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Physical Compatibility of Intravenous Drugs Commonly Used in Intensive Care Units: An Observational Study and Physical Compatibility Laboratory Tests on Anti-Infective Drugs

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Abstract

Background: The objectives were to perform an observation of the administration of injectable drugs in three ICUs, to identify injectable drugs administered by Y-site infusion or mixed in the same container, to compare with physical compatibility data available in the literature and to test the physical compatibility for missing data.

Methods: An observational study was realised over two weeks and patients receiving more than one injectable drug in the same line simultaneously were included. Physical compatibilities were assessed in pairs by comparing with three databases. For some missing data, three tests were realised for pairs including an anti-infective drug. Visual and subvisual evaluations were performed after the preparation, 1 and a 4-hour storage.

Results: A total of 389 combinations between two injectable drugs was observed for Y-site infusions and 31 mixtures in the same container. According to the literature, 21.1% associations were physically compatible, 1.8% as physically compatible potentially, 8.0% as physically incompatible, 6.4% have divergent data according to the databases and 62.7% have no data. Two mixtures were documented. 37 pairs were tested and 70.3% were physically compatible, 8.1% were physically incompatible after visual evaluation and 21.6% after subvisual evaluation.

Conclusions: In the majority of cases, no compatibility data are available in the literature. Laboratory tests give additional information.

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Introduction

Patients hospitalized in Intensive Care Units (ICUs) often require the use of multiple drugs and the intravenous route is the most commonly way of administration. High concentrations of drug solutions with a minimum volume are used to avoid fluid overload and to rapidly obtain an optimal concentration. However, intravenous (I.V) accesses are limited and multiple I.V drugs have to be administered simultaneously to patients, leading to concomitant administration of different drugs in the same infusion line.

For Y-site infusions, drugs must be physically compatible, which means no precipitation, no change of colour or no gas formation [1]. Physical incompatibilities can lead to the formation of precipitate, catheter obstruction, venous irritation, and pulmonary or renal emboli [2]. Incompatibilities of drugs can also result in a decrease in drug activity, change of active drugs or formation of toxic compounds [3].

Bertsche et al. listed the five most important errors for parenteral drugs: hygiene defects, duration of administration, prescribing information (patient, brand, dosage, administration interval and formulation), labeling the preparation for a specific identification and incompatibilities [4]. Taxis et al. have reported that incompatibilities are the most common intravenous medication errors in hospital with a frequency of 25% with 2% having a severe clinical importance [5]. Tissot et al. have assessed medication-administration errors in an ICU: 18.6% of physicochemical compatibility errors were recorded, 63.2% of these errors had a potential clinical effect and 26.3% were potentially life-threatening [6].

The objectives of this study were (1) to perform an observation of the administration of injectable drugs in three adults' ICUs of our hospital, to identify injectable drugs administered by Y-site infusion or mixed in the same container, (2) to compare with

physical compatibility data available in the literature and (3) in some cases, in the absence of physical compatibility data, to test the physical compatibility in our quality control laboratory.

Materials and methods

Observational analysis in ICUs

Between April and June 2018, an observational prospective study was conducted over two weeks in each of three different adults' ICUs selected: one medical ICU and two surgical ICUs (cardiac and polyvalent).

Prescriptions of patients receiving more than one I.V drug in the same line simultaneously (Y-site infusion or drugs mixed in the same container) were included. Each prescription was counted only once per patient to avoid the over-representation of patients who had been hospitalised for a long time. Any modification of prescription for a patient already counted was included. All I.V. drugs were recorded for concentration, solvent and type of container.

The physical compatibility of the drugs used in the Y-site infusions was evaluated in pairs, even if more than two drugs were administered simultaneously in the same IV line. The mixtures in the same container were assessed as a whole, taking into account all the molecules mixed. For comparison with data available in the literature, three databases were used: the 19th edition of the Handbook on Injectable Drugs® [7], the 36th edition of "Stability of injectable drugs in infusion" [8] and Stabilis® [9].

The classification criteria according to the literature data on drug combinations and mixtures observed are presented in Table 1.

Laboratory tests

Many pairs with no data were observed during this study and we focused laboratory tests on pairs including one or two anti-infective drugs (antibiotic, antiviral or antifungal drugs). To simulate the Y-site infusion, each drug in each pair tested was prepared separately at baseline. If the solvent used or the concentration of a drug was different between the three ICUs observed, we tested the different variables in the laboratory. Drugs were mixed and kept in glass tubes at room temperature, not protected from light, to simulate the conditions of storage observed in ICUs. Three tests were realised for each pair studied (drug A/drug B): a) 1 mL/9 mL; b) 9 mL/1 mL; c) 5 mL/5 mL. In the majority of physical compatibility studies, a single 1:1 ratio has been performed [10, 11]. For each pair of drugs tested, we performed these different ratios to simulate cases where the drug flow is different leading to higher or lower concentrations. Mixtures were manually stirred during 30 seconds.

