European Journal of Pharmaceutical Sciences 93 (2016) 56–63

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Dosing errors in preterm neonates due to flow rate variability in multi-infusion syringe pump setups: An in vitro spectrophotometry study☆,☆☆

Roland A. Snijder [a,*], Toine C.G. Egberts [b], Peter Lucas [c], Petra M.A. Lemmers [d], Frank van Bel [d], Annemoon M.D.E. Timmerman [a]

[a] Dept. Medical Technology and Clinical Physics, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Dept. Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands
[c] VSL Dutch Metrology Institute, Delft, The Netherlands
[d] Dept. Neonatology, University Medical Center Utrecht, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 10 March 2016
Received in revised form 1 July 2016
Accepted 29 July 2016
Available online 4 August 2016

Keywords:
Multi-infusion
Dosing error
High-risk medication
Neonatology
Adverse event
Photo spectrometric measurement

ABSTRACT

Background: Drug administration on the neonatal intensive care unit is often associated with adverse events. This may be due to dosing errors caused by multi-infusion setups. We aim to investigate these dosing errors.
Material and methods: N = 3 experiment using a medication schedule, multi-infusion setup (three pumps) and disposables as applied on the NICU. In-line and real-time absorption spectrophotometry was used with dyes as substitutes for pharmaceuticals. Three flow rate changes lasting 1 h were initiated. Subsequently, the possible dosing errors were estimated in the parallel pumps. In addition, startup durations, the times the flow rates required to reach steady state after significant dosing errors, as well as the total dosing error were measured.
Results: Contribution of the start-up delays to the cumulative dosing errors was the largest. However, initiated flow rate changes resulted in significant dosing errors in the parallel pumps as well. The total dosing error was not significant. The significant peak errors were between 48.2% and −32.5% at flow rate increase and decrease, respectively. Startup delays of up to 42.6 min were measured.
Conclusions: Applying multi-infusion while following a neonatal medication schedule may temporarily result in dosing errors, which can be relevant for fast-acting medications. Awareness may mitigate the risks.

1. Introduction

Almost all patients treated on the neonatal intensive care unit (NICU) receive intravenous (IV) infusion therapy (Van Der Eijk et al., 2013). Infusion therapy intended for NICU patients commonly requires the continuous and simultaneous administration of multiple pharmaceuticals such as inotropics, opioids, antibiotics and sedatives. The administration of these drugs using multi-infusion to NICU patients is challenging. For example, these little and often critically ill patients are unable to tolerate the infusion of large quantities of fluid (Bell and Acarregui, 2014). To reduce the amount of fluid delivery but still reach the effective dose, highly concentrated mixtures are delivered at volumetric flow rates as low as 0.5 ml/h. Moreover, these mixtures frequently contain rapid-acting pharmaceuticals with short half-lives and narrow therapeutic margins requiring a stable infusion flow rate, because even a relatively small deviation in flow rate may result in clinically relevant dosing errors. Consequently, accurate motorized syringe pumps are used to meet this demand for precise and accurate drug delivery. Another risk of infusion therapy is the placement of the catheter. With each puncture and accompanying catheter insertion, the probability of systemic infections increases. The number of IV-access sites should therefore be reduced to a minimum, especially in vulnerable patients, such as very and extremely preterm neonates. As such, pharmaceuticals from multiple pumps are often combined into a single central line and catheter before entering the patient's bloodstream. This practice is known as multi-infusion or co-infusion (Décaudin et al., 2009; Lovich et al., 2005). Infusion technology has one of the highest rates of medical errors associated with medical technology (Husch et al., 2005). Previous research has shown that flow rate variability is related to dead time and carrier flow (Décaudin et al., 2009; Lovich et al., 2005; Timmerman et al., 2015), flow interaction between two syringe pumps (Bartels et al.,

☆ **Statement of financial support**: The research leading to the results discussed in this report has received funding from the European Metrology Research Programme (EMRP) HLT07-REG1 (Metrology for Drug Delivery (MeDD)). The EMRP is jointly funded by the EMRP participating countries within Euramet and the European Union.
☆☆ No human or animal subjects nor any biological materials were involved in this study. Approval from the Institutional Review Board, as well as (parental) informed consent, was therefore not applicable for this research.
* Corresponding author at: Dept. of Medical Technology and Clinical Physics, Room C 01.230, University Medical Center Utrecht, 100 Heidelberglaan, Utrecht 3584 CX, The Netherlands.
E-mail address: r.a.snijder-2@umcutrecht.nl (R.A. Snijder).

http://dx.doi.org/10.1016/j.ejps.2016.07.019
0928-0987/

2009; Tsao et al., 2013) and the effects of gravity and vertical displacement (Hall and Roberts, 2005; Neff et al., 2001a). Additionally, several publications addressed the physical effects of a variety of disposables (Murphy and Wilcox, 2010; Neal and Lin, 2009; Van Der Eijk et al., 2014; Weiss et al., 2000a, 2000b). Other studies have already recognized effects as a result of multi-infusion flow interaction in parallel pumps and start-up delays as plausible and possibly clinically relevant in neonatal populations (Levi et al., 2010; Lovich et al., 2013; Medlicott et al., 2013; Sherwin et al., 2014; Tsao et al., 2013).

