Title

Supporting the use of sildenafil infusions in paediatric and neonatal intensive care – a compatibility study.

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Abstract:

Objective: Intravenous (IV) sildenafil, a phosphodiesterase type 5 inhibitor, is increasingly being used for the treatment of pulmonary hypertension (PH) in the paediatric population. Sildenafil (Revatio®) is approved for the treatment of PH in adults where it is administered as a bolus injection. However, in paediatrics it is used off-label and administered by continuous IV infusion. In the critically unwell child, limited IV access necessitates the administration of multiple IV infusions through a single IV lumen. The absence of compatibility data between sildenafil and other IV medications commonly used in this context necessitates the use of a dedicated IV line for sildenafil. The overall aim of this study was to establish the physical and chemical compatibility of sildenafil with commonly administered infusions in the paediatric and neonatal intensive care setting.

Design: This study evaluated the chemical and physical compatibility of binary and multiple combinations (n=42) of sildenafil with adrenaline, noradrenaline, milrinone, vasopressin and heparin. These were tested using three diluents (NaCl 0.9%w/v, Glucose 5%w/v, and Glucose 10%w/v) and two environmental conditions (room temperature and 37°C) frequently encountered in paediatric or neonatal intensive care units. Prior to drug combination analysis, HPLC methods were developed and optimised to allow for the quantification of drugs in accordance with current pharmaceutical guidance. Binary and multiple drug mixtures of sildenafil were examined for physical and chemical compatibility to establish compatibility.

***Measurements and main results*:** Of the drug combinations not containing heparin, all were deemed compatible with the exception of the five drug mix of Sildenafil 800µg/mL, Milrinone 200µg/mL, Vasopressin 0.4Units/mL, Noradrenaline 60µg/mL, Adrenaline 60µg/mL at 37°C, in 10%w/v glucose. All binary or multi drug combinations containing heparin were deemed incompatible.

Conclusions:

This research provides support and information to clinicians looking to co-administer sildenafil with other IV medicines thus removing the requirement to subject their patients to multiple intravenous cannula insertion points where IV access is restricted.

Article Tweet:

New evidence to support administration of sildenafil infusions in #PedsICU and #nicu– collaboration between @RCSIPharmBioMol@FionaSOBrien1 and @OLCHCrumlin @RCSI_Irl @MoninneHowlett #CHI

Introduction

The American Heart Association defines PH as a resting mean pulmonary artery pressure (mPAP) >25 mmHg (1-3). The right ventricle, if subjected to elevated resistance may fail, leading to low cardiac output and death. There are multiple aetiologies for the development of PH in the paediatric population, the definitions and classification of which have recently been updated (2, 4). The forms most commonly requiring intensive care arise either due to a failure of the neonatal circulation to transition (Persistent Pulmonary Hypertension of the Newborn – PPHN) or secondary to cardiac or pulmonary malformations (5). Three major pathways influence pulmonary arterial resistance and form the targets of pharmacotherapy: the nitric oxide (NO), endothelin and prostacyclin pathways (6).

Sildenafil citrate targets the NO pathway by selectively inhibiting the enzyme phosphodiesterase type 5 (PDE5) which metabolizes cGMP. Increased intracellular cGMP concentrations lead to vasodilatation of the smooth muscle in blood vessels via a number of mechanisms (7). Its use has been associated with reduced mortality and improved oxygenation in the treatment of PPHN and a reduction in pulmonary vascular resistance following corrective cardiac surgery for septal defects (8, 9).

The first reported paediatric administration of sildenafil was in 1999 (10, 11). In 2005, IV sildenafil (Revatio®) was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of PH in adults. In 2011 EMA authorisation of oral sildenafil was extended to include paediatric patients aged one year and older. Recently the IV preparation became available in Ireland, again licenced for the treatment of pulmonary arterial hypertension in children over one year. As Revatio® is intended to be administered by IV bolus, compatibility data is currently limited. Evidence for the role of IV sildenafil in the treatment of neonatal pulmonary hypertension continues to emerge;

dosing regimens involve administration of a continuous infusion, often proceeded by a loading dose (12-15). However, this indication remains outside of current licensing.

In the critically unwell child, limited IV access necessitates the administration of multiple IV infusions through a single IV lumen (16). This may be achieved by connecting infusions to a single port using various connectors. This practice is commonly referred to as 'y-siting' or running infusions through a 'gang' (Figure 1 for illustrative purposes only).

