

Intravenous drug incompatibility in intensive care units - A comprehensive review

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Introduction

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.^[1] It is because most of the patients in the ICU are serious/terminally ill/and/or have multiple concomitant diseases.^[2] In ICU, 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.^[3] Effects such as thrombus formation, severe hypersensitivity reactions, and infections are likely to occur when the parenteral drugs are poorly prepared or administered.^[4]

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. Findings from this review are useful in addressing current practice challenges.

Keywords: Drug incompatibility, ICU, preventive strategies

Infusion therapy is associated with a high risk of causing harm for patients. Administration of IV medications may be associated with undesirable effects especially when administered in error.^[5] A medication error has the potential to harm the patient and may lead to lack of success in the therapeutic process. The errors may occur in manufacturing or compounding, relevant transcribing, dispensing, prescribing and administration of a medication, and monitoring of its effects.^[6] Medication errors such as wrong drug, dose, diluents, and cross-contamination errors with IV therapy further lead to death and harm to the patient.^[7] According to a study by Masoumeh *et al.*, in 2015, reported 262 cases (64.38%) of IV medication errors.^[8] In another study by Tissot *et al.* reported 18.6% of the total medication errors to be physicochemical incompatibility.^[9]

This is a narrative review of physical and chemical IV drug incompatibilities and explores the preventive strategies for the same. Findings from this review are useful in addressing current practice challenges.

Aim of narrative review

The aim of this research is to review:

- Incidence of IV drug incompatibility in ICU and their mechanism

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- Interventional methods helpful in preventing its occurrence
- Role of pharmacists in establishing interventions.

Background

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*.^[10]

Drug incompatibility can be classified into

1. Physical incompatibility
2. Chemical incompatibility
3. Therapeutic incompatibility.

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-sulfamethoxazole, 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, or 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.

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.

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.

Mixing solutions

There is a potential for incompatibility and consequent loss of activity of one or both drugs and hence mixing solutions of parenterals are not recommended. Nevertheless, some circumstances compel mixing of two or more parenterals in the same infusion bag, using the same syringe or at a Y-site where two or more IV lines meet. These compelling circumstances include:

- Limited venous access routes available for continuous administration of multiple drugs
- When multiple parenteral medications are to be administered within a short time.

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.

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.

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.

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.

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.

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.

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.

Consequence

The unintended precipitation and toxic products can cause negative aftereffect 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.^[11-17]

Preventive strategies

Patients hospitalized in ICU require multiple IV therapies. A common problem encountered is the limited venous access route complicating

the safe administration of the drug. Each drug should ideally have a different access route.

Drug incompatibility can cause harm to the patient and hence preventing it is important for the safe administration of drugs. The following preventive strategies are helpful:

Usage of multiple lumen catheter

Using separate catheter lumens can prevent contact between incompatible drugs. Using these multi-lumen catheters come at a greater cost compared to a single lumen catheter, due to a slight increase in the risk of infection. Furthermore, because catheter lumen number is lower than the number of parenteral infused, it is necessary to use a multiport manifold.^[18] Studies of the infusion of incompatible drugs through multi-lumen catheters have demonstrated that the staggered orifices of the multi-lumen catheter reduce the phenomena of drug incompatibility.^[19]

Use of these catheters is associated with underappreciated risk of serious and life-threatening complication ranging from mechanical complications to infectious or thrombotic.^[20] Mechanical complications are reported in 5–19% of patients, an infectious complication occurs 5–26%, and thrombotic complication occurs in 2–26% of patients with the central venous catheter.^[21]

Use of in-line infusion filters

Using in-line filters can prevent particle infusion when drug incompatibility result in precipitation. In-line filters have shown to completely prevent particulate infusion and hence improve safety of infusion therapy.

At present, two IV fluid filters are widely used

- 0.2 µm filters for crystalline solutions
- 1.2 µm filters for lipid-containing admixtures.

Furthermore, there is positively charged filters capable of retaining particles, air and microorganisms, and endotoxins.^[22]

Separate IV infusion by time and place is another strategy in preventing the incompatibility issue.

Flushing the IV line with a fluid compatible to the drug administered and the one following it is essential to avoid clogging of catheters and also to prevent the incompatibility.