In summary, the practice of multi-infusion often seems to result in flow rate variability, even when accurate syringe pumps are used. This in turn may result in clinically relevant dosing errors, which is especially true for the (preterm) neonate. Several studies have, for example, reported significant hemodynamic instability and possible adverse effects in neonates in relation to the administration of rapid-acting inotropics (Alderliesten et al., 2013; Dempsey, 2015; Panna et al., 1996; Snijders et al., 2010; Stowe et al., 1996) and propofol (Vanderhaegen et al., 2010). Preterm neonates are known to be particularly susceptible to hemodynamic instability due to their limited ability for cerebral autoregulation in response to changing blood pressure and blood flow (Alderliesten et al., 2013; Caicedo et al., 2011). However, to our knowledge, no substantial research has been performed to quantify multi-infusion flow and dosing rate variability on the NICU.

The objective of this study is therefore to assess dosing errors due to flow rate variability in neonates as a consequence of applying a cascade of multiple infusion pumps intravenously. An absorption spectrophotometry in vitro study was conducted to simulate a multi-infusion setup and neonatal medication schedule.

2. Material and methods

2.1. Experimental setup

IV multi-infusion therapy on the NICU was simulated in a laboratory setting using three infusion pumps, each containing a dye mimicking a pharmaceutical solution. The flow rate, which is linearly related to the dose at the end of the infusion line, was measured with spectrophotometry (Fig. 1A). To simulate the NICU setting, the same disposables were applied in the experimental setup as are used in the daily practice of the NICU of the Wilhemina Children's Hospital of the University Medical Center Utrecht, a tertiary care academic hospital.

Three Perfusor B. Braun syringe pumps (pumps 1–3) (B. Braun, Melsungen AG, Germany) and 50 ml syringes (BD Plastipak, Plymouth, Ireland) were used in the experimental setup. The pumps were connected to a 173 cm central line disposable (Impromediform GmbH, Lüdenscheid, Germany) (Fig. 1B) through the two Luer-Lock access groups for medications (C1 and C2). These access groups were equipped with anti-reflux valves and, subsequently, a filter. Behind the filter there was a specific lipid access (C3) connector which was not used in the experiments. The syringe pump containing the dye solution, mimicking high-risk medication (pump 1, see Fig. 1), e.g. dopamine, was connected to C2, because high-risk medications are commonly administered in

