Hôpitaux Universitaires de Genève

Pharmacie

DRUG INCOMPATIBILITIES : definition, risks and management

Dre Caroline Fonzo-Christe

Pharmacie des HUG

Advanced Studies, Universität Basel

August 26st 2011

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?

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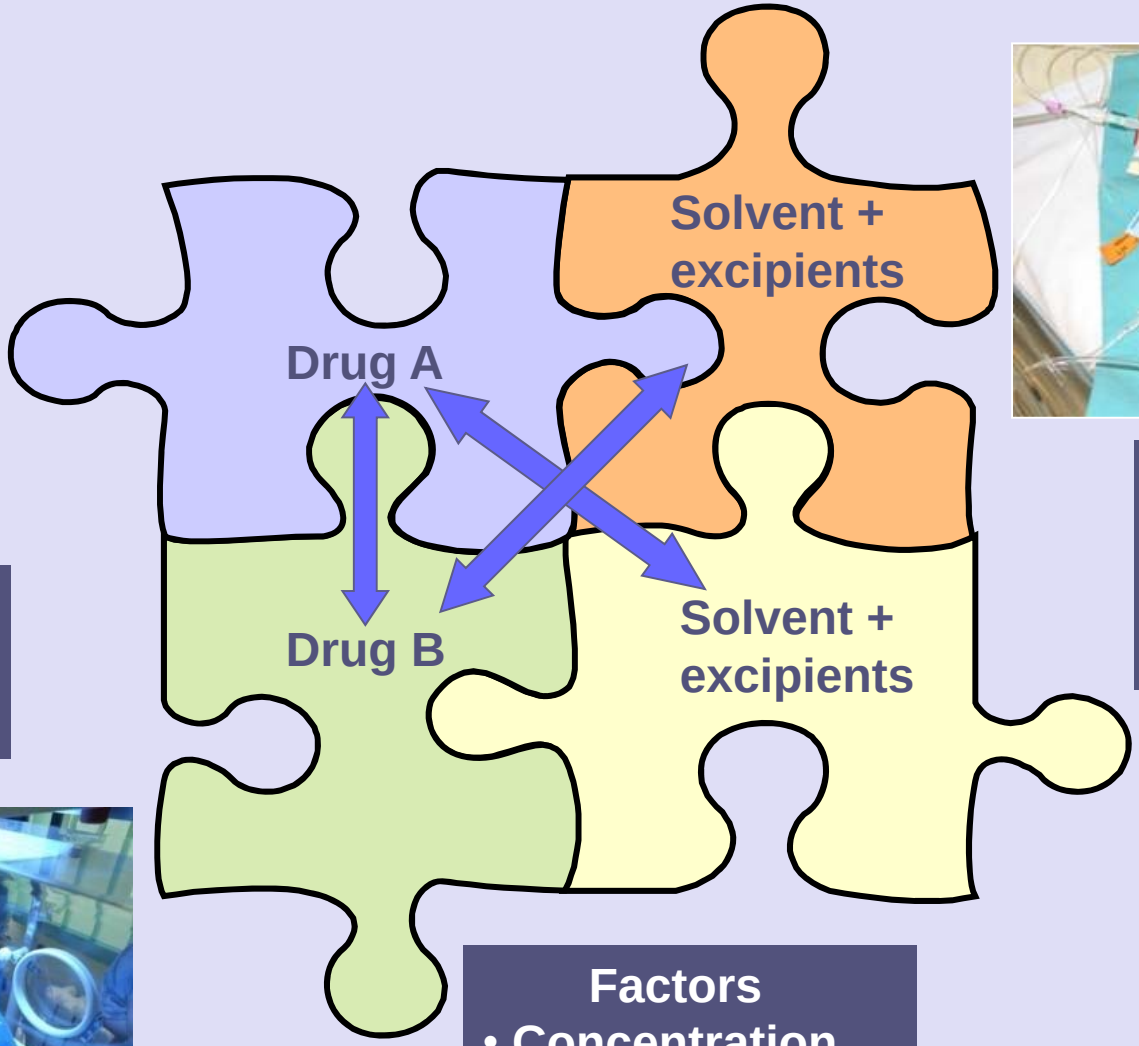
CASE STUDY

- 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?

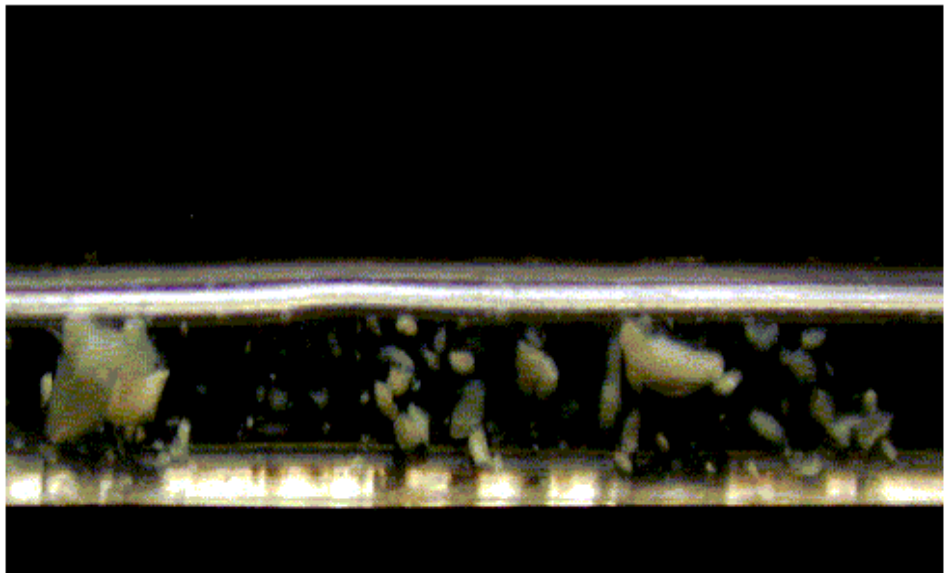
Environment
- Temperature
- Light

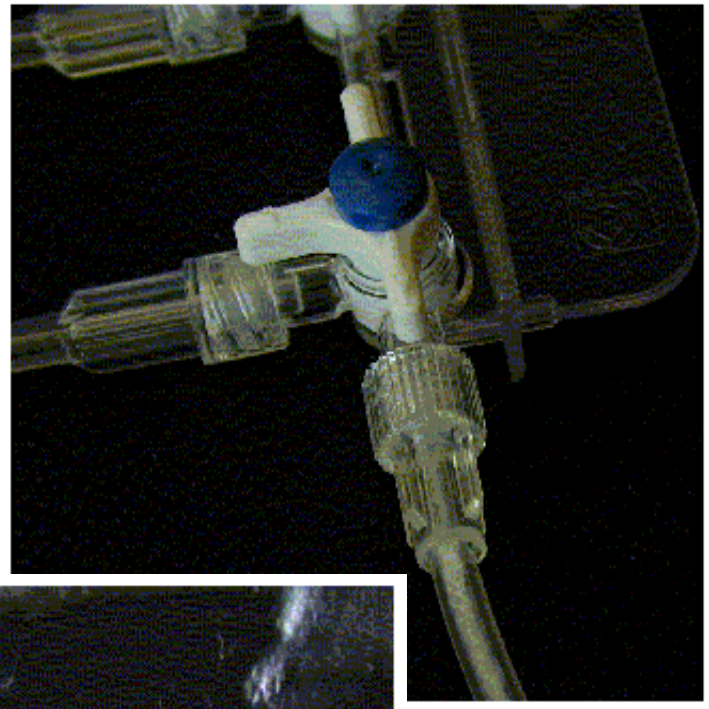
Material
- PVC (DEHP)
- Silicone
- …



Factors
- Concentration
- Time of contact

WHERE?





From: KIK 2.1, BBraun, 2002

WHAT KIND OF REACTIONS?

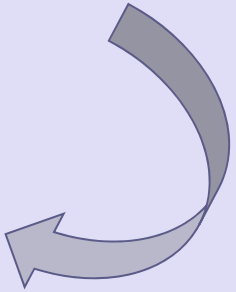
Physico- chemical reactions:

- 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)



patient

INCIDENTS IN PATIENTS?

0148-6071/89/1302-0209$02.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

Vol. 13, No. 2
Printed in U.S.A.

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

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0148-0671/96/2001-0081$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 20, No. 1
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Case Report

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†

From the Departments of †Surgery, ‡Pathology, §Pharmacy, and ‖Clinical Investigation, Tripler Army Medical Center, Honolulu, Hawaii

ABSTRACT. *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. *Methods:* Infusion of TNA into an animal model was undertaken in an effort to reproduce the clinical effect. Laboratory investigation was also performed to isolate a precipitate and identify the factors contributing to precipitation. *Results:* A nonvisible precipitate containing calcium, phosphorus, and organic material was isolated from the TNA 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 precipitate. (*Journal of Parenteral and Enteral Nutrition* **20**:81–87, 1996)

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

TERRY McNEARNEY, MD,*†‡ CHRISTOPHER BAJAJ, DO,* MICHAEL BOYARS, MD,* JOHN COTTINGHAM, MS IV,§ and ABIDA HAQUE, MD§

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

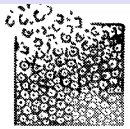
sequence as recommended by American Society for Parenteral and Enteral Nutrition and American Journal of Health System Pharmacy guidelines was as follows: Automix: intralipid 20%, 177 ml; Travesol 10%, 815 ml; dextrose 70%, 457 ml.; sterile wa-

Knowles JB et al. JPEN 1989;13:209-13

Hill SE et al. JPEN 1996;20:81-87

McNearney T et al. Dig Dis Sci 2003;48:1352-4

CEFTRIAXONE- CALCIUM



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) résolutives (2). Deux types d'accidents rares mais graves ont par ailleurs été rapportés chez des patients traités par cet antibiotique.

Néonatalogie : incompatibilité avec d'autres médicaments

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 (3à5).