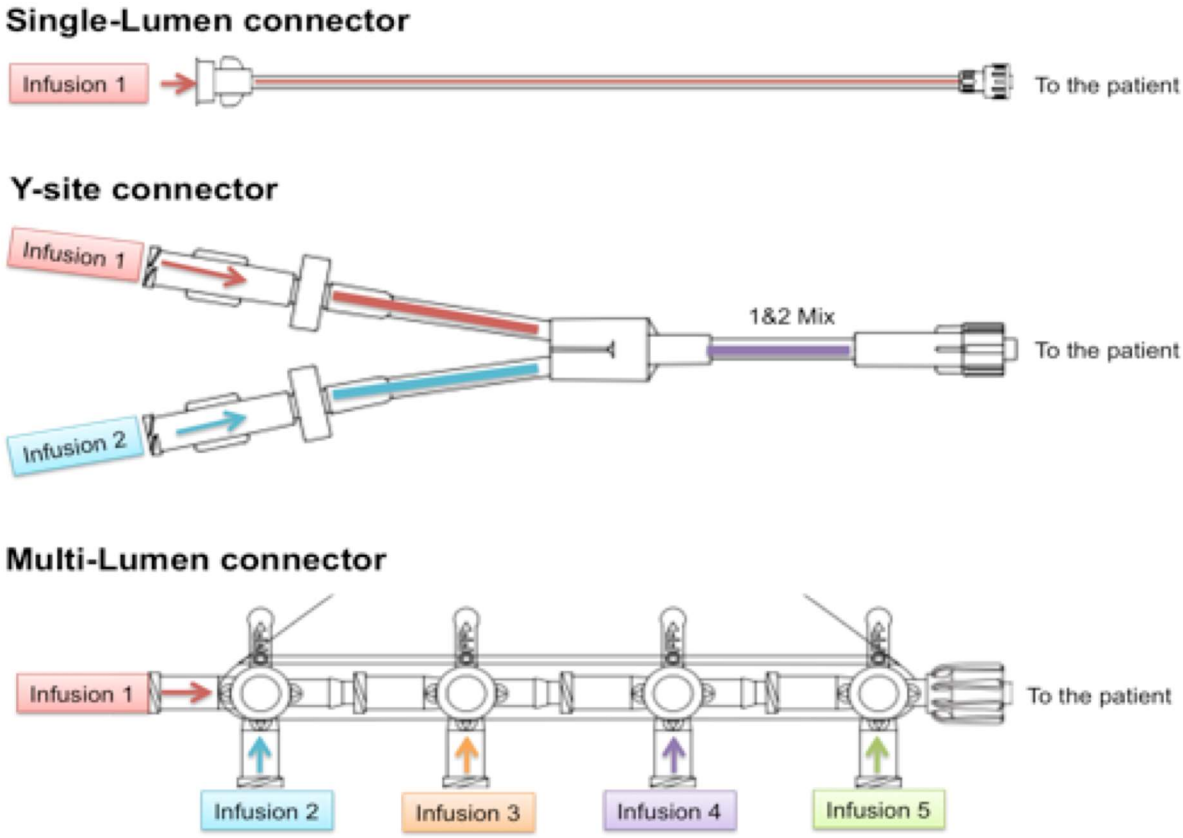

Figure 1 Single, Y-site and multi-lumen devices. The differences between the devices utilised in practice to administer one, two and multiple intravenous drug infusions, respectively.

In cases where drugs have to be infused through a single lumen, it is necessary to determine physical and chemical compatibility of the mixture with the respective diluents and other drugs (17). Incompatibilities can lead to drug degradation or drug-drug interactions, potentially resulting in the loss of therapeutic

drug concentration. Loss of IV access as a result of precipitation of incompatible IV infusions leading to blockage of small vessels has the potential for serious adverse outcomes, particularly in the neonatal population (18-20).

This study examined the physiochemical stability of sildenafil in combination with IV drugs commonly administered in the PICU to facilitate its administration with other commonly used infusions via a single lumen. The IV drugs examined were chosen based on the most commonly used medications in the PICU of Children's Health Ireland (CHI) at Crumlin. Figure 2 illustrates the study process used.