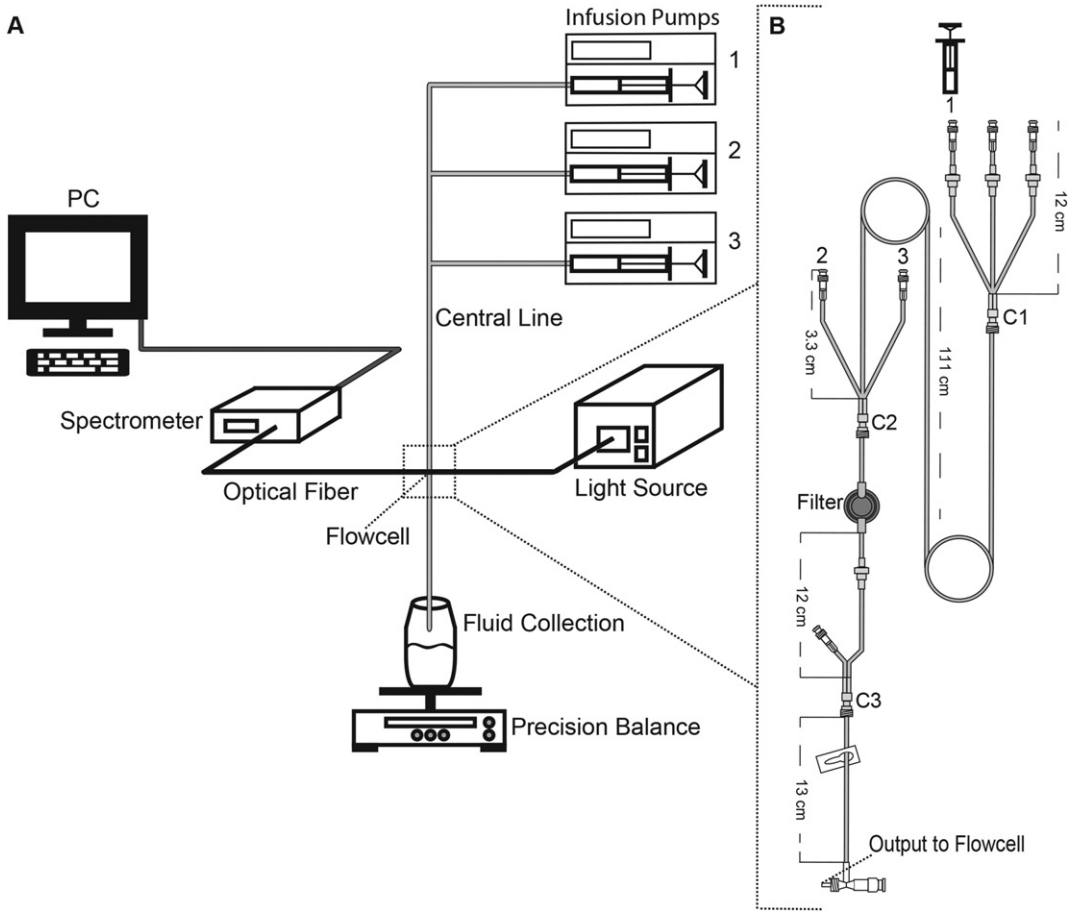

Fig. 1. Measurement setup shown schematically. The dye-filled infusion pumps were connected to the flowcell, shown at the intersection, and, subsequently, to the fluid collection after the flowcell, where the cumulative solution was measured by the precision balance. At the flowcell intersection, a light source was also connected to the same flowcell through optical fibers, which was then connected to a spectrometer. The flowcell enables the light to pass through the dye mixture, which yields an absorption spectrum. The flowcell was shielded from ambient light. The spectrometer and balance data were finally collected by a PC (A). 173 cm central line disposable, C1–C3 are Luer-lock connector groups, C3 is used for lipids. The flow goes from top to bottom in the drawing. Pump 1 (mimicking the critical medication) was connected to access group C2 and pumps 2 and 3 (mimicking "less"-critical medication) to C1. (B).

close proximity to the patient. C1 was used for the pumps containing the dyes mimicking the "less"-critical medications (pumps 2 and 3), e.g. total parenteral nutrition (TPN) and glucose. The central line output was finally connected to a 4 Fr double lumen catheter (Vygon, Ecouen, France), similar to an Umbilical Venous Line used in neonates.

Catheter output concentrations, normally administered to the neonate, were continuously measured using a spectrometric setup (Fig. 1A). The catheter was for this purpose connected to a flowcell (Z flow cell w/SMA 905, 10-mm pathlength, FIAlab, Seattle, WA, USA). The flowcell was connected to a spectrometer (QE65000, Ocean Optics, Dunedin, FL, USA) and a light source (DT-100, Ocean Optics, Dunedin, FL, USA) allowing the spectrometer to obtain a spectrum of the mixture driven through the flowcell. Based on calculations the dyes were expected to be fully mixed, i.e. full diffusion was expected to occur in radial direction of the infusion lines, before entering the flowcell. Finally the fluids from all pumps were collected and measured by the balance (PGW 450, Adam Equipment, Oxford, CT, USA). Both the balance and the spectrometric data were recorded by a PC (×86 32 bits, windows XP, USA) at a sample acquisition period of 10 s (0.1 Hz). The method described was capable to measure the flow rates originating from each specific pump, which is equivalent to the pharmaceutical dose delivered to the patient.

2.2. Medication schedule

To investigate flow rate variability (and thus dosing variability), a medication schedule was simulated in which flow rate changes were initiated and changed back for each pump (Fig. 2). The total duration of the medication schedule was 8 h. Pumps 1–3 were started at flow rates of 6, 2 and 0.5 ml/h, respectively. Six flow rate changes were

