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Y-site compatibility of intravenous medications commonly used in intensive care units: laboratory tests on 75 mixtures involving nine main drugs

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Abstract

Objectives: Patients hospitalized in intensive care units often require multiple drug infusions. Due to limited intravenous accesses, concomitant administration of drugs in the same infusion line is often necessary. Compatibility studies of Y-site administration are available in the literature, but data of several combinations are lacking. Previous work from d'Huart et al. have performed an observation of the administration of injectable drugs in three adults ICUs and identified a list of Y-site administration without compatibility data. The objective of this study was to test the physical compatibility of the main drugs of this list used in pairs in Y-site infusions in critical care units, in order to provide new compatibility data to the literature, and to secure the administration of intravenous drugs.

Methods: The physical compatibility in Y-site of nine drugs with other drugs commonly used in intensive care units has been tested. Examinations were performed on 75 mixtures after their preparation, after 1 and 4-h storage. This evaluation included a visual examination with a search for precipitation formation, color change, gas formation, and a subvisual evaluation: absorbance measurements by UV-visible spectrophotometry at 350, 410 and 550 nm, and Light Obscuration Particle Count Test. The pH evaluation was performed at each time of analysis.

Results: Laboratory tests led to an overall compatibility of 68.0% for all mixtures obtained in this study. Nefopam was found to be quite compatible with other drugs (95.0%). Amiodarone hydrochloride (84.6%), acetylsalicylic acid (80.0%), clonidine hydrochloride (75.0%) and insulin (71.4%) were compatible with other drugs too. Atenolol (42.9%), furosemide (25.0%), heparin sodium (25.0%) showed less compatible results. Pantoprazole sodium (0.0%) was not at all compatible with the other drugs analyzed.

Conclusions: By the results of these laboratory tests, missing compatibility data are now available, providing additional information to the literature.

Keywords: intensive care units; intravenous; physical compatibility; y-site infusion.

Introduction

The intravenous (IV) route is the most common way of drug administration used in intensive care units (ICUs). Indeed, patients hospitalized in these units often require numerous infusions, due to their serious health conditions.

High concentrations of drugs are usually needed to limit the water intake and the infusion volume, using the minimum of IV accesses, as these are limited. For this reason, in most cases multiple IV drugs are administered simultaneously to patients in the same infusion line. For administrations in Y-site, compatibility tests must have been carried out and reliable data should be published in the literature, because incompatibility between drugs can lead to complications for the patient. A physical incompatibility between two drugs can be observed by the formation of a precipitate, a change in color, or the formation of gas [1, 2]. The formation of a precipitate may lead to catheter obstruction, venous irritation and pulmonary renal embolism [3]. In most cases, no physical compatibility data is available in the literature, while incompatibilities are one of the leading causes of IV medication errors in hospital with 25% of errors, including 2% of several clinical adverse effects [4]. Compatibility studies of Y-site administration are available in the literature, but many data are lacking. D'Huart et al. [5] performed an observational study in three different ICUs and have

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highlighted that in most cases (62.7%), physical compatibility data were missing from the literature.

The objective of this study was to test the physical compatibility of the main drugs of the list used in pairs in Y-site infusions in ICUs, in order to provide new compatibility data to the literature and to secure the administration of intravenous drugs.

Materials and methods

Compatibility tests were performed for drugs with the least data in the literature, according to three main databases: the 19th edition of the Handbook on Injectable Drugs® [6], Stabilis® [7] and the 36th edition of "Stability of injectable drugs in infusion" [8]. These tests were carried out on IV drugs the most frequently administered together in ICUs, reported in d'Huart's observational thesis [9].

To simulate Y-site infusion, the physical compatibility of parenteral drugs was evaluated in pairs, even if more than two drugs were commonly administered simultaneously in the same IV line.

Each mixture was carried out according to data from d'Huart's thesis [9]. Each drug was diluted in a solvent (water for injection (WFI), 0.9% sodium chloride (0.9% NaCl), 5% dextrose (D5W), 10% dextrose (D10W), Isofundine® (sodium chloride, potassium chloride, magnesium chloride, calcium chloride) or used pure, according to practices observed in ICUs in this previous work. When the solvent or the concentration of a drug was different between the three ICUs of the hospital, different variables were tested.

Each drug from each pair tested was prepared separately at the baseline. The drugs were reconstituted in their vials or used directly without prerequisite, according to their drug formulation and the corresponding summary of product characteristics. For the preparation of drugs, luer-lock polypropylene syringes identical to those used in ICUs were employed. Dilution with a specific solvent was obtained by using a Vygon® "female luer-lock to female luer-lock connector" between the drug syringe and the solvent syringe. For each pair of a main drug with another drug (drug A/drug B) tested, three ratios (9/1, 1/1 and 1/9) [1] were studied, allowing to simulate cases where the drug flow is different leading to higher or lower concentrations. Drugs were mixed in a 50 mL graduated flask and manually stirred during 30 s. They were kept at room temperature from 20 to 25 °C, upright and not protected from light, to simulate the storage conditions applied in ICUs.

Visual and subvisual evaluations

At each moment of the study, a visual evaluation was carried out on a white and a black background with a flashlight, with the unaided eye by two different technicians, before mixing, after mixing and after 1- and 4-h storage as recommended by the European Consensus Conference [1].

The subvisual aspect was analyzed by measuring the turbidity using a UV-visible spectrophotometer (SAFAS mc^2, Monaco). This method allows to evaluate the formation of microparticles in solution. The absorbance light was scanned at three wavelengths (350, 410 and 550 nm), also recommended by the European Consensus Conference [1]. A change in the initial absorbance of more than 0.1 between the measurement after mixing and after the 4-h of storage was considered as a turbidity and so incompatibility of the two drugs involved.

A second subvisual test was performed applying the Light Obscuration Particle Count Test (PAMAS SVSS). The particle counter is based on the principle of light blocking which allows the automatic determination of the number of particles according to their size. Requirements exist for the number of particles larger than 10 µm and larger than 25 µm. According to European Pharmacopoeia Reference Standards [10], for containers of ≤100 mL, the values to be respected were ≤6,000 particles of ≥10 µm and ≤600 particles of ≥25 µm per container. For containers of >100 mL, the values were ≤25 particles of ≥10 µm per milliliter and ≤3 particles of ≥25 µm per milliliter. Measurements were carried out in 10 mL glass tubes. Before each measurement, the outer surfaces of the glass tube were cleaned with a water jet from E-POD® "Pure Water Remote Dispenser". Before proceeding with particle counting, the contents of each sample were mixed by 20 successive slow inversions of the container, then the mixture was left to stand for 2 min to avoid the possible presence of bubbles which may be generated by agitation. A first portion of 1 mL of the mixture was removed and the number of particles was evaluated on the three next portions of 1 mL. The mean number of particles of these three portions (total volume of 3 mL) represented the number of particles in the mixture. Between each measurement, the particle counter tubing was flushed with two portions of 1 mL of water from the E-POD® "Pure Water Remote Dispenser". Measurements for each pair were repeated three times and the mean number represented the particle count.