Physical compatibility was defined as the absence of particulate formation, haze, colour change and gas evolution [1]. As recommended by the European Pharmacopeia [12], the samples were visually inspected against a white/black background with the unaided eye by two different technicians after the mixture and after a 1-hour and 4-hour storage. The subvisual aspect was assessed by using a UV spectrophotometer (Safas mc^2, Monaco). The absorbance light was scanned at 350, 410 and 550 nm as recommended by the European Consensus Conference at each time of the analysis [1]. Drugs were considered as physically compatible if no visible change was detectable within 4 hours. A modification in absorbance value of the initial concentration was considered as turbidity. Table 2 gives the list of drugs and solvents used for laboratory tests.

Table 1: Criteria for the classification of drug combinations and mixtures observed in ICUs according to literature data.

Pairs observed in Y-site infusion					Mixture observed in the same container	
Compatible	**Potentially compatible**	**Incompatible**	**Controversial**	**No data**	**Stable or not stable**	**No data**
Compatibility data available in the literature with concentrations equal to or higher than those observed	Compatibility data available in the literature with concentrations lower than those observed	Incompatibility data available in the literature regardless of the concentrations, the solvent and the container	Compatibility and incompatibility data available in the literature		Physico-chemical stability data available in the literature with identical concentrations or closer than observed	

Table 2: List of drugs and solvents used for laboratory tests.

	Laboratory	Batch
Anti-infective drugs		
Amoxicillin 1 g	Panpharma	305141, 305173
Amoxicillin 2 g	Panpharma	304826
Amphothericin B liposomal (Ambisome®)	Gilead sciences	0121476D1
Cefazolin 2 g	Mylan	171109, 171110
Cefepim 2 g	Mylan	4M2098FR
Cefotaxime 2 g	Mylan	R3051
Cotrimoxazole (Bactrim®) 400/80 mg 5 mL	Roche	F3069F03
Daptomycin 350 mg	Accord	290/18
Fluconazole 2 mg/mL	Fresenius Kabi	15MF225F4
Gentamicine 40 mg/mL	Panpharma	70595
Gentamicine 80 mg/mL	Panpharma	70700
Levofloxacine 250 mg/50 mL	Fresenius Kabi	15ME507R22
Linezolid 600 mg/300 mL	Fresenius kabi	15MF170I1
Ornidazole 1 g 6 mL	SERB/CSP	2476
Ornidazole 500 mg 3 mL	SERB/CSP	2448
Piperacillin/tazobactam 4 g	Mylan	5M2914FR
Spiramycine (Rovamycine®) 1.5 MUI	Sanofi	85088
Vancomycin 1 g	Sandoz	EC0109
Vancomycin 500 mg	Sandoz	CB0124
Voriconazole (Vfend®) 200 mg	Pfizer	Z499509
Other drugs		
Heparin sodium 5000 UI/1 mL	Sanofi	5A013
Insulin (Umuline®) 100 UI/mL	Lilly	C875902
Levetiracetam 100 mg/5 mL	Mylan	F2046
Magnesium sulfate 15 % (1.5 g/10 mL)	Aguettant	1802267
Nefopam (Acupan®) 20 mg/mL	Biocodex	F0226
Pantoprazole 40 mg	Arrow	PAG14
Pyridoxine hydrochloride 250 mg/5 mL	Renaudin	205548
Thiamine (Bevitine®) 100 mg/2 mL	D.B Pharma	F1112
Solvents		
Water for injection 20 mL	Chaix et du marais	8P345
Water for injection 250 mL	Lavoisier	8F031
Sodium chloride 0.9 % 10 mL Proamp®	Aguettant	1803445
Sodium chloride 0.9 % 100 mL Ecoflac®	BBraun	18281451
Sodium chloride 0.9 % 250 mL	Lavoisier	8F323
Sodium chloride 0.9 % 500 mL	Lavoisier	8F031, 8F368
Sodium chloride 0.9 % 500 mL Ecoflac®	BBraun	183358162
Glucose 5 % 100 mL Ecoflac®	BBraun	182018131
Glucose 5 % 100 mL	Lavoisier	4F1933
Glucose 5 % 250 mL	Lavoisier	4F1932
Glucose 5 % 250 mL Easyflex®	MacoPharma	BMAF272
Glucose 5 % 500 mL Ecoflac®	BBraun	18314450

Results

Observational analysis in ICUs

Y-site evaluation

A total of 74 medical prescriptions were analysed. 389 different associations between two IV drugs have been reported and compared to physical compatibility data available in the three databases. According to the literature, the physical compatibility results obtained for the Y-site combinations are presented in Figure 1.