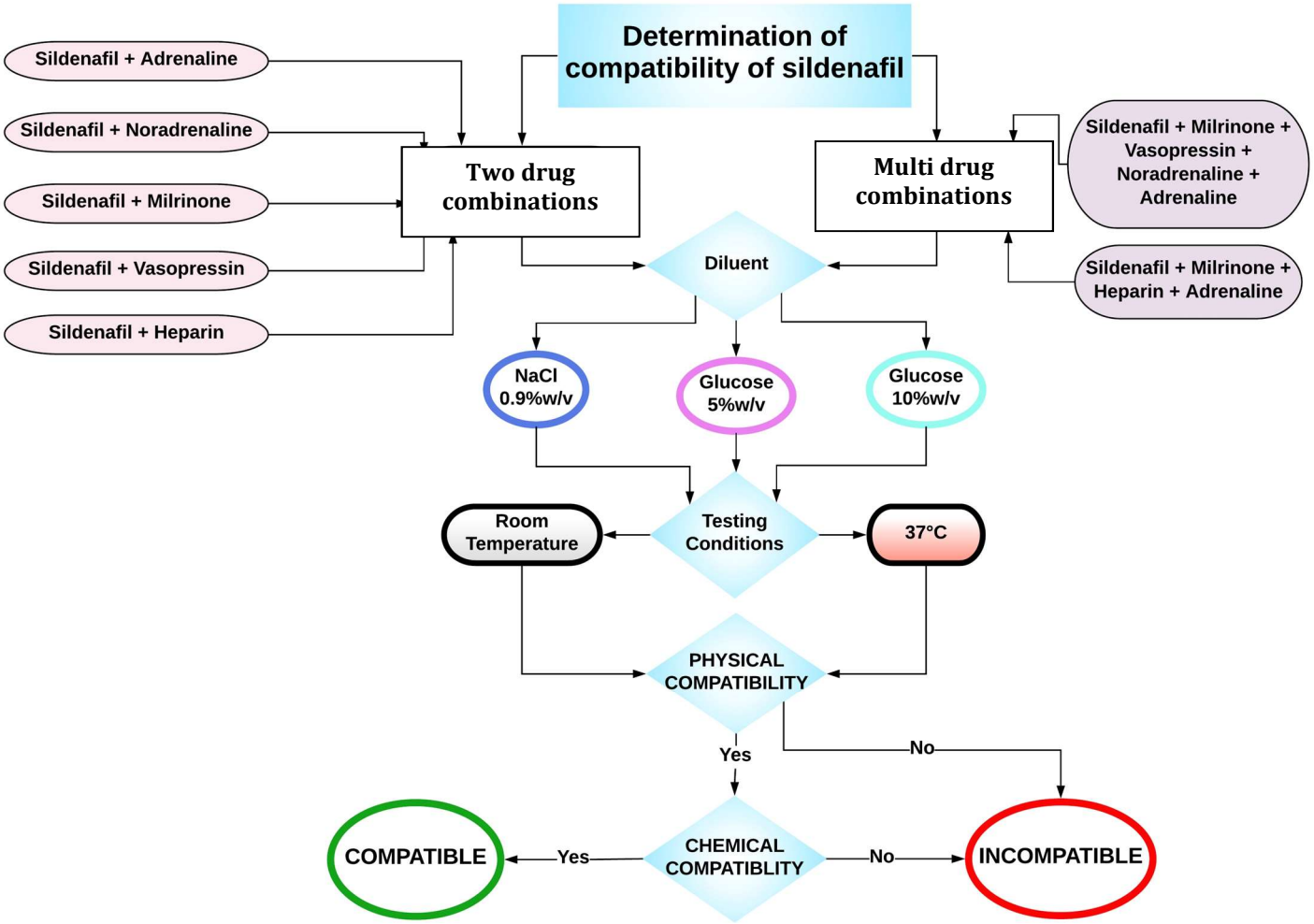

Figure 2 Study overview of the study process to establish sildenafil compatibility/incompatibility.
Test admixtures were classified as binary or multiple, with combinations tested in three diluents Sodium Chloride (NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v) and at two temperature conditions Room Temperature (18 - 22°C) or 37°C. Physicochemical testing was used to establish sildenafil and secondary drug compatibility in the test combinations.

Materials and Methods

Sildenafil citrate injection (Revatio® 10mg/12.5mL) was supplied by Pfizer Ireland (Investigator Led Research Grant). Adrenaline bitartrate injection (epinephrine 1:1000) was obtained from Mercury Pharma International Ltd, Ireland. Noradrenaline bitartrate injection (norepinephrine 1:1000) was obtained from Hospira UK Ltd, UK. Milrinone lactate injection (Primacor® 10mg/10mL) was obtained from Sanofi, UK. Heparin sodium injection (Heparin 5000/5mL) was obtained from Wockhardt UK Limited, UK. Vasopressin injection (20 USP units/mL) was obtained from Fresnius Kabi, Canada. The diluents Sodium Chloride (NaCl) 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v were obtained from Baxter, Ireland. HPLC grade Acetonitrile and other mobile phase components were all purchased from Thermo Fisher Scientific Inc.

Sample preparation and storage conditions

In this study, the concentrations tested, were based on the current standardised infusion concentrations used in the PICU in CHI for patients weighing ≤ 5kg with PH. In accordance with European Pharmacopoeial methods, drug mixtures were prepared in transparent colourless borosilicate glass test tubes with a flat base and an internal diameter of 16 mm (Merck KGaA, Germany) (21). Each drug was drawn from the ampoules using a filter needle and reconstituted in one of the three test diluents; NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v to achieve the desired clinical concentration (Table 1). The concentrations used in this study are listed below:

- Sildenafil citrate 800 µg/mL (Pfizer)
- Adrenaline bitartrate 60 µg/mL (Mercury Pharma International Ltd)
- Noradrenaline bitartrate 60 µg/mL (Hospira UK Ltd)
- Milrinone lactate 200 µg/mL (Sanofi, UK)
- Heparin sodium 100 Units/mL (Wockhardt UK Limited)
- Vasopressin 0.4 Units/mL (Fresnius Kabi, Canada)

Sildenafil IV solution was combined with the secondary drug solution to be tested in a 1:1 ratio (22). Simulations of multiple drug combinations were carried out by mixing drug combinations in a 1:1 ratio.

The effects of two environmental conditions encountered in clinical practice were investigated (Table 1). To reflect real-world conditions, room temperature (RT) test mixtures were stored in uncontrolled temperature of 18 – 22°C without light protection over the duration of the study, 24 h. The second environmental condition examined, reflected where temperature controlled incubators are used in the intensive care unit. To mimic this higher temperature, experiments were conducted in a 37°C temperature controlled incubator without light protection over the duration of the study. Modelling of contact times between drugs at minimal flow rates (0.1mL/hr) and maximum combined dead-space of catheter, tubing and connectors, determined maximum contact time to be 8 hours. Based on this, studies were carried out over 24 h with samples or recordings taken at 0, 2, 4, 8 and 24 h.

Table 1: various drug combinations tested

Drug combination (s)	**Diluent**		
Sildenafil citrate 800 µg/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v

Adrenaline bitartrate 60 µg/mL			
Sildenafil citrate 800 µg/mL Noradrenaline bitartrate 60 µg/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v
Sildenafil citrate 800 µg/mL Milrinone lactate 200 µg/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v
Sildenafil citrate 800 µg/mL Heparin sodium 100 Units/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v
Sildenafil citrate 800 µg/mL Vasopressin 0.4 Units/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v
Sildenafil citrate 800 µg/mL Milrinone lactate 200 µg/mL Heparin sodium 100 Units/mL Adrenaline bitartrate 60 µg/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v
Sildenafil citrate 800 µg/mL Milrinone lactate 200 µg/mL Vasopressin 0.4 Units/mL Adrenaline bitartrate 60 µg/mL Noradrenaline bitartrate 60 µg/mL	NaCl 0.9%w/v	Glucose 5%w/v	Glucose 10%w/v

Physical compatibility testing

Visual inspection

Tubes were inspected macroscopically, firstly against a white background to observe any colour changes or gas elution, and secondly against a black background with fluorescent light to examine for precipitation, haze or strands. Physical incompatibility was defined as the observation of gross precipitation, visual particulate matter, haze, gas formation, or colour change in accordance with the

European and United States Pharmacopoeial specifications (21, 23).

Turbidity

Turbidity of the drug combinations was measured using a calibrated laboratory-grade turbidimeter (Hach, Colorado USA). Prior to the turbidity assessment of test samples the tubes were inverted twice to resuspend any settled particles, when bubbles disappeared the turbidity was tested. Measurements were obtained six times per tube and mean turbidity calculated. Incompatibility was defined as a change in turbidity by 0.5 nephelometric turbidity units (NTU) as defined by Trissel and Bready (24).

