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Intravenous Drug Incompatibilities in the Intensive Care Unit- A Review

Reshma Ramesan[1], Dhanya Dharman[2]
[1.] *Sixth year Pharm D student,Ezhuthachan college of Pharmaceutical Sciences,Marayamuttom,Neyyattinkara,Trivandrum,Kerala,India*
[2.] *Assisstant Professor,Department of Pharmacy Practice*
reshmasr96@gmail.com

Abstract
In intensive care unit, intravenous (IV) therapy is preferred over oral therapy for a faster therapeutic action. IV therapy is complex and error prone, requiring strategies to reduce the risk and complications. Once injected, reversing the action is not possible unless an antidote exists. 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 the change of solution color, precipitation, or turbidity. Incompatibility occurs in vitro, which differentiates it from real drug interactions that occur in vivo. Medication errors such as wrong drug, dose, diluents, and cross-contamination errors with IV therapy further lead to death and harm to the patient. This is a narrative review of physical and chemical IV drug incompatibilities and explores the preventive strategies for the same.

INTRODUCTION

The clinical condition of hospitalized patients often requires intravenous drug therapy, with potential exposure of patients to several risks and harms. The complexity of intravenous drug therapy, drug administration in particular, is the major cause of such problems. Intravenous medication administration is a complex procedure involving several steps, and is therefore prone to error.(1)In critical care, the majority of medications (>70%) are administered parenterally for faster action or due to patient's inability to swallow oral medications.It is known that many patients will receive an average of 10 different medications in multiple doses during a single admission.(2)
The Intensive Care Unit (ICU) presents substantial patient safety challenges.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. 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]
From various studies,it has been reported that about 18.6% of the total medication errors (MEs) belong to the category physicochemical incompatibility. 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 change of solution color, precipitation, or turbidity. 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.(3)
Drug incompatibilities can lead to reduced drug activity or inactivity, the formation of a new toxic or nontoxic active ingredient, increased toxicity of one or more of the involved drugs, and organoleptic changes.(4) Numerous factors should be considered before concurrently administering two or more drugs to reduce the risk of incompatibility. The use of multilumen catheters might allow different intravenous drugs to be administered separately but simultaneously. Adjusting the drug administration schedules is also a key factor to be analyzed, as is whether the administration of a specific drug can be temporarily discontinued without compromising patient care while another medication is administered.(5) Two incompatible drugs can also be administered consecutively, which makes it important to flush the infusion line with a compatible fluid between each administration. Another way to minimize the risk of incompatibilities includes the use of electronic prescriptions with alerts regarding the possible incompatibilities between the drugs prescribed. Some studies have already demonstrated that computerized alerts can influence drug prescriptions and avoid possible adverse events.(6)
Drug incompatibility can be classified into
1. Physical incompatibility
2. Chemical incompatibility
3. Therapeutic incompatibility.

1.Physical incompatibility
As long as the concentration of a drug is less than its saturation solubility, it can be maintained in aqueous solution. Immediate precipitation of the drug from its supersaturated solution is not necessary. However, this may happen at any time. Variable and erratic precipitation time is exhibited by Trimethoprim-sulfomethoxazole, etoposide, etc.
Physical reactions of drugs usually refer to either phase separation or precipitation (e.g., after the dilution of alcoholic solutions) due to a change of the relationship between ionization and non-ionization and solubility.
The alteration may result in:
Synergism: Increase in the drug effectiveness, resulting in a greater combined effect than the sum of each drug acting independently.

Antagonism: Decrease in drug effectiveness, resulting in lesser combined effect of two or more agents than the sum of each drug acting alone

New effect: An effect that neither drug shows on its own (e.g., toxicity)

The pH-value and the buffer capacity (pKa value) of the parenterals are major factors resulting in physical interactions. Usually, the drug has the greatest influence on the pH of the solution infused. Several drugs are weak bases and are formulated as the aqueous soluble salts of the corresponding acids. Any change in the pH-value in the infusion tubing, for example, from the simultaneous addition of another drug, may result in the release of the bases from their salts. Such bases have low aqueous solubility and thus precipitate on pH change. Relative quantity of drugs added and their buffering capacity influences the process of precipitation. In the infusion tubing system, these kind of rapidly occurring pH dependent precipitation reactions can be identified. These precipitation reactions are visible and can be observed as crystals, haziness and turbidity. In ICU, precipitations based on drug incompatibilities are responsible for the most common particle formation. Reactions between drugs and plastic materials (adsorption effects) are one of the reasons for invisible physical incompatibilities. Due to this, the drugs become immobilized at the inner surface of infusion containers or infusion lines thereby lowering the concentration and severely decreasing the quantity of the drug administered to a patient.