Ces accidents ont été imputés à un[e] entre la *c* d'autres méd recevaient ce *conate de cal* zépine, aminc mine, macrolid

La lettre de se que « *dan un précipité être visualisé et/ou a été re parenchyme rénal)* », et s recommandé *ceftriaxone* voie séparée. mélanger les antibiotique à caments ou à contenant du

Il ne nous sible d'obteni sions sur les cas rapportés. On peut noter que dans le dictionnaire Vidal, ces pré-

Prescrire 1997;17:506

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

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

What's Known on This Subject

The package label for ceftriaxone was changed in August 2007 to contraindicate the co-administration of ceftriaxone with calcium-containing intravenous solution.

What This Study Adds

The cases reported to the FDA and the FDA AERS database search are provided and discussed to provide clinicians the basis for these new precautions.

ABSTRACT

OBJECTIVES. Unsolicited reports regarding potentially serious adverse drug reactions in neonates and young infants were 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:e609–e613

www.pediatrics.org/cgi/doi/10.1542/peds.2008-3080

doi:10.1542/peds.2008-3080

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Food and Drug Administration.

Key Words

ceftriaxone, calcium, newborn, drug therapy/adverse event, cardiopulmonary arrest

Abbreviations

FDA—Food and Drug Administration
AERS—Adverse Event Reporting System

Accepted for publication Dec 17, 2008

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Bradley JS et al. Pediatrics 2009;123:609-13

PEROXIDES

Toxic Hydroperoxides in Intravenous Lipid Emulsions Used in Preterm Infants

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

+ Author Affiliations

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.

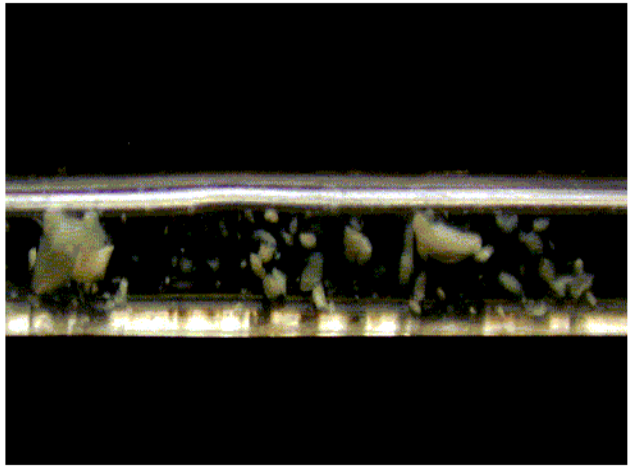
Helbock H et al. Pediatrics 1993;91;83-7

pH AND DRUGS

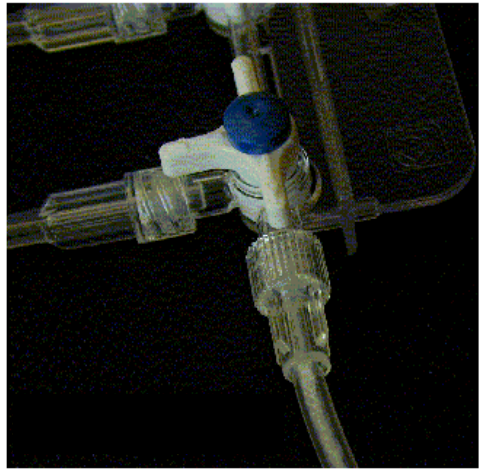
Acidic drugs low pH < 7		Basic drugs high pH > 7	
Amiodarone (Cordarone®)	pH = 4	Aciclovir (Zovirax®)	pH = 11
Adrenaline	pH = 3	Cotrimoxazole (Bactrim®)	pH = 10
Dobutamine (Dobutrex®)	pH = 3	Furosemide (Lasix®)	pH = 9
Midazolam (Dormicum®)	pH = 4	Ganciclovir (Cymevene®)	pH = 9
Morphine HUG	pH = 3.5	Omeprazole (Antra®)	pH = 9
Vancomycine (Vancocin®)	pH = 3	Phenytoin (Phenhydan®)	pH = 12

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



furosemide sodique (pH 9)
+ vancomycine HCl (pH 3)



From: KIK 2.1, BBraun, 2002

furosemide sodique (pH 9)
+ midazolam HCl (pH 4)

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

SOLVENT (DILUENT)

Solvent	pH	Appropriate for
Glucose 5%-20%	pH = 4.0 - 6.0	amiodarone, amphotericine B
NaCl 0,9%	pH = 7.0 - 7.5	aciclovir, phenytoin, furosemide

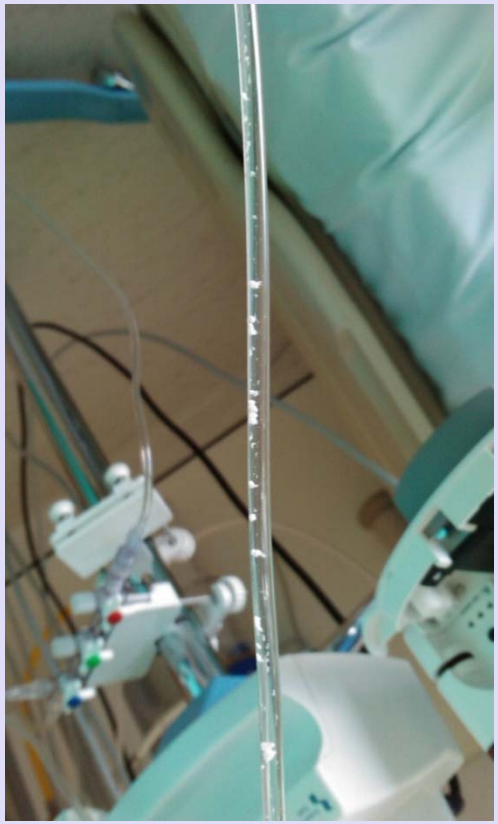
From: KIK 2.1, BBraun, 2002

Be careful with solvent pH !

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 »

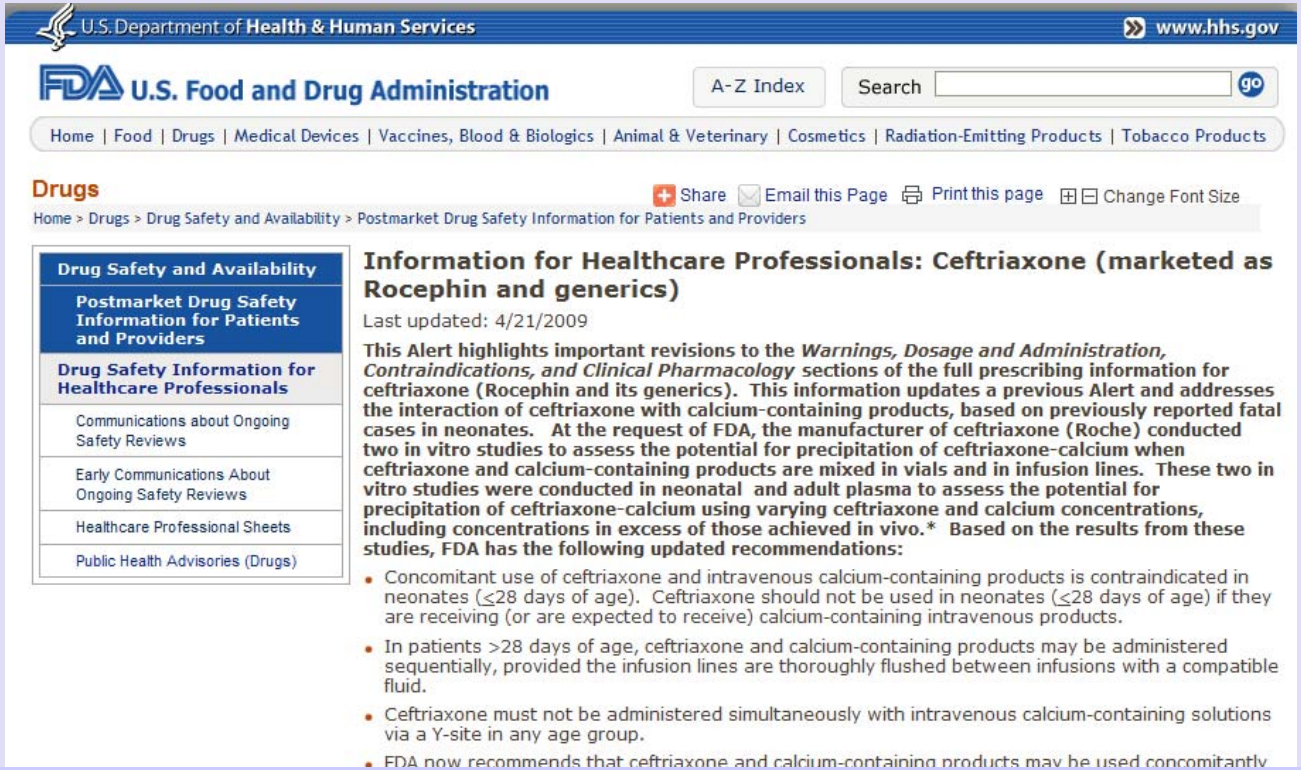
Co-solvent and/or adjusting pH can increase the solubility of drugs in solution

drug		excipient
amiodarone	**Cordarone®**	polysorbate (tween)
paracetamol	**Perfalgan®**	mannitol, phosphate, NaOH
esomeprazole	**Nexium®**	NaOH, EDTA
phenytoin	**Phenhydan®**	glycofurol-75, EDTA
clonazepam	**Rivotril®**	propyleneglycol, acetic acid

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

COMPLEXATION

Formation of insoluble calcium-ceftriaxone complex



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Postmarket Drug Safety Information for Patients and Providers
Drug Safety Information for Healthcare Professionals
Communications about Ongoing Safety Reviews
Early Communications About Ongoing Safety Reviews
Healthcare Professional Sheets
Public Health Advisories (Drugs)

Information for Healthcare Professionals: Ceftriaxone (marketed as Rocephin and generics)

