Incompatibility of IV Drugs

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Definition

Drug Incompatibility refers to interactions between two or more substances which lead to changes in chemical, physical, therapeutic properties of the pharmaceutical dosage form.

Types of Drug Incompatibility

1. Therapeutic incompatibility

   modification of the therapeutic effect of one drug by the prior concomitant administration of another (Drug interactions).

2. Physical incompatibility

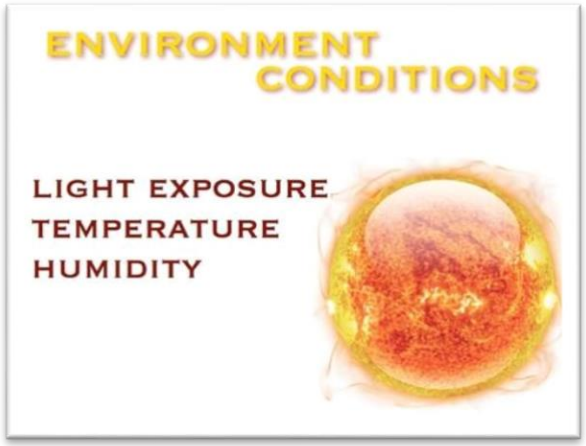
   Interaction between two or more substances which lead to change in color, odor, taste, viscosity and morphology (pharmaceutical incompatibilities).

3. Chemical incompatibility

   Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form.

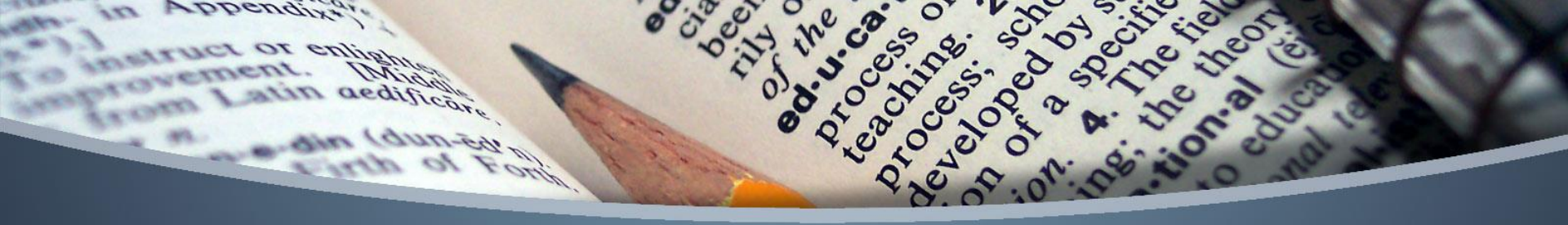
Physical Incompatibility

- Insolubility
  - Change in **pH**
  - Any change that may lead to precipitation of drugs and change in their properties.



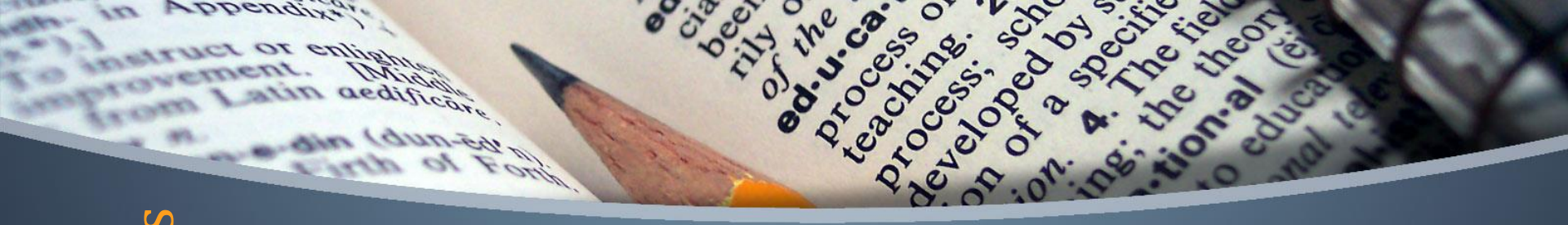
Chemical Incompatibility

- Oxidation
  - **Light** → photo-chemical reactions
  - **pH** : each drug has its ideal pH for stability. Any change in pH affect drug stability and may accelerate oxidation reaction.



- Physical incompatibilities result in visible (precipitate, color change, gas production) and invisible (sub-visible particles, variations in pH) reactions, and even in the absence of precipitate could result in a significant reduction in the amount of drug delivered to the patient.

- Chemical incompatibilities can lead to a decrease in drug delivery, drug degradation, and/or formation of toxic products.