Chemical compatibility testing

pH

In line with USP guidance and reflecting the significant impact of pH on compatibility, a narrow pH tolerance was used in this project (23). Incompatibility was defined as a change in mean pH by >0.5 units from the initial pH. Aliquots of the drug combinations were withdrawn at 0 h, 2 h, 4 h, 8 h and 24 h and tested for pH using a calibrated laboratory-grade pH-meter (Testo SE & Co. KgaA, Germany). Duplicate combinations were tested and triplicate values obtained per sample from which the mean pH was then calculated.

Drug concentration determination via HPLC analysis

High performance liquid chromatography (HPLC) methods were developed, optimised and validated to ensure system suitability and precision for analytical determination of drug concentration (Table 2). Briefly, HPLC methodology was

developed in accordance with European Pharmacopoeial standards, the inter-day and intra-day precision, accuracy, linearity, tailing factor, theoretical plates, limit of detection and quantitation were all established for each HPLC method of each drug to ensure reliability and validity of the methods utilised and that the results obtained are statistically sound. Using these validated methods, samples were filtered using 0.45 µm filters (Phenomenex Inc. California USA) prior to HPLC analysis. Triplicate measurements were performed on duplicate samples of each test admixture. HPLC determination was used to detected drug concentrations at time 0 h, 2 h, 4 h, 8 h and 24 h after mixing. Results of peak area generated by the OpenLab software v2.0 (Agilent Technologies Inc., California USA) were analysed using Microsoft Excel® to calculate concentration and percentage recovery of the drugs. Drug concentrations were expressed as a percentage of the initial concentration detected. Altered concentration >10% was deemed an incompatibility as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (25, 26).

Table 2 High performance liquid chromatography methods utilised for quantification of sildenafil and secondary paediatric intensive care drugs

Variable	**Sildenafil**	**Adrenaline**	**Noradrenaline**	**Milrinone**	**Vasopressin**
Column	Kinetex 5µm C18 100Å (150x 4.6mm) column				
Mobile phase	Acetonitrile: ammonium	Phosphate buffer (pH7):	Sodium heptane	Phosphate buffer (pH7.5)	Phosphate buffer (pH3) :

	acetate buffer (pH7) (1:1)	Acetonitrile (85:15)	sulfonate: methanol (80:20) (pH3)	: acetonitrile (80:20)	acetonitrile (87:13)
Flow rate	1mL/min	1mL/min	1mL/min	1mL/min	1mL/min
Detection wavelength	280nm	280nm	280nm	220nm	195nm
Injection Volume	20µL	20µL	20µL	20µL	60µL
Range	50 - 400 µg/mL	10 - 60 µg/mL	10 - 60 µg/mL	10 - 200 µg/mL	0.025 - 0.4 Units/mL
Linearity	>0.99	>0.99	>0.99	>0.99	>0.99

Results

Visual appearance, turbidity and pH compatibility

According to the European Medicines Agency (EMA), sildenafil exhibits a pH dependent solubility profile and an increase in pH is proportional to an increase in sildenafil insolubility with the pH of sildenafil of around 3.8 (27). As per USP guidance and reflecting the critical nature of pH in stability, incompatibility in this study was defined as a change in mean pH by >0.5 units from the initial pH. The initial pH reading for sildenafil was 4.02 and the acceptable limits using the USP guidelines were set between pH 3.52 to 4.52.

Of the drug combinations not containing heparin, all were deemed compatible with the exception of the five drug mix of Sildenafil 800µg/mL, Milrinone 200µg/mL, Vasopressin 0.4 Units/mL, Noradrenaline 60µg/mL, Adrenaline 60µg/mL (Table 3). This multi drug mix at 37°C and in 10%w/v glucose showed fluctuation in concentrations and high standard deviations, which require further investigation (further discussed below).

All binary or multi drug combinations containing heparin were deemed incompatible.

Table 3 Visual appearance, turbidity and pH results of the Y-site and multi-infusion drug admixtures in three diluents and two temperature conditions. Shaded results indicate an incompatibility. Incompatibility was recorded as change in visual appearance, a change in turbidity >0.5NTU (25) and a change pH of 0.5 from the initial pH of the drug which was set between pH 3.52 to 4.52 as per USP guidelines

Drug Admixtures		**Visual inspection**		**Turbidity (NTU)[a] (mean ± SD[b])**			**pH**		
		Time (h)							
	Temperature & Diluent	***0***	***24***	***0***	***8***	***24***	***0***	***8***	***24***
Sildenafil 800µg/mL + Heparin 100Units/ mL	RT NaCl 0.9%w/v	White precipitate	White precipitate	203.33 ± 3.27	303.50 ± 0.84	305.5 ± 10.2	4.17 ± 0.05	4.22 ± 0.2	4.26 ± 0.2
	37°C NaCl 0.9%w/v	Clear	Clear	0.28 ± 0.02	0.13 ± 0.02	0.12 ± 0.02	4.06 ± 0.2	4.17 ± 0.3	4.17 ± 0.3
	RT Glucose 5%w/v	Clear	Slightly cloudy	1.84 ± 0.1	16.55 ± 0.42	28.5 ± 0.1	4.66 ± 0.1	4.71 ± 0.2	4.76 ± 0.3
	37°C Glucose 5%w/v	Clear	Slightly cloudy	0.65 ± 0.03	3.71 ± 0.18	5.55 ± 0.24	4.52 ± 0.2	4.60 ± 0.3	4.64 ± 0.3
	RT Glucose 10%w/v	Clear	Slightly cloudy	1.16 ± 0.03	12.15 ± 0.37	28.1 ± 0.6	4.63 ± 0.03	4.65 ± 0.1	4.7 ± 0.2
	37°C Glucose 10%w/v	Clear	Slightly cloudy	0.98 ± 0.02	3.99 ± 0.28	6.1 ± 0.3	4.46 ± 0.2	4.52 ± 0.4	4.58 ± 0.3
Sildenafil 800µg/mL	RT NaCl 0.9%w/v	Clear	Clear	0.01 ± 0.004	0.003 ± 0.01	0.02 ± 0.02	3.69 ± 0.02	3.74 ± 0.03	3.74 ± 0.04
	37°C NaCl 0.9%w/v	Clear	Clear	0.01 ± 0.008	0.00 ± 0.00	0.01 ± 0.02	3.71 ± 0.08	3.70 ± 0.1	3.69 ± 0.13

