MAIN POINTS

- What are drug incompatibilities?
- How frequent in the hospital?
- How can we prevent them?
- How can we treat them?
- What should you know?
MAIN POINTS

- What are drug incompatibilities?
- How frequent in the hospital?
- How can we prevent them?
- How can we treat them?
- What should you know?
CASE STUDY

- ICU patient with GVH (graft-versus-host disease)
- Central IV catheter, 3 lumen
- IV drugs infused **over 24h**: Nutriflex Lipid special, Nexium (1.6mg/ml), Sandimmun (1mg/ml) et Trandate (5mg/ml).
- Other drugs as **bolus ou short infusion**: Bactrim, Cancidas, Cellcept, Cymevene, Lasix, Solumedrol, Tazobac
- Reserve drugs: morphine, Perfalgan et Droperidol
- New drug: blood
WHICH PARTNERS?

Drug incompatibility

Environment
• Temperature
• Light

Material
• PVC (DEHP)
• Silicone
• …

Factors
• Concentration
• Time of contact
WHERE?

Drug incompatibility

From: KIK 2.1, BBraun, 2002
# WHAT KIND OF REACTIONS?

**Physico-chemical reactions:**
- Acid-base reactions (pH)
- Solubility changes
- Emulsion cracking
- Oxido-reduction
- ...

**Consequences**
- precipitates *(visible)*
- coloration *(visible)*
- gas formation *(visible)*
- pH change *(invisible)*
- ↓ drug concentration *(invisible)*

- Catheter occlusion
- Particles emboli *(renal, pulmonary)*
- ↓ therapeutic effect
- Toxic effect *(ex. peroxide)*

**Drug incompatibility**
INCIDENTS IN PATIENTS?

Drug incompatibility

Pulmonary Deposition of Calcium Phosphate Crystals as a Complication of Home Total Parenteral Nutrition

JAROL B. KNOWLES, M.D., GIL CUSSON, B.S., R.P.H., MARILYN SMITH, R.N., and MICHAEL D. SITRIN, M.D.

From the Nutrition Support Service and Clinical Nutrition Research Unit, Department of Medicine, University of Chicago, Chicago, Illinois

Pulmonary Deposition of Calcium Phosphate Crystals as a Complication of Home Total Parenteral Nutrition

ABSTRACT: Background: Pneumocystal respiratory failure and death occurred in two young adult females with pelvic infections. Autopsy revealed an amorphous material containing calcium obstructing the pulmonary microvasculature of each patient. Both patients received an identical total parenteral admixture (TPA) solution before their deaths. Methods: Infusion of TPA into an animal model was undertaken in an effort to reproduce the clinical effect. Laboratory investigation was also performed to isolate precipitate and identify the factors contributing to precipitation. Results: A noncrystalline precipitate containing calcium, phosphorus, and organic material was isolated from the TPA solution. Infusion of the formulation into healthy pigs resulted in sudden death within 4 hours. Alteration of the amino acid component, mix sequence, agitation technique, and mixing container influenced precipitate formation. Conclusion: Pulmonary embolization of a precipitate containing calcium phosphate resulted in the death of two patients. The pH of the amino acid component, transient elevation of calcium and phosphorus concentrations during mixing, and the lack of agitation during automated preparation of the formulation were identified as the etiologic factors producing the fatal precipitation. (Journal of Parenteral and Enteral Nutrition 20:81-87, 1996)

Case Report

Fatal Microvascular Pulmonary Emboli From Precipitation of a Total Nutrient Admixture Solution


From the Departments of Surgery, Pathology, Urology, and Clinical Investigation, Tripler Army Medical Center, Honolulu, Hawaii

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Case Report

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From the Departments of Surgery, Pathology, Urology, and Clinical Investigation, Tripler Army Medical Center, Honolulu, Hawaii

Total Parenteral Nutrition Associated Crystalline Precipitates Resulting in Pulmonary Artery Occlusions and Alveolar Granulomas

TERRY MCNEARNEY, M.D.; CHRISTOPHER RAJAI, D.O.; MICHAEL BOYARS, M.D.; JOHN COTTINGHAM, M.S., IV, and ABIDA RAQUE, M.D.