Table 3 illustrates the top 10 pharmacological classes used in Y-site infusion and Table 4 represents the main pharmacological classes with missing compatibility data in the literature, in descending order.

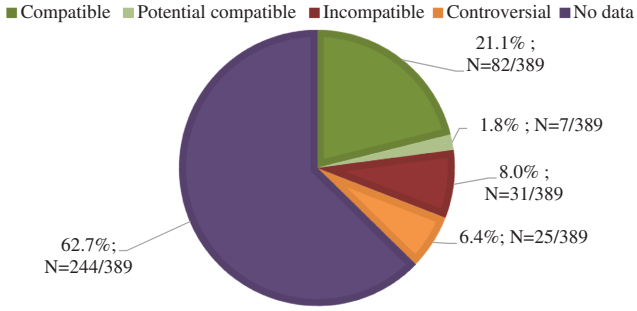

Figure 1: Drugs combinations for Y-site infusions: comparison with physical compatibility data in the literature.

Table 3: The top 10 pharmacological classes and the main drugs used in Y-site infusion classified by ATC codes, in descending order.

ATC Codes	Most used in Y-site infusion	Drugs
B05	Blood substitutes and perfusion solutions	Cernevit®, Nutryelt®, magnesium sulfate, calcium chloride, potassium chloride, Phocytan®, Dipeptiven®, albumin
J01	Antibiotics	Amikacin, amoxicilline, cefazolin, cefepim, cefotaxime, ceftazidime, ceftriaxone, cotrimoxazole, daptomycin, gentamicin, levofloxacin, linezolid, meropenem, metronidazole, ornidazole, piperacillin/tazobactam, spiramycine, vancomycin
N02	Analgesics	Acetylsalicylic acid, morphine, nefopam, paracetamol, tramadol
A11	Vitamins	Ascorbic acid, pyridoxine, thiamine
B01	Anticoagulants	Heparin sodium
A10	Antidiabetics	Insulin
C01	Cardioactive drugs	Amiodarone, dobutamine, isosorbide dinitrate, isoprenaline, norepinephrine
A02	Drugs for acid related disorders	Pantoprazole
A12	Mineral supplements	Selenium, zinc
J02	Antimycotics for systemic use	Caspofungin, fluconazole, voriconazole

Mixtures evaluation

A total of 31 drug mixtures in the same container were reported during this study. On average, 3.2 drugs were mixed in the same container and two mixtures have already been studied in the literature (6.5%; N = 2/31). The stability of the droperidol-morphine mixture was evaluated by Williams et al. [13] and the metoclopramide-ondansetron mixture by Stewart et al. [14]. For other mixtures, no data were reported. All the mixtures observed during this study with missing data in the literature are presented in Table 5.

Table 4: The 10 pharmacological classes with the least compatibility data in the literature classified by ATC codes, in descending order.

ATC Codes	With missing compatibility data in the literature
B05	Blood substitutes and perfusion solutions
J01	Antibiotics
N02	Analgesics
A11	Vitamins
A12	Mineral supplements
J02	Antimycotics for systemic use
C01	Cardioactive drugs
A10	Antidiabetics
A02	Drugs for acid related disorders
B01	Anticoagulants

Laboratory tests

37 pairs were tested in the laboratory. 70.3% of pairs (N = 26/37) were evaluated as physically compatible after visual and subvisual evaluation. 8.1% of pairs (N = 3/37) were found to be incompatible after the visual evaluation and 21.6% of pairs (N = 8/37) after only the subvisual evaluation. The results obtained are presented in Table 6.

Figure 2 presents the large white precipitate occurring immediately after mixing amoxicillin with vancomycin. Figure 3 presents the precipitation formed after the mixture of cotrimoxazole with heparin sodium. This precipitation occurs after a 4-hour contact.

Discussion

Patients in ICUs are subjected to a high rate of incompatibilities.

Despite many physical compatibility studies published in the literature, physical compatibility data between injectable drugs are not always available.

Observational study

Patients admitted to ICUs constitute a high-risk population, with higher drug concentrations in the majority of cases than for other patients. The observational study

Table 5: Mixtures of drugs in the same container, observed in ICUs, with missing data in the literature.

