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ORIGINAL ARTICLE

Physical compatibility of alprostadil with selected drugs commonly used in the neonatal intensive care units

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Abstract

This study aimed to determine the physical compatibility of alprostadil with 17 continuous infusion drugs commonly administered in neonatal intensive care units. Test samples were prepared in a laminar airflow hood. Alprostadil 20 mcg/ml was mixed with each drug in a 1:1 ratio, in two orders of mixing. Physical stability of the admixtures was assessed by visual examination and by measuring turbidity. Visual examination was conducted by two observers by two methods: visual examination against a black and white background under normal fluorescent light and using a high-intensity monodirectional light. pH was measured as chemical stability predictor. Evaluations were performed immediately and 4 h after mixing. An additional visual control was performed at 24 h. Visual examination was positive or doubtful for the four drug combinations not considered compatible. Turbidity values were under 0.5 NTU throughout the study in all samples. No modifications of one pH unit or more was detected in any drug pair over time.

Conclusion: Alprostadil was considered physical compatible with 13 drugs (adrenalin, amiodarone, calcium gluconate, dobutamine, dopamine, fentanyl, flecainide, furosemide, heparin, ketamine, midazolam, milrinone and morphine). Incompatibility could not be ruled out for 3 drugs (cisatracurium, dexmedetomidine and noradrenalin), and insulin was considered incompatible with alprostadil.

What is Known:
- *Y-site administration is common in neonatal intensive care units, and volume of diluents and rate of infusions in newborns were lower than in adults which might result in high concentrations and prolonged contact time at Y-site administration.*
- *Available data about compatibility of alprostadil with other drugs was scarce.*

What is New:
- *Alprostadil was compatible with 13 drugs commonly used in neonatal intensive care units.*
- *Insulin was considered incompatible with alprostadil, and incompatibility cannot be ruled out for cisatracurium, dexmedetomidine and noradrenalin with alprostadil.*

Keywords Alprostadil · Y-site administration · Neonates · Intravenous drug · Safety

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Abbreviations

IV	Intravenous
NTU	Nephelometric turbidity unit
NICUs	Neonatal intensive care units

Introduction

Alprostadil is a synthetic prostaglandin E1 and possesses a wide variety of pharmacological actions including vasodilation and inhibition of platelet aggregation. Alprostadil is indicated to temporarily maintain the patency of the ductus arteriosus until corrective or palliative surgery can be performed in neonates with congenital heart defects (e.g. pulmonary atresia or stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, transposition of the great vessels with or without other defect) who are dependent on the patent ductus for survival [1].

Alprostadil is administered as a continuous infusion into a large vein or through the umbilical catheter. It is recommended to start at 0.05 to 0.1 mcg/kg/min and, once therapeutic response is achieved, reduce rate to the lowest effective dosage. In the case of unsatisfactory response, dose could be increased gradually to 0.4 mcg/kg/min. Therapeutic response is indicated by an increase in systemic blood pressure and pH in those with restricted systemic blood flow and acidosis, or by an increase in oxygenation (pO_2) in those with restricted pulmonary blood flow [1].

Alprostadil is available in Spain as an injectable solution of 500 mcg/ml in dehydrated alcohol. It is recommended to dilute the drug in either 5% dextrose or 0.9% NaCl in the range of 2–20 mcg/ml prior to administration [1].

The availability of intravenous access is limited in neonates, and multiple intravenous (IV) drugs have to be administered simultaneously to these patients, leading to concomitant administration of different drugs in the same infusion line [2]. This practice is known as "Y-site" administration. For Y-site infusions, drugs must be physically compatible, which means no precipitation, no change of colour or no gas formation [3]. In the case of lipid-containing products, emulsion stabilization should be evaluated [4, 5]. However, the information is not always available or sometimes can reveal controversial data when verified at more than one source [6, 7]. Kalikstad et al. [2] found that 59% of the drug-drug co-infusions used in their neonatal intensive care unit (NICU) had no compatibility data in the literature. From the 26% co-infusions of drugs that were considered compatible, 93% had restrictions on concentration, contact time or infusion fluid for the administration to their patients. In 2018, similar results were obtained by Leopoldino et al. [6]; 42.1% from the drug combinations identified were restricted compatibilities and 31.2% unknown compatibilities.