2.Chemical incompatibility

In chemical incompatibility, the drug may undergo many chemical degradation pathways such as oxidation, reduction, hydrolysis, photolysis, or racemization. Chemical reactions can be perceived as turbidity, precipitation, and color changes. As an aftercome, the amount of the active drug decreases and/or toxic by-products form.

Hydrolysis is a common pathway of chemical decomposition. It involves an attack by water molecules on labile bonds resulting molecular changes. Examples include phosphate ester like hydrocortisone sodium phosphate hydrolyzes at acidic pH.

Oxidation and reduction: Steroids, tricyclic compounds, and phenolic drugs such as epinephrine undergo spontaneous oxidation. Displacement of aluminum from needles by cisplatin thus precipitates platinum steel.

Photolysis photodegradation: Drugs such as Amphotericin B, dacarbazine, and doxorubicin undergo degradation in the presence of light as a catalyst.

Racemization: Occurs in optically active drugs like epinephrine in which l-isomer is more active than d-isomer.

3.Therapeutic incompatibility

When drugs are administered concurrently, therapeutic incompatibility may occur resulting in undesirable antagonistic or synergistic pharmacological activity.

For example, the antibiotics chloramphenicol and penicillin are not compatible; as chloramphenicol antagonizes penicillin's antibacterial effects. Hence, penicillin should be infused at least 1 h before chloramphenicol.(6,7,8)

Mechanisms of incompatibility

Small concentrated volumes when mixed would elicit incompatibility problems rather than mixing in larger volume infusion bag. This occurs due to higher mutual drug concentration and greater potential changes in pH.

a)Precipitation of drugs on dilution

Some injections are formulated in non-aqueous solvents to dissolve poorly water-soluble substances in a small volume. In such cases, diluting the non-aqueous injection with saline or water many results in precipitation.

Diazepam is a classic example of this kind of mechanism. Diazepam is formulated as 5 mg/mL injection with vehicle composed of propylene glycol 40%, ethanol 10%, benzyl alcohol 1.5%, and water for injection. Dilution of diazepam may result in precipitation at some concentration. However, its sufficient dilution to below its saturation solubility results in stable solution. Morris in his study of "compatibility and stability of diazepam injection following dilution from IV fluids" reported that visible precipitation is produced in dilutions of 1:1–1:10.

Digoxin, lorazepam, phenytoin, amiodarone, phytomenadione, and clonazepam are other drugs which show solubility problems and are formulated in injection vehicles other than aqueous vehicles. Manufacture may sometimes recommend administering the drug undiluted.

b)Precipitation of drugs due to pH change on mixing

Aqueous solubility of drugs is enhanced by ionization of the molecule. For a Bronsted Lowry base, formulating as a low pH solution such as hydrochloride would enhance solubility. Bronsted-Lowry acids are formulated as sodium or potassium salt (high pH solution) to increase the aqueous solubility of the drug. Whenever there is a change in the pH toward the end of the scale, the proportion of ionized and unionized drug in solution will reduce and so does the water solubility of the drug.

An example of this category of drugs is furosemide. Furosemide 20 mg/2 mL solution is stable at a pH of 8.0–9.3. Altering the pH of the solution can result in precipitation of the drug especially when in acidic media. Furosemide precipitates on diluting with glucose 5% solution.

c)Ionic reactions forming insoluble substances

The salts of monovalent cations (sodium and potassium) are more soluble than their divalent cation salts (calcium and magnesium). When solutions containing calcium or magnesium ions are mixed, there is a material risk of forming insoluble calcium or magnesium salts.

Insoluble calcium sulfate is formed when calcium chloride 10% and magnesium sulfate 50% are mixed. It is imperative that mixing of drug salts of calcium or magnesium with carbonates, bicarbonates, phosphates, tartrates, and sulfates be avoided. Ceftriaxone forms insoluble ceftriaxone-calcium complex when mixed with calcium containing solutions including Hartmann's Solution (containing sodium lactate,potassium chloride, sodium chloride, and calcium dehydrate). When ceftriaxone sodium is diluted with Ringer's lactate, precipitation can occur in spite of alkaline pH of RL maintaining the ionized water-soluble form of ceftriaxone.

d)Denaturation of biological molecules

Variations in pH and osmolality would result in the degradation of biological substances such as blood products and insulin. Literature on the compatibility of insulin's and biological products exists. Newly marketed monoclonal antibodies, interferons and recombinant coagulation factors lack such compatibility data; hence, mixing of these with other drugs is not recommended.