The color coding system for drug pH was used in a Swiss hospital for 5 years, and this has made it possible to diminish the incompatible mixture risk from 15% to 2% with Y-site administration.^[23]

Methodology

Search strategy

Databases used in our search strategy included PubMed, Medline, and International Pharmaceutical Abstracts from 2000 to July 2018. Databases were searched using the terms “drug incompatibility in

ICU,” “pH and drug stability,” “physical incompatibility,” “chemical incompatibility,” and “Y-site.” Electronic drug compatibility databases such as Micromedex, King’s Guide, and Trissel’s tables were manually screened for additional data. Searches were limited to articles in English, German, and Spanish.

The findings from the search are presented as a narrative review.

Results and Discussion

Of the articles surveyed, the following articles met the selection criteria established by this review, such as incidence of drug incompatibility, common IV drugs involved in incompatibility, and preventive strategies for the same.

In the prospective cross-sectional study conducted by Marsilio *et al.* (2016) entitled “drug incompatibilities in the adult ICU” to identify physical and chemical incompatibilities among the IV drug administered in ICU. They observed that the most frequent incompatibility was between midazolam and hydrocortisone (8.9%) followed by hydrocortisone and vancomycin (5.2%). The most common incompatibility was between continuous and intermittent infusion (50%). They, thus, concluded by enforcing the role of the clinical pharmacist in a multidisciplinary team to reduce the undesirable IV drug incompatibility.^[24]

In another study, Nagaraju *et al.* (2015) carried out a prospective observational study on the “assessment of IV admixtures incompatibilities and the incidence of IV drug administration errors” in a tertiary care teaching hospital. They collected the data for a period of 6 months by chart review method and observed 28.94% incompatibility. Pantoprazole-furosemide (13.11%) combination occurred the most followed by Amikacin-pantoprazole (10.62%). They concluded that it important to make health-care professionals aware of compatibility problems, daily prescription review by a clinical pharmacist and providing unbiased information from reliable references could possibly prevent compatibility errors in the wards.^[25]

Lopez *et al.* (2014) in their study “physicochemical compatibility of high concentration drugs usually Y-site administered in ICU s” assessed the physical incompatibility of 83 binary mixture of drugs usually administered through Y-site and evaluated the chemical stability of the relevant mixtures. The study demonstrated the physical incompatibility of dopamine or dobutamine with methadone and midazolam and also methadone with midazolam and pantoprazole/esomeprazole. The study also demonstrated about the physical and pH compatibility of other common medications in ICU.^[26]

Ramanath and Hymavathi (2012) performed an observational prospective study on “assessment of IV admixtures in hospitalized patients of rural tertiary care teaching hospital” and found that incompatibilities consisted of 28.28% of the total combination of the drugs. Amikacin-ceftriaxone (25%) combination occurred the most followed by amikacin-pantoprazole (14%). They found that undocumented combinations constituted the major portion when compared to compatible, incompatible, and variable combinations. This study showed that clinical

pharmacist can play a pivotal role in the assessment in IV admixture thus reducing the IV incompatibility occurrence.^[27]

Neininger *et al.* in their study aimed to identify the IV drug combinations and evaluate the knowledge of physician and nurses. They identified incompatible drug administration in 10% of the 87 patients studied. They observed 26 incompatible pairs frequent being cefotaxime, pantoprazole, and vancomycin. They concluded that there was a knowledge deficit among the health-care personnel thus requiring urgent implementation of quality improvement strategies by the clinical pharmacists.^[28]

From the above studies, it is evident that pantoprazole, vancomycin, midazolam, and amikacin are the frequent medications involved in incompatibility in ICU. Pantoprazole, a proton-pump inhibitor is indicated for drug-induced gastrointestinal disturbances; Vancomycin, a glycopeptide antibiotic indicated for bacterial infections; Midazolam, for induction of sedation and anesthesia; and Aminoglycoside amikacin is given for various bacterial infections encountered in ICU.

From the data analyzed, it is apparent that incompatibility can occur at any time if the medications are not properly administered. When a number of medications is greater than IV access routes, one can use multi-lumen catheter, allowing infusion of more than one drug through the same line. In such cases, proper care must be in administering medications simultaneously.

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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