In neonatal patients, volume of diluents and rate of infusions must be lower than in adults which might result in high concentrations and prolonged contact time between medications during the infusion; suitable published data on this is difficult to find [6]. Physical incompatibilities can lead to the formation of precipitates; the following clinical effects have been described with their infusion: catheter obstruction, venous irritation, pulmonary or renal emboli, infarction and even death [8–10]. In addition, it has been proposed that neonates are particularly at risk for particulate matter-related sequelae because they have fewer alveoli and capillaries in the lungs compared with adults [11]. Incompatibilities of drugs can also result in decrease in drug activity, change of active drugs or formation of toxic compounds [8], and particles can activate the immune system and lead to the development of a systemic inflammatory response syndrome [10].

Very little information is available about the compatibility of alprostadil with IV solutions and medications commonly used in neonates with congenital heart diseases. Most of data was published by JE Dice in 2006 [12]. They studied the physical compatibility of alprostadil 15 mcg/ml with 13 drugs commonly used in neonatal intensive care units (NICUs), some IV solutions containing potassium chloride and a parenteral nutrition (PN) solution without lipids. Alprostadil was mixed 1:1 with solutions, PN and medications. Physical compatibility was evaluated by visual examination and gross temperature change detection touching the test tube, over 60 min. No incompatibilities with alprostadil were detected. However, the duration of the study does not permit us to know the compatibility of alprostadil with these drugs if the contact time is longer. In addition, although a standard methodology for Y-site studies was not established, the two methods used in the study was not enough to confirm the full compatibility, as micro-precipitation and chemical compatibility was not tested.

The purpose of this study was to evaluate the physical stability of alprostadil 20 mcg/ml diluted in 5% dextrose with 17 continuous infusion drugs commonly used in NICUs, during Y-site administration.

Materials and methods

Selection of the drugs, concentration and diluent was based on the information collected by a survey answered by nine Spanish NICUs in 2018 about IV drugs frequently used in their units [13]. For the study, we selected exclusively continuous infusion drugs. Frequency of use, according to the survey, and probability of Y-site infusion with alprostadil, based on clinical experience of the multidisciplinary local group, were taken into account to prioritize experimental studies. Regarding concentration, a wide variability of drug concentrations was detected on the survey [14]. The maximum concentration reported on the survey for each drug was selected

because high drug concentrations are in most cases more prone to lead to incompatibility [3, 15]. Regarding diluent, the multidisciplinary group decided to use 5% dextrose for all the drugs, since this diluent is the one preferred in NICUs. For those medications in which 5% dextrose dilution is not recommended, normal saline was used. Photosensitive drugs were protected for light during the study, covered with an aluminium foil.

Sample preparation

The samples were prepared in a laminar airflow hood in order to minimize contamination by environmental particles. The individual drug solutions were prepared by dilution of each drug in the selected diluent and by gentle mixing. Drugs were mixed in a 1:1 ratio since Allen et al. [16] reported that the mixing of an intravenous fluid in an administration set with a secondary additive through a Y-injection site occurs at that ratio. Before mixing, drugs were filtered 0.22 μm to reduce the background noise of particles [17]. The two-order mixing was studied: alprostadil (Alp) on study drug (drug B) (Alp + B) and study drug on alprostadil (B + Alp). The following control samples were used in the study: alprostadil mixture, B drug mixture and Milli-Q water as negative control. Three samples were prepared for each mixing order for the visual examination. For turbidity and pH measurement, a different sample was prepared for each mixing order and each time point, since ambient contamination could be produced when performing the measurements.

To simulate the inline mixing, samples were mixed in sterile 50-ml polypropylene tubes for turbidimetry and pH measurement. For visual examinations, samples were mixed in colourless 15-ml borosilicate glass screw-cap culture tubes with aluminium caps. Mixing and analysis were performed under ambient laboratory conditions (temperature 22–25 °C).

Stability assessment

Samples were subjected to an established panel of methods and acceptance criteria to assess physical incompatibility in terms of potential precipitation [4, 18]. The physical stability of the admixtures was assessed by visual examination and by measuring turbidity and pH. Samples were tested within 1 h after mixing (t_0) and after 4 h (t_4). As an additional check, visual examinations were also performed after 24 h (t_{24}).

Visual examinations were performed by two different observers with two methods: in a normally diffused fluorescent room light with the unaided eye against a black and white background, according to the European Pharmacopeia (Chapter 2.9.20, 10th edition), and with a high-intensity monodirectional light (Tyndall beam) (Schott KL 1600 LED, Mainz, Germany) in a dark room. The turbidity of each sample was measured using a formazin-calibrated colour-correcting turbidimeter (2100Qis Turbidimeter; Hach Lange GmbH, Dusseldorf, Germany). Triplicate determinations were made for each of the samples at each time point. A calibrated electrode (HI 5221; Hanna Instruments, Eibar, Guipuzcoa, Spain) was used for pH measurement in triplicate for each of the samples at each time point.

