) caused hypokalemia, and furosemide and insulin (1.73%, n=2) increased blood glucose by reducing the effect of insulin. Other notable incompatibilities included heparin and tenecteplase (1.73%, n=2), which increased the risk of bleeding, and amoxicillin-clavulanate and ranitidine (0.86%, n=1), where ranitidine decreased the serum concentration of amoxicillin. A total of 115 incompatibilities were identified, which emphasizes the necessity of close monitoring and adjustment of drug combinations to avoid adverse effects.

TABLE 1: DISTRIBUTION OF PATIENTS WHO WHERE EXPERIENCED THERAPEUTIC INCOMPATIBILITIES DURING ICU STAY (N=49)

Incompatible drug combinations	Symptoms/Events	No. of Patients	Percentage of patients(%)
Tramadol+Ondansetron	Diaphoresis	9	18.6
Levofloxacin+Ondansetron	Bradycardia	5	10.2
Tramadol + Paracetamol	Increased body temperature	5	10.2

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Ondansetron+Metoclopramide	Decreased heart rate	4	8.16
Amikacin+Diclofenac	Increased serum creatinine	4	8.16
Cefoperazone sulbactam + Furosemide	Increased serum creatinine	4	8.16
Furosmide + Hydrocortisone	Hypokalemia	3	6.12
Insulin+ hydrocortisone	Hyperglycemia	3	6.12
Tramadol + Buscopan	Unconscious	2	4.08
Furosemide + Tramadol	Increased blood pressure	2	4.08
Levofloxacin+Dexamethasone	Knee and elbow pain	1	2.04
Heparin+Tenecteplase	Gum bleeding	1	2.04
Torsemide+Hydrocortisone	Decreased potassium level	1	2.04
Furosemide + Fentanyl	Increased blood pressure	1	2.04
Fentanyl+ketamine	Difficulty in breathing	1	2.04
Nitroprusside+Furosemide	decreased blood pressure	1	2.04
Atropine+Glycopyrrolate	Urinary retention	1	2.04
Pheniramine+Metaclopramide	Drowsiness	1	2.04
TOTAL		**49**	**100**

Medical Conditions and Causes of Extended ICU Stay on Account of Drug Interactions

A 27 patients had a prolonged ICU stay due to drug interactions. Different medical conditions were contributing to this extended period of stay for the patients. For those with coronary artery disease, the causes were bradycardia, potassium levels being decreased, and gum bleeding. For those with stroke, the complications ranged from decreased potassium levels, hyperglycemia, and knee-elbow pain. Those with acute inferior wall myocardial infarction had bradycardia, peripheral tremors, and decreased blood pressure. Other conditions like chronic liver disease, hernia, reactive airway disease, and chronic kidney failure caused problems like increased blood pressure, bradycardia, and increased serum creatinine. The patients with chronic obstructive pulmonary disease became unconscious, while those with acute appendicitis had hand tremors, decreased GFR, and diaphoresis. Subacute intestinal obstruction caused diaphoresis and drowsiness, whereas ureteric calculus triggered sweating and breathing problems. Additionally, peripheral tremors are caused due to UTI, Parkinson's disease, and C5-C6 disc prolapse with a consequent progressive pain and increase in serum creatinine. Urinary retention due to opioid poisoning.

TABLE 2: DISTRIBUTION OF INCOMPATIBLE DRUG COMBINATIONS AMONG TWO STUDY GROUPS

Drug combinations	**No.of patients experienced therapeutic incompatibility with prolonged ICU stay (N=27)**	**Percentage of patients (%)**	**No. of patients experienced therapeutic incompatibility with no prolonged ICU stay (N=22)**	**Percentage of patients (%)**
Tramadol+Ondansetron	4	14.81	5	22.73
Amikacin+Diclofenac	3	11.11	2	9.09
Levofloxacin+	3	11.11	2	9.09