The last test performed at any time was the pH measurement (Bioblock Scientific pH meter) of each solitary drug before it was combined, and then after having mixed the drugs in pairs. For each pair, the pH had to show no change of more than 0.5 pH unit within 4 h to be stable.

These compatibility tests were assessed at different times: after mixing the two drugs (T 0H), 1 h after preparation (T 1H), and after a 4-h storage (T 4H), as 60% of the compatibility studies published in the literature are carried out over a 4-h period [11].

Results

Seventy-five mixtures involving nine main drugs and 34 other drugs commonly used in ICUs were evaluated. Table 1 gives the list of all the drugs tested in Y-site and the solvents used. The pairwise compatibility results are all presented in Table 2, which shows the details of combinations evaluated.

Acetylsalicylic acid

Acetylsalicylic acid is a drug compatible in pairs with 80.0% (8/10) of the drugs tested presented in Table 2. The acetylsalicylic acid/potassium canreonate mixture was incompatible because of visible precipitation at the 9/1 ratio after preparation and at the 1/1 ratio after a 1-h storage. Practices also revealed the frequent combination of

Table 1: List of drugs and solvents used for laboratory tests.

	Tradename	Dosage	Laboratory	Batchs
Main drugs				
Acetylsalicylic acid	ASPEGIC INJECTABLE 500 mg/5 mL	500 mg	Sanofi Aventis	HY202/J710A
Amiodarone hydrochloride	CORDARONE 150 mg/3 mL sol inj	150 mg/3 mL	Sanofi Aventis	H1963/J0860
Atenonol	TENORMINE 5 mg/10 mL sol inj	5 mg/10 mL	Astrazeneca	F1016-1/F1021-1
Clonidine hydrochloride	CATAPRESSAN 0.15 mg/mL sol inj	0.15 mg/1 mL	Boehringer Ingelheim	C13508/C13509
Furosemide	FUROSEMIDE RENAUDIN 20 mg/2 mL sol inj	20 mg/2 mL	Renaudin	207536/207685
Heparin sodium	HEPARINE CHOAY 5000 UI/1 mL sol inj	5000 IU/1 mL	Labo Choay	AA003A
Heparin sodium	HEPARINE CHOAY 25 000 UI/5 mL sol inj	25000 IU/ 5 mL	Labo Choay	676
Insulin (human)	UMULINE RAPIDE 100 UI/mL sol inj	100 IU/1 mL	Lilly	D257313/D262785
Nefopam	ACUPAN 20 mg/2 mL sol inj	20 mg/2 mL	Biocodex	D8004
Pantoprazole sodium	EUPANTOL 40 mg pdre p sol inj	40 mg	Takeda	479857/488939
Other drugs				
Bumetanide	BURINEX 2 mg/4 mL sol inj	2 mg/4 mL	Karo Pharma AD	F1032FP1
Calcium chloride	CHLORURE DE CALCIUM RENAUDIN 10% sol inj	1 g/10 mL	Renaudin	207379
Cefazoline sodium	CEFAZOLINE MYLAN 2 g pdre p sol inj IM IV	2 g	Mylan	200520
Cefotaxime sodium	CEFOTAXIME MYLAN 2 g pdre p sol inj	2 g	Mylan	200656/200935/200936
Ciclosporine	SANDIMMUN 50 mg/mL sol diluer p perf	50 mg/1 mL	Novartis SAS	SVP16/SCCU8
Furosemide	FUROSEMIDE RENAUDIN 20 mg/2 mL sol inj	20 mg/2 mL	Renaudin	207242
Hydrocortisone sodium succinate	HYDROCORTISONE UPJOHN 100 mg prép inj	100 mg	Serb	2708-W2T30/2685-W2T28/ 3012-W2S87/3012-W2T47
Insulin (human)	UMULINE RAPIDE 100 UI/mL sol inj	100 IU	Lilly	D262785/D257313
Isofundine®	ISOFUNDINE sol p perf	500 mL	Renaudin	20045454/21084452
Isosorbide dinitrate	ISOSORBIDE MEDISOL 10 mg/10 mL sol inj	10 mg/10 mL	Medisol Labo	H028/H025/H030
Levetiracetam	LEVETIRACETAM MYLAN 100 mg/mL, solution à diluer pour perfusion	100 mg/1 mL	Mylan	5002235/5002260
Levofloxacine hemihydrate	LEVOFLOXACINE ARROW 5 mg/mL sol p perf en poche	250 mg/ 50 mL	Arrow	156
Levofloxacine hemihydrate	LEVOFLOXACINE ARROW 5 mg/mL sol p perf en poche	500 mg/ 100 mL	Arrow	43
Magnesium sulfate	SULFATE DE MAGNESIUM PROAMP 0.15 g/mL, solution injectable	1.5 g	Chaix et du Marais	0P207/0P208/0P138/ 0P189/0P189/1 P100
Methylprednisolone hemisuccinate	METHYLPREDNISOLONE MYLAN 20 mg, poudre pour solution injectable	20 mg	Mylan	B1156/206450/B1165
Metronidazole	METRONIDAZOLE B BRAUN 0.5%, solution pour perfusion	500 mg	Braun Medical	200738131
Midazolam hydrochloride	MIDAZOLAM MYLAN 50 mg/10 mL sol inj	50 mg/10 mL	Mylan	F3573/F3585
Mycophenolate mofetil hydrochloride	CELLCEPT 500 mg pdre p sol diluer p perf	500 mg	Roche	H3541/H3549/B8022
Nefopam	ACUPAN 20 mg/2 mL sol inj	20 mg	Biocodex	D777/D783/D787/D798/ H1047
Nicardipine	NICARDIPINE ARROW 10 mg/10 mL sol inj	10 mg/10 mL	Arrow	173
Nutryelt®	NUTRYELT sol diluer p perf	10 mL	Aguettant	D0023A01/D0025A07
Pantoprazole sodium	EUPANTOL 40 mg pdre p sol inj IV	40 mg	Takeda	490195
Paracetamol	PARACETAMOL B. BRAUN 10 mg/mL, solution pour perfusion	1 g/100 mL	Braun Medical	20501450/20427451/ 20504452/20352453/ 21104453
Phloroglucinol	PHLOROGLUCINOL/TRIMETHYLPHLOR-OGLUCINOL ARROW 40 mg/0.04 mg/4 mL sol inj	40 mg, 0.04 mg/4 mL	Arrow	1163 / 1173 / 1177
Phytomenadione	VITAMINE K1 CHEPLAPHARM 10 mg/1 mL sol buv/ inj	10 mg/1 mL	Cheplapharm	F4029F01/F4046F03/ F4061F02
Potassium canreonate	SOLUDACTONE 200 mg, lyophilisat et solution pour usage parentéral	200 mg	Pfizer	25A29D711

