Drug Incompatibility

Risk Prevention in Infusion Therapy

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**Drug Incompatibility**

**Definition of incompatibilities**
Incompatibility is an undesirable reaction that occurs between the drug and the solution, container or another drug. The two types of incompatibilities associated with intravenous administration are physical and chemical [Josephson 2006, RCN 2005, Douglas et al. 2001].

**Definition of interactions**
A drug interaction describes the alteration of a drug effect due to the influence of another substance (i.e. drug, chemical substance, nutrition) resulting in a solution that is no longer optimal for the patient after the substances are mixed [Craven et al. 2007a, Josephson 2006, Douglas et al. 2001, Nemec et al. 2008].

**The difference between interactions and incompatibilities**
The preparation of intravenous drugs and solutions is accompanied with the risk of undesirable reactions of the drug interacting with other substances. In this context it is important to distinguish an incompatibility reaction from an interaction.

An interaction occurs inside the body and therefore cannot be seen. In contrast to the interaction, an incompatibility reaction occurs inside a fluid container or infusion line and is usually visible. This text will focus on drug incompatibilities associated with IV therapy.

**The two types of incompatibilities**
1. Physical reactions
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 relation between ionization and nonionization and solubility [Newton 2009].

The alteration may result in
- **Synergism**
  Increased drug effectiveness, as the combined effect is greater than the sum of each drug acting independently
- **Antagonism**
  Decreased drug effectiveness, as the combined effect of two or more agents is less than the sum of each drug acting alone
- **New effect**
  An effect that neither drug shows on its own (e.g. toxicity)
Fig. 1a: Chemical precipitation of Midazolam (turbidity) and Ketamin (particle formation) [Riemann et al. 2005].

Fig. 1b: Physical precipitation of Midazolam as a result of an unfavorable pH medium [Riemann et al. 2005].
Drug Incompatibility

1. Physical reactions continued ...

The pH-value and the buffer capacity (pKa value) of the IV solutions and the drugs used are major factors responsible for physical interactions [Newton 2009].

The situation in an infusion regimen is specific to the combination of drugs and solution used. Usually, the drug has the greatest influence and therefore defines the pH-value of the solution infused. Many drugs are weak bases, present as the water soluble salts of the corresponding acids. Changes in pH-value in the infusion tubing, e.g. from simultaneous addition of another drug, may release the bases from their salts. Because of the low aqueous solubility of such bases, particles may precipitate (Fig.1). The process of precipitation is influenced by the relative quantity of the drugs added, as well as their buffering capacity. These pH-dependent precipitation reactions are usually very rapid and can be identified within a few centimeters in the infusion tubing system. They can visibly be observed as crystals, haziness or turbidity (Fig.1+2) [Newton 2009]. Precipitations based on drug incompatibilities are responsible for the most common particle formation seen in complex ICU infusion lines [Schröder 1994].

Further invisible physical incompatibilities are reactions between drugs and plastic materials (adsorption effects). This leads to the drugs becoming immobilized at the inner surface of infusion containers or infusion lines and so lowers the concentration and drastically decreases the quantity of the drug administered to a patient [Trissel 1996].

2. Chemical reactions

A chemical incompatibility means that the drug is chemically degraded, due to oxidation, reduction, hydrolysis, or decomposition. Chemical reactions can manifest themselves through turbidity, precipitation and color changes.

As a consequence, the amount of the active agent decreases and / or toxic by-products form [RCN 2005, Douglas et al. 2001, Höpner et al. 2003].
Fig. 2a: Physical incompatibilities of Diazepam. Picture by courtesy of F. Schröder, Pharmacist Bremen, Germany.

Fig. 2b: Precipitation of Midazolam (Turbidity). Picture by courtesy of F. Schröder, Pharmacist Bremen, Germany.
### Causes

Incompatibilities of drugs can occur between

- drugs and inappropriate IV solutions as diluent
- two drugs (drug-drug incompatibility) when they are
  - mixed together, e.g. within the same infusion line (simultaneous infusion) and/or IV container
  - administered one after the other, but within the same infusion line
- drugs and adjuvants (preservative, buffer, stabilizer, solvent)
- drugs and materials of IV containers (e.g. PVC) or medical devices, which can concern the nature of the material used and/or reactions at the inner surface (e.g. adsorption)


### Examples of drug-drug incompatibilities

[Josephson 2006, Höpner et al. 2003]

<table>
<thead>
<tr>
<th>Incompatible drugs in combination with any other drug</th>
<th>Drugs with limited compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Alprostadile</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Doxaprame</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>Glycerol trinitrate</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Milrinon</td>
</tr>
<tr>
<td>Theophylline derivatives</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>Sodium nitroprusside</td>
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</tbody>
</table>
Causes

Incompatibilities of drugs can occur between drugs and inappropriate IV solutions as diluent two drugs (drug-drug incompatibility) when they are mixed together, e.g. within the same infusion line (simultaneous infusion) and/or IV container—drugs and adjuvants (preservative, buffer, stabilizer, solvent)—drugs and materials of IV containers (e.g. PVC) or medical devices, which can concern the nature of the material used and/or reactions at the inner surface (e.g. adsorption) [Trissel 1996, Giki et al. 2000, Newton 2009].