+ Milrinone 200µg/mL + Heparin 100Units/ mL + Adrenaline 60µg/mL	RT Glucose 5%w/v	Clear	Slightly cloudy	0.26 ± 0.02	13.90 ± 0.09	23.9 ± 0.33	3.97 ± 0.1	3.98 ± 0.1	3.956 ± 0.1
	37°C Glucose 5%w/v	Clear	Cloudy	0.21 ± 0.04	3.47 ± 0.18	4.44 ± 0.28	3.92 ± 0.08	3.93 ± 0.1	3.93 ± 0.08
	RT Glucose 10%w/v	Clear	Slightly cloudy	0.23 ± 0.03	9.69 ± 0.11	18.6 ± 0.3	3.79 ± 0.2	3.79 ± 0.2	3.76 ± 0.2
	37°C Glucose 10%w/v	Clear	Cloudy	0.15 ± 0.01	3.71 ± 0.19	5.17 ± 0.18	3.87 ± 0.2	3.94 ± 0.2	3.98 ± 0.3

In relation to studies including heparin, visual appearance turbidity and pH results showed the following incompatibilities:

1. Sildenafil 800 µg/mL + Heparin 100 Units/mL in NaCl 0.9%w/v at RT conditions (Table 3, Figure 3)

   This solution was instantly cloudy with white precipitate and strands forming as soon as the heparin was added (Figure 3). Conversely, in the same diluent at 37°C the heparin and sildenafil combination was clear at all time points, indicating a possible temperature dependant reaction. Turbidity measurements of the same solution showed a significant difference in the turbidity of the mix at RT (0 h: 203.33 ± 3.27 NTU) when compared with the 37°C result (0 h: 0.28 ± 0.02 NTU) indicating incompatibility between the drugs (Table 3). All pH measurements were within acceptable limits (Table 3).

2. Sildenafil 800 µg/mL + Heparin 100 Units/mL in Glucose 5%w/v and Glucose 10%w/v in both RT and 37°C (Table 3, Figure 3)

   Visual changes in appearance were observed when sildenafil and heparin were mixed in both Glucose 5%w/v and Glucose 10%w/v 2 h after mixing at both temperatures (RT and 37°C). All solutions were slightly cloudy. No effervescence was noted; the colour of the precipitate was white (Figure 3). Again turbidity measurements of these solutions showed an increase in turbidity of >0.5 NTUs indicating incompatibility in these combinations at these temperatures (Table 3). pH measurements at all times point were outside the limits with the exception of 37°C Glucose 10%w/v at 0 h indicating incompatibility (Table 3).

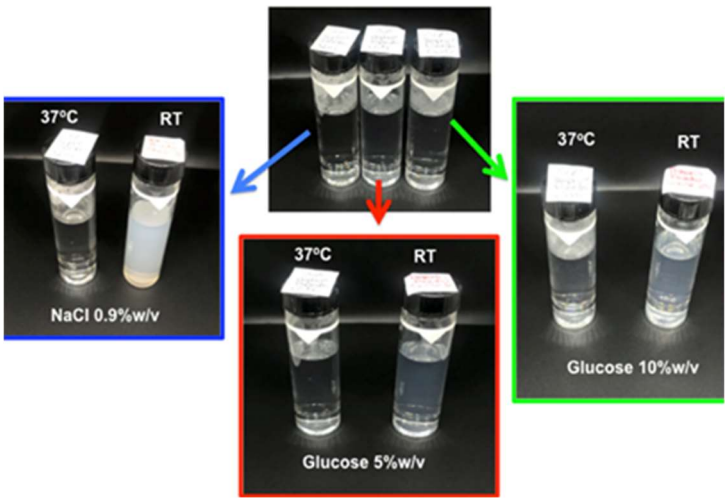

Figure 3: Sildenafil (0.8 mg/ml) and Heparin (100 Units/ml) combination at (A) RT and (B) 37°C in three test diluents (NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v) at 24 h. RT = room temperature

3. Sildenafil 800µg/mL + Milrinone 200µg/mL + Heparin 100 Units/ml + Adrenaline 60 µg/mL in Glucose 5%w/v and Glucose 10%w/v in both RT and 37°C (Table 3, Figure 4)

   The 4 drug mix was cloudy at 24 h in both Glucose 5%w/v and Glucose 10%w/v at RT and 37°C (Figure 4). Turbidity measurements of these solutions in these conditions indicate physical incompatibility in the combinations (Table 3). All pH measurements were within acceptable limits (Table 3). No turbidity was seen in the 4-drug combination in NaCl 0.9%w/v however, it was already established in the y-site combination (Figure 3) that Heparin and sildenafil are incompatible and therefore for the purpose of this study turbidity in NaCl of this 4 drug combination was deemed inconclusive.