e)Evolution of gas

On mixing of acidic drug solutions with a parenteral solution containing carbonate or bicarbonate, carbon dioxide gas evolves. This evolution of gas is normal in the reconstitution of many drugs like ceftazidime.(8)

Causes of incompatibility

Incompatibility generally occurs between:

•Drugs and inappropriate diluents
•Two drugs (drug-drug incompatibility)
•When these are mixed together 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 adjuvants such as stabilizer and solvent
•Drugs and materials of IV containers like PVC.(9)

Consequences of incompatibilities

The unintended precipitation and toxic products can cause negative aftercome for the patient. The consequence of incompatibility ranges from thrombophlebitis up to multi-organ failure. When an inactive entity is formed, it can lead to therapeutic failure. The severity of the damage caused by incompatibility depends on the patient's condition (age, weight, nature, severity of the disease, etc.) and the type of drug administered. Major consequences of incompatibility are listed below:

•Multi-organ failure
•Severe liver dysfunction
•Toxic shock
•Local embolus
•Myocarditis
•Respiratory difficulties
•Systemic allergic reactions
•Local allergic reactions
•Thrombosis
•Thrombophlebitis
•Phlebitis
•Local redness(10)

Incompatibilities regarding intravenous drug administration

Errors in the administration of intravenous drugs have been analyzed in a number of studies, with intravenous drug incompatibilities comprising one subgroup of these problems. Especially in intensive care, during which parenteral drug administration is often complicated by the fact that the number of the concurrently administered drugs exceeds the number of available infusion lines, intravenous drug incompatibilities represent a significant problem. Although the frequency of the incompatibilities does not seem particularly high, the substances found most frequently were often vital drugs like insulin, antibiotics, antiarrhythmics and catecholamines. Even a small decrease in the efficiency of these drugs can cause a significant impact on patients in ICUs.(10)

Intravenous access is usually limited and often need to have medications administered simultaneously through the same line. This is facilitated by a y-site connector where the medications mix in the lumen of the tubing for up to 1 min prior to being infused into the patient. Not all medications can be mixed together as all are not compatible with each other.[11] Incompatibility is an undesirable reaction that occurs between the drug and the solution, container or another drug. Administering incompatible medications together through the same line can result in negative consequences and even death in some extreme cases. The three incompatibilities associated with IV administration are physical, chemical and therapeutic incompatibility.(11)

Intravenous therapy presents a potential risk to patient safety with associated risks varying from minor complications to death. As more number of patients are becoming acutely ill, the numbers of patients requiring IV therapies are increasing. Maintaining the patient's vascular access throughout treatment is difficult because a number of complications including phlebitis, infiltration, extravasations, and infections may occur.[12] Complications increase hospital stays, duration of therapy, and can also put the patients at risk of other medical problems.(12)

The intensive care unit (ICU) presents substantial patient safety challenges. It is complex, pressing the need for high-risk decision making. This may lead to higher medical error rates. Furthermore, these patients may be prone to iatrogenic injury due to the severity of their illness and their need for frequent high-risk medications and interventions.(13)

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. The incompatibilities involving these drugs might be critical because they affect vital drugs such as sedatives, steroids, and antimicrobials.(13)

Midazolam is widely used in the ICU as the first-choice drug for the continuous sedation of patients subjected to invasive procedures.This drug requires increased caution in its preparation and administration because it is commonly associated with serious adverse events.(14)Corticosteroids have been used for more than 60 years as adjunctive treatments of infections to mitigate local and systemic inflammatory responses. These drugs are commonly used among critically ill patients, and a significant number of studies have demonstrated the benefits of using corticosteroids for patients in septic shock because they are associated with initial shock reversal, the mitigation of systemic inflammatory response indicators, and significant decreases in mortality.(15)

ICU patients receive injections and commonly require antimicrobial therapy. Approximately 20% to 40% of patients are estimated to receive antimicrobials to treat and prevent infections during hospitalization. The precipitation, inactivation, and change in stability caused by other drugs can reduce drug efficacy, leading to a low therapeutic index that is detrimental to antimicrobial therapy.(14,15)

Pharmaceutical intervention contributed to the prevention and reduction of the occurrence of incompatibility reactions because adherence to guidelines (66.2%) led to the administration of incompatible drugs via different routes, at different times, or both. Incomplete adherence to guidelines (22.0%) was attributed to situations when one or more drugs were not administered via the indicated route or when any of the suggested times of drug administration was not accepted. No cases of non-adherence to the guidelines were observed. By performing a pharmaceutical intervention in the form of guidelines, the pharmacy department contributed to patient safety and promoted the increased integration of the pharmacist into the multidisciplinary team.(16)