Last updated: 4/21/2009

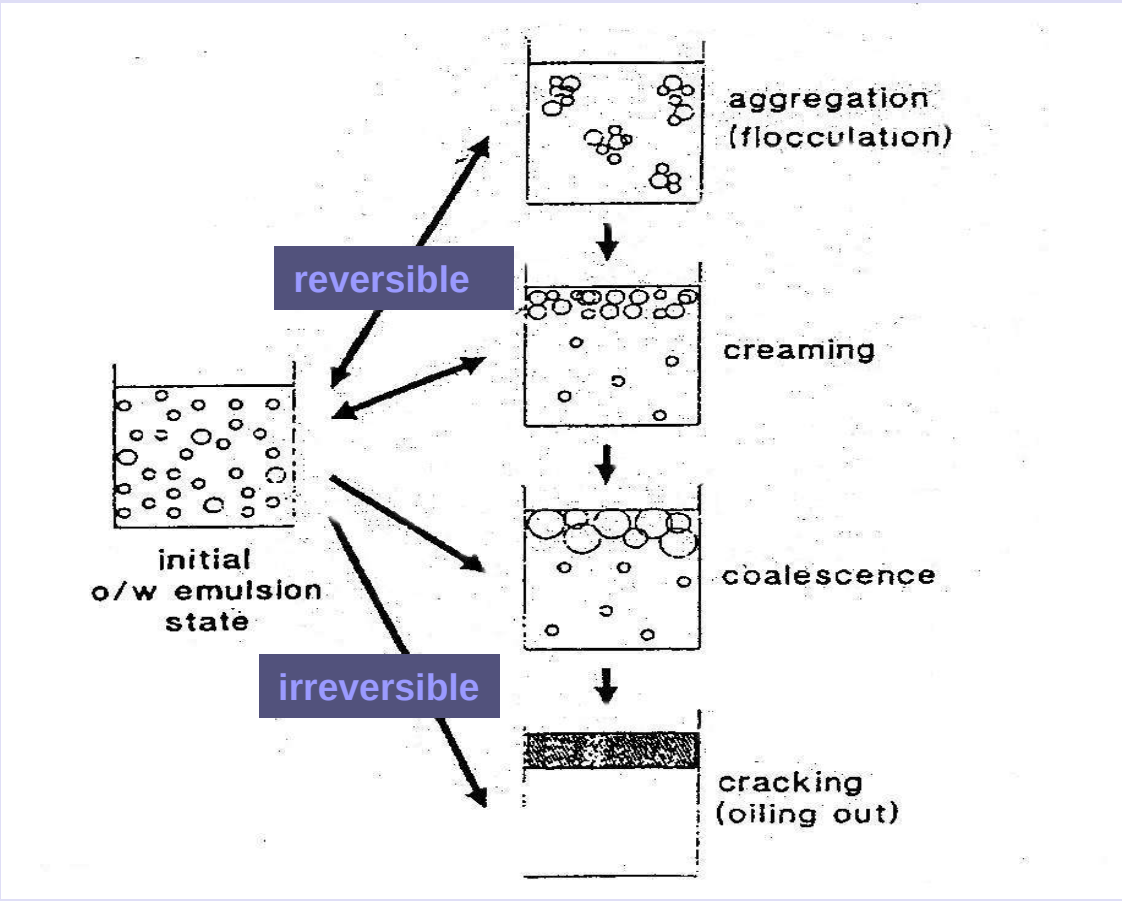
This Alert highlights important revisions to the *Warnings, Dosage and Administration, Contraindications, and Clinical Pharmacology* sections of the full prescribing information for ceftriaxone (Rocephin and its generics). This information updates a previous Alert and addresses the interaction of ceftriaxone with calcium-containing products, based on previously reported fatal cases in neonates. At the request of FDA, the manufacturer of ceftriaxone (Roche) conducted two in vitro studies to assess the potential for precipitation of ceftriaxone-calcium when ceftriaxone and calcium-containing products are mixed in vials and in infusion lines. These two in vitro studies were conducted in neonatal and adult plasma to assess the potential for precipitation of ceftriaxone-calcium using varying ceftriaxone and calcium concentrations, including concentrations in excess of those achieved in vivo.* Based on the results from these studies, FDA has the following updated recommendations:

- Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (≤28 days of age). Ceftriaxone should not be used in neonates (≤28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products.
- In patients >28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group.
- FDA now recommends that ceftriaxone and calcium-containing products may be used concomitantly

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

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

Lipofundin or Disoprivan

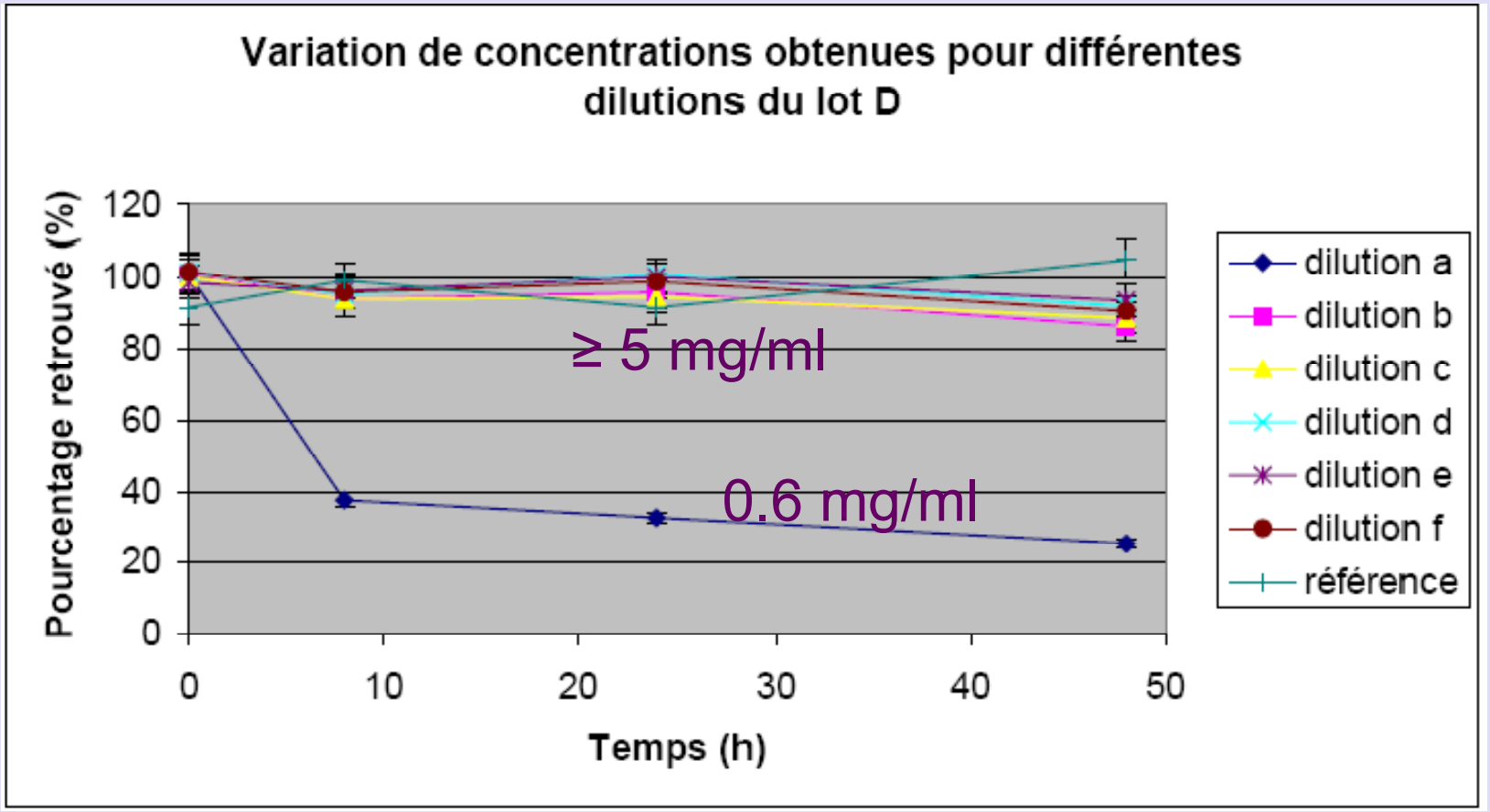
+ Garamycine

- Phase separation over 24h

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



N.Marcoz 2003, http://pharmacie.hug-ge.ch/ens/travmaitrise/2003_nm_amiodarone_po.pdf

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 syrines in PE

  adsorption to in-line filter
  - Ex. phenobarbital

LEACHING (DESORPTION)

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

DEHP-free material (NoDEHP) !

LEACHING

Health Care Without Harm

ISSUES

PVC and Phthalates

Potential exposures to DEHP from medical procedures and nutrition in a neonatal intensive care unit

Source of DEHP Exposure	Exposure (mg DEHP/kg body weight)	Unit	Total Exposure or Concentration in Product	Source	TI/dose*
Artificial ventilation in preterm infants (PVC respiratory tubing; not polyethylene)	NR	Hour (inhalation)	0.001-4.2 mg(est. total exposure)	1	
Neonatal blood replacement transfusion; short-term, acute	0.3 (0.14-0.72)	treatment period	NR	2	2
Neonatal blood replacement transfusion; double volume; short term, acute	1.8 (0.84-3.3)	treatment period	NR	3	0.3
Platelet concentrates in newborns	1.9	treatment	NR	4	0.3
Extracorporeal oxygenation in infants	14-140	treatment	NR	5	0.04-0.004
Extracorporeal oxygenation in infants	4.7-34.9	Treatment	NR	6	0.12-0.02
Congenital heart repair (neonates)		1-4 hours	0.3-4.7 µg/mL/hr(change in level in whole blood during procedure)	7	
IV crystalloid solution	0.03	From tubing	NR	8	20
Total parenteral nutritional formula (TPN), with lipid	2.5	NR	3.1 µg/mL (concentration in TPN formula); more from tubing	9	0.2
TPN/IV Tubing	5	day	10 mg/2-kg baby/day	10	0.12
Multiple IV Sources: packed red blood cells, platelet rich plasma, fresh frozen plasma, and medications	5	day	10 mg/2-kg baby/day	11	0.12
Breast milk	0.0015-0.0165	Day	0.01-0.11 mg/kg (concentration in breast milk)	12	27-2.4
Infant formula	0.015	Day	0.004-0.06 mg/kg wet weight	13	2.6
Infant formula	0.0087-0.035	NR	0.33-0.98 mg/kg dry weight	14	4.5-1.1