Physical incompatibility was defined as visible particulate matter, haze, colour change or gas formation detected in the visual examination. A change (increase or decrease) in measured turbidity of 0.5 nephelometric turbidity unit (NTU) or more, compared with unmixed controls (drug solutions) or along the study period, was considered as physical incompatibility. According to Staven et al. [17], values under 0.2–0.3 NTU were considered for individual evaluation, since some obvious precipitations they observed lead to lower turbidity values than 0.5 NTU. Changes in pH were evaluated related to pKa and solubility of drug. Modifications of one pH unit or more during the 4-h observational period could indicate the presence of chemical reactions that implies physical instability.

Results

Seventeen drugs administered by continuous infusion were selected for the compatibility study with alprostadil. The drugs studied with their concentrations and diluents used are listed in Table 1.

Alprostadil 20 mcg/ml in 5% dextrose solution was a colourless solution without haze. Turbidity was about 0.13 NTU and pH mean 4.37 (± 0.13). Milli-Q water has a mean turbidity value of 0.08 NTU (± 0,01).

Most of drugs tested were compatible (n = 13) with alprostadil. Only insulin was considered incompatible, and for three drugs incompatibility could not be ruled out in this study due to visual examination results. Results are shown in Tables 2 and 3.

All combinations had turbidity values of less than 0.5 NTU. No modifications of one pH unit or more were detected in any drug pair over time.

Visual examination was positive or uncertain for the four drug combinations not considered compatible. Colour change and gas formation were not detected visually in any sample. In the positive visual tests, small particles were observed.

For insulin, particles were detected visually in the six samples by the two observers at 0, 4 and 24 h of the study using the Tyndall beam. The Pharmacopeia method did not allow definitive detection of particles in the samples. Turbidity did not change over time and in mixing samples compared with controls.

For noradrenalin, signs of precipitation, definitive or doubtfully, were detected by the two observers in the six mixing samples at 4 and 24 h using the Tyndall beam.

Table 1 Drugs included in the study: manufacturer, diluent, concentration and protection for light

Drug	Manufacturer	Diluent	Concentration studied (mg/ml)	Protection from light
Alprostadil	Pfizer	D5W	0.02	No
Adrenalin	Braun	D5W	0.2	Yes
Amiodarone	Sanofi Aventis	D5W	6	No
Calcium gluconate	Braun	D10W	0.04[a]	No
Cisatracurium	Normon	D5W	1.2	No
Dexmedetomidine	Orion Corporation	D5W	0.004	No
Dobutamine	Hospira	D5W	10	No
Dopamine	Grifols	D5W	10	No
Fentanyl	Kern Pharma	NS	0.04	No
Flecainide	Meda Pharma SL	D5W	2	No
Furosemide	Genfarma	NS	5	Yes
Heparin	Hospira	NS	1[b]	No
Insulin	Novo Nordisk	NS	1[b]	No
Ketamine	Parke Davis	D5W	5	No
Midazolam	Normon	D5W	2.5	No
Milrinone	Sanofi Aventis	D5W	0.5	No
Morphine	Braun	NS	2	Yes
Noradrenalin	Normon	D5W	0.5	Yes

D5W 5% dextrose, *D10W* 10% dextrose, *NS* normal saline

[a] Milliequivalents per millilitre

[b] International units per millilitre

In the case of cisatracurium, detection of particles grew over time by the Pharmacopeia method, which seemed to imply an increase in the number of particles. By the Tyndall method, the first observer notified signs of precipitation since t_0 in the six samples and the second observer only in five at t_0 and four of the samples at t_4.

Two combinations had turbidities over 0.2 NTU and changed over time: alprostadil + fentanyl and dexmedetomidine + alprostadil.

In the case of fentanyl, visual examination was classified as negative by the two methods for the two observers at the three time points (t_0, t_4 and t_{24}). Because of this, despite the positive trend observed in turbidity for one mixing ratio, we considered fentanyl to be compatible with alprostadil within 4 h. This positive trend in turbidity should be studied for a longer time period.