KEY WORDS: parenteral nutrition; crystalline precipitates; pulmonary artery occlusion; alveolar granulomas.

Crystal precipitation from total parental nutrition (TPN) and systemic embolization has been described in patients on TPN, including in the lung (1-4). This is a rare and unexpected complication of TPN (1). The following case reports illustrate the spectrum of this complication.

ACCIDENTS MORTELS SOUS CEFTRIAXONE (ROCÉPHINE® I.V.)

Des accidents rares mais graves, la plupart du temps évitables.

La ceftriaxone (Rocéphine®) est une céphalosporine de troisième génération utilisable par voie injectable (1). Sa longue demi-vie rend possible une seule administration quotidienne. Cet antibiotique est largement utilisé dans le traitement d’infections graves, particulièrement en pédiatrie. Ses effets indésirables sont le plus souvent bénins.

Nous avons signalé l’existence de précipitations biliaires (et rénales) résolutive (2). Deux types d’accidents rares mais graves ont par ailleurs été rapportés chez des patients traités par cet antibiotique.

Néonatologie : incompatibilité avec d’autres medicaments

Une lettre de l’Agence française du médicament (faisant suite à un courrier des laboratoires Produits Roche) a signalé trois décès et un accident grave chez des nouveau-nés hospitalisés en réanimation (3,5).

Ces accidents ont été imputés à un entre la c d’autres médecins recevaient ce concomitant entre la ceno de la zépine, aminoside, macrolide.

La lettre de se que « dar un précipité être visualisé et/ou a été n paracétamol rénale », et s recommandé ceftriaxon : voir séparément, mélanges antibiotique à camétiens ou contaminant du il ne nous sable d’obteni

sions sur les cas rapportés. On peut noter que dans le dictionnaire Vidal, ces pré-

Intravenous Ceftriaxone and Calcium in the Neonate: Assessing the Risk for Cardiopulmonary Adverse Events

John S. Bradley, MD*, Ronald T. Wason, PharmD†, Lucile Lee, MD,‡ Simret Nembhard, MD, MPH§

*Rady Children’s Hospital San Diego, San Diego, California; †Office of Surveillance and Epidemiology and Office of New Drugs, Office of Antimicrobial Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland; ‡Office of Maternal, Reproductive, and Human Development, Center for Biology Evaluation and Research, US Food and Drug Administration, Rockville, Maryland

The authors have indicated they have no financial relationships relevant to this article to disclose.

What’s known on this subject

The package insert for ceftriaxone was changed August 2009 to recommend the co-administration of calcium with calcium-containing intravenous solutions.

What this study adds

This case reported to the FDA and the FDA/ARS database search were provided and discussed to provide clinicians the basis for these new precautions.

ABSTRACT

OBJECTIVES Unintended reports regarding potentially serious adverse drug reactions in neonates and young infants are reported to the Food and Drug Administration, leading to changes in the package label for ceftriaxone. This report describes and summarizes the reported cases that led to safety concerns regarding the concurrent administration of intravenous ceftriaxone and calcium in this age group.

METHODS Nine reported cases were assessed. The Food and Drug Administration Adverse Event Reporting System database was searched for potential drug interactions in patients who were receiving concomitant ceftriaxone and calcium therapy.

RESULTS Eight of the reported 9 cases (7 were ≤2 months of age) represented possible or probable adverse drug events. There were 7 deaths. None of the cases were reported from the United States. The dosage of ceftriaxone that was administered to 4 of 6 infants for whom this information was available was between 150 and 200 mg/kg per day. The rate of occurrence of these serious adverse drug reactions cannot be accurately determined from available data.