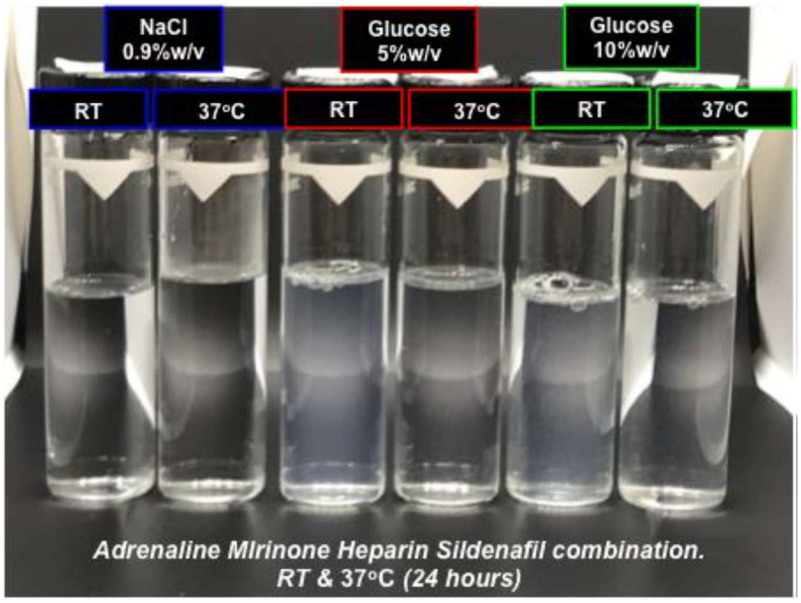

Figure 4 Visual appearance of the four-drug combination. Sildenafil Adrenaline Milrinone and Heparin combinations in the three diluents tested at 24 h at RT and 37°C.

Chemical compatibility results – drug content

The analytical determination of drug content for the simulated Y-site and multi-infusion drug mixtures in NaCl 0.9%w/v, Glucose 5%w/v, and Glucose 10%w/v at two temperature conditions (RT and 37°C) was carried out. Drug content of sildenafil, adrenaline, noradrenaline, vasopressin and milrinone were determined.

The concentrations of all drugs analysed within the various combinations remained within 90 – 110% drug content or acceptable limits with the exception of:

1. Sildenafil 800µg/mL + Heparin 100 Units/ml at RT in NaCl 0.9%w/v (Figure 5)

   Recovery of sildenafil in the simulated Y-site heparin sildenafil combination at RT in NaCl 0.9%w/v was initially 64% at 0 h and further decreased to 50.6% and 43.9% at 8 h and 24 h respectively.

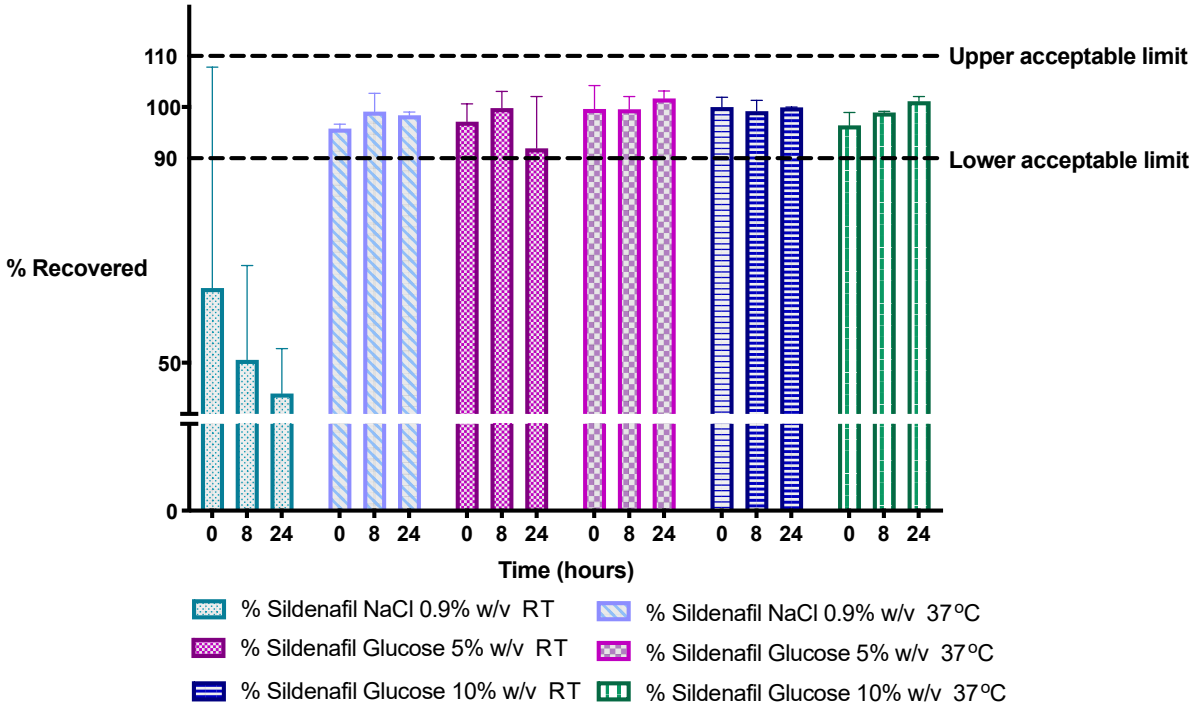

Figure 5 Simulated Y-site (0.8 mg/ml sildenafil + 100 Units/ml heparin) admixtures recovery profiles at 0 h, 8 h and 24 h, in NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v at RT and 37°C.

2. <u>Sildenafil 800µg/mL + Milrinone 200µg/mL + Heparin 100 Units/ml + Adrenaline 60µg/mL at RT Glucose 10%w/v (Figure 6):</u>

   Drug content for the 4 drug mix of sildenafil, heparin, adrenaline and milrinone demonstrated sildenafil incompatibility in the mix in glucose 10%w/v (Figure 6) at RT but not at 37°C indicating a possible temperature dependent process. All other analysis demonstrated compatibility between the drugs in this mix however as can be seen from the results displayed below many of the concentrations measured were close to the lower acceptable limit of 90% drug content.