NR = Not Reported *TI/dose: based on FDA's TI of 0.6 mg/kg/day for parenteral exposures and 0.04 mg/kg/day for intestinal exposures; TI/dose ratios < 1 imply that the TI has been exceeded for the given source of exposure

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
http://www.noharm.org/lib/downloads/pvc/DEHP_Exposure_of_Infants.pdf

MAIN POINTS

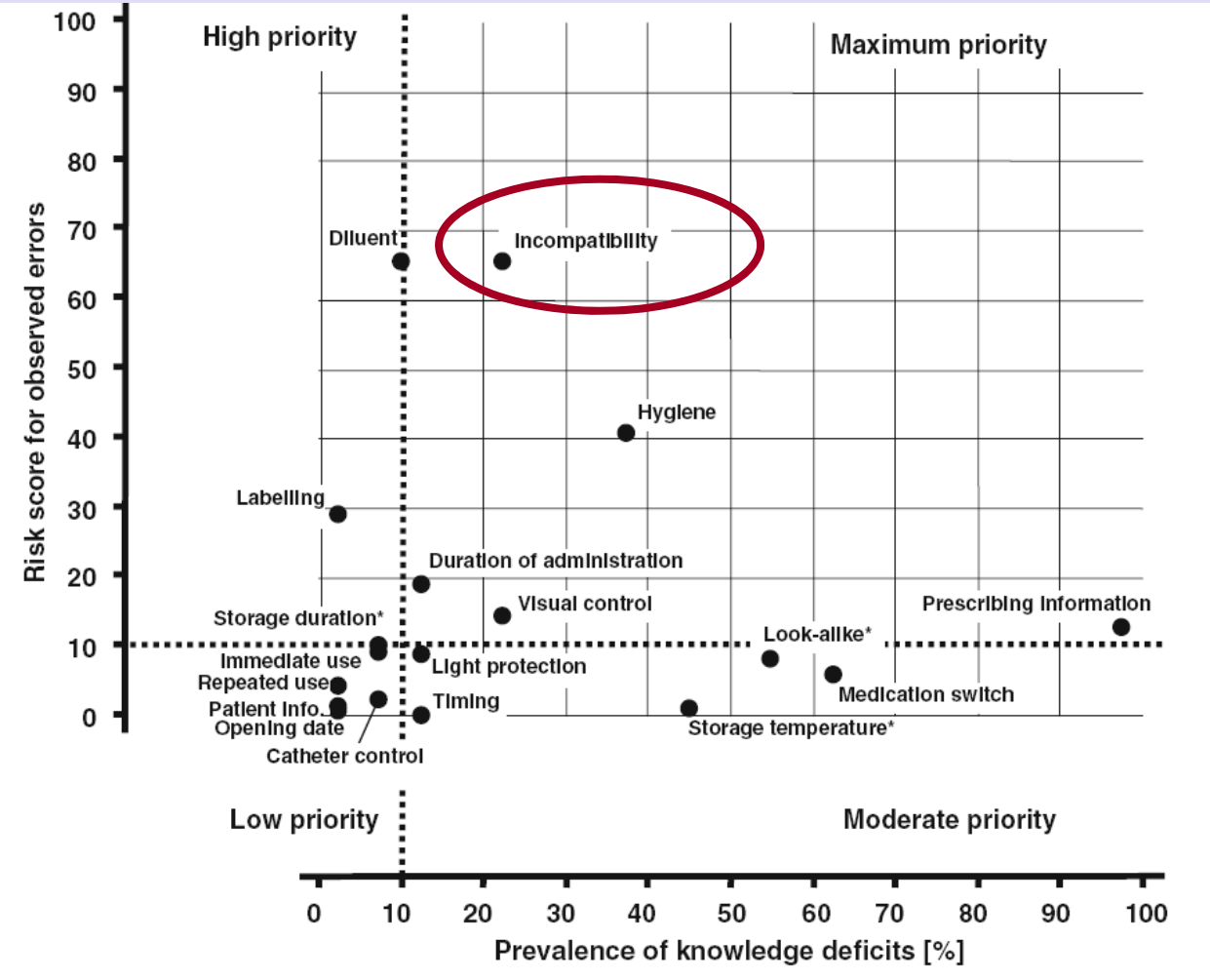
- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
- How can we treat them?
- What should you know?

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*
[2] *Bertsche T et al. Am J Health Syst Pharm 2008;65:1834-40*
[3] *Tissot E et al. Intensive Care Med 1999;25:353-9*
[4] *Vogel Kahmann I et al. Anaesthesist 2003;52:409-12*
[5] *Gikic M et al. Pharm World Sci 2002;22:88-91*
[6] *Kalikstad B et al. Arch Dis Child 2010;95:745-8*

PRIORITY FOR QUALITY IMPROVEMENT



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

MAIN POINTS

- What are drug incompatibilities?
- How frequent in the ICU?
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  - in the ward
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TOOLS

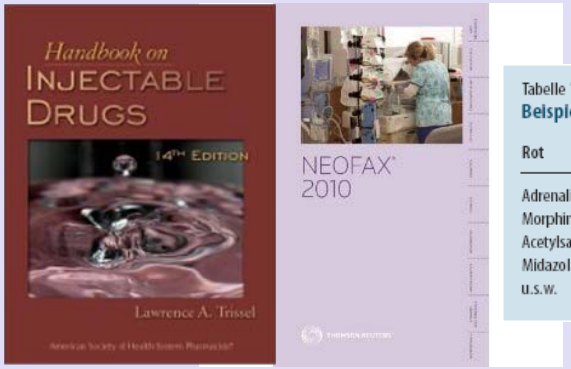
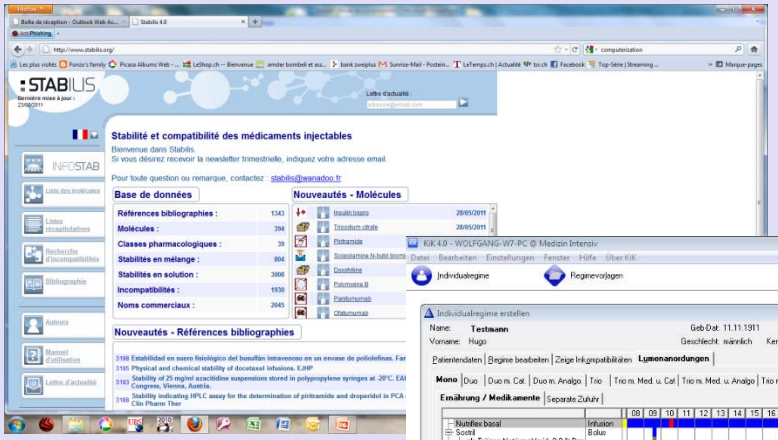
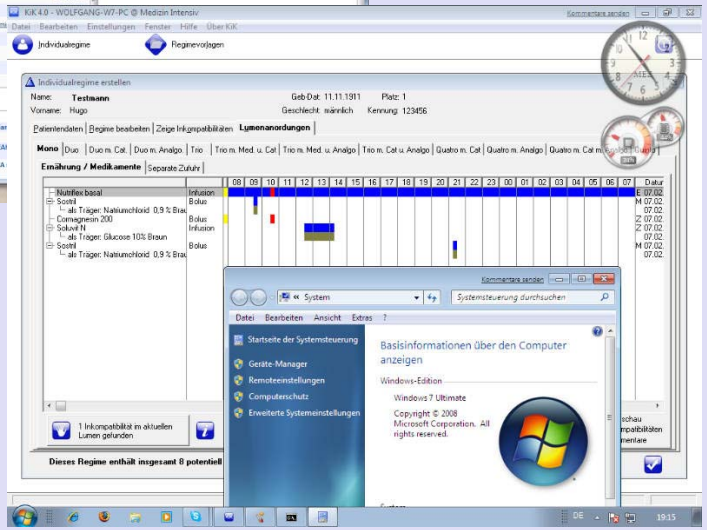


Tabelle 1
Beispiele der Farbzuordnung einiger Medikamente

Rot	Blau	Gelb	Schwarz
Adrenalin	Furosemid	Imipenem/Cilastatin	Blutprodukte
Morphin	Heparin	Cefazolin	TPN
Acetylsalicylat	Insulin	Amoxicillin	Propofol
Midazolam	Natriumbicarbonat	Spironolacton	Diazepam
u.s.w.	u.s.w.	u.s.w.	u.s.w.





TOOLS

Reference and its abreviation	
Trissel handbook 14th ed.	Ref
Tools and their abreviations	
CHUV 9.0 cross-table	CHUV
KIK 3.0 database	KIK
King 2008 cross-table	King
Neofax 2007 handbook	NeoF
Perfysi 2 database	Perf
pH 2007 cross-table	pH
Stabilis 3 database	Stab
Thériaque 2007 database	Thé

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

Table 4 Tool-evaluation summary

Tool	Accuracy score[a]	Completeness score[a]	Comprehensiveness score[a]	Applicability score[a]	Global score[a]
Ref	250	250	250	250	1000
Thé	234	200	218	188	840
pH	175	200	134	298	807
CHUV	213	150	174	266	803
Perf	230	138	218	191	776
NeoF	190	181	116	191	678
King	192	131	108	211	642
Stab	179	144	149	112	584
KIK	105	156	157	105	523

Ref Trissel's Handbook

Thé Thériaque database, *Perf* Perfysi database, *CHUV* CHUV's cross-table *King* King cross-table wall chart, *NeoF* Neofax handbook, *Stab* Stabilis database, *pH* pH cross-table, *KIK* software