CONCLUSIONS The concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and young infant may result in a life-threatening adverse drug reaction. Contributing factors for infants in this report may include the use of ceftriaxone at dosages higher than those approved by the Food and Drug Administration, intravenous “push” administration, and administration of the total daily dosage as a single infusion. Pediatrics 2009;123:609–613

PEROXIDES

Toxic Hydroperoxides in Intravenous Lipid Emulsions Used in Preterm Infants

Harold J. Helbok, Paul A. Motchnik, Bruce N. Ames

ABSTRACT

The unsaturated fatty acids that make up a large component of the lipid emulsion Intralipid are highly susceptible to peroxidation, and the products of this reaction could explain the toxicity that has been associated with the administration of some emulsions. Lipid peroxidation produces hydroperoxides, which can alter arachidonic acid metabolism or react to form organic free radicals, which then stimulate a cascade of damage to endogenous lipids. The lipid hydroperoxides and their breakdown products are also mutagens and carcinogens. To determine the degree of lipid peroxidation in Intralipid, we measured the lipid hydroperoxide content of three lots of 20% Intralipid using high-performance liquid chromatography with chemiluminescence detection. The average concentration was 290 ± 29 μmol/L (SEM) lipid hydroperoxides (n = 15), a large portion of which was made up of trilinoleate derivatives. Measurements made on Intralipid samples collected from the end of the intravenous tubing after a 20-hour infusion cycle were not significantly different from measurements made on newly opened bottles. The lipid hydroperoxide content of some lipid emulsions may represent a clinically significant risk to premature infants, particularly those with preexisting lung disease.

Helbok H et al. Pediatrics 1993;91;83-7
# pH AND DRUGS

<table>
<thead>
<tr>
<th>Acidic drugs</th>
<th>Basic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>low pH &lt; 7</td>
<td>high pH &gt; 7</td>
</tr>
<tr>
<td>Amiodarone (Cordarone®) pH = 4</td>
<td>Aciclovir (Zovirax®) pH = 11</td>
</tr>
<tr>
<td>Adrenaline pH = 3</td>
<td>Cotrimoxazole (Bactrim®) pH = 10</td>
</tr>
<tr>
<td>Dobutamine (Dobutrex®) pH = 3</td>
<td>Furosemide (Lasix®) pH = 9</td>
</tr>
<tr>
<td>Midazolam (Dormicum®) pH = 4</td>
<td>Ganciclovir (Cymevene®) pH = 9</td>
</tr>
<tr>
<td>Morphine HUG pH = 3.5</td>
<td>Omeprazole (Antra®) pH = 9</td>
</tr>
<tr>
<td>Vancomycine (Vancocin®) pH = 3</td>
<td>Phenytoin (Phenydan®) pH = 12</td>
</tr>
</tbody>
</table>
ACIDIC AND BASIC DRUGS

To be put in solution, **salts** of active substances are used:
- An acid is soluble in a basic solution → drug solution is basic
- A base is soluble in an acidic solution → drug solution is acidic

Don’t mix or infuse on Y-site acidic with basic drug solutions!

from KIK 2.1, BBraun, 2002
# SOLVENT (DILUENT)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>pH</th>
<th>Appropriate for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 5%-20%</td>
<td><strong>pH = 4.0 - 6.0</strong></td>
<td>amiodarone, amphotericine B</td>
</tr>
<tr>
<td></td>
<td><strong>pH = 7.0 - 7.5</strong></td>
<td>aciclovir, phenytoin, furosemide</td>
</tr>
<tr>
<td>NaCl 0,9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Be careful with solvent pH!