Adults admitted to intensive care units are subjected to a high rate of drug incompatibilities that might be related to the numerous intravenous drugs prescribed. Importantly, a significant number of untested drug combinations still exists, highlighting the need for additional studies on this subject to provide increased safety regarding intravenous drug administration.(16)

Drug incompatibilities most commonly found among some prescriptions analyzed

Drug incompatibilities
Hydrocortisone x Midazolam
Cefepime x Midazolam
Hydrocortisone x Vancomycin
Cefepime x Vancomycin
Omeprazol x Vancomycin
Calcium chloride x Hydrocortisone
Midazolam x Omeprazole
Phenytoin x Ranitidine
Phenytoin x Midazolam
Phenytoin x Noradrenaline
Hydrocortisone x Vitamin B1
Sulfamethoxazole-Trimethoprim x Vancomycin
Phenytoin x Fentanyl
Sulfamethoxazole-Trimethoprim x Fentanyl
Sulfamethoxazole-Trimethoprim x Hydrocortisone
Sulfamethoxazole-Trimethoprim x Ranitidine

(4)

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

Sl no	**Continuous infusion**	**Bolus dose**	**Effect / Result**
1	Meropenem	Pantoprazole	Precipitation
2	Clindamycin	Pantoprazole	Red precipitation
3	Piperacillin/Tazobactam	Pantoprazole	Precipitation
4	Metronidazole	Pantoprazole	Reddish brown discoloration
5	Meropenem	Ondansetron	White precipitation
6	Amikacin	Pantoprazole	Precipitation
7	Ceftriaxone	Ondansetron	Haziness with micro precipitation
8	Glycopyrrolate	Pantoprazole	Orange discoloration
9	Fluconazole	Pantoprazole	Haziness and micro-precipitation
10	Levofloxacin	Pantoprazole	Orangish-yellowish discoloration
11	Piperacillin/Tazobactam	Midazolam	White haze
12	Thiamine	Furosemide	Haze/Turbidity

(3)

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

Sl no.	**Infusion 1**	**Infusion 2**	**Effect/Result**
1	Paracetamol	Metronidazole	Turbidity
2	Meropenem	Acyclovir	Precipitation
3	Paracetamol	Acyclovir	Particulate formation
4	Meropenem	Calcium gluconate	Yellow color

(3)

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

Sl no	Bolus 1	Bolus 2	Effect
1	Ondansetron	Pantoprazole	Turbid precipitation+Yellow discoloration
2	Furosemide	Pantoprazole	Haze/turbidity
3	Ketorolac	Pantoprazole	Haze,Microparticulates,Yellow discoloration
4	Dexamethasone	Pantoprazole	Precipitation
5	Fentanyl	Pantoprazole	Haze and Microprecipitation

(3)

Pharmacist role in intravenous administration

The mission of the profession of pharmacy is to improve public health through ensuring safe, effective, and appropriate use of medications.(14) Clinical Pharmacist can play a significant role in nurse training as an effective method to reduce the rate of errors in the hospital. One obvious solution to aid in the process of DRPs could be considering pharmacy services in IV product preparation by implementing protocol prepared by Clinical Pharmacist and establishment of reporting error systems.(15)

Pharmacist role to provide expert advice on compatibility and stability for the use of multiple drugs if required for IV administration, update staff on new clinical practice guidelines and help to interpret guidelines as they apply to patients with advanced illness. Thus, permanent supervision and involvement of Clinical Pharmacist is important.(16)

CONCLUSION

Patients admitted to ICU are more prone to incompatibilities due to the high number of IV medications they are subjected to. Several studies show that a significant number of drug incompatibilities occurs in ICU. The occurrence of these incompatibilities can be prevented by adhering to proper medication administration techniques such as flushing the line using compatible fluid, through multi-lumen catheter, through multiple IV access, using in-line infusion filters, spacing of medication, or color coding system. Increased safety regarding IV administration of drugs is required as there is a significant number of untested drug combinations still exists, highlighting the need for additional studies on this subject. There is a large gap in terms of studies seeking to investigate how nursing staff could minimize incompatibilities. Hence, investments in the area of health-care professionals' training are essential. Predicting all incompatibilities may seem impossible, but their occurrence can be minimized by the active participation of CP in ward rounds, thus enhancing patient safety.

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