TOOLS

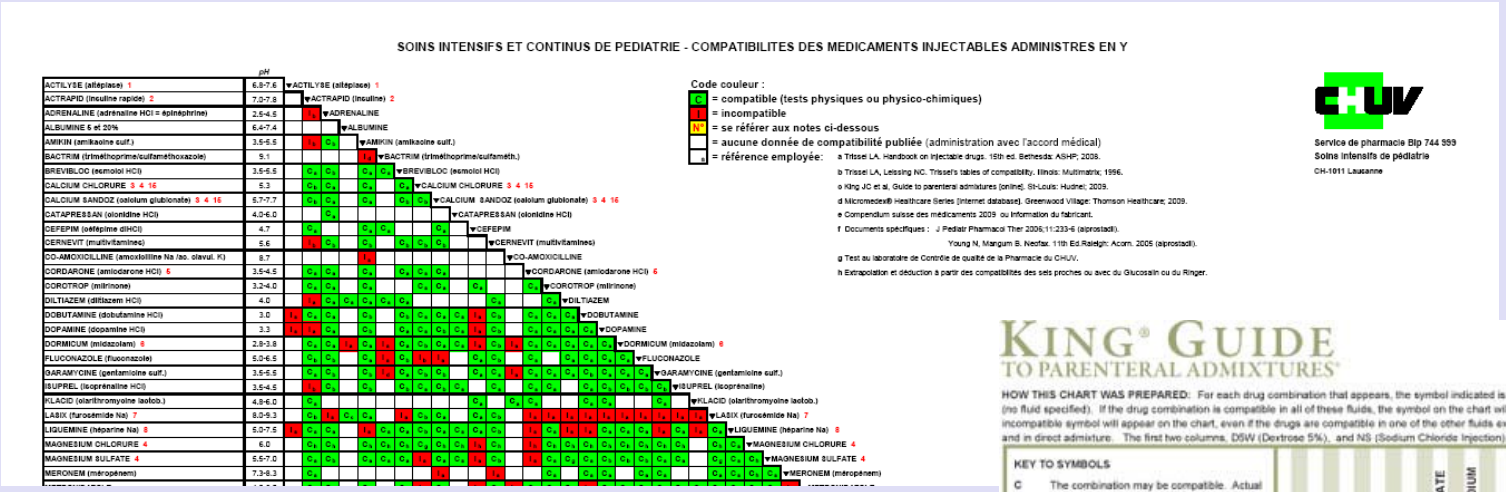
- Assessment ➔ interpretation

➔ adapted cross-tables (charts)

➔ pH- color code (Schaffhausen Model)

- Main problems: - exhaustiveness
  - assessment of drug pairs

CROSS-TABLES



SOINS INTENSIFS ET CONTINUS DE PEDIATRIE - COMPATIBILITES DES MEDICAMENTS INJECTABLES ADMINISTRES EN Y

Code couleur :

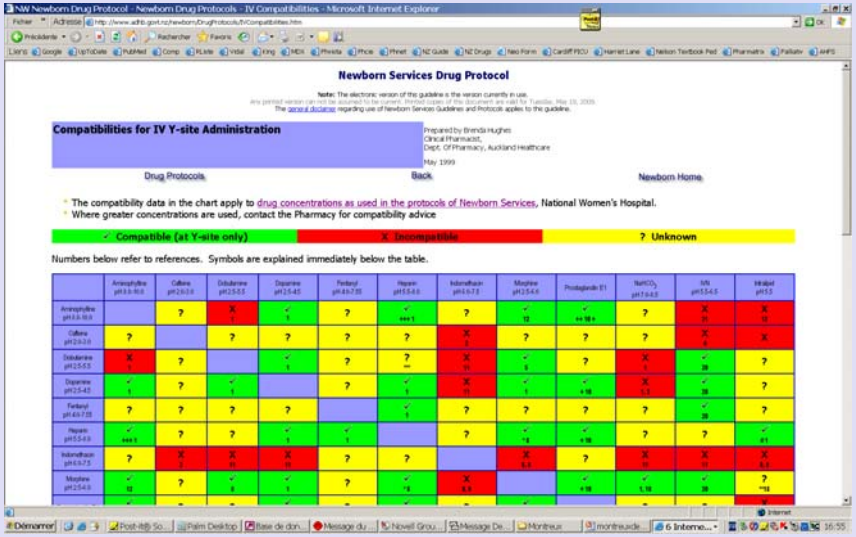
- C = compatible (tests physiques ou physico-chimiques)
- I = incompatible
- N° = se référer aux notes ci-dessous
- = aucune donnée de compatibilité publiée (administration avec l'accord médical)
- = référence employée:

a Trissel LA. Handbook on injectable drugs. 15th ed. Bethesda: ASHP; 2008.
b Trissel LA, Leissing NC. Trissel's tables of compatibility. Illinois: Multimatrix; 1996.
c King JC et al. Guide to parenteral admixtures [online]. St-Louis: Hudnet; 2009.
d Micromedex® Healthcare Series [Internet database]. Greenwood Village: Thomson Healthcare; 2009.
e Compendium suisse des médicaments 2009 ou Information du fabricant.
f Documents spécifiques : J Pediatr Pharmacol Ther 2006;11:233-6 (alprostadil).
Young N, Mangum B. Neofax. 11th Ed.Raleigh: Acorn. 2005 (alprostadil).
g Test au laboratoire de Contrôle de qualité de la Pharmacie du CHUV.
h Extrapolation et déduction à partir des compatibilités des sels proches ou avec du Glucosalin ou du Ringer.

CHUV
Service de pharmacie Bip 744 999
Soins intensifs de pédiatrie
CH-1011 Lausanne

http://files.chuv.ch/internet-docs/pha/medicaments/pha_phatab_compatibilitessip.pdf

http://www.adhb.govt.nz/newborn/DrugProtocols/IVCompatibilities.htm



Newborn Drug Protocol - Newborn Drug Protocols - IV Compatibilities - Microsoft Internet Explorer

Newborn Services Drug Protocol

Compatibilities for IV Y-site Administration

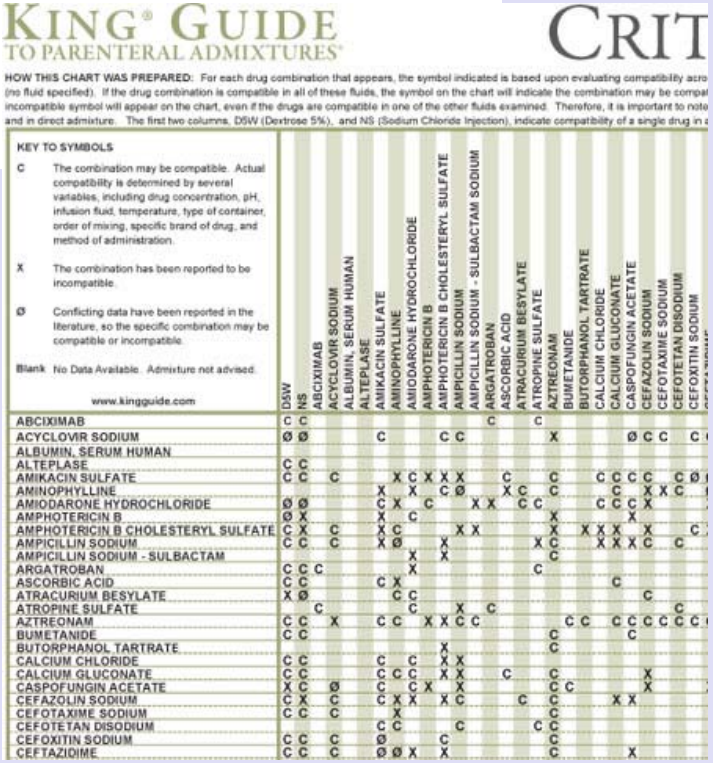
Prepared by Brenda Hughes
Clinical Pharmacist,
Dept. Of Pharmacy, Auckland Healthcare
May 1999

Drug Protocols Back Newborn Home

The compatibility data in the chart apply to drug concentrations as used in the protocols of Newborn Services, National Women's Hospital.
Where greater concentrations are used, contact the Pharmacy for compatibility advice

✓ Compatible (at Y-site only) X Incompatible ? Unknown

Numbers below refer to references. Symbols are explained immediately below the table.



KING® GUIDE TO PARENTERAL ADMIXTURES®

CRIT

HOW THIS CHART WAS PREPARED: For each drug combination that appears, the symbol indicated is based upon evaluating compatibility acro (no fluid specified). If the drug combination is compatible in all of these fluids, the symbol on the chart will indicate the combination may be compa incompatible symbol will appear on the chart, even if the drugs are compatible in one of the other fluids examined. Therefore, it is important to note and in direct admixture. The first two columns, D5W (Dextrose 5%), and NS (Sodium Chloride Injection), indicate compatibility of a single drug in a

KEY TO SYMBOLS

C The combination may be compatible. Actual compatibility is determined by several variables, including drug concentration, pH, infusion fluid, temperature, type of container, order of mixing, specific brand of drug, and method of administration.

X The combination has been reported to be incompatible.

Ø Conflicting data have been reported in the literature, so the specific combination may be compatible or incompatible.

Blank No Data Available. Admixture not advised.

www.kingguide.com

	D5W	NS	ABCIXIMAB	ACYCLOVIR SODIUM	ALBUMIN, SERUM HUMAN	ALTEPLASE	AMIKACIN SULFATE	AMINOPHYLLINE	AMIODARONE HYDROCHLORIDE	AMPHOTERICIN B	AMPHOTERICIN B CHOLESTERYL SULFATE	AMPICILLIN SODIUM	AMPICILLIN SODIUM - SULBACTAM SODIUM	ARGATROBAN	ASCORBIC ACID	ATRACURIUM BESYLATE	ATROPINE SULFATE	AZTREONAM	BUMETANIDE	BUTORPHANOL TARTRATE	CALCIUM CHLORIDE	CALCIUM GLUCONATE	CASPOFUNGIN ACETATE	CEFAZOLIN SODIUM	CEFOTAXIME SODIUM	CEFOTETAN DISODIUM	CEFOXITIN SODIUM
ABCIXIMAB	C	C												C			C										
ACYCLOVIR SODIUM	Ø	Ø					C				C	C						X					Ø	C	C		C
ALBUMIN, SERUM HUMAN																											
ALTEPLASE	C	C																									
AMIKACIN SULFATE	C	C		C			X	C	X	X	X				C		C				C	C	C	C		C	Ø
AMINOPHYLLINE						X		X			C	Ø			X	C		C				C	X	X	C		
AMIODARONE HYDROCHLORIDE	Ø	Ø				C	X		C			X	X		C	C						C	C	X				
AMPHOTERICIN B	Ø	X				X	C			C							X						X				
AMPHOTERICIN B CHOLESTERYL SULFATE	C	X		C		X	C				X	X						X	X	X		X		X			C
AMPICILLIN SODIUM	C	C		C		X	Ø			X							X	C			X	X	X	C		C	
AMPICILLIN SODIUM - SULBACTAM								X		X								C									
ARGATROBAN	C	C	C				X										C										
ASCORBIC ACID	C	C				C	X															C					
ATRACURIUM BESYLATE	X	Ø					C	C																C			
ATROPINE SULFATE			C				C				X	C														C	
AZTREONAM	C	C		X			C	C		X	X	C	C					C	C			C	C	C	C	C	C
BUMETANIDE	C	C															C					C					
BUTORPHANOL TARTRATE											X						C										
CALCIUM CHLORIDE	C	C					C				X	X															
CALCIUM GLUCONATE	C	C					C	C	C		X	X			C		C						X				
CASPOFUNGIN ACETATE	X	C		Ø			C	X			X						C	C						X			
CEFAZOLIN SODIUM	C	X		C			C	X	X		X	C			C		C					X	X				
CEFOTAXIME SODIUM	C	C		C			X										C										
CEFOTETAN DISODIUM							C	C			C						C	C									
CEFOXITIN SODIUM	C	C		C			Ø				C						C										
CEFTAZIDIME	C	C		C			Ø	Ø	X		X						C						X				