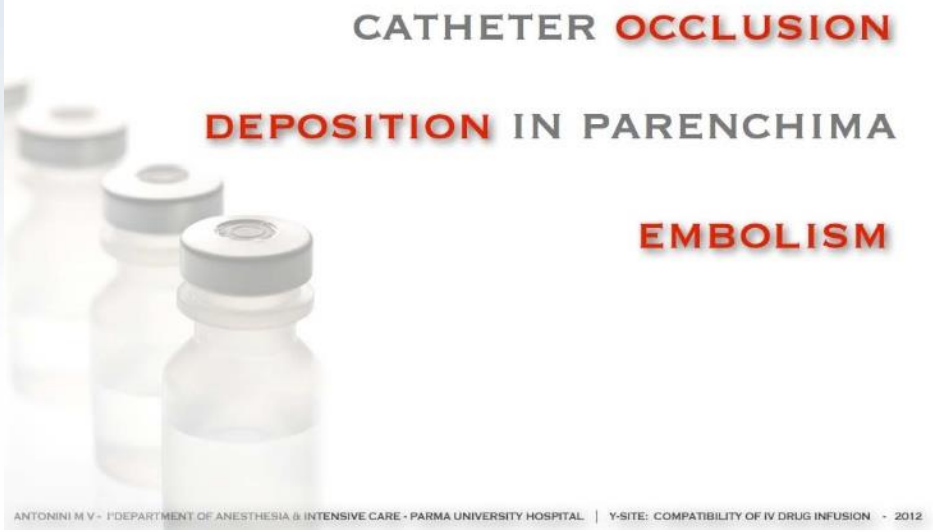
Mixing incompatible medications

- Mixing incompatible medications is a major IV medication error.
- Although critically ill patients usually have multiple central IV lines, several medications have to be infused simultaneously through the same lines.
- Investigations have shown that mixing an IV drug with the wrong diluents can occur in up to 80% of the cases.
- This is alarming especially in the ICU where 25% of the IV incompatibilities are highly significant and 26% are life-threatening.

انواع و ویژگی‌های فیزیکوشیمیایی محلول‌های تزریقی

IV Solution	Glucose (g/L)	Na (mEq/L)	Cl (mEq/L)	K (mEq/L)	Ca	Osmolality (mOsm/L)
Normal Saline (NS)	0	**154**	154	0	0	308
Ringer's Lactate (RL)	0	130	109	4	3	272
Dextrose Water, 5% (DW 5%)	50	0	0	0	0	278
DW5% in Saline (0.9%)	50	154	154	0	0	560
Half Saline (HS)	0	**77**	77	0	0	154
DW 3.33% + Saline 0.3%	33	51	51	0	0	270

COMPLICATIONS



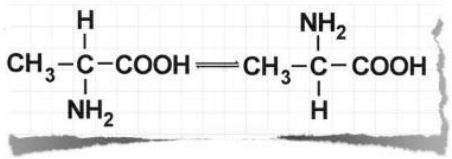
Reaction of IV medications when mixed together resulting in solutions that are no longer optimal for the patient.

- The stability is altered by physico-chemical reactions leading to decreased effectiveness of the drug or an increased micro-particles load leading ultimately to therapeutic failure, catheter occlusion or embolism.

CVC OCCLUSION

INVISIBLE REACTIONS

pH Δ



↓ A.P. **BIOAVAILABILITY**

↓ **THERAPEUTIC ACTIVITY**

TOXIC COMPOUNDS

COMPATIBILITY

IMPACT ON CLINICAL & NURSING PRACTICE

Results 33/820 (4%) co-infusions were documented as compatible without any restrictions. 212/820 (26%) drug co-infusions were compatible, but 196 of the 212 (93%) had restrictions on infusion fluid, concentration or contact time. 608/820 (74%) drug co-infusions in neonates have either been shown to be incompatible or have not been tested. Among those not tested, 163/486 (34%) entailed major differences in pH level which could cause co-infusion instability.

Conclusion There is a lack of data on compatibility for the majority of drugs used for co-infusions in neonates. [...] Our results suggest that further studies on drug compatibility are needed to reduce possible ADRs and toxicity, and avoid precipitation and occlusion of infusion lines in critically ill neonates.

Compatibility of drug infusions in the NICU
Arch. Dis. Child. 2010; 95:9 745-748

When the dilution or mixing of the salt or ionized forms of organic drugs results in precipitation, the most likely cause is formation of the non-ionized drug forms.

Intravenous Ceftriaxone (marketed as Rocephin and generics) and Calcium drug-drug interaction

FDA received seven case reports of serious cardiopulmonary adverse events in neonates associated with precipitation of a ceftriaxone-calcium salt in the lung and/or kidneys. Six neonates died. [...]

Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions in any age group.

when ceftriaxone sodium is diluted in lactated Ringer's injection, precipitation can occur despite the alkaline pH of lactated Ringer's maintaining the ionized

water-soluble form of ceftriaxone.

The problem in this case is the formation of a poorly soluble calcium salt of

ceftriaxone, the ionized form of which is a divalent anion.

recent warning !

DRUG SAFETY: incompatibility of ceftriaxone and calcium

„The French drug agency reported on deaths of premature infants and neonates after the intravenous application of ceftriaxone and calcium.

Precipitates were found in lungs and kidney of the patients."