Drugs	Dose	Concentration	Container	Solvent	Final volume
Mixtures of 2 drugs					
Cernevit®		*one vial*	Syringe	NaCl 0.9 %	50 mL
Nutryelt®		*one vial*			
Calcium chloride	2 g	4 mg/mL	Bag	G5 %	500 mL
Thiamine	100 mg	0.2 mg/mL			
Potassium chloride	2 g–4 g	8–16 mg/mL	Bag	G5 %	250 mL
Thiamine	100 mg	0.4 mg/mL			
Dobutamine	500 mg	10 mg/mL	Syringe	G5 %	50 mL
Norepinephrine	8 mg	0.16 mg/mL			
Droperidol	1.25–2.5 mg	0.025–0.052 mg/mL	Syringe	NaCl 0,9 %	50 mL
Nefopam	120 mg	2,4 mg/mL			
Glucose phosphate	13.2 mmol	0.053 mmol/mL	Bag	G5 %	250 mL
Thiamine	100 mg	0.4 mg/mL			
Magnesium sulfate	1.5 g	1,5 g/L	Bag	NaCl 0.9 %	1000 mL
Thiamine	100 mg	0,1 mg/mL			
Mixtures of 3 drugs					
Cernevit®		*one vial*	Bag	Parenteral	2000 mL
Clorazepate dipotassium	10 mg	5 µg/mL		nutrition	
Nutryelt®		*one vial*			
Cernevit		*one vial*	Bag	Parenteral	1477 mL
Nutryelt®		*one vial*		nutrition	
Magnesium sulfate	4,5 g				
Cernevit®		*one vial*	Syringe	NaCl 0.9 %	100 mL
Nutryelt®		*one vial*			
Thiamine	100 mg	1 mg/mL			
Calcium chloride	2 g	16–2 g/L	Bag	NaCl 0.9 %(1) –	125 mL(1) –
Nefopam	80 mg	0,64–0.08 mg/mL		Glucose 10 %(2) –	1000 mL(2)(3)
Magnesium sulfate	3 g	24–3 g/L		Isofundine® (3)	
Calcium chloride	2 g	2 g/L	Bag	Isofundine®	1000 mL
Nefopam	80–100 mg	0.08–0.1 mg/mL			
Magnesium sulfate	3–4.5 g	3–4.5 g/L			
Droperidol	1.25–2.5 mg	0.025–0.05 mg/mL	Syringe	NaCl 0.9 %	50 mL
Ketamine	30–45–50 mg	0.6–0.9–1 mg/mL			
Morphine sulfate	20–50 mg	0.4–1 mg/mL			
Nefopam	80 mg	0.16 mg/mL	Bag	Isofundine®	500 mL
Pyridoxine	250 mg	0.5 mg/mL			
Thiamine	250 mg	0.5 mg/mL			
Metoclopramide	10 mg	0.5 mg/mL	Syringe	–	20 mL
Pantoprazole	40 mg	2 mg/mL			
Phloroglucinol	80 mg	4 mg/mL			
Pyridoxine	250 mg	0.5 mg/mL	Bag	NaCl 0,9 %	500 mL
Magnesium sulfate	3 g	6 g/L			
Thiamine	100 mg	0.2 mg/mL			
Mixtures of 4 drugs					
Cernevit®		*one vial*	Syringe	NaCl 0.9 %	100 mL
Nutryelt®		*one vial*			
Magnesium sulfate	4.5 g	45 g/mL			
Thiamine	100 mg	1 mg/mL			

(*continued*)

Table 5: (*continued*)

Drugs	Dose	Concentration	Container	Solvent	Final volume
Cernevit®		*one vial*	Syringe	NaCl 0.9 %	100 mL
Nutryelt®		*one vial*			
Pyridoxine	250 mg	2.5 mg/mL			
Thiamine	100 mg	1 mg/mL			
Cernevit®		*one vial*	Bag	NaCl 0.9 %	100 mL
Nutryelt®		*one vial*			
Zinc	10 mg	0.1 mg/mL			
Selenium	100 µg	1 µg/mL			
Mixture of more than 4 drugs					
Ascorbic acid	1g	10 mg/mL	Bag	NaCl 0.9 %	100 mL
Cernevit®		*one vial*			
Calcium folinate	5 mg	0.05 mg/mL			
Nutryelt®		*one vial*			
Thiamine	100 mg	1 mg/mL			
Pyridoxine	250 mg	2.5 mg/mL			
Selenium	100 µg	0.1 mg/mL			
Zinc	10 mg	0.1 mg/mL			

NaCl 0.9 %: sodium chloride 0.9 %; G5 %: glucose 5 %

Table 6: Physical compatibility tests performed in laboratory.