pH COLOR CODE

- Adult ICU in Schaffhausen (Switzerland) since 10 years

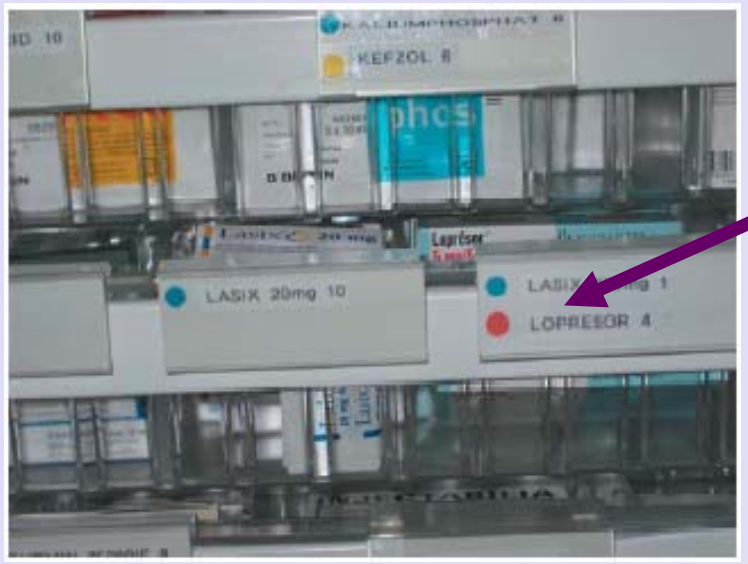
Tabelle 1

Beispiele der Farbzuordnung einiger Medikamente

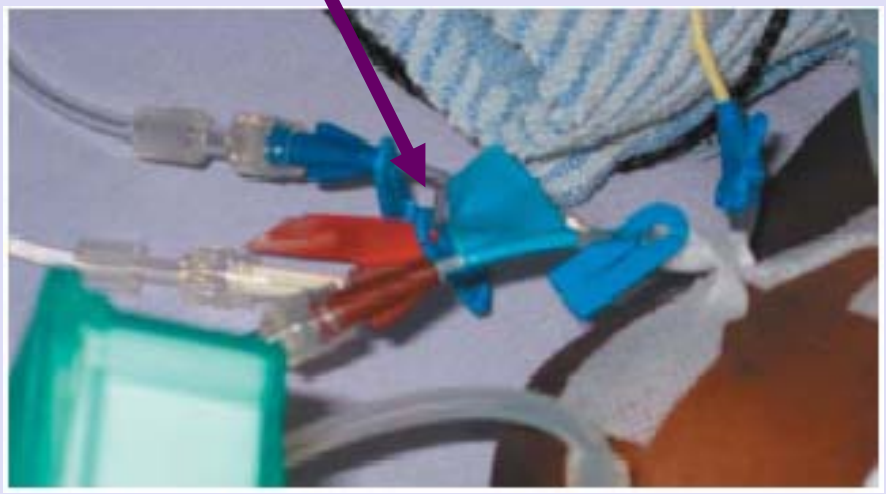
Rot	Blau	Gelb	Schwarz
Adrenalin	Furosemid	Imipenem/Cilastatin	Blutprodukte
Morphin	Heparin	Cefazolin	TPN
Acetylsalicylat	Insulin	Amoxicillin	Propofol
Midazolam	Natriumbicarbonat	Spironolacton	Diazepam
u.s.w.	u.s.w.	u.s.w.	u.s.w.

Vogel Kahmann I. et al. Anaesthesist 2003;52:409-12

pH COLOR CODE



Pharmacy ward

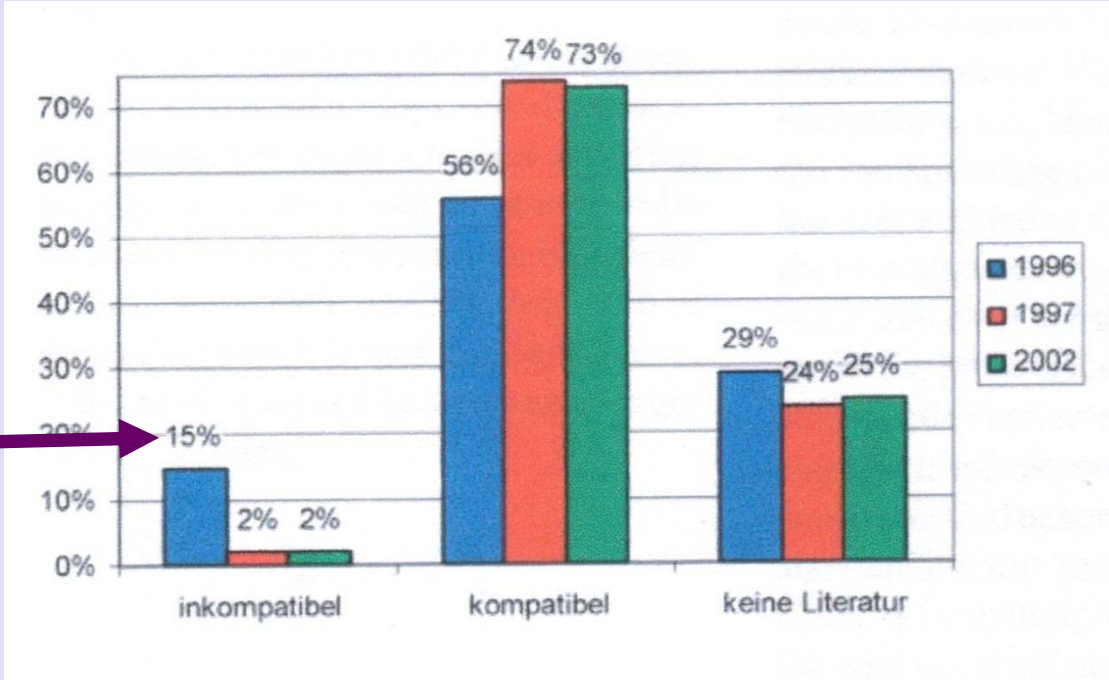


On IV-lines

Vogel Kahmann I. et al. Anaesthesist 2003;52:409-12

pH COLOR CODE

- About 78 drug combinations (636 different drugs)



⬇ Y-site infusion of potentially incompatible drugs

Vogel Kahmann I. et al. Anaesthesist 2003;52:409-12

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[1].

- Scientific accuracy

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.