Ceftriaxone must not be infused simultaneously with calcium containing infusion fluids or IV drug solutions

Source: swissmedic online, Oct. 22nd 2006

Background Paroxysmal 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 nutrient admixture (TNA) solution before their deaths [...]

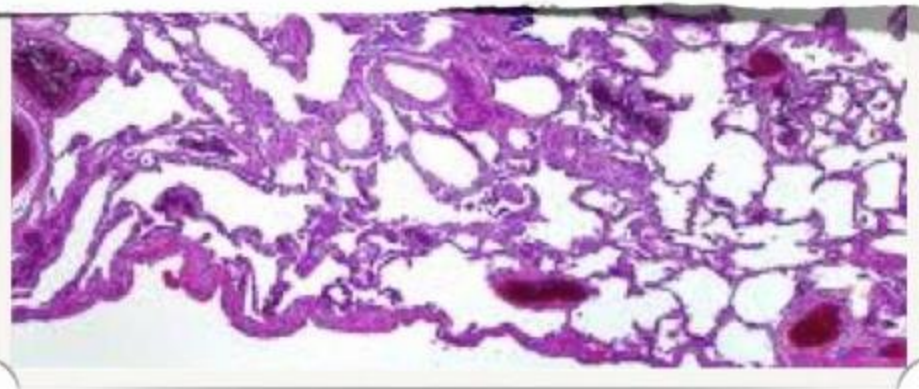
Conclusion Pulmonary embolization of a precipitate containing calcium phosphate resulted in the death of two patients.

Fatal microvascular pulmonary emboli from precipitation of a total nutrient admixture solution, JPEN J Parenter Enteral Nutr. 1996 Jan-Feb;20(1):81-7

FDA SAFETY ALERT:
Hazards of Precipitation Associated with Parenteral Nutrition

This is to alert you of a concern that precipitate formation in total parenteral nutrition (TPN) admixtures may present a life-threatening hazard to your patients.

The Food and Drug Administration has received a report from one institution of 2 deaths and at least 2 cases of respiratory distress, which developed during peripheral infusion of a three-in-one (amino acids, carbohydrate and lipids) TPN admixture. The admixture contained 10% FreAmine III, dextrose, calcium gluconate, potassium phosphate, other minerals, and a lipid emulsion all of which were combined using an automated compounder. The solution may have contained a *precipitate of calcium phosphate. Autopsies revealed diffuse microvascular pulmonary emboli* containing calcium phosphate. One literature report cites an adult case of subacute interstitial pneumonitis associated with calcium phosphate precipitates.[1]

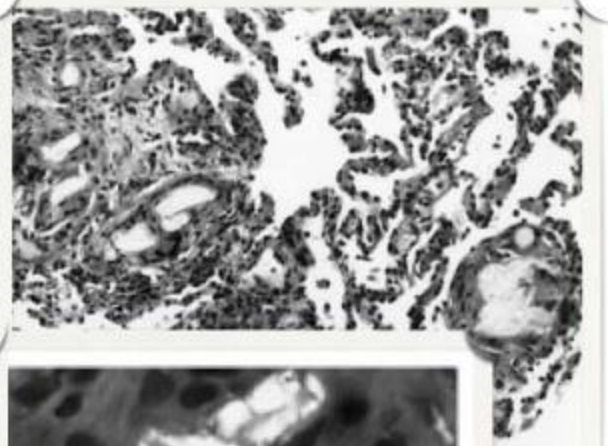


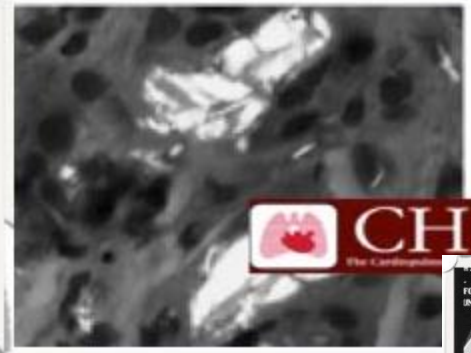
Microvascular Pulmonary Emboli Secondary to Precipitated Crystals in a Patient Receiving Total Parenteral Nutrition* : A Case Report and Description of the High-Resolution CT Findings

Jeremiah S. Reedy, MD; Janet E. Kuhlman, MD; and Marta Voytovich, MD

A patient with a history of a small-bowel transplant that was subsequently resected required total parenteral nutrition for nutritional supplementation. While receiving therapy, he developed chest tightness, shortness of breath, and fever. The chest radiograph showed bilateral reticulonodular opacities, and the high-resolution CT scan demonstrated diffuse, poorly marginated micronodular opacities in a miliary pattern. Pathology specimens obtained by transbronchial biopsy revealed amorphous material obstructing the pulmonary microvasculature. Microvascular emboli secondary to precipitated crystals is a potential complication of total parenteral nutrition. An awareness of the factors that influence crystal solubility may prevent adverse interactions in patients who require parenteral nutrition.