From: KIK 2.1, BBraun, 2002
HEPARIN FLUSHING

Solvent:
NaCl 0,9% + heparine 20 UI/ml!

heparine + caspofungine ➔ precipitation

Ask careful what has been added to the solution!
**SOLUBILITY**

« Pastis effect »

Co-solvent and/or adjusting pH can increase the solubility of drugs in solution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiodarone</td>
<td>Cordarone®</td>
</tr>
<tr>
<td>paracetamol</td>
<td>Perfalgan®</td>
</tr>
<tr>
<td>esomeprazole</td>
<td>Nexium®</td>
</tr>
<tr>
<td>phenytoin</td>
<td>Phenyldan®</td>
</tr>
<tr>
<td>clonazepam</td>
<td>Rivotril®</td>
</tr>
</tbody>
</table>

polysorbate (tween)  
mannitol, phosphate, NaOH  
NaOH, EDTA  
glycofurol-75, EDTA  
propyleneglycol, acetic acid

Dilution of drugs ➔ dilution of co-solvents ➔ pH change ➔ **Risk of precipitation**!
COMPLEXATION

Formation of insoluble calcium-ceftriaxone complex

No administration of calcium and ceftriaxone by the same IV line!

Neonates: no calcium infusion if ceftriaxone has been administered (48h wash out period)!
LIPID EMULSION

Increased risk of coalescence:

- ↓ pH
- ↓ conc. AA
- electrolytes with high valence (Ca\(^{2+}\), Mg\(^{2+}\), PO\(_4^{3-}\))

Lipid emulsion is not water!
LIPID EMULSION

Lipofundin or Disoprivan + Garamycine

- Phase separation over 24h

Drug incompatibility

Oil phase + fat soluble-dye (Sudan red III)
PHOTODEGRADATION

- Degradation of drug under light exposition (sun, phototherapy)
  - Store in the dark
    - Ex. furosemide, adrenaline, vecuronium
  - Protection during administration
    - nifedipine, isoprenaline, nitroprussiate
    - lipides (neonatology)
Cordarone and Light

Variation de concentrations obtenues pour différentes dilutions du lot D

- ≥ 5 mg/ml
- 0.6 mg/ml

CORDARONE AND LIGHT

- NICU and PICU: 15 mg*BW ad 50 ml
- Stability if conc. > 5 mg/ml (patients >15kg)
- But:
  - No 10 or 20 ml amber syringe on the market
  - Pediatric references: stable over 24h without light protection

HUG: No protection, even if conc. < 5 mg/ml
SORPTION

- Physical interaction between molecule and material (adsorption onto surface)
- Sorption ⇒ loss of drug

adsorption to PVC
- Ex: amiodarone, nitroglycerine, tacrolimus
- HUG:
  - Flexs Bioren and syringues BD in PP
  - Standard iv-lines in PVC
  - Connecting lines for syringes in PE

adsorption to in-line filter
- Ex. phenobarbital
LEACHING (DESORPTION)

- Leaching of DEHP from PVC by cosolvent
- DEHP: diethylhexylphthalate (plasticizer):
  - hepatotoxic, carcinogen, toxic for reproduction
  - friability of material, particles in solution
- Cosolvent: castor oil, PEG-35 castor oil, Cremophor, polysorbate 80
  - Ex: Taxol, Sandimmun, Prograf

DEHP-free material (NoDEHP)!
LEACHING

Increase with:
- Temperature
- Lipid content
- Contact time (storage)
- Amount of fluid

High – risk:
- Preterm neonates and critically ill patient
- IV therapy
- Parenteral and enteral feedings
- Ventilation
- Blood transfusion
- Long hospital stay, prolonged therapies