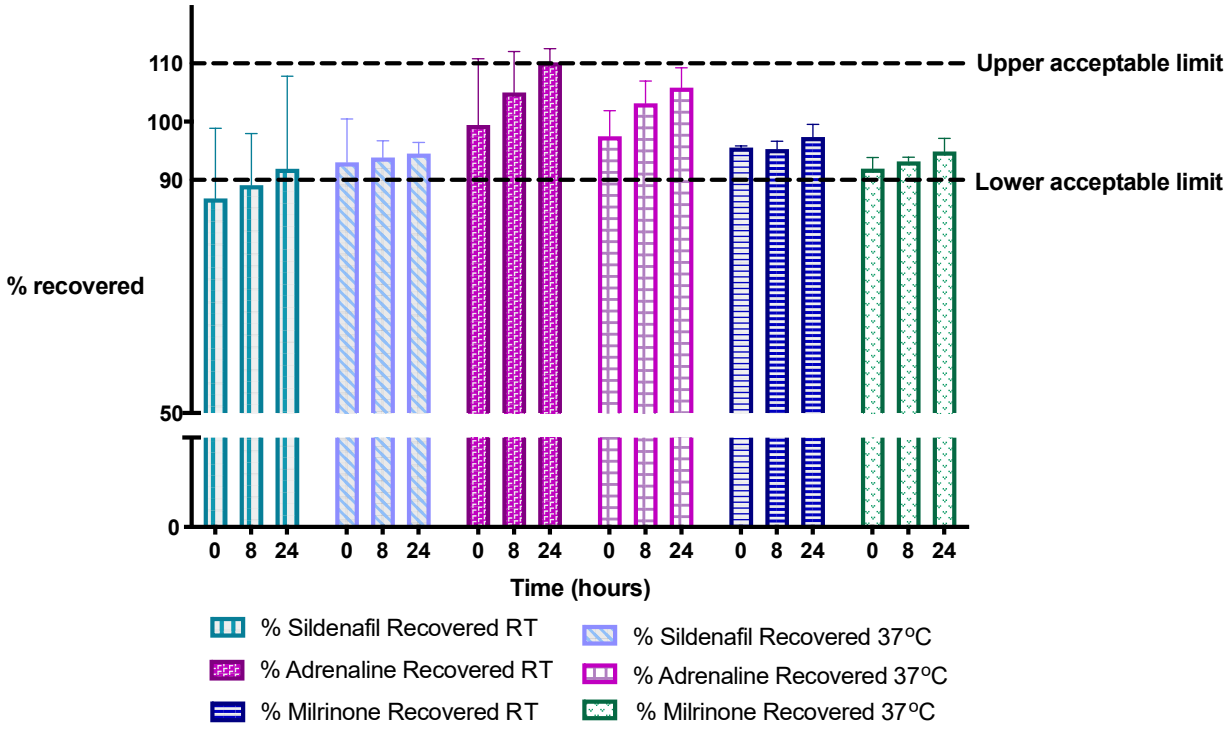

Figure 6 Simulated multi-infusion (Sildenafil 800µg/mL + Heparin 100 Units/mL + Milrinone 200µg/mL + Adrenaline 60µg/mL) admixtures recovery profiles at 0 h, 8 h and 24 h in Glucose 10%w/v at RT and 37°C

In addition to the results above where incompatibility was clearly identified, there were 4 scenarios which the compatibility of the drug combinations were classified as inconclusive and requiring of further investigation. These were:

1. Sildenafil 800µg/mL and Heparin 100 units/mL at 37°C in NaCl 0.9%w/v

   Analysis of this combination of sildenafil and heparin at RT resulted in an incompatible result and as such a similar result at 37°C was expected but didn't materialise. However, when the drug concentration results are examined, they fluctuate extensively from 0 h – 24 h with large standard deviations.

2. Sildenafil 800µg/mL + Milrinone 200µg/mL + Heparin 100 Units/ml + Adrenaline 60µg/mL at RT in NaCl 0.9%w/v.

3. Sildenafil 800µg/mL + Milrinone 200µg/mL + Heparin 100 Units/ml + Adrenaline 60µg/mL at 37°C in NaCl 0.9%w/v.

This mixture has been classified as inconclusive in this study due to the presence of heparin in the mixture and the physical incompatibility results seen both in this combination in Glucose 5% and Glucose 10%w/v (Table 3) and in the incompatibility results observed when sildenafil and heparin are combined in NaCl (Figure 5). Further investigation of this 4 drug combination is required before classifying the mixture.

4. Sildenafil 800µg/mL, Milrinone 200µg/mL, Vasopressin 0.4 Units/ mL, Noradrenaline 60µg/mL, Adrenaline 60µg/mL at 37°C in Glucose 10%w/v.
   Increased fluctuation in recovery and high standard deviation between the duplicate samples in the Glucose 10%w/v five-drug samples at 37°C, provided results that were deemed to be inconclusive and requiring further investigation.

Discussion

The aim of this study was to determine the physical and chemical compatibility of sildenafil with commonly administered drugs in PICU-specific conditions. Assessment of forty-two combinations was undertaken to achieve the study aim as shown in Figure 7.