	Drugs	Concentration	Solvent		Results
1	Amphothericin B liposomal (Ambisome®)	1.16 mg/mL	G5 %	Incompatible	Precipitation
	Vancomycin	10, 62.5 and 83.3 mg/mL	G5 %		
2	Amoxicillin	20.83 and 83.3 mg/mL	NaCl 0.9 %	Physically compatible	
	Heparin sodium	208 UI/mL	NaCl 0.9 %		
3	Amoxicillin	20.83 and 83.3 mg/mL	NaCl 0.9 %	Physically compatible	
	Insulin (Umuline®)	1 UI/mL	NaCl 0.9 %		
4	Amoxicillin	20.83 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Magnesium sulfate	6 mg/mL	NaCl 0.9 %		
5	Amoxicillin	20.83 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Nefopam	0.16 mg/mL	NaCl 0.9 %		
6	Amoxicillin	20.83 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Pyridoxine	0.5 mg/mL	NaCl 0.9 %		
7	Amoxicillin	20.83 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Thiamine (Bevitine®)	0.2 mg/mL	G5 %		
8	Amoxicillin	20.83 mg/mL	G5 %	Incompatible	Precipitation (Figure 2)
	Vancomycin	31.25 mg/mL	G5 %		
9	Cefazolin	41.6 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Cotrimoxazole (Bactrim®)	3.2/0.64 and 80/16 mg/mL	G5 % or none		
10	Cefazolin	41.6 mg/mL	G5 %	Physically compatible	
	Levetiracetam	5.21 and 20.83 mg/mL	NaCl 0.9 %		
11	Cefazolin	41.6 mg/mL	G5 %	Physically compatible	
	Levofloxacine	5 mg/mL	–		
12	Cefazolin	41.6 mg/mL	G5 %	Incompatible	Increase of UV absorbance
	Nefopam	0.16 mg/mL	NaCl 0.9 %		

(*continued*)

Table 6: (*continued*)

	Drugs	Concentration	Solvent		Results
13	Cefazolin Pantoprazole	41.6 mg/mL 4 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
14	Cefepim Daptomycin	83.3 mg/mL 21 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
15	Cefepim Thiamine (Bevitine®)	83.3 mg/mL 0.2 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
16	Cefepim Voriconazole	83.3 mg/mL 8 mg/mL	G5 % G5 %	Physically compatible	
17	Cefotaxime Heparin sodium	41.6 and 125 mg/mL 208 UI/mL	G5 % or NaCl 0.9 % NaCl 0.9 %	Physically compatible	
18	Cefotaxime Hydrocortisone	83.3 mg/mL 2 mg/mL	G5 % NaCl 0.9 %	Incompatible	Increase of UV absorbance
19	Cefotaxime Insulin (Umuline®)	83.3 mg/mL 1 UI/mL	G5 % NaCl 0.9 %	Physically compatible	
20	Cefotaxime Levetiracetam	83,3 mg/mL 20.83 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
21	Cefotaxime Ornidazole	41.6 mg/mL 31.25 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
22	Cefotaxime Thiamine (Bevitine®)	83.3 mg/mL 0.4 mg/mL	G5 % G5 %	Physically compatible	
23	Cotrimoxazole (Bactrim®) Heparin sodium	3.2/0.64 and 80/16 mg/mL 208 UI/mL	G5 % or none NaCl 0.9 %	Incompatible	Precipitation for undiluted Bactrim® (Figure 3)
24	Cotrimoxazole (Bactrim®) Insulin (Umuline®)	3.2/0.64 and 80/16 mg/mL 1 UI/mL	G5 % NaCl 0.9 %	Incompatible	Increase of UV absorbance
25	Daptomycin Thiamine (Bevitine®)	21 mg/mL 0.2 mg/mL	NaCl 0.9 % NaCl 0.9 %	Physically compatible	
26	Fluconazole Thiamine (Bevitine®)	2 mg/mL 0.2 mg/mL	– NaCl 0.9 %	Physically compatible	
27	Gentamicin Nefopam	4.17 mg/mL 0.16 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
28	Linezolid Insulin (Umuline®)	2 mg/mL 1 UI/mL	– NaCl 0.9 %	Physically compatible	
29	Ornidazole Heparin sodium	31.25 mg/mL 208 UI/mL	NaCl 0.9 % NaCl 0.9 %	Physically compatible	
30	Ornidazole Insulin (Umuline®)	31.25 mg/mL 1 UI/mL	NaCl 0.9 % NaCl 0.9 %	Physically compatible	
31	Piperacillin/tazobactam Insulin (Umuline®)	166/20.83 mg/mL 1 UI/mL	G5 % NaCl 0.9 %	Physically compatible	
32	Piperacillin/tazobactam Levetiracetam	166/20.83 mg/mL 20.83 mg/mL	G5 % NaCl 0.9 %	Physically compatible	
33	Piperacillin/tazobactam Thiamine (Bevitine®)	166/20.83 mg/mL 0.4 mg/ml	G5 % G5 %	Physically compatible	
34	Spiramycine (Rovamycine®) Heparin sodium	0.0625 MUI/mL 208 UI/mL	NaCl 0.9 % NaCl 0.9 %	Physically compatible	