Schettler T. 2002

<table>
<thead>
<tr>
<th>Source of DEHP Exposure</th>
<th>Exposure (ng DEHP/kg body weight)</th>
<th>Unit</th>
<th>Total Exposure or Concentration in Product</th>
<th>Source</th>
<th>Tdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial ventilation in preterm infants (PVC respiratory tubing; not polyethylene)</td>
<td>NR</td>
<td>Hour (insulation)</td>
<td>0.001-4.2 ng</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neonatal blood replacement transfusions: short-term, acute</td>
<td>0.3 (0.14-0.72)</td>
<td>treatment period</td>
<td>NR</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Neonatal blood replacement transfusions: double volume short term, acute</td>
<td>1.8 (0.8-3.3)</td>
<td>treatment period</td>
<td>NR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total intravascular volume</td>
<td>1.9</td>
<td>treatment</td>
<td>NR</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Extracorporeal oxygenation in infants</td>
<td>14-340</td>
<td>treatment</td>
<td>NR</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Extracorporeal oxygenation in infants</td>
<td>4.7-34.9</td>
<td>Treatment</td>
<td>NR</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Congenital heart repair (neonates)</td>
<td>1-6 hours</td>
<td>0.3-4.7 µg/mL</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV crystalloid solution</td>
<td>0.3</td>
<td>From tubing</td>
<td>NR</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total parenteral nutritional formula (TPN), with lipid</td>
<td>2.5</td>
<td>NR</td>
<td>3.3 µg/mL (concentration in TPN formula)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>TPN/IV tubing</td>
<td>5</td>
<td>day</td>
<td>10 mg/2-kg body/day</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Multiple IV Sources: packed red blood cells, platelet rich plasma, fresh frozen plasma, and medications</td>
<td>5</td>
<td>day</td>
<td>10 mg/2-kg body/day</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>0.0055-0.0165</td>
<td>Day</td>
<td>0.01-0.025 mg/kg (concentration in breast milk)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Infant formula</td>
<td>0.015</td>
<td>Day</td>
<td>0.004-0.04 mg/kg weight</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Infant formula</td>
<td>0.0087-0.035</td>
<td>NR</td>
<td>0.33-0.08 mg/kg dry weight</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported

* Tdose = ratio of Tdose to 0.6-2 mg/kg/day for parenteral exposures and 0.06 mg/kg/day for intestinal exposures. Tdose ratio = 1 imply that the Tdose has been exceeded for the given source of exposure.
MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
- How can we treat them?
- What should you know?
MEDICATION ERRORS

- Adult ward
  - $3\%^1$ incompatible drug combinations
- Adult ICU
  - $7.2 - 18.6\%^{2-4}$ incompatible drug combinations, $26.3\%^2$ potentially life-threatening, $29\%$ no information$^4$
- Pediatric ICU
  - $3.6\%^5$ incompatible combinations
- Neonatal ICU
  - $14.9\%^6$ incompatible combinations, $59.3\%$ no information

$^1$ Westbrook JI. BMJ Qual Saf 2011; doi10.1136/bmjqs-2011-000089
$^4$ Vogel Kahmann I et al. Anaesthesist 2003;52:409-12
PRIORITY FOR QUALITY IMPROVEMENT

Bertsche T et al. PWS 2008;30:907-15
MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
  - in the ward
- How can we treat them?
- What should you know?
TOOLS

- Evaluation by 2 pharmacists
- 40 drug pairs usually used in NICU and PICU
- Trissel’s as gold reference
TOOLS

Assessment ➔ interpretation

➔ adapted cross-tables (charts)
➔ pH- color code (Schaffhausen Model)

Main problems: - exhaustiveness
               - assessment of drug pairs
pH COLOR CODE

- Adult ICU in Schaffhausen (Switzerland) since 10 years


Tabelle 1
Beispiele der Farbzuordnung einiger Medikamente

<table>
<thead>
<tr>
<th>Rot</th>
<th>Blau</th>
<th>Gelb</th>
<th>Schwarz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalin</td>
<td>Furosemid</td>
<td>Imipenem/Cilastatin</td>
<td>Blutprodukte</td>
</tr>
<tr>
<td>Morphin</td>
<td>Heparin</td>
<td>Cefazolin</td>
<td>TPN</td>
</tr>
<tr>
<td>Acetylsalicylat</td>
<td>Insulin</td>
<td>Amoxicillin</td>
<td>Propofol</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Natriumbicarbonat</td>
<td>Spironolacton</td>
<td>Diazepam</td>
</tr>
<tr>
<td>u.s.w.</td>
<td>u.s.w.</td>
<td>u.s.w.</td>
<td>u.s.w.</td>
</tr>
</tbody>
</table>