(CHEST 1999; 115:892–895)





Digestive Diseases and Sciences, Vol. 48, No. 7 (July 2003), pp. 1352–1354 (© 2003)

CASE REPORT

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

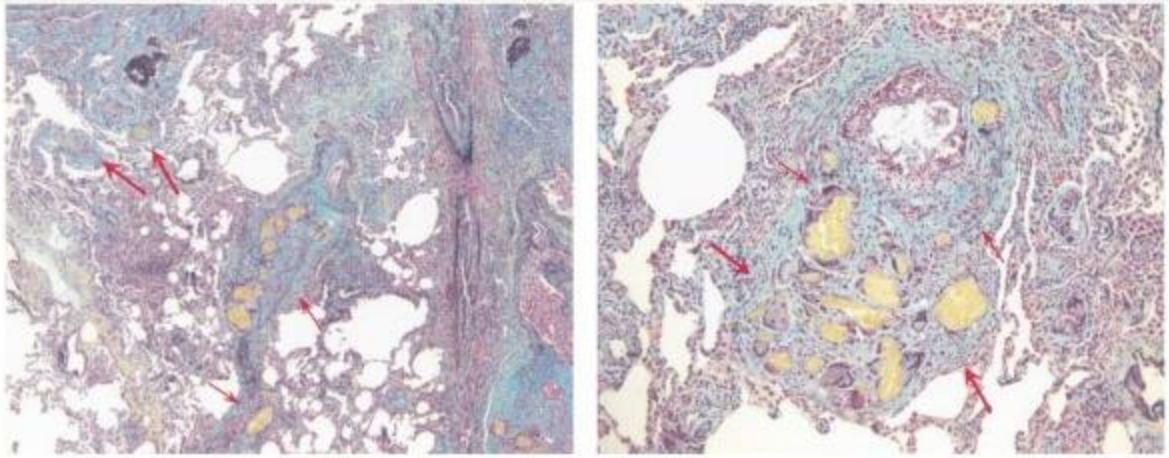


Fig 1. (A) Open lung biopsy of the lingula demonstrating organizing occlusions in pulmonary artery branches containing crystalline precipitates that appear yellow in the Movat stain. (thin arrows). Crystalline precipitates are also appreciated in the alveolar tissue (thick arrows). 40×, MOVAT pentachrome stain. (B) Open lung biopsy of the lingula demonstrating alveolar foreign body giant cell granulomas containing crystalline precipitates, from disruption of the vascular wall, noted by perturbation of the elastin stain (thin arrow). The granuloma is invading into the alveolar tissue (thick arrows). 100×, Movat pentachrome stain.

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

STEVEN E. HILL, MD†; LESLIE S. HELDMAN, MD‡; ELWIN D. H. GOO, PHARMD§; PAUL E. WHIPPO, DVM‖; AND JOSEPH C. PERKINSON, MD†

JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION 20 (1996)

Microvascular Pulmonary Emboli Secondary to Precipitated Crystals in a Patient Receiving Total Parenteral Nutrition: A Case Report and Description of the High-Resolution CT Findings

Jeremiah S. Reedy, Janet E. Kuhlman and Marta Voytovich

Chest 1999; 115;892-895

& DEVICES
MATERIALS

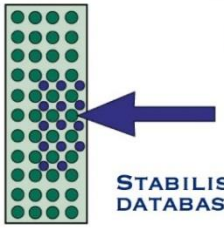
LEACHING

E.G. AMIODARONE &
PROPOFOL IN
PVC CONTAINER

STABILIS
DATABASE

ABSORPTION

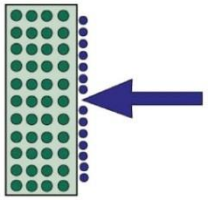
E.G. NIMODIPINE &
NYTROGLICERIN IN
PVC CONTAINER