Table 1: (continued)

	Tradename	Dosage	Laboratory	Batchs
Potassium chloride	CHLORURE DE POTASSIUM LAVOISIER 10% (0.10 g/mL) sol diluer p perf	2 g/20 mL	Lavoisier	9P266/0P213
Pyridoxine hydrochloride	PYRIDOXINE RENAUDIN 250 mg/5 mL sol inj	250 mg/5 mL	Renaudin	207731
Remifentanil hydrochloride	ULTIVA 2 mg pdre p sol inj ou perf	2 mg	Aspen	9F7C/7H2N
Sodium selenite	SELENIUM INJECTABLE 10 µg/mL sol diluer p perf	100 µg/10 mL	Aguettant	4505451/G0136A01/ 105152
Spiramycine adipate	ROVAMYCINE 1,5 MUI lyoph p us parentér	1.5 M IU	Sanofi Aventis	A5170
Thiamine hydrochloride	BEVITINE 100 mg/2 mL sol inj	100 mg/2 mL	DB Pharma	F1441/F1138/F1142/ F1143/F1145/F1146/ F1154/F1155
Tramadol hydrochloride	CONTRAMAL 100 mg/2 mL sol inj	100 mg/2 mL	DB	00071S
Urapidil	URAPIDIL STRAGEN 50 mg/10 mL sol inj	50 mg/10 mL	Stragen	F2112-01/F2101-01/F7130-02
Vancomycine hydrochloride	VANCOMYCINE MYLAN 500 mg pdre p sol diluer p perf	500 mg	Mylan	B1601
Vancomycine hydrochloride	VANCOMYCINE MYLAN 1000 mg pdre p sol diluer p perf	1 g	Mylan	B2398/B2434
Solvents				
Water for injection	EAU POUR PREPARATIONS INJECTABLES LAVOISIER sol ppi	250 mL	Chaix et du Marais	8F447
Water for injection	EAU POUR PREPARATIONS INJECTABLES LAVOISIER sol ppi	500 mL	Chaix et du Marais	0F632
5% Dextrose	GLUCOSE LAVOISIER 5% sol p perf	250 mL	Chaix et du Marais	9F591
5% Dextrose	GLUCOSE B BRAUN 5% sol p perf	250 mL	Macopharma	19I27A/20H31B
0.9% Sodium chloride	CHLORURE DE SODIUM 0.9% LAVOISIER sol p perf	500 mL	Chaix et du Marais	0F648
0.9% Sodium chloride	CHLORURE DE SODIUM 0.9% LAVOISIER sol p perf	250 mL	Chaix et du Marais	0F654
0.9% Sodium chloride	CHLORURE DE SODIUM B BRAUN 0.9% sol p perf	250 mL	Macopharma	20C05C/20B11D
Isofundine®	ISOFUNDINE sol p perf	500 mL	B Braun	20442452/173338131/ 2000685/21084452
10% Dextrose	GLUCOSE B BRAUN 10% sol p perf	500 mL	B Braun	21063406

acetylsalicylic acid with Nutryelt®, which is a nutritional intake of micro-nutrients: iron, copper, manganese, zinc, fluorine, iodine, selenium, chromium, molybdenum [12]. The acetylsalicylic acid/Nutryelt® combination in pair was pink at 9/1 and 1/1 ratios after the preparation within 4 h, while the ordinary Nutryelt® color is yellow. In the absence of chemical data and by applying the precautionary principle, this mixture was considered incompatible.

Amiodarone hydrochloride

Results for mixtures of amiodarone hydrochloride with other drugs tested were 84.6% compatible (11/13). The amiodarone hydrochloride/cefazolin mixture at 1/1 and 1/9 ratios demonstrated turbidity at all times of analysis. The absorbance variation between T 0H and T 4H was 0.48 at 350 nm, 1.29 at 410 nm and 1.10 at 550 nm at the 1/1 ratio and 0.37 at 350 nm, 0.23 at 410 nm and 0.12 at the 1/9 ratio. Figure 1 shows that the mixture was whitish at the 1/1 ratio and opalescent at the 1/9 ratio from T 0H and at each time of analysis. The amiodarone hydrochloride/furosemide mixture was whitish at the 1/9 ratio at all times studied and also exhibited turbidity. The absorbance variation between T 0H and T 4H was 1.42 at 410 nm and 1.71 at 550 nm to the 1/9 ratio. These mixtures were also considered incompatible and should be administered separately.

Some mixtures with amiodarone hydrochloride were visually and at spectrophotometer compatible, while subvisual particles were counted. In this situation, it concerned mixtures with bumetanide, cefotaxime sodium, potassium chloride, hydrocortisone sodium succinate, insulin, magnesium sulfate, nefopam, paracetamol, thiamine and vancomycine hydrochloride, detailed in Table 2. These poor

Table 2: Mixtures of drugs performed in this study and results of compatibility.