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Ondansetron				
Tramadol + Buscopan	2	7.41	0	0
Tramadol + Paracetamol	2	7.41	3	13.64
Furosemide + Tramadol	2	7.41	0	0
Furosmide + Hydrocortisone	1	3.7	2	9.09
Insulin+ hydrocortisone	1	3.7	2	9.09
Ondansetron+ Metoclopramide	1	3.7	3	13.64
Levofloxacin+ Dexamethasone	1	3.7	0	0
Heparin+Tenecteplase	1	3.7	0	0
Torsemide+ Hydrocortisone	1	3.7	0	0
Furosemide + Fentanyl , Fentanyl + Ketamine	1	3.7	0	0
Nitroprusside+ Furosemide	1	3.7	0	0
Atropine+Glycopyrrolate	1	3.7	0	0
Pheniramine+ Metaclopramide	1	3.7	0	0
Cefoperazone sulbactam + Furosemide	1	3.7	3	13.64
TOTAL	**27**	**100**	**22**	**100**

Distribution of Study Groups Based on Economic Status

The distribution of patients in the study groups based on economic status was assessed using the Modified Kuppusamy Scale. Out of the first group of 27 patients, 22.22% came under the upper middle-class category, 70.37% under the lower middle-class category, and 7.41% under the upper lower-class category, with none in the upper or the lower economic classes. In the second group of 22 patients, 9.09% were classified as upper middle class, 72.73% as lower middle class, and 18.18% as upper lower class, with no patients in the upper or lower economic classes. There was a highly significant difference in economic status between the two groups in the lower middle class (p=0.0002), with no significant difference in the other classes (p=0.0631).

Cost of Illness Analysis for Patients with Prolonged ICU Stay Due to Therapeutic Incompatibility

The cost of illness analysis for patients with prolonged ICU stays due to therapeutic incompatibility was conducted for 22 patients. The analysis revealed the average costs for monitoring, management, and indirect expenses associated with various drug combinations. For *Tramadol+Ondansetron*, the average monitoring cost was 1500 INR, with no management cost and an indirect cost of 1960 INR, totaling 17,300 INR for 5 patients. *Ondansetron+Metoclopramide* had a monitoring cost of 450 INR, a management cost of 50 INR, and an indirect cost of 1960 INR, totaling 14,145 INR for 3 patients. *Cefoperazone Sulbactam+Furosemide* incurred monitoring costs of 950 INR, management costs of 44 INR, and indirect costs of 1960 INR, totaling 8862 INR for 3 patients. *Tramadol+Paracetamol* had monitoring costs of 700 INR, management costs of 86 INR, and indirect costs of 1960 INR, with a total of 8238 INR for 3 patients. The combination of *Amikacin+Diclofenac* resulted in monitoring costs of 950 INR, management costs of 224 INR, and indirect costs of 1960 INR, totaling 6268 INR for 2 patients. *Levofloxacin+Ondansetron* incurred a monitoring cost of 450 INR, a management cost of 50 INR, and an indirect cost of 1960 INR, totaling

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4920 INR for 2 patients. *Furosemide+Hydrocortisone* led to monitoring costs of 400 INR, management costs of 95 INR, and indirect costs of 1960 INR, totaling 4910 INR for 2 patients. Lastly, *Insulin+Hydrocortisone* had monitoring costs of 150 INR, management costs of 150 INR, and indirect costs of 1960 INR, totaling 4520 INR for 2 patients. Overall, the total cost for all 22 patients amounted to 69,163 INR, with an average monitoring cost of 7950 INR, management costs of 1168 INR, and total indirect costs of 15,680 INR.

Average Cost of Treatment Based on Socioeconomic Classification

The average cost of treatment was evaluated for two groups based on the socioeconomic classification. For the upper-middle economic class, the average cost was 30,631 INR for the first group (N=27) and 3,730 INR for the second group (N=22), with a p-value of 0.0313, which was considered to be significant. The average treatment cost of the lower-middle class was 27,759 INR in the first group and 3,072 INR in the second group, and had a p-value of 0.0108, indicating significant difference also. The upper-lower class had an average cost of 29,240 INR in the first group and 3,141 INR in the second group. There were no patients in the lower socioeconomic class group, and no treatment cost was recorded for them.