Drugs with limited compatibility

- Alprostadile
- Clonidine
- Dobutamine
- Dopamine
- Doxapram
- Epinephrine
- Glycerol trinitrate
- Milrinon
- Norepinephrine
- Sodium nitroprusside

Fig. 3: Main causes of incompatibilities in standard IV therapy.
Drug Incompatibility

Consequences

Consequences for the patient

- damage from toxic products
- particulate emboli from crystallization and separation
- tissue irritation due to major pH changes
- therapeutic failure

The unintended presence of precipitation and toxic products can cause various negative consequences for the patient. This can range from thrombophlebitis up to multi-organ failure. The reduction or elimination of the active drug can lead to a therapeutic failure. The extent of the damage mainly depends on the patient’s condition (age, weight, nature, severity of the disease etc.) and on the type of drug administered. Consequences of physicochemical drug incompatibilities are particularly severe in neonate and pediatric patients [Höpner 2007].

There is little published scientific information about the frequency of drug incompatibility reactions. In one study, incompatibility was investigated in a pediatric intensive care ward showing that 3.4% of drug combinations were incompatible and thus potentially dangerous [Gikic et al. 2000]. A life threatening nature was found for 26% of incompatibilities in an intensive care unit (ICU) by Tissot et al. [2004]. Another survey collected 78 different medication regimes and found 15% with incompatibility reactions [Vogel Kahmann et al. 2003]. Taxis and Barber [2004] reported that in the ICU clinical incompatibilities can contribute to 25% of medication errors. Further publications showed that, depending on the ward type, up to 80% of IV drug doses were prepared with the wrong diluent [Cousins et al. 2005, Hoppe-Tichy et al. 2002].
Drug Incompatibility

Financial impact

Adverse effects of drug incompatibilities extend periods of patients’ hospitalization and the total costs for hospitals. Severe respiratory complications caused by toxic drug-drug interactions may lead to an additional cost for the healthcare provider of up to 56,670 € per single case.

Risk related costs for the healthcare institution

A cost evaluation of the risk can be done by assigning costs to their related clinical treatment and resulting extended length of stay. The cost can be calculated using the average daily cost [Gianino 2007, Bertolini 2005] of the expected clinical treatment. Fig. 4 shows the results of such a calculation for selected examples of complications.

Conclusion

The prevention of adverse drug events due to drug-drug interactions can result in budget savings for the healthcare provider. In the case of severe complications which require full ICU treatment for diverse days of hospitalization, a hospital may save between 7,556 € and 56,670 € per single case.

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**Fig. 4:** Estimation of possible additional costs as a consequence of complications caused by drug incompatibilities. In order to facilitate the attribution of each complication to the cost calculation, severity levels were introduced. RICU: Respiratory Intermediate Care Unit
Drug Incompatibility

Fig. 5: Assessment and planning of regimes to avoid mixing of drugs, which have to be administered separately.

Fig. 6: Compatibility checking using available literature, databases, services and information material.

Fig. 7: Color coding and drug separation to prevent drug incompatibilities through a clear indication of the drug.
Preventive strategies

Dangerous incompatibilities can be prevented by

- a plausibility check regarding the SPC and available sources on compatibility information, also considering the material used for therapy (e.g. diluent, IV container, IV lines) and the infusion regimen (Fig. 5)

- individual labeling for each drug preparation (including drug, concentration, patient name) (Fig. 7)

- consistently checking alternative modes of administration and/or using multi-lumen catheters (Fig. 6)

- separating the drug doses by time and place. This can include the rinsing of the infusion system with a neutral IV solution prior to the application of another drug (Fig. 5) [Craven et al. 2007b, RCN 2005, Riemann et al. 2005, Höpner et al. 2003, Vogel Kahmann et al. 2003, Hoppe-Tichy et al. 2002]

Furthermore, in-line filters can reduce influx of particles which result from incompatibilities. Moreover, they can be used to monitor physical and chemical incompatibilities. In-line filters are able to retain solid particles of at least 0.2 µm [Schröder 1993, Schröder 1994]. As a consequence, the filter may block. This is not a malfunction of the filter, but should initiate a check of the medication in order to eliminate any incompatibility.
Drug Incompatibility

**Ecoflac® plus**
The state of the art IV solution container that offers safe and convenient application of all IV procedures from drug admixture to drug delivery. Container based incompatibilities are prevented by a special polyethylene container material which is:
- Chemically inert.
- Toxicologically safe
- Free from plasticizers, additives and other compounds.
- Free from substances that may potentially migrate into the finished preparation.

**ConComp®**
Free database on drugs compatible with Ecoflac® plus.
- Offers information on interactions between certain drugs, carrier solutions and container materials.
- Offers overview of scientific literature on drug compatibility with the container.

**Intrafix® SafeSet Neutrapur® (PVC free)**
Prevention of interactions between certain drugs and material:
- These infusion lines may be used with drugs which are not recommended to be applied with PVC material, e.g. Taxol.
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Omniflush®
Prefilled flush syringe for safe and convenient flushings with saline solution.

Certofix® Multilumen Catheters
Central venous catheters for high-level and versatile IV therapy.
Multilumen catheters prevent drug incompatibilities by
- Separate lumens (distal, middle, proximal) averting the mixing of solutions and drugs.
- Separate vents achieving an immediate dilution of the individual solution/drug in the blood, high enough to prevent further incompatibility reaction.

Intrapur® and Sterifix® Infusion Filters
A whole range of filters for safe infusion therapy.
- Retains solid particles and precipitations of drug incompatibilities preventing their influx into the organism.
- Functions like an indicator when filter blocks as a result of chemical or physical reactions.

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Drug Incompatibility

Literature


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The summarized scientific information in this document has been prepared for healthcare professionals. It is based on an analysis of public literature and guidelines. The intention is to give an introduction to the risks commonly associated with infusion therapy and to increase the awareness of healthcare workers to these kinds of problems. Due to its summary nature, this text is limited to an overview and does not take into account all types of local conditions. B. Braun does not assume responsibility for any consequences that may result from therapeutical interventions based on this overview.