STABILIS
DATABASE

ADSORPTION

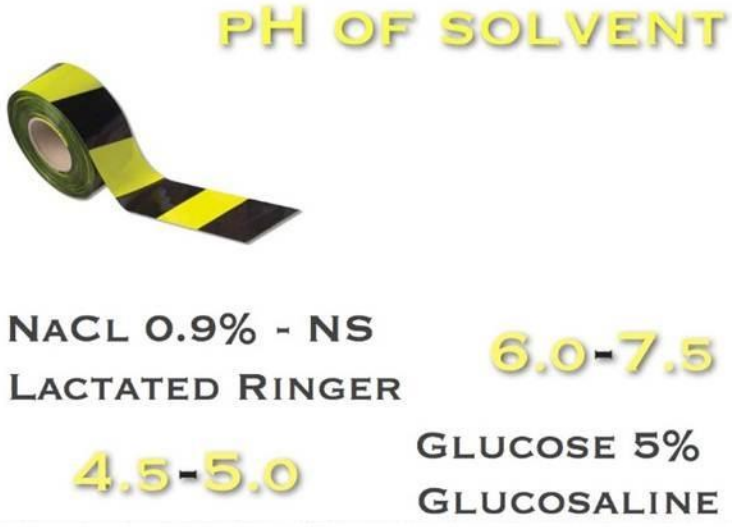
STABILIS
DATABASE



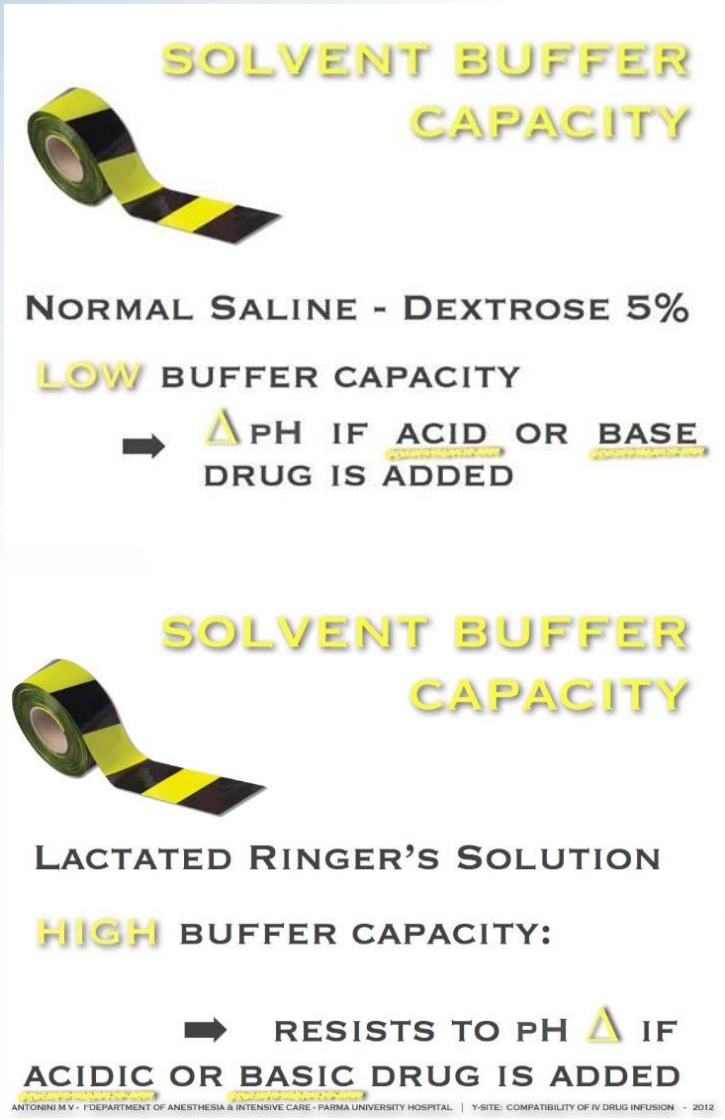
E.G. INSULINE IN
PVC-EVA-PE-GLASS
& HEPARIN SODIUM IN
PVC-GLASS CONTAINER

IV drug compatibilities based on the pH

The pH of solution was one of the compatibility measure used in the establishment of standard concentrations of medications commonly given by continuous infusion and prepared at the bedside.



Vilma Loubnan, Soumana C Nasser.
[Lebanese American University, Beirut, Lebanon]
A Guide on Intravenous Drug Compatibilities Based on Their pH.
International Journal of Comprehensive Pharmacy (IJCP) 2010; 1(5): 1-9.



Medications admixture into a solution could alter the pH to acidic or basic depending on the solution buffer capacity.

- Normal Saline (NS) and Dextrose 5% in water (D5W) solutions have low buffer capacity, so that the solution will turn acidic with the admixture of an acidic medication, and it will turn basic with the admixture of a basic medication.
- Lactated Ringer's (LR) solution has a high buffer capacity, so that when adding an acidic medication, the solution will either remain neutral or the pH will drop to a lesser extent than that observed with NS or D5W solution.

↑ pH > 8.0

AMINOPHYLLINE
AMOXICILLIN/CLAVULANATE
AMPICILLIN SODIUM
AMPICILLIN SODIUM/SULBACTAM SODIUM
FUROSEMIDE

↑↑ pH > 9.0 - 10.0

PHENYTOIN SODIUM
THIOPENTAL SODIUM
PANTOPRAZOLE SODIUM
OMEPRAZOLE SODIUM
LANSOPRAZOLE SODIUM
ESOMEPRAZOLE SODIUM
ACYCLOVIR SODIUM
GANCICLOVIR SODIUM
TRIMETHOPRIM/SULFAMETHOXAZOLE

CISATRACURIUM BESYLATE
DOBUTAMINE HCL
DOPAMINE & EPINEPHRINE HCL
ESMOLOL HCL
FENOLDOPAM MESYLATE
FLUMAZENIL
ISOPRENALINE HCL
MIDAZOLAM HCL
MORPHINE HCL
NOREPINEPHRINE BITARTRATE
ONDANSETRON HCL
PANCUROMIUM/ROCURONIUM/VECURONIUM BR
REMIFENTANIL HCL
SUCCINYLCHOLINE CL
VANCOMYCIN HCL