Regarding dexmedetomidine, we cannot rule out incompatibility because visual examination using the Tyndall beam was positive for the same mixing ratio. Previous information in the literature has not been published, and an additional method to measure subvisible particles would be necessary to confirm this compatibility. However, it is important to note that pH of dexmedetomidine mixture was 4.31 and that of alprostadil mixture 4.37, which would predict the compatibility of the two drugs.

Amiodarone mixed on alprostadil at 1:1 ratio has a doubtful visual test. However, no samples were identified as clear precipitation by observers.

Discussion

There is no a standard protocol or consensus to which tests should be performed to judge compatibility/incompatibility of intravenous drugs administered by Y-site infusion. Differences in the methodology of compatibility studies in the literature likely contribute to the common finding of conflicting data for specific combinations of drugs [7]. This highlights the need for a consensus on the methodology for compatibility studies.

For safe Y-site administration of a drug combination, it should be physically compatible. Chemical degradation of ingredients is less relevant for Y-site administration because of the short contact time. Relatively few drug combinations are so chemically unstable that Y-site administration of the combination is precluded [3]. The calculated in-line contact time between drugs at the Y-site is at most 4 h [19], and for this reason, study time of the majority of Y-site compatibility studies was established as 4 h [18, 20, 21].

Table 2 Results from the investigation of possible precipitation of the seventeen drugs with alprostadil

DRUG B (B)	Mixing ratio	VISUAL INSPECTION (+/-)				TURBIDITY (NTU)				PH			
		Er.Ph		Tyndall effect		(mean±SD)				(mean±SD)			
		t_0	t_4	t_0	t_4	t_0		t_4		t_0		t_4	
Adrenalin	Control (B)	-	-	-	-	0.08		0.08		3.71		3.69	
	Alp + B	-	-	-	-	0.08	0.01	0.10	0.00	3.04	0.02	3.85	0.02
	B + Alp	-	-	-	-	0.07	0.1	0.9	0.02	3.96	0.02	3.90	0.01
Amiodarone	Control (B)	-		-		0.2		0.17		3,65		3,7	
	Alp + B	-	-	-	-	0.13	0.01	0.12	0.00	3.76	0.01	3.75	0
	B + Alp	+/-	+/-	+/-	+/-	0.13	0.03	0.12	0.1	3.75	0.01	33.73	0
Calcium Gluconate	Control (B)	-	-	-	-	0.11		0.13		5.92		5.67	
	Alp + B	-	-	-	-	0.08	0.01	0.09	0.01	5.76	0.00	5.78	0.02
	B + Alp	-	-	-	-	0.09	0.02	0.10	0.01	5.73	0.02	5.77	0.02
Cisatracurium	Control (B)	-	-	-	-	0.12		0.08		3.89		3.88	
	Alp + B	-	-	+/-	+/-	0.11	0.01	0.08	0.01	3.98	0.01	4.01	0.07
	B + Alp	-	-	+/-	+/-	0.08	0.02	0.07	0.1	3.93	0.02	3.94	0.01
Dexmedetomidine	Control (B)	-	-	-	-	0.8		0.2		4.31		4.31	
	Alp + B	-	-	-	-	0.14	0.01	0.08	0.01	4.31	0.03	4.33	0.02
	B + Alp	-	-	+/-	+	0.21	0.04	0.26	0.05	4.34	0.02	4.28	0.02
Dobutamine	Control (B)	-	-	-	-	0.7		0.08		3.41		3.36	
	Alp + B	-	-	-	-	0.11	0.01	0.09	0/01	3.61	0.02	3.59	0.02
	B + Alp	-	-	-	-	0.13	0.03	0.08	0/01	3.2	0.05	3.61	0.01
Dopamine	Control (B)	-	-	-	-	0.07		0.9		3.57		3.43	
	Alp + B	-	-	-	-	0.08	0.1	0.08	0.02	3.5	0.04	3.64	0.02
	B + Alp	-	-	-	-	0.07	0.01	0.08	0.01	3.78	0.02	3.73	0.01
Fentanyl	Control (B)	-	-	-	-	0.08		0.08		4.55		4.49	
	Alp + B	-	-	-	-	0.28	0.01	0,.6	0.01	4.41	0.01	4.42	0.02
	B + Alp	-	-	-	-	0.13	0.00	0.10	0.01	4.41	0	4.41	0.01
Flecainide	Control (B)	-	-	-	-	0,.3		0.14		5.51		5.54	
	Alp + B	-	-	-	-	0.08	0.01	0.13	0.01	5.56	0.03	5.57	0.01
	B + Alp	-	-	-	-	0.09	0.01	0.11	0.01	5.60	0.01	5.66	0.03
Furosemide	Control (B)	-	-	-	-	0.07		0.9		8.6		8.44	
	Alp + B	-	-	-	-	0.09	0.00	0.11	0..04	7.86	0.01	7.54	0.04
	B + Alp	-	-	-	-	0.08	0.00	0.08	0.02	7.62	0,03	7.32	0.05
Heparin	Control (B)	-	-	-	-	0.09		0.07		6.27		6.25	
	Alp + B	-	-	-	-	0006	0.00	0.08	0.01	4.5	0.09	4.65	0.03
	B + Alp	-	-	-	-	0.07	0.00	0.07	0.01	4.2	0.02	4.65	0
Insulin	Control (B)		-	+/-	-	0.15		0.07		5.17		5.62	
	Alp + B	-	+/-	+	+	0.12	0.02	0.16	0.01	4.69	0.02	4.73	0.02
	B + Alp	+/-	+/-	+	+	0.10	0.02	0.12	0.03	4.74	0.02	4.71	0,03
Ketamine	Control (B)	-	-	-	-	0.13		0.06		4.23		4.29	
	Alp + B	-	-	-	-	0.07	0.00	0.09	0.01	4.24	0.03	4.34	0.12
	B + Alp	-	-	-	-	0.13	0.01	0.17	0.01	4.21	0.02	4.28	0.02
Midazolam	Control (B)	-	-	-	-	0.12		0.09		3.09		3.06	
	Alp + B	-	-	-	-	0.11	0.02	0.13	0.02	3.22	0.01	3.17	0.03
	B + Alp	-	-	-	-	0.09	0.02	0.14	0.01	3.18	0.02	3.23	0.01
Milrinone	Control (B)	-	-	-	-	0.09		0.08		3.64		3.58	
	Alp + B	-	-	-	-	0.11	0.01	0.07	0.1	3.66	0.01	3.65	0.04
	B + Alp	-	-	-	-	0.09	0.01	0.08	0.01	3.69	0.02	3.67	0.01
Morphine	Control (B)	-	-	-	-	0.08		0.07		6.05		5.35	
	Alp + B	-	-	-	-	0.9	0.01	0.08	0.01	4.74	0.09	4.55	0.02
	B + Alp	-	-	-	-	0.09	0.01	0.07	0.00	4.55	0.01	4.59	0.06
Noradrenalin	Control (B)	-	-	-	-	0.07		0.15		3.17		3.2	
	Alp + B	+/-	+/-	+/-	+/-	0.07	0.01	0.12	0.02	3.34	0.02	3.33	0.02
	B + Alp	+/-	+/-	+/-	+/-	0.10	0.01	0.08	0.02	3.36	0.04	3.36	0.02