Compatibility chart		RT	37°C	RT	37°C	RT	37°C	RT	37°C	RT	37°C	RT	37°C	RT	37°C
		Adrenaline bitartrate (0.06mg/ml)	Adrenaline bitartrate (0.06mg/ml)	Noradrenaline Bitartrate (0.06mg/ml)	Noradrenaline Bitartrate (0.06mg/ml)	Vasopressin (0.4 Units/ml)	Vasopressin (0.4 Units/ml)	Heparin Sodium (100 Units/ml)	Heparin Sodium (100 Units/ml)	Milrinone Lactate (0.2mg/ml)	Milrinone Lactate (0.2mg/ml)	Sil + Mil + Hep +Ad*	Sil + Mil + Hep +Ad*	Sil + Mil + Vaso + Norad +Ad*	Sil + Mil + Vaso + Norad +Ad*
NaCl 0.9%w/v	Sildenafil citrate 0.8mg/ml	c	c	c	c	c	c	i	?	c	c	?	?	c	c
Glucose 5%w/v	Sildenafil citrate 0.8mg/ml	c	c	c	c	c	c	i	i	c	c	i	i	c	c
Glucose 10%w/v	Sildenafil citrate 0.8mg/ml	c	c	c	c	c	c	i	i	c	c	i	i	c	?

Figure 7 Compatibility chart generated from this study.

Y-site combinations (binary admixtures) and multi-infusion combinations at two temperature conditions (RT & 37°C) and three diluents (Sodium chloride (NaCl) 0.9%w/v, Glucose 5%w/v & Glucose 10%w/v). *Sil = sildenafil, Mil = milrinone, Hep = Heparin, Ad = Adrenaline, Norad = Noradrenaline, Vaso = vasopressin, i = incompatible, c = compatible, ? = inconclusive.

In addition to the results as outlined, this study highlights three main points:

1. Due to an observed physical incompatibility, heparin was essentially considered unsuitable for administration via Y-site and multi-infusion connectors in clinical practice and therefore further testing was deemed irrelevant for the purposes of this study to inform clinical judgement in the PICU setting. In order to further examine and elucidate the causes of this incompatibility, advanced analytical testing would be required.
2. The study results highlight the importance of taking into account PICU-specific environmental factors that can affect IV drug stability and efficacy when utilising Y-site and multi-infusion connectors. For instance, PICU incubators and the effect temperature may have on the degradation process of drug products. This was observed in the mixture of sildenafil and heparin in NaCl 0.9%w/v, where at RT conditions an instant white precipitate was observed upon mixture, however at 37°C the solution remained clear and colourless throughout the 24 h test period, possibly

indicating a temperature dependant physical incompatibility (Figure 3). A temperature dependant fluctuation in drug recovery was also seen in the five-drug simulated multi-infusion combination in Glucose 10%w/v at 37°C compared to the stable recovery at RT conditions and was deemed inconclusive. However in clinical practice the temperature of the IV infusions cannot be reliably determined when they combine and as such vigilance in the clinical setting is important.

3. There are important limitations to note in this study:
    - Although sildenafil demonstrated chemical and physical compatibility in most of the combinations (with the exception of those containing heparin), it is still important to note study-specificity. In this study, the concentrations utilised, the drug brands and the diluents used are all important factors that lead to the determination of compatibility.
    - The choice of drugs examined reflects local practice and is not an exhaustive list of infusions or diluents used in the neonatal/paediatric setting.
    - This study was carried according to guidelines published by Trissel (29) but nonetheless, it is important to note that experiments were carried out in an academic research laboratory and while local implementation of these findings is planned, responsibility for translation of these results into the wider setting rests with local clinicians.

Conclusion

Currently there are no available Y-site compatibility studies for sildenafil in combination with other commonly administered PICU infusions. This is due to the recent introduction of sildenafil as a mainstay treatment of paediatric PH and also that adults generally would not require sildenafil to be Y-sited.

In paediatrics, sildenafil is currently administered as a continuous infusion via a dedicated line, often proceeded by a loading dose over 30 - 180 minutes (9, 28, 30). Current practices in this patient cohort emphasise the importance of Y-site studies and the need for compatibility data to allow intensivists to co-administer sildenafil with other drugs via Y-site safely.

Figure legends

Figure 1	Single, Y-site and multi-lumen devices. The differences between the devices utilised in practice to administer one, two and multiple intravenous drug infusions, respectively.
Figure 2	Study overview of the study process to establish sildenafil compatibility/incompatibility. Test admixtures were classified as binary or multiple, with combinations tested in three diluents Sodium Chloride (NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v) and at two temperature conditions Room Temperature (18 - 22°C) or 37°C. Physicochemical testing was used to establish sildenafil and secondary drug compatibility in the test combinations.
Figure 3	Sildenafil (0.8 mg/ml) and Heparin (100 Units/ml) combination at (A) Room Temperature and (B) 37°C in three test diluents (NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v) at 24 h. RT = room temperature
Figure 4	**Figure 4** Visual appearance of the four-drug combination. Sildenafil Adrenaline Milrinone and Heparin combinations in the three diluents tested at 24 h at RT and 37°C.
Figure 5	Simulated Y-site (0.8 mg/ml sildenafil + 100 Units/ml heparin) admixtures recovery profiles at 0 h, 8 h and 24 h, in NaCl 0.9%w/v, Glucose 5%w/v and Glucose 10%w/v at Room Temperature and 37°C.
Figure 6	Simulated multi-infusion (Sildenafil 800µg/mL + Heparin 100 Units/mL + Milrinone 200µg/mL_+Adrenaline 60µg/mL) admixtures recovery profiles at 0 h, 8 h and 24 h in Glucose 10%w/v at Room Temperature and 37°C
Figure 7	Compatibility chart generated from this study. Y-site combinations (binary admixtures) and multi-infusion combinations at two temperature conditions (RT & 37°C) and three diluents (Sodium chloride (NaCl) 0.9%w/v, Glucose 5%w/v & Glucose 10%w/v). *Sil = sildenafil, Mil = milrinone, Hep = Heparin, Ad = Adrenaline, Norad = Noradrenaline, Vaso = vasopressin, i = incompatible, c = compatible ? = inconclusive.

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