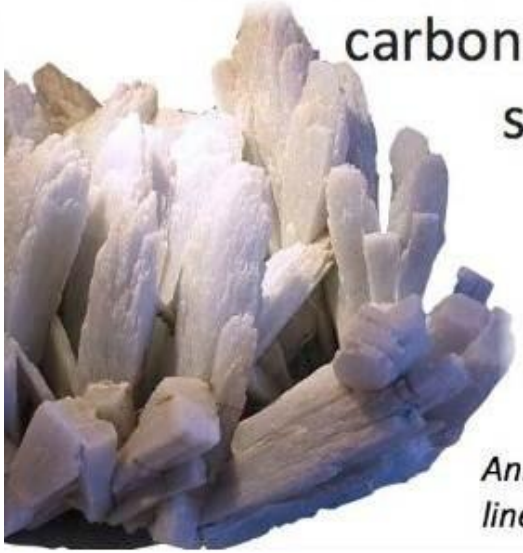
↓↓ pH

2.5-5.0

$MgSO_4 + CaCl \rightarrow CaSO_4$

INSOLUBILE!

The mixing of drug salts of calcium, and to a lesser extent magnesium, with phosphates, carbonates, bicarbonates, tartrates or sulfates should also be avoided.



Murney P, To mix or not to mix – compatibilities of parenteral drug solutions, Australian Prescriber; 2008 Aug; 4(31), 98-101

Anhydrite rock ($CaSO_4$ mineral) not so nice in CVC lines!

Hemolysis Associated with 25% Human Albumin Diluted with Sterile Water -United States, 1994-1998

[...] if sterile water alone is used as the diluent, the osmolarity (tonicity) of the albumin solution is reduced and may cause hemolysis in recipients. This report describes two of 10 episodes of hemolysis (one fatal) * among persons who received 25% human albumin diluted with sterile water and emphasizes that sterile water alone should not be used to dilute albumin.

Centers for Disease Control and Prevention, "Hemolysis Associated with 25% Human Albumin Diluted with Sterile Water - United States, 1994-1998,"MMWR Morbidity & Mortality Weekly Report, March 5, 1999, 48(8):157-1599

A 5% Glucose Infusion Fluid Provokes Significant Precipitation of Phenytoin Sodium Injection *via* Interruption of the Cosolvent Effect of Propylene Glycol.

Yoshinori Onuki,*[a] Mayumi Ikegami-Kawai,[b] Kazumi Ishitsuka,[a] Yoshihiro Hayashi,[a] and Kozo Takayama[a]

[a]*Department of Pharmaceutics, Hoshi University; and* [b]*Faculty of Pharmaceutical Sciences, Hoshi University; 2–4–41 Ebara, Shinagawa, Tokyo 142–8501, Japan.*

Received August 25, 2011; accepted October 31, 2011; published online November 4, 2011

The precipitation of phenytoin sodium injection provoked by mixing with infusion fluids renders its use in clinical practice difficult, as rapid intravenous (i.v.) push and i.v. infusion are supposed to be avoided. As some of its aspects remain unclear, this study tried to elucidate this precipitation mechanism. In particular, this study focused on the significant precipitation induced by glucose infusion fluid. The precipitation pro-

Chemical and Pharmaceutical Bulletin
Vol. 60 (2012) , No. 1 86

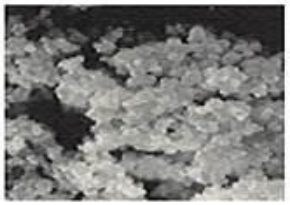
Dilution of injectable phenytoin by adding it to an infusion bag lowers its pH and therefore reduces its solubility resulting in precipitation of the drug. Glucose 5% infusion solution, which has a pH of 4.3–4.5, will precipitate phenytoin almost immediately.

Murney P, To mix or not to mix – compatibilities of parenteral drug solutions, Australian Prescriber; 2008 Aug; 4(31), 98-101

Parenteral nutrition (PN)

3 risk factors for incompatibilities with parenteral nutrition

- Precipitation of calcium with phosphate

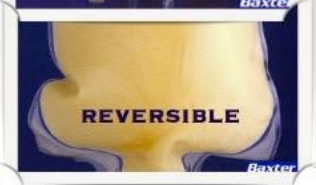


- Creaming/breaking of the lipid emulsion

- Addition/simultaneous application of drugs to/with the PN

FAT EMULSIONS

CREAMING



AGGREGATION

TG

COALESCENCE

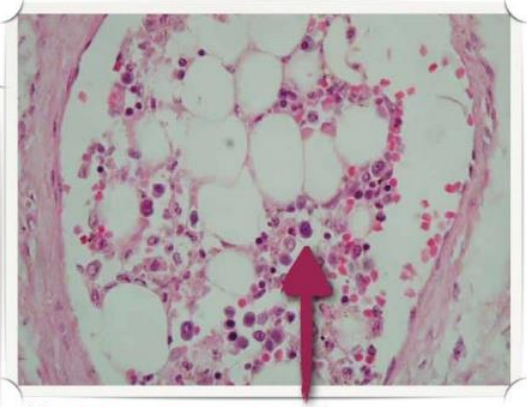
CRACKING

ANTONINI M V - I°DEPARTMENT OF ANESTHESIA & INTENSIVE CARE - PARMA UNIVERSITY HOSPITAL | Y-SITE: COMPATIBILITY O

LIPID EMULSIONS

FAT EMBOLISM

PHARMACIE.HUG-GE.CH



"CRACKING" PHASE SEPARATION

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incompatibility between drugs and PN