	Drugs	Concentration	Solvent	Initial pH drugs value	Initial pH mixtures value (9/1, 1/1, 1/9)	Results	Type of incompatibility
1	Acetylsalicylic acid	5 mg/mL	0.9% NaCl	5.27	7.28/7.98/8.62	Incompatible	Precipitation at 9/1 and 1/1 ratios
	Potassium canreonate	10 mg/mL	0.9% NaCl	8.92			
2	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.29/5.33/5.35	Physically compatible	
	Isofundine®	–	–	5.35			
3	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.24/5.22/5.23	Physically compatible	
	Potassium chloride	100 mg/mL	None	5.61			
4	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.24/5.24/5.23	Physically compatible	
	Insulin (human)	1 IU/mL	0.9% NaCl	5.44			
5	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.16/5.15/5.07	Physically compatible	
	Magnesium sulfate	6 mg/mL	5% Dextrose	4.58			
6	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.28/5.25/5.23	Physically compatible	
	Nefopam	80 µg/mL	0.9% NaCl	5.24			
7	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.06/4.63/3.86	Incompatible	Pink at 9/1 and 1/1 ratios
	Nutryelt®	–	0.9% NaCl	3.22			
8	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.01/5.45/6.83	Physically compatible	
	Hydrocortisone sodium succinate	2 mg/mL	0.9% NaCl	7.35			
9	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.23/5.26/5.45	Physically compatible	
	Phytomenadione	0.2 mg/mL	0.9% NaCl	5.61			
10	Acetylsalicylic acid	10 mg/mL	0.9% NaCl	5.27	5.07/4.77/4.23	Physically compatible	
	Thiamine hydrochloride	1 mg/mL	0.9% NaCl	3.65			
11	Amiodarone hydrochloride	3 mg/mL	5% Dextrose	4.10	4.37/5.61/6.62	Physically compatible	Particle count at the 9/1 ratio*
	Bumetanide	0.2 mg/mL	0.9% NaCl	6.78			
12	Amiodarone hydrochloride	3 mg/mL	5% Dextrose	4.10	4.40/4.89/4.98	Incompatible	Whitish at the 1/1 ratio and opalescent at the 1/9 ratio.
	Cefazolin sodium	40 mg/mL	5% Dextrose	5.01			Turbidity at 1/1 and 1/9 ratios
13	Amiodarone hydrochloride	9 mg/mL	5% Dextrose	4.10	4.36/5.05/5.20	Physically compatible	Particle count at all ratios*
	Cefotaxime sodium	40 mg/mL	5% Dextrose	5.23			
14	Amiodarone hydrochloride	3 mg/mL	5% Dextrose	4.10	4.18/4.47/5.11	Physically compatible	Particle count at 9/1 and 1/1 ratios*
	Potassium chloride	100 mg/mL	None	6.44			
15	Amiodarone hydrochloride	18 mg/mL	5% Dextrose	4.10	4.37/5.1/7.21	Incompatible	Whitish at the 1/9 ratio at T 4H. Turbidity at the 1/9 ratio
	Furosemide	5 mg/mL	0.9% NaCl	8.72			
16	Amiodarone hydrochloride	9 mg/mL	5% Dextrose	4.10	4.24/5.44/6.52	Physically compatible	Particle count at 9/1 and 1/1 ratios*
	Hydrocortisone sodium succinate	2 mg/mL	0.9% NaCl	7.47			
17	Amiodarone hydrochloride	6 mg/mL	5% Dextrose	4.10	3.90/4.21/4.71	Physically compatible	Particle count at 9/1 and 1/1 ratios*
	Insulin (human)	1 IU/mL	0.9% NaCl	5.83			
18	Amiodarone hydrochloride	3 mg/mL	5% Dextrose	4.10	4.10/4.59/4.78	Physically compatible	
	Levofloxacine hemihydrate	5 mg/mL	None	4.82			
19	Amiodarone hydrochloride	9 mg/mL	5% Dextrose	4.10	4.84/5.26/5.31	Physically compatible	Particle count at 9/1 and 1/1 ratios*
	Magnesium sulfate	1.5 mg/mL	Isofundine®	5.32			

Table 2: (continued)

	Drugs	Concentration	Solvent	Initial pH drugs value	Initial pH mixtures value (9/1, 1/1, 1/9)	Results	Type of incompatibility
20	Amiodarone hydrochloride	9 mg/mL	5% Dextrose	4.10	4.78/5.23/5.29	Physically compatible	Particle count at the 9/1 ratio*
	Nefopam	160 µg/mL	Isofundine®	5.29			
21	Amiodarone hydrochloride	18 mg/mL	5% Dextrose	4.10	4.27/4.61/4.84	Physically compatible	Particle count at the 9/1 ratio*
	Paracetamol	10 mg/mL	None	5.09			
22	Amiodarone hydrochloride	3 mg/mL	5% Dextrose	4.10	3.91/3.77/3.71	Physically compatible	Particle count at the 9/1 ratio*
	Thiamine hydrochloride	2 mg/mL	0.9% NaCl	3.9			
23	Amiodarone hydrochloride	9 mg/mL	5% Dextrose	4.10	3.64/3.37/3.27	Physically compatible	Particle count at 9/1 and 1/1 ratios*
	Vancomycine hydrochloride	31.3 mg/mL	5% Dextrose	3.24			
24	Atenolol	100 µg/mL	0.9% NaCl	5.91	5.96/6.25/6.82	Incompatible	Non- compliant particle count at all ratios except for 1/9 at T4H
	Ciclosporine	10 mg/mL	5% Dextrose	6.98			
25	Atenolol	100 µg/mL	0.9% NaCl	5.91	5.91/5.97/6.45	Physically compatible	
	Methylprednisolone hemisuccinate	200 µg/mL	0.9% NaCl	7.05			
26	Atenolol	50 µg/mL	0.9% NaCl	5.91	5.63/5.24/4.92	Incompatible	Non-compliant particle count at the 9/1 ratio at T 0H and T1H
	Metronidazole	5 mg/mL	None	4.85			
27	Atenolol	100 µg/mL	0.9% NaCl	5.91	5.72/5.05/4.25	Incompatible	Haze at the 1/1 ratio
	Mycophenolate mofetil	10 mg/mL	5% Dextrose	3.75			
28	Atenolol	100 µg/mL	NaCl 0.9%	5.91	5.63/4.67/3.39	Incompatible	Slightly yellow color*
	Nutryelt®	-	0.9% NaCl	3.18			
29	Atenolol	100 µg/mL	0.9% NaCl	5.91	5.86/5.27/4.17	Physically compatible	
	Thiamine hydrochloride	1 mg/mL	0.9% NaCl	4.59			
30	Atenolol	100 µg/mL	0.9% NaCl	5.91	5.96/5.99/6.02	Physically compatible	
	Urapidil	5 mg/mL	None	6.03			
31	Clonidine hydrochloride	12.5 µg/mL	0.9% NaCl	5.10	5.72/6.76/7.00	Incompatible	Non-compliant particle count at the 1/9 ratio
	Methylprednisolone hemisuccinate	0.2 mg/mL	0.9% NaCl	7.13			
32	Clonidine hydrochloride	12.5 µg/mL	0.9% NaCl	5.10	4.26/3.97/3.86	Physically compatible	Particle count at 1/1 and 1/9 ratios*
	Mycophenolate mofetil hydrochloride	10 mg/mL	5% Dextrose	3.84			
33	Clonidine hydrochloride	12.5 µg/mL	0.9% NaCl	5.10	4.23/3.89/3.77	Physically compatible	
	Thiamine hydrochloride	1 mg/mL	5% Dextrose	3.76			
34	Clonidine hydrochloride	12.5 µg/mL	0.9% NaCl	5.10	5.85/5.99/6.09	Physically compatible	
	Urapidil	5 mg/mL	None	6.13			
35	Furosemide	10 mg/mL	None	8.96	8.24/5.49/5.49	Incompatible	Turbidity at the 1/1 ratio
	Magnesium Sulfate	6 mg/mL	Isofundine®	5.26			
36	Furosemide	10 mg/mL	None	8.96	6.71/6.01/5.50	Incompatible	Turbidity at 1/1 and 1/9 ratios. Opalescence at 1/9
	Nefopam	1.7 mg/mL	0.9% NaCl	5.40			
37	Furosemide	10 mg/mL	None	8.96	8.37/6.02/5.34	Physically compatible	
	Paracetamol	10 mg/mL	None	5.21			
38	Furosemide	10 mg/mL	None	8.96	7.69/7.03/6.87	Incompatible	Whiteness and turbidity at the 1/1 ratio. Opalescence at the 9/1 ratio.
	Spiramycine adipate	60 mIU/mL	0.9% NaCl	6.86			