(*continued*)

Table 6: (*continued*)

	Drugs	Concentration	Solvent	Results
35	Vancomycin Nefopam	31.25 mg/mL 0.16 mg/mL	G5 % NaCl 0.9 %	Physically compatible
36	Voriconazole (Vfend®) Heparin sodium	8 mg/mL 208 UI/mL	G5 % NaCl 0.9 %	Physically compatible
37	Voriconazole (Vfend®) Thiamine (Bevitine®)	8 mg/mL 0.2 mg/mL	G5 % NaCl 0.9 %	Physically compatible

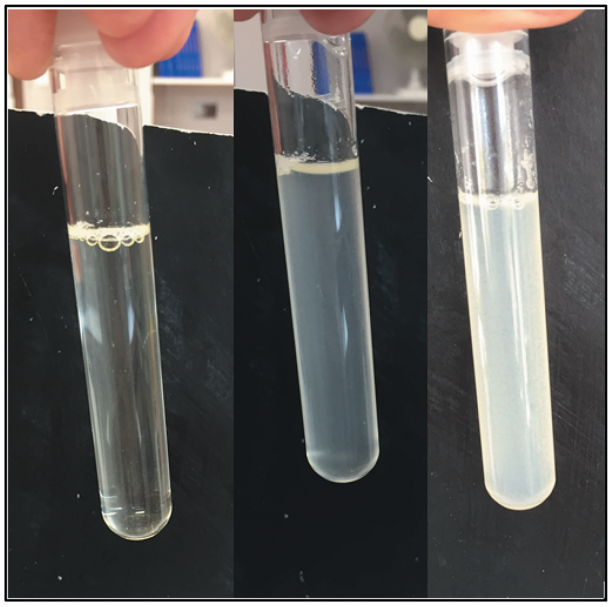

Figure 2: Mixture of amoxicillin (A) 20.83 mg/mL diluted in 5 % glucose with vancomycin (V) 31.25 mg/mL diluted in 5 % glucose after the mixture (left), after 5 minutes (middle) et after 30 minutes (right) (A:V (v:v): 5:5).

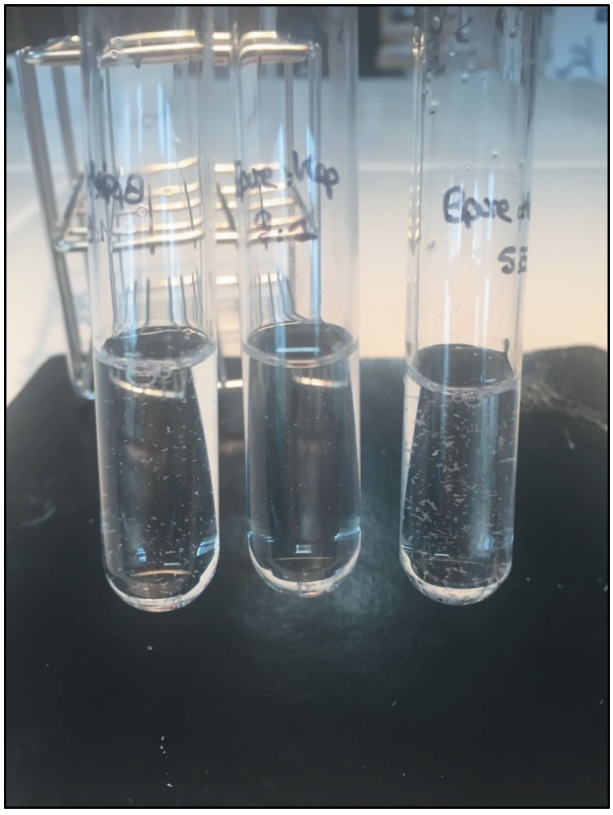

Figure 3: Mixture of cotrimoxazole (C) undiluted with heparin sodium (H) at 208 UI/mL diluted in 0.9 % sodium chloride after 4 hours (C:H (v:v): glass tube left to right, n°1: 1:9; n°2: 9:1; n°3: 5:5).

has demonstrated that in the majority of cases, no physical compatibility data were available in the literature with only 22.9 % of the combinations documented as physically compatible and 8.0 % as incompatible. After laboratory tests, the percentage of combinations with missing data was 56.0 %. We obtained a final percentage of incompatible and physical compatible combinations of 9.8 % and 27.8 % respectively.

A previous similar study was performed in 2006 in the same hospital center in two ICUs. After consulting literature, Serrurier et al. had obtained 23 % of Y-site admixtures physically compatible, 5 % were physically incompatible, 2 % with conflict between two literature references and 70 % without any data about stability or compatibility. We can notice that the percentage of combinations without data has decreased by 14 %. On the other hand, a more important percentage of associations documented as incompatible are administered in this study compared to 2006 [15].