- drugs „commonly" added to PN admixtures

  eg. insulin, heparin, albumin

  4 criteria for addition:

  2. stable PN infusion rate
  3. pharmacokinetic profile supporting a 24h infusion
  4. stable dosage regimen over 24h
  5. documented physical/chemical stability over 24h

Lester LE et al. Am J Health-Syst Pharm 2006; 63: 1656-61

- drugs infused simultaneously with PN admixtures

  ⇒ precipitation, eg. calcium with ciprofloxacin

  ⇒ breaking of lipid emulsion, eg. with acyclovir

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FDA SAFETY ALERT:

Hazards of Precipitation Associated with Parenteral Nutrition

To: **Hospital Pharmacists**
Hospital Risk Managers
Hospital Nutritional Support Teams
Home Health Care Nutrition Support Services
Hospital Directors of Nursing
Home Care Pharmacists
Home Care Nurses
Physicians

April 18, 1994

This is to alert you of a concern that precipitate formation in total parenteral nutrition (TPN) admixtures may present a life-threatening hazard to your patients.

Example from the ICU

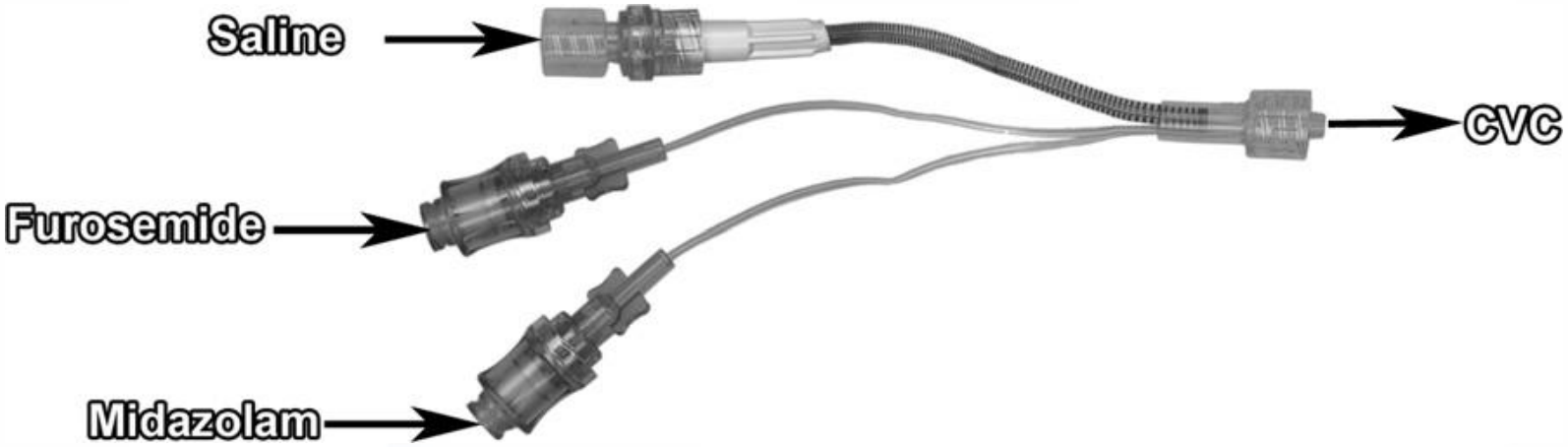
Patient with three-line CVC, IV drug therapy:

Continuous infusion:
- morphine
- midazolam
- clonidine
- norepinephrine
- TPN
- insulin
- heparin
- hydrocortisone

Short infusion/bolus:
- pantoprazole 40mg 1x
- clindamycin 900mg 2x
- ciprofloxacin 400mg 3x

Furosemide-Midazolam incompatibility

- Even in the absence of visible particles, precipitation of furosemide led to a drug loss estimated at between 10 % and 15 %.
- Furosemide is more impacted by interaction because the pH of the mixture is acid and this form is poorly soluble in an aqueous solution.
- Physical incompatibility between furosemide and midazolam leads to a significant reduction in drug delivered to the patient and may result in treatment failure.

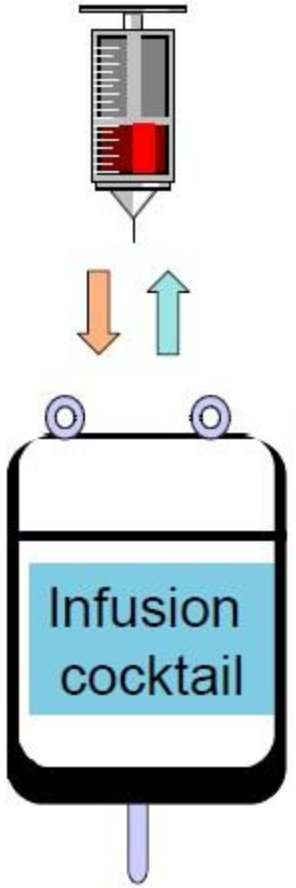


what can we do to prevent them ?