Visual inspection results: + (positive for precipitation); − (negative for precipitation); +/− (doubtful for precipitation); Red colour: incompatibility data. Orange colour: doubtful compatibility data; *NTU* nephelometric turbidity unit

Physical incompatibility, which is precipitation of particles, could be evaluated by several methods. Staven et al. [4] evaluated and established a test program suitable for investigating physical compatibility of drugs and TPN mixed at the Y-site. Based on this article, together with stability guidelines [22, 23], European Pharmacopeia and reference literature [18],

Table 3 Compatibility of alprostadil with the seventeen drugs studied

Drug B	
Adrenalin	*Compatible*
Amiodarone	*Compatible*
Calcium gluconate	*Compatible*
Cisatracurium	**Not conclusive**
Dexmedetomidine	**Not conclusive**
Dobutamine	*Compatible*
Dopamine	*Compatible*
Fentanyl	*Compatible*
Flecainide	*Compatible*
Furosemide	*Compatible*
Heparin	*Compatible*
Insulin	***Incompatible***
Ketamine	*Compatible*
Midazolam	*Compatible*
Milrinone	*Compatible*
Morphine	*Compatible*
Noradrenalin	**Not conclusive**

we selected our panel of methods. For detection of visible particles, the visual examination method established for the European Pharmacopeia was selected and made by two observers. For subvisible particles detection (particles ≤ 25 μ), a Tyndall beam was used in the visual examination [24, 25] and turbidity was measured. Evaluation of pH was selected because it might help to understand and predict precipitation upon mixing with drugs. pH variation is a classical test which could be a simple indicating method for physical stability related to chemical reactions. A modification of 1 or 2 pH units should not be considered as a "slight modification in pH values" and should be explained [22].