Prevention: ward
pH COLOR CODE

Pharmacy ward

On IV-lines

pH COLOR CODE

- About 78 drug combinations (636 different drugs)

↓ Y-site infusion of potentially incompatible drugs

HUG NURSE EVALUATION

MATERIALS & METHODS
Assessment of two tools (fig.2) by 48 nurses in 5 units (PICU, adult and geriatric intensive care, surgery, onco-hematology) using a standardized form.

- Scientific accuracy
- Ergonomics
- Applicability
- Design
- Reliability

Evaluation by determining the compatibility of five drugs pairs (fig.2): rate of correct answers according to the Trissel’s Handbook on Injectable Drugs 15th ed, chi-square test.

Evaluation using visual analogue scales (VAS 0-10; 0 = null, 10 = excellent). Results are expressed as the median and interquartile range (IQR) for 25% and 75% (Wilcoxon rank sum test).

HUG NURSE EVALUATION

Fig. 3: Ergonomics

Fig. 4: Applicability

Fig. 5: Design

Fig. 6: Reliability

CHOICE OF NURSE TOOL

- Should be adapted to the hospital
  - Type of patients
  - Type of medications
  - Clinical pharmacist presence
  - Language
  - Computerization of prescription, electronic medical record

⇒ « Individualized » tool for each hospital
IN-LINE FILTERS

Potential difficulties for implementation

• at least two types of filters (0.2 and 1.2 µm)
• technical aspects (priming, flushing)
• aseptic risks
• no filtration for some products
• blocked filters

⇒ Teaching, operating procedures and follow-up are essential
Drugs incompatibility:

- Nexium® + Dormicum® + Morphine®
- Esomeprazole discoloration ± precipitation in acidic solutions

Prevention: ward
MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
  - in the hospital pharmacy
- How can we treat them?
- What should you know?
IN VITRO STUDY

Fig. 2 – Drug compatibility tests realised in the quality control laboratory

4 tests for each pair of drugs:
- 1:1 mix with agitation
- 1:4 mix with agitation
- 4:1 mix with agitation
- 1:1 mix without agitation (mixing an IV bag administration, where mixing is not necessarily homogeneous)

Fig. 3 – Visual incompatible drugs (left) or compatible drugs (right)

Fig. 5 – Evaluation of (in)compatibilities between drugs administered in the same IVL, based only on literature data (pink dotted bars) and after laboratory tests (purple streaked bars)

IN VITRO STUDY

Compatibility lipid emulsions and drugs

Granulometry
- mean size < 500 nm
- % globule > 5µm ≤ 0.4%

Zeta potential measurement
pH measure
Visual inspection (microscope)
## NUTRIFLEX LIPID SPECIAL

<table>
<thead>
<tr>
<th>DCI</th>
<th>Concentration tested</th>
<th>Y-site Compatibility with NPT / 1h</th>
<th>Y-site Compatibility with NPT / 4h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>417 UI/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>0.8 mg/ml</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Octreotide</td>
<td>25 µg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.5 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Cefepime</td>
<td>100 mg/ml</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Meropenemene</td>
<td>50 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Co-Amoxicilline</td>
<td>50 mg/ml (amox.)</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>5 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>10 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Vancomycine</td>
<td>10 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2.5 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2 mg/ml</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