Review of observational studies performed in ICUs

In the literature, other studies have identified the percentage of drug incompatibilities in ICUs. We obtained a similar percentage of incompatibilities to that found in a retrospective ICU study performed by Bertsche et al. with 7.2 % of physically incompatible pairs administered [16].

Tardy et al. observed 12% of incompatible combinations and 50% of these incompatible combinations included an anti-infective drug [17]. Neininger et al. analysed prescriptions in pediatric ICUs and identified 10% of incompatible drug administration [18]. The most common drugs involved were cefotaxime, pantoprazole and vancomycin. Kanji et al. conducted an observational study in thirteen ICUs and observed a prevalence of inappropriate associations in 18.7% of patients with more than one drug infusion [19]. They also quantified the published physical and chemical stability data for drugs commonly used in continuous infusion in ICUs. Physical and/or chemical compatibility data existed for 54% of the combinations with 15% of incompatible combinations and 9% of conflicting data [20]. Bertsche et al. have cited a publication of Kähny-Simonius et al. who observed that compatibility is unknown or ambiguous for up to 45% of co-infusions in an ICU [16, 21].

A study obtained a more important percentage of incompatible combinations. Marisilio et al. found a percentage of incompatibilities in 68% of prescriptions analysed in an ICU [22]. One study found a lower percentage of incompatibilities. After comparing clinical practices in ICUs with the literature, Humbert-Delaloye et al. obtained 4.8% of incompatible combinations [23].

Data available in the literature

In this study, antibiotics are one of the most commonly used pharmacologic classes for Y-site infusion. This class is both the one that contains the most compatibility data available in the literature for responding to ICUs' combinations, but also one of the classes in which the data was the most missing. This can be explained by the large number of molecules present in this class and used in ICUs. In our study, out of 77 molecules, 18 were antibiotics (23.4%; N = 18/77). The same observation can be made for the class of blood substitutes and perfusion solutions.

For the class of anticoagulants represented only by heparin sodium in this study, in the majority of cases, physical compatibility data are available in the literature to respond to the combinations performed in ICUs. For mineral supplements or anti-mycotics for systemic use, in the majority of cases, no compatibility data are available in the literature.

One of the limits of this study is that physical compatibility data in the literature often relate to drug pairs and the information available on triplets or quadruplets is limited. Overall, in clinical practice, more than two drugs are infused simultaneously by Y-site infusion or mixed in the same container. In this study, a mean of 3 drugs were mixed in the same container.

Incompatible combinations in our ICUs

Of the 31 combinations performed in ICUs and reported as incompatible in the literature, 9 combinations included heparin sodium (29.0%; N = 9/31). Stabilis® database reported 132 physical incompatibilities including heparin sodium [9]. Regarding the incompatible associations observed in ICUs, the incompatible association of heparin sodium with caspofungin has been demonstrated by Chan et al. with the formation of a large white precipitate immediately after contact between the two drugs [24]. For the combination of heparin sodium with vancomycin, the Summary of Product Characteristics of vancomycin reports this association as incompatible [25]. The association of heparin sodium with amiodarone has been demonstrated as incompatible by Perez Juan et al. [11] and Charlmers et al. [26].

We observed 8 incompatible combinations including pantoprazole (25.8%; N = 8/31). Pere et al. tested the compatibility of pantoprazole with other injectable drugs during Y-site infusion [27]. Among the mixtures observed in ICUs during our study, they had already observed a significant precipitation of the pantoprazole-amiodarone combination, a precipitation formed after 15 minutes for the association of pantoprazole with metoclopramide and a precipitation after one hour during the combination of pantoprazole with heparin or piperacillin/tazobactam. Neininger et al. had also highlighted the significant risk of precipitation with this molecule [18].

Of the 25 molecules observed in an incompatible combination, 9 anti-infective drugs were involved (caspofungin, cefazolin, cefotaxime, cefepim, cotrimoxazole, gentamicine, meropenem, metronidazole, vancomycin). The combination of cotrimoxazole with caspofungin has already been demonstrated to be incompatible, with the formation of a significant white precipitate formed immediately after the contact [24].