We tested the compatibility of each drug pair for the two orders of mixing because there are some combinations where precipitation only occurs in one of them. In the Y-site administration, an order of mixing does not exist and, for this reason, in case of incompatibility detection in one of the orders, the Y-site administration of the drug pair will be contraindicated.

Alprostadil is more stable at acidic pH values compared with neutral and especially alkaline pH. The pH of maximum stability has been reported to be pH 3 [26]. Combination of alprostadil with the seventeen drugs resulted in pH values between 3 and 6, except for furosemide. Measured pH of the mixing of alprostadil with furosemide was between 7 and 8, which could predict a less stable combination. However, no visual signs of precipitation and high turbidity values were detected in our study. In the recent study of Greenhill et al. [27], the combination of furosemide (1 mg/ml) with alprostadil (10 mcg/ml) in normal saline displayed a slight positive trending slope in measured turbidity which could have potentially exceeded 1 NTU but not until some point well beyond 240 min. Despite this, they concluded that the combination was compatible for the study period but longer contact times should be not safe. In our study, this trend in turbidity was not detected during 4 h.

In our study, 13 drugs were considered compatible with alprostadil for Y-site administration. Compatibility information of six of them (adrenalin, dobutamine, dopamine, fentanyl, furosemide and midazolam) with alprostadil was available in the literature. Study times were shorter and concentration and diluents were different, but all combinations were identified also as compatible [12, 27].

We used high concentrated drug infusions in our study, corresponding with the maximum concentration reported on the survey by nine Spanish NICUs [13, 14]. Selection of concentrated drugs would be more interesting for neonates, especially in children with heart defects, since their fluid needs are very small and concentrated solutions are common. One of the highest problems reported by some authors related to compatibility data is the lack of compatibility studies at the concentration normally used in children [2, 7]. In addition, analysis of concentrated drugs comprehends a wide concentration range, covering more information gaps presents in clinical practice.

According to Leopoldino et al. [6], 80% of newborns were exposed to potential drug incompatibility during their stay in the NICU, with an expectation of one potential drug incompatibility per patient each day. It is expected that our study will increase the information available, and will impact in clinical practice and patient safety.

It was remarkable that our incompatible drug pair (insulin and alprostadil) was not identified by an objective method (turbidity). On the one hand, particles observed could have been too small and scarce for reaching a turbidity value over 0.5 NTU. However, this would not be coherent with the previous studies and the established criteria. On the other hand, one of the most important factors that influence insulin stability is the recipient used. Glass tubes were used for visual samples, while turbidity samples were contained in polypropylene tubes. Adsorption phenomena happen in glass containers and not in polypropylene recipients, so one possibility for this result is that observations registered in the visual examination tests were produced for the adsorption phenomena, and not due to precipitates. One observer had doubts in the visual examination of insulin control, which supports that hypothesis. Summarizing, we considered necessary one additional objective method to confirm the compatibility of alprostadil with insulin.

The main limitation of this study is that a light obscuration particle counter was not used. In case of having obtained the number and size of the particles per millilitre, drug pairs with not conclusive results in this study could have been resolved. In addition, we studied only the 1:1 ratio of mixing, but in clinical setting other different ratios can be placed, depending

on the infusion rates of the different drugs [28]. This is an important factor to take into account when a pharmacist evaluates the compatibility data of Y-site co-infusion drugs. The concentrations of the drug and the degradation products have not been evaluated in our study, so chemical stability could not be confirmed.

Conclusion

In conclusion, this study demonstrates the physical Y-site compatibility of alprostadil with the following thirteen drugs at the administration conditions (concentration and diluent) previously indicated (Table 1) with the double visual test, and turbidity and pH measurements were used: adrenalin, amiodarone, calcium gluconate, dobutamine, dopamine, fentanyl, flecainide, furosemide, heparin, ketamine, midazolam, milrinone and morphine hydrochloride. Insulin was identified as incompatible with alprostadil by the visual examination method. Incompatibility of alprostadil with cisatracurium, dexmedetomidine and noradrenalin could not be totally ruled out when the visual examination test resulted unfavourable and turbidity and pH tests favourable.

These results will contribute to an increase in the Y-site compatibility data available in the literature, which will improve drug safety in NICUs.

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Data availability Data and materials are not in a public depository and are available upon request.

Compliance with ethical standards

Conflicts of interests The authors declare that they have no conflict of interest.

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