# DISOPRIVAN

## Prevention:

**Pharmacy**

### Incompatible Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Appearance</th>
<th>pH</th>
<th>Zeta pot.</th>
<th>Glob. size</th>
<th>Total</th>
<th>Probable Incompatible Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin 50mg/ml (Amikin®)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>Atrivan 1mg/ml (HUG)</td>
</tr>
<tr>
<td>CaCO2 75mg/ml (CaCO2 HUG®)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>23</td>
<td>Gatifloxacin 50mg/ml (Rocophine®)</td>
</tr>
<tr>
<td>Gentamicin 60mg/ml (Garamycin®)</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>21</td>
<td>Ephegin HCL 10mg/ml (Bischel)</td>
</tr>
<tr>
<td>HCl 7.25% (Salza 6% 7.25% Brown)</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>Fluocacillin (Fluocar®)</td>
</tr>
<tr>
<td>MgSO4 100mg/ml (Bichse)</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>21</td>
<td>Meropenem 50mg/ml (Meronem®)</td>
</tr>
<tr>
<td>MgSO4 500mg/ml (Bichse)</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>23</td>
<td>Nitroglycerin 1mg/ml (Perilanti®)</td>
</tr>
<tr>
<td>Vancomycin 50mg/ml (Sandoz)</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td>26</td>
<td>Phenylephrin HCL 10mg/ml (Bicehol)</td>
</tr>
<tr>
<td>Dopamin 25mg/ml (Sintetica)</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>14</td>
<td>Thiapental 50mg/ml (fentanyl®)</td>
</tr>
</tbody>
</table>

### Probably Incompatible Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Appearance</th>
<th>pH</th>
<th>Zeta pot.</th>
<th>Glob. size</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalin 1mg/ml (Sintetica)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Ciprofloxacín 2mg/ml (Ciprocin®)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Dobutamin 5mg/ml (Fresenius)</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Salcin O (Hanseler)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Lidocaine 20mg/ml (Rapidocain®)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Phenytoin 50mg/ml (Phenydan®)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Suxazethonum 50mg/ml (Lytech®)</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Vecuronium 2mg/ml (Norcuron®)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Ganciclovir 50mg/ml (Cymeven®)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Metronidazol 5mg/ml (HUG)</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Milozol 5mg/ml (Dorific®)</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

---

PN: reduced risk of precipitation

Use of organic calcium and phosphates salts

MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
- How can we treat them?
- What should you know?
CATHETER RESCUE

Non–thrombotic catheter occlusions in pediatric patients:

Drug precipitates

Acidic drugs

0.2 to 1 ml
0.1 N HCl

Basic drugs

1 ml 0.1 N NaOH or Na-bicarbonate

Lipid Residue

0.55 ml/kg
70% ethanol, max 3 ml

Kerner J et al. JPEN 2006;30: S73-S81
MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
- How can we treat them?
- What should you know?
WHICH DRUGS?

- Always ALONE:
  - Blood and derivates: agglutination and hemolysis risks

- Be careful WITH:
  - Low and high pH: precipitation risks → crystal deposit in kidney, lung, liver
  - Drugs with co-solvent: precipitation risks → crystal deposit in kidney, lung, liver
  - Lipid emulsions: cracking risks → fat embolism

Reduce contact time to a minimum!
- Connexion near to the patient
# CASE STUDY: resolution

<table>
<thead>
<tr>
<th>Lumen 1 (nutrition)</th>
<th>Lumen 2 (basic pH)</th>
<th>Lumen 3 (acidic pH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nutriflex</td>
<td>• Nexium</td>
<td>• Trandate</td>
</tr>
<tr>
<td>• Sandimmun</td>
<td>• Cymevene</td>
<td>• Cellcept</td>
</tr>
<tr>
<td>• Bactrim</td>
<td>• Lasix</td>
<td>• Solumedrol</td>
</tr>
<tr>
<td>• Cancidas (stop Nutriflex)</td>
<td>• In-line filter 0.2 μm</td>
<td>• Tazobac</td>
</tr>
<tr>
<td></td>
<td>• Blood (stop Nexium for 1h, no filter)</td>
<td>• In-line filter 0.2 μm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reserve drugs</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

Hospital and clinical pharmacists can help!