DISCUSSION:

The study reveals that males (53.34%) were more likely to be admitted to the ICU than females (46.67%), a finding which is in contrast with other studies like Modra L et al., (2021), where females represented the majority of ICU admissions.[8] The most common medical conditions leading to ICU admissions were gastrointestinal disorders (24.01%), cardiac disorders (21.33%), and neurological conditions (18.65%), which is consistent with studies by Yang K.,(2022) although the latter study focused on cerebral vascular accidents and cardiovascular diseases.[9] Inj. Pantoprazole (12.68%) was the most commonly prescribed parenteral drug, which is consistent with its wide usage in ICU settings for the treatment of GI disorders. Therapeutic incompatibilities were also brought to light, and Paracetamol & Ondansetron (16.67%) was the most common followed by other drug combinations such as Ondansetron & Metronidazole (8.82%) and Tramadol & Ondansetron (8.82%), which is in line with findings from studies by Stevens AJ et al., (2014), regarding other common drug interactions in ICUs.[10]

The patients who experienced therapeutic incompatibilities had a significantly longer ICU stay, with average stays being notably higher for those with drug interactions. This is consistent with the study by Cristiano Moura et al., where the prolonged ICU stays due to drug interactions were reported.[11] Most therapeutic incompatibilities identified in this study were moderate in degree (82.5%); this finding is concordant with that of Aline Teotonio Rodrigues et al.,(2015) who also identified moderate interactions to be the most prevalent in ICUs.[12] The socioeconomic impact of therapeutic incompatibilities was evident, as patients from lower middle-class backgrounds (70.37%) experienced longer ICU stays and higher treatment costs, a finding that matches trends observed in studies by Khwannimit B et al. regarding the financial burden of ICU care.[13,14] The total cost for patients having a prolonged ICU stay because of the interaction of drugs was ₹731,827, in contrast to the ₹69,163 spent by patients who had no prolonged stay, furthering the economic burden caused by drug interactions in the ICU setting.[15] The study in its whole essence stresses that careful medication management must be done in ICUs to avoid therapeutic incompatibility, lower the health costs, and ensure proper clinical outcomes, especially among lower socio-economic patients.

CONCLUSION:

This research indicates that therapeutic incompatibilities have a major effect on patient outcomes and the costs of healthcare in an ICU setting. The statistics obtained indicate that 53.34% of the men and 46.67% of the women had been admitted to the ICU within the period under investigation, with most (45.34%) aged 41-65 years old. Therapeutic incompatibilities were found in several drug combinations, with the most common being Tramadol & Ondansetron (16.67%). These interactions caused several adverse effects, including diaphoresis (20%), hypokalemia (7.5%), and decreased heart rate (7.5%).

The study also shows that patients who had drug interactions stayed longer in the ICU, with 55.1% of these patients staying for 4-7 days. The total cost of drug interactions in patients with prolonged ICU stays was approximately ₹731,827, compared to ₹69,163 for those

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without prolonged ICU stays. This reflects an additional cost of ₹405,000 for patients with prolonged stays, indicating the financial burden of drug interactions. Furthermore, patients from lower middle-class socioeconomic backgrounds (70.37%) experienced the highest financial burden, as ICU care is often unaffordable for those in this category. Overall, the findings stress the importance of minimizing therapeutic incompatibilities through careful medication management and monitoring. Reducing drug interactions can improve clinical outcomes, shorten ICU stays, and reduce the overall cost of care, especially for economically vulnerable patients. This study underscores the need for healthcare providers to implement stringent protocols for drug administration in ICUs to prevent adverse drug events, improve patient safety, and reduce the financial burden on healthcare systems.

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