Mixtures of drugs in the same container in our ICUs

Physical compatibility data are not sufficient to evaluate a mixture and physico-chemical stability data are necessary. In the majority of cases, no information is available

in the literature on the physicochemical stability of a mixture. Only two mixtures observed in ICUs have already been studied in the literature. Humbert-Delaloye et al. studied the mixture of 5 mg/mL dobutamine and 0.06 mg/mL norepinephrine [28]. This mixture was observed during our study but with higher concentrations of dobutamine (10 mg/mL) and norepinephrine (0.16 mg/mL). A new stability study should be performed to confirm the physicochemical stability with higher concentrations. Another mixture was also observed in ICUs, combining droperidol, ketamine and morphine sulfate. In the literature, a study evaluated the stability of a comparable mixture of droperidol, ketamine and fentanyl with a 30-day stability at 25 °C [29].

More than a third of the mixtures observed include thiamine (vitamin B1) (33.3 %; N = 10/31), a molecule with limited stability data in literature. The mixture of nefopam with droperidol was observed in 12 different patients during this study, without any stability data published to date.

Laboratory tests

Physical compatibility tests on anti-infective drugs

In this work, we focused on laboratory tests including an anti-infective drug. Antibiotics and antifungal drugs are in the top 10 of the most-used pharmacological classes in Y-site infusion in ICUs, as well as in the top 10 of pharmacological class for which physical compatibility data are the most missing. Schneider et al. observed that parenteral drugs and particularly anti-infective agents were more frequently involved in administration errors than other compounds or forms of administration [30]. Bertsche et al. also observed that antibiotics were the most common incompatible pairs of drugs [4]. As demonstrated by Roberts et al. [31], continued administration of antibiotics such as β-lactams versus intermittent administration is associated with decreased hospital mortality in critically ill patients with severe sepsis. In contrast, continued administration of antibiotics may increase the risk of incompatibility.

Visually incompatible pairs

The duration of a physical compatibility study is different between the authors in the literature. Trissel et al. observed the tests at different intervals up to 4 hours [32]. As explained by Nemec et al., the in-line contact time between drugs in the Y-infusion is at most four hours [33].

In our study, for the majority of laboratory tests, pairs of drugs were physically compatible. Three pairs were visually incompatible: amphotericin B liposomal with vancomycin (pair 1), amoxicillin with vancomycin (pair 2) and undiluted cotrimoxazole with heparin sodium (pair 3). The precipitation occured immediately after mixing for pair 1, after 5 minutes for pair 2 and after 4 hours for pair 3. For each test performed with cotrimoxazole, we studied two concentrations used in ICUs: undiluted concentration for patients with fluid restriction and diluted concentration as recommended by the Summary of Product Characteristics. There was no visual precipitation for the diluted cotrimoxazole solution with heparin sodium but an increase of absorbance during the subvisual evaluation was observed. For cotrimoxazole, the risk of precipitation is higher with undiluted solution.

Subvisually incompatible pairs

No visual precipitation occurred but an increase of absorbance was observed after a 1-hour or a 4-hour contact. These combinations cannot be recommended safely.

Critical drugs

Of the three tests performed for cotrimoxazole, all were considered as incompatible. Two out of three tests performed on vancomycin were visually incompatible. Of the 7 tests performed on amoxicillin with another drug, five combinations were considered as incompatible.

Solutions and limits

Stabilis® has also created a tool for creating compatibility charts for clinicians [9]. This tool has already shown its usefulness [11, 34]. Conducting compatibility studies is one of the scientific missions of pharmacists [2, 35]. In the ICUs of our Hospital, the prescriptions are not fully computerised. The handwritten prescriptions are realised and accessible only in the care units, which limits the knowledge of all the drugs administered to a patient by the pharmacist. In addition, the administration scheme is not specified on the handwritten prescriptions.

One of the limitations of this study is that only physical compatibility has been evaluated. The absence of physical modification does not allow to conclude to the chemical stability. The concentrations of the drug and the degradation products have not been evaluated in our study. Another limitation is that the evaluation has been investigated only by pairs and the results cannot be extrapolated for mixtures of 3 drugs or more.

Additional Y-site compatibility studies have to be performed after this evaluation. A program of stability studies will be set up to evaluate the stability of frequently-used mixtures observed during this evaluation.

Conclusion

The present study provides new information on the physical compatibility of anti-infective drugs used in Y-infusion and on mixtures performed in ICUs. Physical compatibility data can contribute to safe medication practices.

This observational study highlighted that in most cases, physical compatibility data were missing from the literature and did not meet the clinical needs of ICUs.

The laboratory tests carried out focused on anti-infective drugs, one of the most-used pharmacological classes in ICUs care and represented by a large number of molecules. Many other compatibility tests need to be performed, especially on blood substitutes and perfusion solutions, mineral supplements and antifungal drugs. Mixture studies must also be performed, especially on vitamins, such as thiamine or pyridoxine. Critical molecules with high precipitation potential have been identified, including amoxicillin, cotrimoxazole, heparin sodium, pantoprazole and vancomycin.

In the absence of compatibility data, these drugs must be infused alone.

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