Table 2: (continued)

	Drugs	Concentration	Solvent	Initial pH drugs value	Initial pH mixtures value (9/1, 1/1, 1/9)	Results	Type of incompatibility
39	Heparin sodium	208.3 IU/mL	0.9% NaCl	5.90	5.69/5.52/5.49	Incompatible	Non-compliant particle count at the 1/9 ratio at T 0H and T1H
	Levetiracetam	15 mg/mL	0.9% NaCl	5.51			
40	Heparin sodium	208.3 IU/mL	0.9% NaCl	5.90	5.06/4.28/3.69	Incompatible	Non-compliant particle count at 1/1 and 1/9 ratios at T 0H and T1H
	Midazolam hydrochloride	1 mg/mL	0.9% NaCl	3.65			
41	Heparin sodium	208.3 IU/mL	0.9% NaCl	5.90	5.50/5.45/5.43	Incompatible	Non-compliant particle count at the 1/9 ratio at T 0H and T1H
	Nefopam	1.7 mg/mL	0.9% NaCl	5.43			
42	Heparin sodium	208.3 IU/mL	0.9% NaCl	5.90	5.19/5.01/5.04	Physically compatible	
	Paracetamol	10 mg/mL	0.9% NaCl	5.12			
43	Insulin (human)	1 IU/mL	0.9% NaCl	5.60	5.69/5.56/5.58	Physically compatible	
	Isosorbide dinitrate	1 mg/mL	None	5.53			
44	Insulin (human)	1 IU/mL	0.9% NaCl	5.60	5.42/5.40/5.41	Physically compatible	
	Nefopam	160 µg/mL	Isofundine®	5.36			
45	Insulin (human)	1 IU/mL	0.9% NaCl	5.60	5.78/5.14/5.09	Physically compatible	
	Paracetamol	10 mg/mL	None	5.16			
46	Insulin (human)	1 IU/mL	0.9% NaCl	5.60	8.9/9.50/9.68	Incompatible	Turbidity at the 1/9 ratio
	Pantoprazole sodium	1 mg/mL	None	9.70			
47	Insulin (human)	2 IU/mL	0.9% NaCl	5.60	4.56/3.55/3.20	Physically compatible	
	Phloroglucinol	10 mg/mL	None	3.11			
48	Insulin (human)	3 IU/mL	0.9% NaCl	5.60	4.49/3.78/3.59	Incompatible	Non-compliant particle count: T 0H at all ratios, T 1H at 1/1 and 1/9, T 4H at 1/9
	Remifentanil hydrochloride	100 µg/mL	0.9% NaCl	3.58			
49	Insulin (human)	3 IU/mL	0.9% NaCl	5.60	5.79/5.77/5.80	Physically compatible	
	Sodium Selenite	1 µg/mL	0.9% NaCl	6.22			
50	Nefopam	160 µg/mL	Isofundine®	5.32	5.28/5.02/4.41	Physically compatible	
	Nicardipine hydrochloride	1 mg/mL	None	3.61			
51	Nefopam	160 µg/mL	0.9% NaCl	5.32	4.21/3.60/3.57	Physically compatible	
	Nicardipine hydrochloride	1 mg/mL	None	3.61			
52	Nefopam	160 µg/mL	Isofundine®	5.32	5.29/5.27/5.18	Physically compatible	
	Pyridoxine hydrochloride	0.5 mg/mL	Isofundine®	5.15			
53	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.21/5.12/5.06	Physically compatible	
	Pyridoxine hydrochloride	0.5 mg/mL	Isofundine®	5.15			
54	Nefopam	160 µg/mL	0.9% NaCl	5.32	4.92/4.11/3.90	Physically compatible	
	Pyridoxine hydrochloride	0.5 mg/mL	0.9% NaCl	5.15			
55	Nefopam	160 µg/mL	Isofundine®	5.32	5.33/5.25/5.23	Physically compatible	
	Thiamine hydrochloride	0.5 mg/mL	Isofundine®	3.89			
56	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.23/5.21/5.20	Physically compatible	
	Thiamine hydrochloride	0.5 mg/mL	Isofundine®	3.89			
57	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.10/4.32/3.93	Physically compatible	
	Thiamine hydrochloride	0.5 mg/mL	0.9% NaCl	3.95			
58	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.55/5.64/5.85	Physically compatible	
	Tramadol hydrochloride	6.3 mg/mL	0.9% NaCl	6.79			
59	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.27/5.18/5.20	Incompatible	Non-compliant particle count at the 1/9 ratio
	Cefotaxime sodium	40 mg/mL	5% Dextrose	5.26			
60	Nefopam	80 µg/mL	Isofundine®	5.32	5.39/5.39/5.38	Physically compatible	
	Calcium chloride	2 mg/mL	Isofundine®	5.44			
61	Nefopam	80 µg/mL	0.9% NaCl	5.32	5.46/5.39/5.37	Physically compatible	
	Calcium chloride	2 mg/mL	Isofundine®	5.46			
62	Nefopam	80 µg/mL	0.9% NaCl	5.32	5.70/5.80/6.15	Physically compatible	
	Calcium chloride	2 mg/mL	0.9% NaCl	5.46			