- Ergonomics
- Applicability
- Design
- Reliability

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

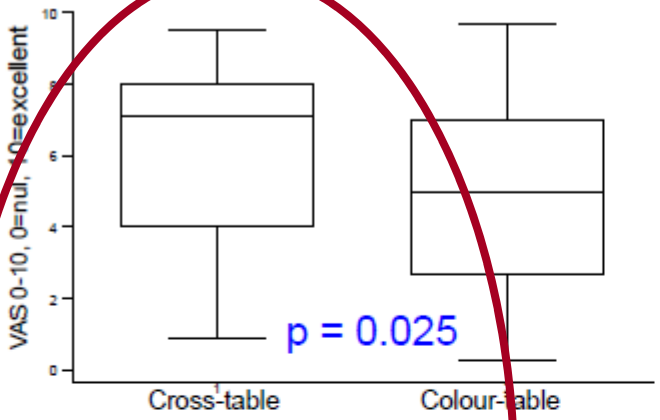


***Fig.3** : Ergonomics*

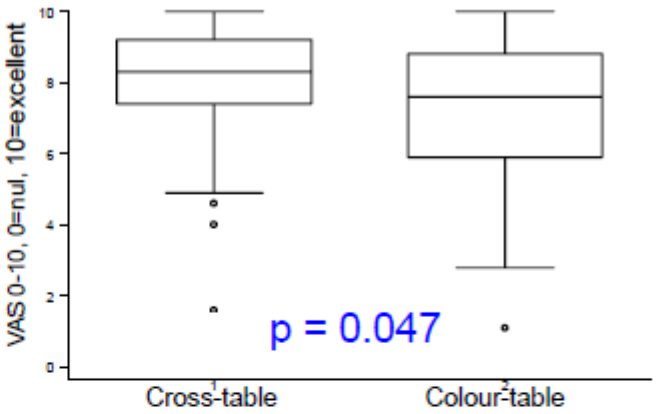


***Fig.4:** Applicability*

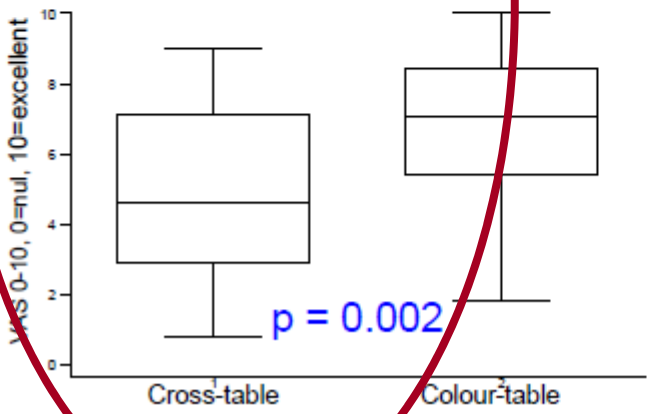


***Fig.5:** Design*

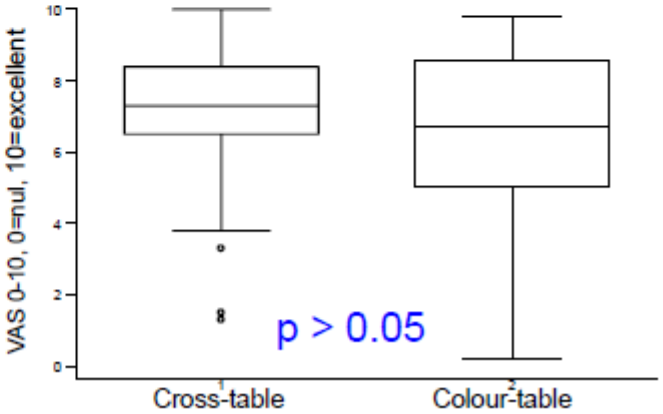


***Fig.6:** Reliability*

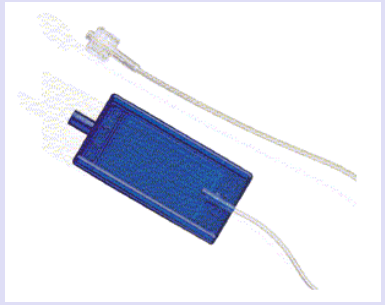
Gschwind L et al. ESCP 2010. http://pharmacie.hug-ge.ch/rd/posters/ESCP2010_lg_incompat.pdf

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



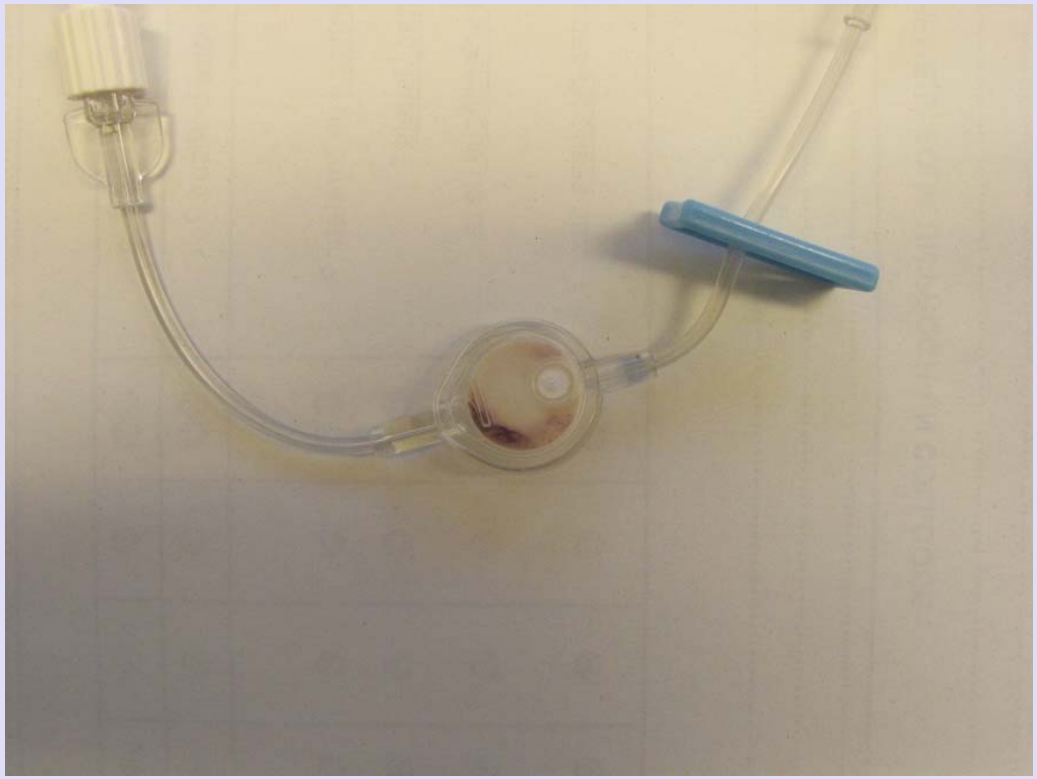
Potential difficulties for implementation

- 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

BLOCKED FILTERS

- Drug incompatibility:



Nexium® + Dormicum® + Morphine®

➔ Esomeprazole discoloration ± precipitation in acidic solutions

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

g. 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 (mimicking an Y-site administration, where mixing is not necessarily homogeneous)

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

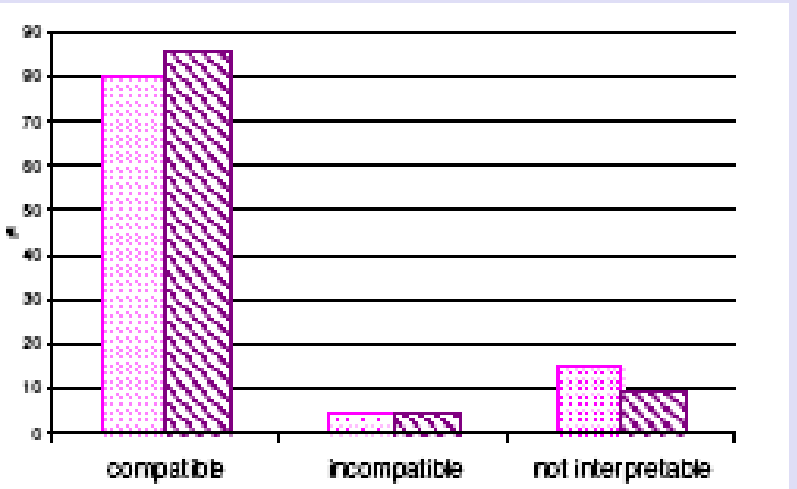


Fig. 5 – Evaluation of (in)compatibilities between drugs administered in the same IVL, based only on literature data (pink dotted bars) and after laboratory tests (purple streaked bars)

Humbert Delaloye V et al. ESCP 2009. http://files.chuv.ch/internet-docs/pha/recherche/pha_poster_2009escp_compatibilites.pdf

IN VITRO STUDY

Compatibility lipid emulsions and drugs

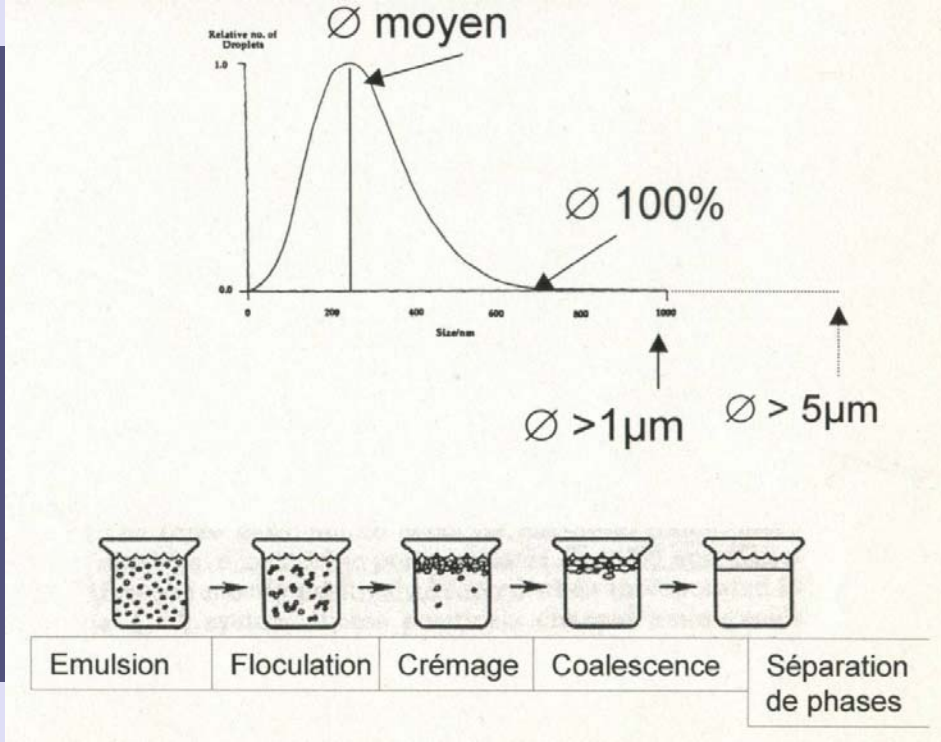
Granulometry

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

Zeta potential measurement

pH measure

Visual inspection (microscope)



NUTRIFLEX LIPID SPECIAL

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

Bouchoud L et al. SFNEP 2009. http://pharmacie.hug-ge.ch/ens/conferences/lb_incomp_sfnep.pdf