"is this combination of drugs compatible ?"

how to deal with such tasks

- what questions to ask
- where to look for compatibility data
- how to interpret compatibility data



avoiding incompatibility on the ward

- no combination of drugs in an infusion
  the more drugs, the higher the risk for incompatibility
- determination of 1 or 2 „standard cocktails"
  defined, standardised composition in a fixed infusion fluid
  Testing for compatibility !
  CAUTION change of manufacturer !
- saline solution 0,9% or dextrose 5% as infusion fluid
  CAUTION pH !
  avoid complex infusion fluids (Ringer, amino acid solutions)
- rapid switch to oral application of drugs

avoiding incompatibility in the ICU

- use of multi-lumen central venous catheters
- peripheral venous catheters for short time application
- minimising contact time (= reaction time)
- measures adapted to the wards´ needs
  according to available literatur data on compatibility
- standardising IV drug therapy
  - drug sortiment of well-known physical/chemical properties
  - check of stability/compatibility by the pharmacist

avoiding incompatibility in the ICU

measures adapted to the wards´ needs

- classification of drugs according to their pH
- implementation of a „colour code system" according to drugs´ pH and available literature on compatibility
  Vogel Kahmann I et al. Anaesthesist 2003; 52:409-412
- individual compatibility charts resulting from literature data and own testing
  Serrurier C et al. EJHPScience 2006; 12:96-99
  Wedekind CA, Fidler BD, Critical Care Nurse 2001, 21:45-51

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avoiding incompatibility with PN

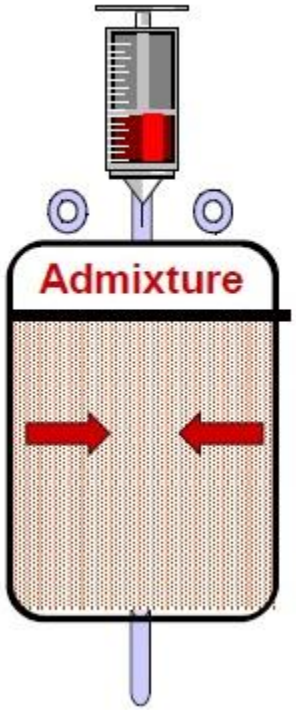
- never use parenteral nutrition for electrolyte therapy

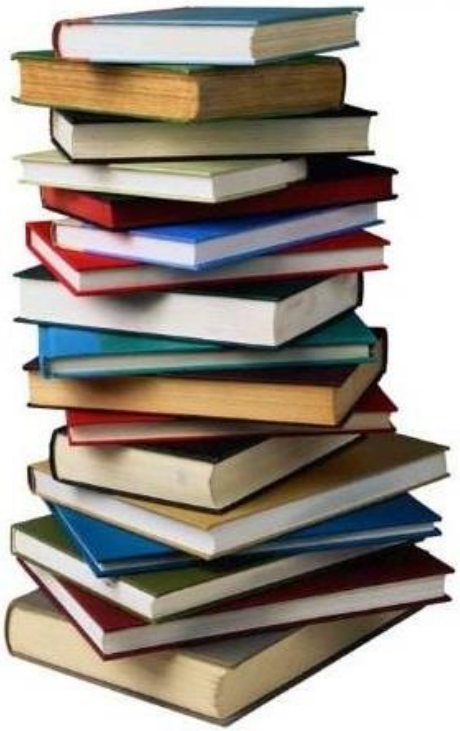
  keep to manufacturers´ recommendations

- add divalent cations (calcium, magnesium) and phosphate as organic bound salts (eg gluconate or glycerophosphate)

- no addition of drugs to PN

- no simultaneous application via Y-line





FDA

Lexicomp
Smart data. Better decisions.

MICROMEDEX
DRUG
INFORMATION

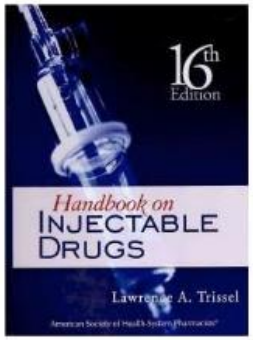
HUG
Hôpitaux Universitaires de Genève

PubMed

National
Library
of Medicine
NLM

AIFA

thériaque



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Stabilis

CHUV

KING® GUIDE
To Parenteral Admixtures®
current IV

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where to look for compatibility data ?

- manufacturer, product information

  provide very little information on compatibility (solvents)

- databases

  eg. KIK®, Stabilis®

- internet sites

  eg. www.rphworld.com

- reference books, literature

  eg. EJHP Science
  Trissel®, King Guide®, AJHP
  - mostly data from the USA