Table 2: (continued)

	Drugs	Concentration	Solvent	Initial pH drugs value	Initial pH mixtures value (9/1, 1/1, 1/9)	Results	Type of incompatibility
63	Nefopam	160 µg/mL	Isofundine®	5.32	5.38/5.51/6.64	Physically compatible	
	Hydrocortisone sodium succinate	2 mg/mL	0.9% NaCl	7.55			
64	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.98/6.62/7.28	Physically compatible	
	Hydrocortisone sodium succinate	2 mg/mL	0.9% NaCl	7.55			
65	Nefopam	2.5 mg/mL	0.9% NaCl	5.32	5.49/5.54/5.62	Physically compatible	
	Isosorbide dinitrate	1 mg/mL	None	5.65			
66	Nefopam	160 µg/mL	Isofundine®	5.32	5.36/5.36/5.34	Physically compatible	
	Magnesium sulfate	3 mg/mL	10% Dextrose	4.89			
67	Nefopam	160 µg/mL	0.9% NaCl	5.32	5.58/5.35/4.90	Physically compatible	
	Magnesium sulfate	3 mg/mL	10% Dextrose	4.89			
68	Nefopam	160 µg/mL	Isofundine®	5.32	5.36/5.35/5.32	Physically compatible	
	Magnesium sulfate	4.5 mg/mL	10% Dextrose	4.93			
69	Nefopam	160 µg/mL	Isofundine®	5.32	5.57/5.37/4.99	Physically compatible	
	Magnesium sulfate	4.5 mg/mL	0.9% NaCl	4.93			
70	Pantoprazole sodium	80 µg/mL	0.9% NaCl	9.70	7.70/6.18/4.76	Incompatible	Yellowish at 1/1 and 1/9 ratios at T 4H. Turbidity at the 1/9 ratio
	Paracetamol	10 mg/mL	None	4.74			
71	Pantoprazole sodium	4 mg/mL	0.9% NaCl	9.70	5.56/4.02/3.17	Incompatible	Orange at all ratios at T 1H. Precipitation at 9/1. Turbidity at 1/1 and 1/9 ratios
	Pyridoxine hydrochloride	2.5 µg/mL	0.9% NaCl	2.84			
72	Pantoprazole sodium	4 mg/mL	0.9% NaCl	9.70	9.72/9.59/9.17	Incompatible	Turbidity at 9/1 and 1/1 ratios
	Sodium Selenite	1 µg/mL	0.9% NaCl	5.32			
73	Pantoprazole sodium	4 mg/mL	0.9% NaCl	9.70	9.36/8.56/4.82	Incompatible	Orange at the 1/9 ratio at T 4H. Turbidity at the 1/9 ratio
	Thiamine hydrochloride	1 mg/mL	0.9% NaCl	3.75			
74	Pantoprazole sodium	4 mg/mL	0.9% NaCl	9.70	9.67/9.54/8.93	Incompatible	Non-compliant particle count at all ratios
	Phytomenadione	200 µg/mL	0.9% NaCl	5.80			
75	Pantoprazole sodium	4 mg/mL	0.9% NaCl	9.70	9.50/8.80/8.10	Incompatible	Precipitation and turbidity at all ratios at T 1H and T 4H
	Phloroglucinol	400 µg/mL	0.9% NaCl	4.57			

*Method of Particle counter non applicable to amiodarone hydrochloride and mycophenolate mofetil because of the production of gas bubbles induced by polysorbate 80.

particle counter results could be correlated to the production of gas bubbles in solution induced by polysorbate 80 in amiodarone hydrochloride which should not be considered as a particulate contamination. These results by the particle counter were also not interpretable, because this method was unsuitable to mixtures containing amiodarone hydrochloride [10]. Eur Ph suggests the use of method 2 (microscopic evaluation) for these preparations. This technic was not available in our laboratory, however, according to the absence of turbidity nor visible particle, these 10 mixtures were considered as physically compatible.

Atenolol

Regarding drugs mixed with atenolol, only 3/7 pairs (42.9%) were compatible. The atenolol/mycophenolate mofetil mixture showed a haze at the 1/1 ratio from T 1H. The atenolol/Nutryelt® pair was incompatible because of the slightly yellow color of the mixture for the same reason as the acetylsalicylic acid Nutryelt® pair. More than 6,000 particles of ≥10 µm were counted by the particle counter in the container of the atenolol/ciclosporine pair at all ratios at all times studied, except for the 1/9 ratio at T 4H.

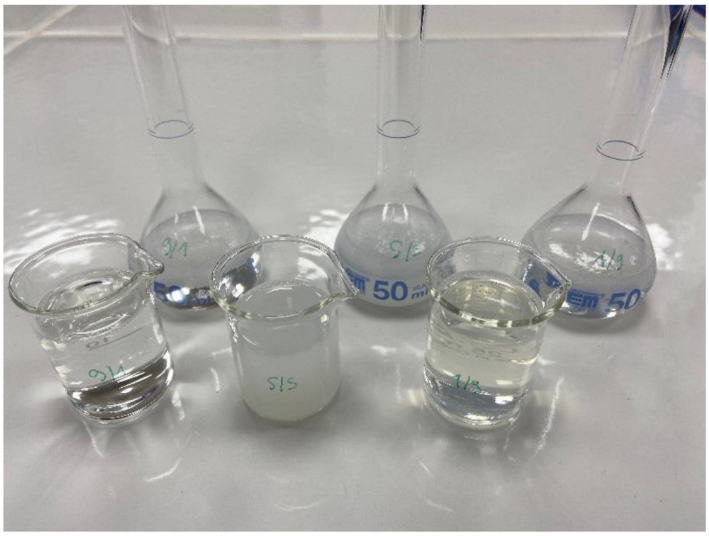

Figure 1: The amiodarone hydrochloride – cefazolin sodium pair was whitish at the 1/1 ratio (in the middle) and opalescent at the 1/9 ratio (right) at T 0H.

According to European Pharmacopoeia Recommendations, it caused the incompatibility of these two drugs in the same IV line. For the atenolol/metronidazole mixture, more than 6,000 particles of ≥10 µm per container were also counted at the 9/1 ratio at T 0H and T 1H. These three mixtures containing atenolol were also not considered to be physically compatible and should not be administered in the same infusion line.