DISOPRIVAN

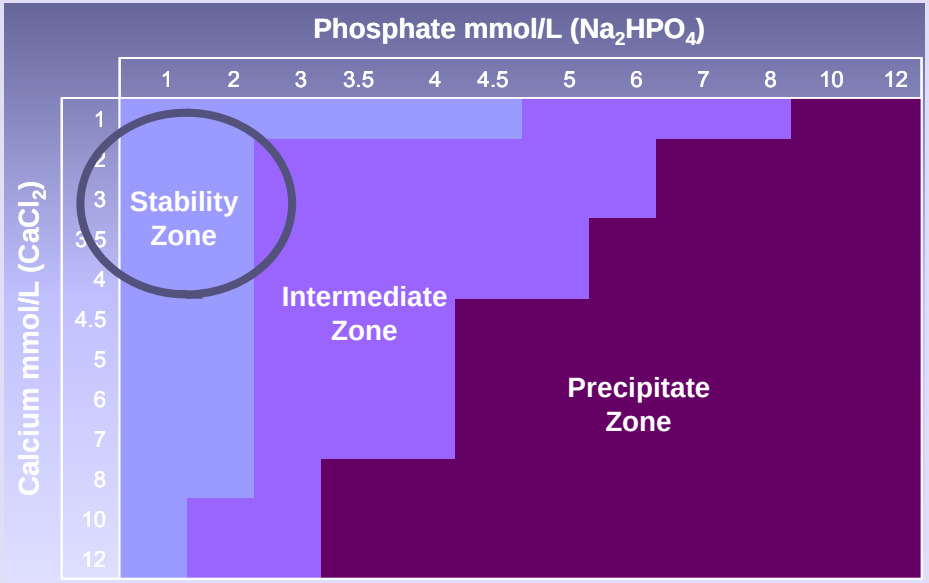
Incompatible Drugs	Appearance	pH	Zeta pot.	Glob. size	Total
Amikacine 50mg/ml (Amikin®)	3	0	10	10	20
CaCl2 75mg/ml (CaCl2 HUG®)	3	0	10	10	23
Gentamycin 60mg/1,5ml (Garamycin®)	2	0	10	10	22
HCl 7,25% (Salzsäure 7,25% Braun)	2	3	10	10	25
MgSO4 100mg/ml (Bichsel)	1	0	10	10	21
MgSO4 500mg/ml (Bichsel)	3	0	10	10	23
Vancomycin 50mg/ml (Sandoz)	3	3	10	10	26
Dopamin 25mg/ml (Sintetica)	1	3	0	10	14
Probably Incompatible Drugs					
Adrenalin 1mg/ml (Sintetica)	0	3	0	7	10
Ciprofloxacin 2mg/ml (Ciproxine®)	1	0	0	10	11
Dobutamin 5mg/ml (Fresenius)	1	3	0	7	11
Silicon Oil (Hanseler)	3	0	0	6	9
Lidocain 20mg/ml (Rapidocain®)	1	0	0	6	7
Phenytoin 50mg/ml (Phenydan®)	1	0	0	8	9
Suxamethonium 50mg/ml (Lysthenon®)	0	0	8	3	11
Vecuronium 2mg/ml (Norcuron®)	2	0	0	5	7
Ganciclovir 50mg/1ml (Cymevene®)	0	0	0	6	6
Metronidazol 5mg/ml (HUG)	0	0	0	5	5
Midazolam 5mg/5ml (Dormicum®)	0	0	0	5	5

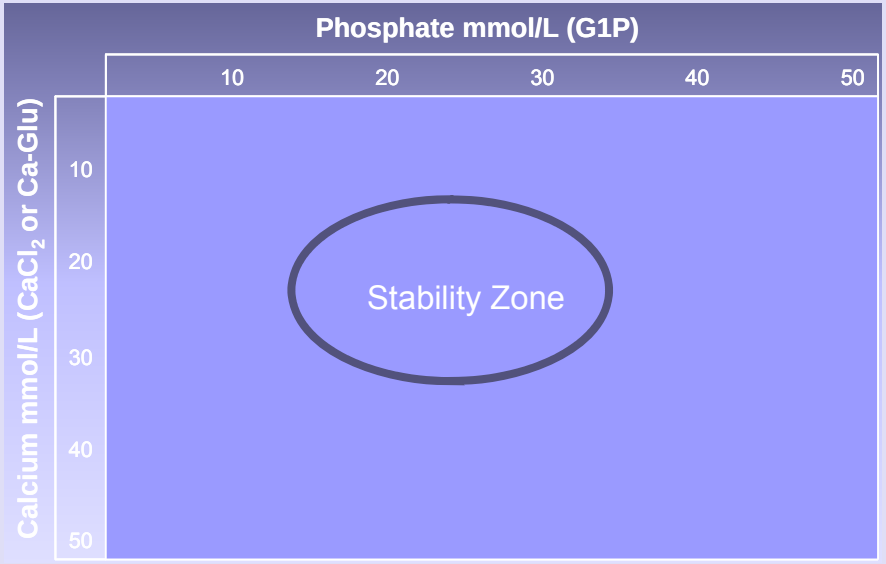
Probably Compatible Drugs	Appearance	pH	Zeta pot.	Glob. size	Total
Atropin 1mg/ml (HUG)	0	0	2	2	4
Ceftriaxon 50mg/ml (Rocephine®)	0	0	0	2	2
Ephedrin HCL 10mg/ml (Bischel)	0	0	0	1	1
Flucoxacillin (Floxapen®)	0	0	0	1	1
Meropenem 50mg/ml (Meronem®)	0	0	0	1	1
Nitroglycerin 1mg/ml (Perlinganit®)	0	0	0	1	1
Phenylephrin HCL 10mg/ml (Bischel)	0	0	0	2	2
Thiopental 50mg/ml (Penthotal®)	0	0	0	3	3
Trimetho/sulfamet 400/80mg/5ml (Bactrim®)	0	0	1	0	1
Compatible Drugs					
Amoxicilline/Acid clavulanic 1,2g/20ml (Augmentin®)	0	0	0	0	0
Water for injection (Braun)	0	0	0	0	0
Fentanyl 50ug/ml (Sintenyl®)	0	0	0	0	0
Furosemid 40mg/4ml (Lasix®)	0	0	0	0	0
Noradrenalin 1mg/ml (Sintetica)	0	0	0	0	0

Stucki C et al. ESCP 2009 http://pharmacie.hug-ge.ch/rd/posters/escp09poster_cs.pdf

PN: reduced risk of precipitation

Use of organic calcium and phosphates salts





Bouchoud L et al. JPEN J Parenter Enteral Nutr. 2010;4:542-5

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

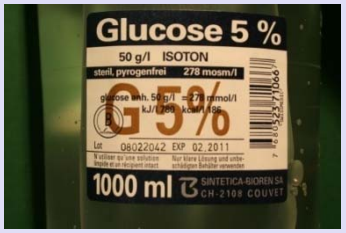
MAIN POINTS

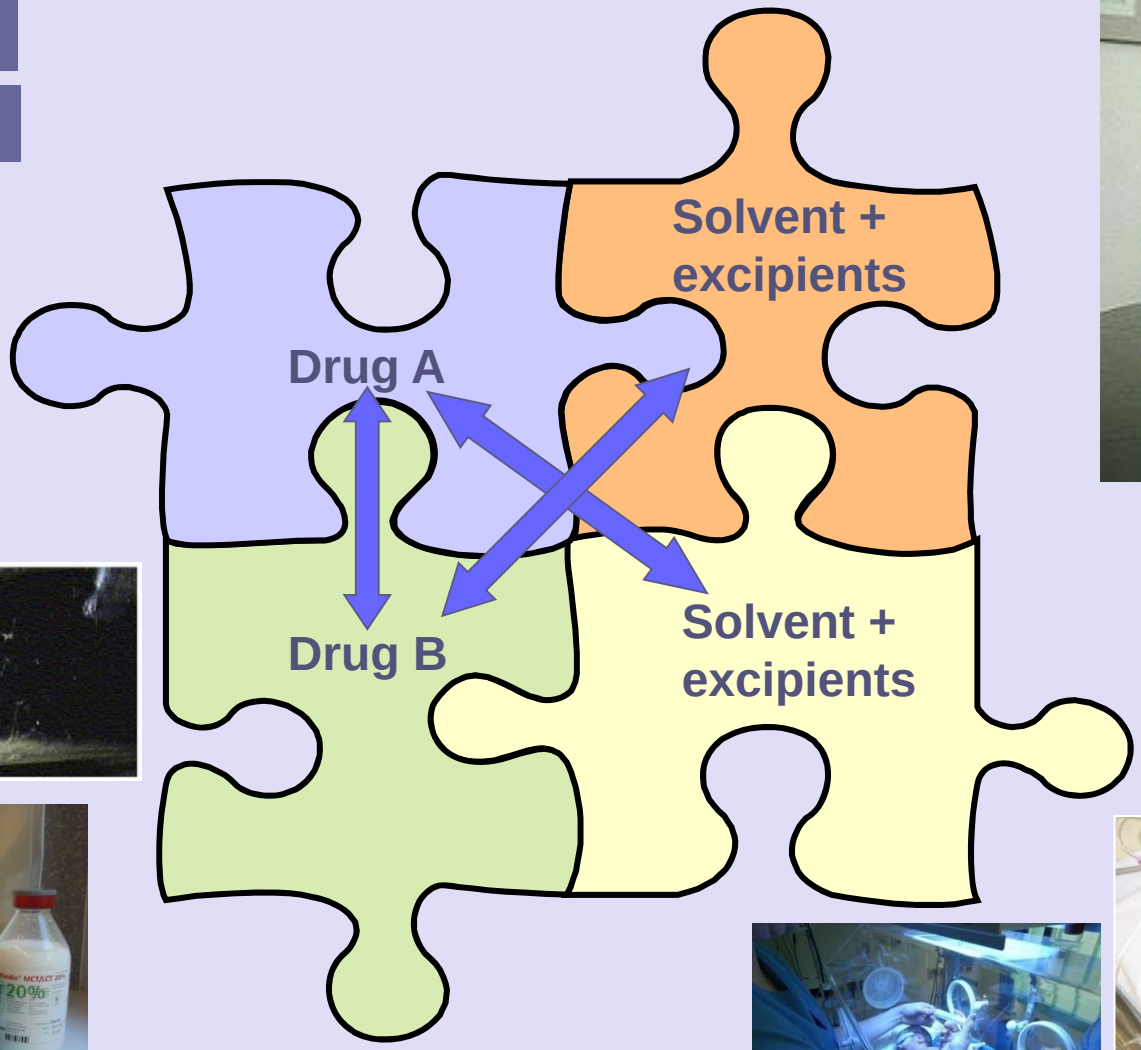
- What are drug incompatibilities?
- How frequent in the ICU?
- How can we prevent them?
- How can we treat them?
- What should you know?

TO REMEMBER

Acidic drugs

Basic drugs





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

continuous

intermittent

material

Lumen 1 (nutrition)	Lumen 2 (basic pH)	Lumen 3 (acidic pH)
• Nutriflex • Sandimmun	• Nexium	• Trandate
• Bactrim • Cancidas (stop Nutriflex)	• Cymevene • Lasix	• Cellcept • Solumedrol • Tazobac
	• In-line filter 0.2 γm	• In-line filter 0.2 γm
	• Blood (stop Nexium for 1h, no filter)	• Reserve drugs

TAKE HOME MESSAGE

Hospital and clinical pharmacists can help!