Clonidine hydrochloride

Clonidine hydrochloride results were compatible for 50.0% of the mixtures tested (3/4). The clonidine hydrochloride/methylprednisolone pair was incompatible due to particle count at the 1/9 ratio outside of European Pharmacopeia Recommendations at each time of the analysis. The clonidine hydrochloride/mycophenolate mofetil mixture showed more than 6,000 subvisible particles of ≥10 µm and more than 600 subvisible particles of ≥25 µm per container at 1/1 and 1/9 ratios at each time. As amiodarone hydrochloride, mycophenolate mofetil contains polysorbate 80 in its excipients producing gas bubbles, which could distort results by the light obscuration particle test. Excluding the particle counter results which were not operable, this mixture was physically compatible by spectrophotometry and by the visual evaluation.

Furosemide

Among the mixtures tested with furosemide, only the furosemide/paracetamol pair was compatible, representing 25.0% of the mixtures (1/4). Opalescence and white mixtures were observed for the three other pairs. The furosemide/magnesium sulfate pair showed turbidity at the 1/1 ratio with an absorbance variation of 0.43 from T 0H to T 4H at 550 nm. For the furosemide/nefopam pair, the absorbance variation from T 0H to T 4H was 0.19 at 410 nm and 0.45 at 550 nm at the 1/9 ratio and 1.93 at 550 nm at the 1/1 ratio. This mixture showed whiteness at the 1/1 ratio and opalescence at the 1/9 ratio after the preparation, visible on Figure 2. The mixture furosemide/spiramycine was white and produced haze at the 1/1 ratio with an absorbance variation of 0.78 at 410 nm and of 0.56 at 550 nm from T 0H to T 4H. This pair was opalescent at the 9/1 ratio. The subvisual evaluation made it possible to classify the pairs of furosemide/magnesium sulfate,

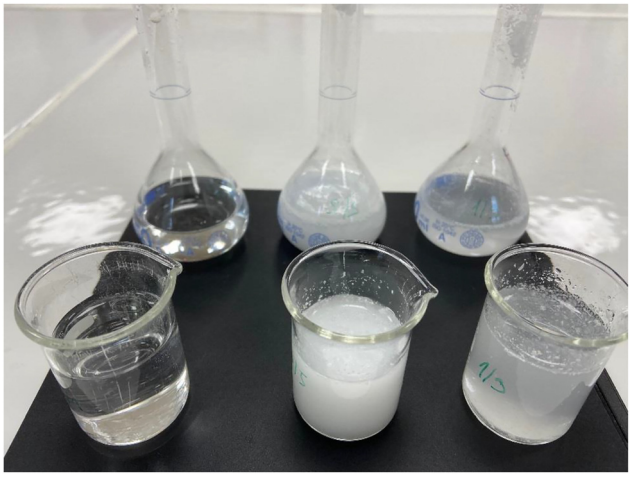

Figure 2: For the furosemide – nefopam mixture, the 1/9 ratio (right) was opalescent and the 1/1 ratio (in the middle) was whitish after its preparation (T 0H).

furosemide/nefopam and furosemide/spiramycine as incompatible mixtures for the concentrations studied.

Heparin sodium

The heparin sodium/paracetamol pair was the only pair with heparin sodium that was physically compatible (25.0%, 1/4). Other results for heparin sodium mixtures were wrong. The heparin sodium/levetiracetam mixture suggested the presence of subvisual incompatibility at the 1/9 ratio at T 0H and T 1H with more than 6,000 subvisible particles of ≥10 µm per container counted, same for the heparin sodium/midazolam pair at 1/1 and 1/9 ratios at T 0H and T 1H, and for the heparin sodium/nefopam pair at the 1/9 ratio at T 0H and T 1H. Based on European Pharmacopeia Recommendations, these three pairs could not be considered as compatible even if the results of the particle counter at T 4H were in conformity, because in practice, the mixture of drugs is supposed to be infused to the patient after its preparation.

Insulin

Regarding the mixtures made with insulin, 71.4% of them were compatible (5/7). The insulin/pantoprazole sodium pair was incompatible because of haze at the 1/9 ratio showing an absorbance variation of 0.46 at 350 nm from T 0H to T 4H. The insulin/remifentanil pair was also incompatible because of more than 6,000 subvisible particles of ≥10 µm per container counted at T 0H at all ratios, T 1H at 1/1 and 1/9 ratios, and at T 4H at the 1/9 ratio.

Nefopam

Of the 20 mixtures made with nefopam, 95.0% were physically compatible (19/20). Only the nefopam/cefotaxime sodium pair was incompatible due to a count of more than 6,000 subvisible particles of ≥10 µm per container at the 1/9 ratio at each time of the analysis.

Pantoprazole sodium

None of the mixtures obtained with pantoprazole sodium were compatible (0/6). The pantoprazole sodium/paracetamol pair became yellow at 1/1 and 1/9 ratios at T 4H and presented turbidity at the 1/9 ratio with an absorbance variation of 0.24 at 350 nm and of 0.13 at 410 nm from T 0H to T 4H. The pantoprazole sodium/pyridoxine mixture changed from white to orange after a 1-h storage at all ratios, and precipitated at the 9/1 ratio, visible on Figure 3. This pair also was incompatible at the 1/1 ratio with an absorbance variation of 0.87 at 350 nm, 1.94 at 410 nm and 0.83 at 550 nm, and at the 1/9 ratio with a variation of 0.98 unit at 350 nm, 0.92 at 410 nm and 0.27 at 550 nm. The pantoprazole sodium/sodium selenite pair also showed turbidity at 9/1 and 1/1 ratios with an absorbance variation at the 9/1 ratio of 0.15 at 350 nm and at the 1/1 ratio of 0.13 at 350 nm, while no change was visible to the naked eye. The pantoprazole sodium/thiamine mixture became orange at the 1/9 ratio at T 4H and the absorbance variation at this ratio was 1.85 at 350 nm, 0.68 at 410 nm and 0.37 at 550 nm. The pantoprazole sodium/phloroglucinol pair precipitated at all ratios after a 1-h storage. The pantoprazole sodium/phytomenadione mixture produced more than 6,000 particles of ≥10 µm per container at

Figure 3: Pantoprazole sodium – pyridoxine turned from white to orange after a 1-h storage and precipitated at the 9/1 ratio (left: T 0H, middle: T 1H, right: T 4H).

all ratios and at each time of the analysis leading to the incompatibility of this mixture according to European Pharmacopeia Recommendations.

Table 3 summarizes the results of combinations with these nine main drugs presented above and allows the conclusion of an overall compatibility of 68.0% for all the mixtures included in this study (51/75).

Discussion

Use of main drugs in ICUs

Systemic anticoagulation such as acetylsalicylic acid reduces mortality in patients on mechanical ventilation, decreasing cardiovascular events and preventing organ failure [13].

Amiodarone hydrochloride is widely used in ICUs for the treatment of arrhythmias, especially since its use in combination is usually effective and safe [14].

Atenolol is a commonly used β-blocker in the treatment of cardiovascular diseases and to reduce the risk of re-infarction and the related mortality after myocardial infarction. Its cardioselectivity reduces the risk of inducing a respiratory deficiency problem, making atenolol a drug of first choice in ICUs [15].

Clonidine hydrochloride is usually used in ICUs for its sedative, analgesic and anxiolytic effects, outside of its approved indications [16]. It also gets combined with other drugs in the same IV route.

Furosemide is used in ICUs to reduce short-term patient mortality. It helps limiting excessive fluid gain, while excessive fluid administration in post-operative and post-traumatic patients is a common occurrence [17].

Injectable anticoagulation such as heparin sodium is one of the most commonly prescribed therapies in ICUs. A low dose of heparin sodium is often needed to prevent a venous disease, which can contribute to the deterioration of organ functions. Higher doses treat a venous disease or an acute coronary syndrome [18].

Critically ill patients frequently develop high levels of sugar in the blood. An intensive insulin therapy with a tight blood sugar control reduces patient mortality in ICUs [19].

Nefopam is a centrally acting non-opioid analgesic agent commonly used for patients admitted in ICUs getting mechanical ventilation and receiving sedative and analgesic medications. They are integral parts of the complex management of these patients, to minimize their discomfort and to reduce the risk of agitation and accidental self-extubation [20]. Nefopam could be a safe and effective pain reliever in regards with the high risk of organ vulnerability of patients [21].

Critically ill patients in ICUs are at risk of developing gastrointestinal bleeding due to mechanical ventilation and coagulopathy. A low dose of heparin sodium is often required to prevent a venous disease, which can contribute to the deterioration of organ functions and liver or kidney failure. Proton-pump inhibitors, such as pantoprazole sodium are the most commonly used prophylactic acid suppressants in these circumstances [22].

Table 3: Summary of the overall compatibility for each main drug.

Main drugs	Number of mixtures with other drugs		Compatibility, %
Acetylsalicylic acid	10	8	80.0%
Amiodarone hydrochloride	13	11	84.6%
Atenonol	7	3	42.9%
Clonidine hydrochloride	4	3	75.0%
Furosemide	4	1	25.0%
Heparin sodium	4	1	25.0%
Insulin	7	5	71.4%
Nefopam	20	19	95.0%
Pantoprazole sodium	6	0	0.0%
Total	75	51	**68.0%**

Observational study

In this study, only mixtures which were visually and subvisually compatible by UV-visible spectrophotometer were tested using the particle counter, otherwise they were physically incompatible and the latter was not performed.

Sometimes, Isofundine® was employed as a drug in combination with another drug, e.g., acetylsalicylic acid/Isofundine®, sometimes it was used as a solvent, e.g., for the dilution of nefopam. Tests were not repeated on different batches of medications.

For combinations with amiodarone hydrochloride and mycophenolate mofetil, the presence of polysorbate 80, as an excipient contained in the formulation of these two drugs, led to the production of gas bubbles which could have been wrongly detected as particles by the particle counter. The production of bubbles was not due to a particulate contamination. For this type of mixture producing bubbles, a more suitable particle counting method would be a Microscopic Particle Count Test [10].

Large differences in pH between two drugs studied in Y-site were noticed, shown in Table 2. Pantoprazole sodium (4 mg/mL in 0.9% NaCl) pH was 9.70, while the pH of other drugs mixed with pantoprazole sodium was between 2.84 and 5.80. All seven mixtures containing pantoprazole

sodium were incompatible. Furosemide had also an alkaline pH of 8.96 (in pure solution at 10 mg/mL resulting in large differences of pH with other mixed drugs. Four of five mixtures containing furosemide were incompatible. The combination of two drugs with opposite pH can also be a cause of drug incompatibility which should dissuade us from mixing two drugs with distant pH unless their Y-site compatibility is certain. This hypothesis is currently under study in our laboratory.

Data available in the literature

An incompatibility with the Light Obscuration Particle Test could equally represent an evolution of size, shape or count of particles, while the UV-visible spectrophotometer is useful for assessing subvisible aggregation and correlates to a visual incompatibility such as opalescence [1].

Care should be taken regarding intravenous administration of furosemide, as many drugs can interact with furosemide ranging from opalescence to precipitation, especially in combination with acid drugs, which can lead to vessel obstructions [23].

According to the summary of product characteristics, pantoprazole sodium powder should not be mixed with other drugs except for its dilution in 0.9% sodium chloride [24]. It was already known from other studies that pantoprazole sodium was often incompatible with other drugs [1]. No administration of mixture with pantoprazole sodium should be observed unless compatibility data can ensure this.

Many other combinations with heparin sodium and pantoprazole sodium are known to be incompatible in the literature. Heparin sodium is also a drug which must be administered alone when compatibility data are not available [25].

Limits

Only the physical compatibility has been tested. It cannot conclude on the chemical stability of these binary combinations, nor can it be extrapolated to associations of more than two drugs, nor to mixtures achieved in the same vial.

Physical compatibility studies should be performed for other drugs mixtures for which data are lacking. New requests must continue to be collected in ICUs and other units to achieve new Y-site compatibility assessments. In all cases, drug combination should always be administered with caution taking into account qualified data from the literature.

Conclusions

By the results of these laboratory tests, compatibility data which were lacking are now available, providing additional information to the literature and securing IV administrations in ICUs. An incompatibility could be due to a visible change, opalescence, precipitation, subvisual turbidity or particle count. Nefopam was found to be quite compatible with other drugs (95.0%). Amiodarone hydrochloride (84.6%), acetylsalicylic acid (80.0%), clonidine hydrochloride (75.0%) and insulin (71.4%) were compatible with other drugs too. Atenolol (42.9%), furosemide (25.0%), heparin sodium (25.0%) showed less compatible results. Pantoprazole sodium (0.0%) was not at all compatible with the other drugs analyzed.

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Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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