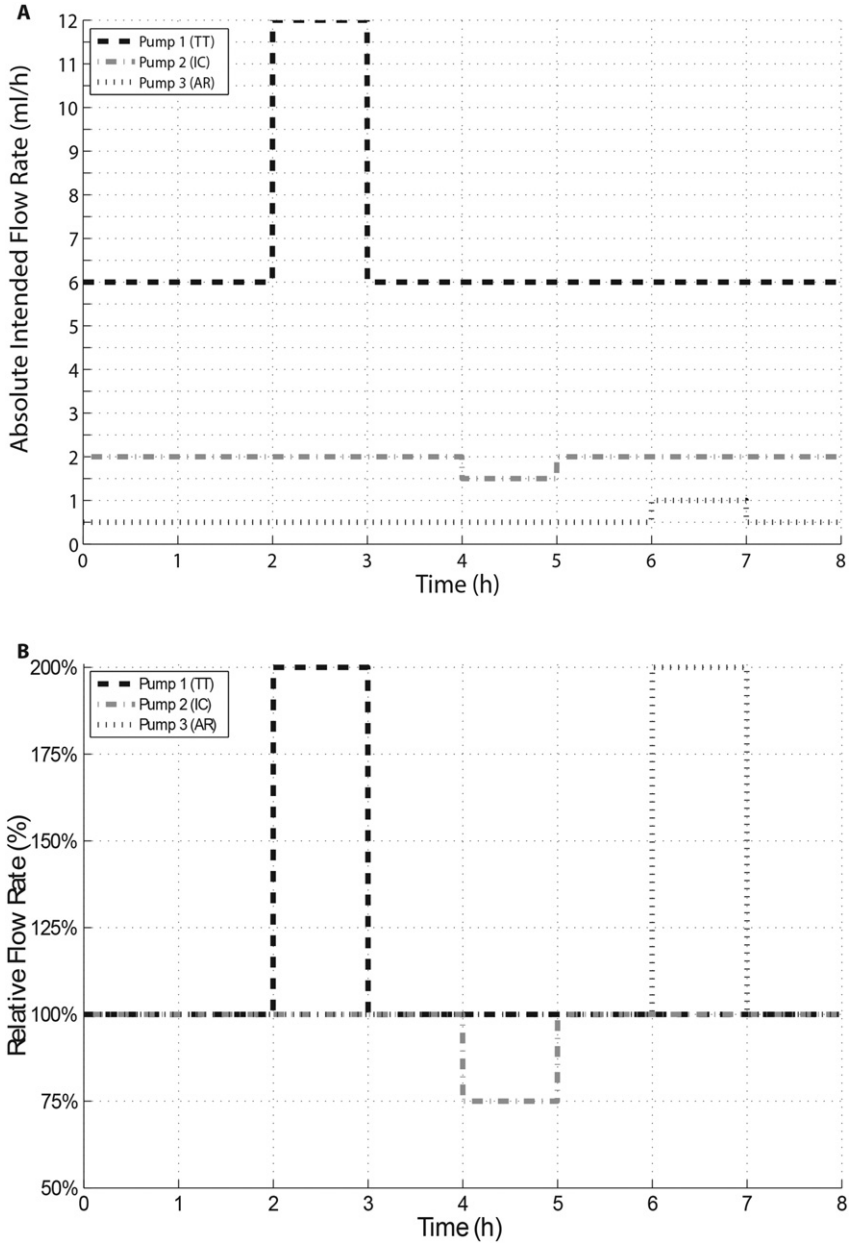

Fig. 2. Graphical representation of medication schedule set point values. Absolute intended flow rate (A) and relative flow rate changes (B). The flow rate in pump 1 was increased at t = 2 h from 6.0 to 12 ml/h and back to 6.0 ml/h at t = 3 h (a 100% change). Pump 2 was decreased from 2.0 to 1.5 ml/h at t = 4 h and back to 2 ml/h at t = 5 h (a 25% change). Pump 3 was increased from 0.5 ml/h to 1.0 ml/h at t = 6 h and changed back to 0.5 ml/h at t = 7 h (a 100% change). As a substitute for the pharmaceuticals Tartrazine (TT, 0.02 mg/l), Allura Red (AR, 0.1 mg/l) and Indigo Carmine (IC, 0.2 mg/l).

manually executed according to the medication schedule; first these were initiated and, next, changed back after 1 h. During the flow rate changes the other two pumps, in which no flow rate change was intentionally initiated, were considered the 'parallel pumps'. The experiment was repeated three times (N = 3).

Tartrazine (TT), Allura Red (AR) and Indigo Carmine (IC) laser dyes were used as substitutes for the pharmaceuticals. The dyes were selected on the basis of their distinctive absorption spectra, i.e. the overlap of the absorption spectra was minimal. Dye concentrations (Fig. 2) were chosen according to the linear range agreement between concentration and absorption by which the absorption spectrum can be related to flow rate and thus the flow and dosing rate variability of each individual pump.

2.3. Dosing errors

In clinical practice a dose is defined as the amount of a pharmaceutical administered in a certain time interval. It is usually denoted as mg or mg per kg patient weight. In infusion therapy the concentration of the pharmaceutical in the syringe pump is usually kept constant. Therefore, the dose intended to administer during a time interval is realized by setting and, if necessary, adjusting, the flow rate. This means that a dose is delivered per unit time (dosing rate), often denoted as mg/h or mg/kg/h. Consequently, if the patient receiving infusion therapy requires a different dose, the clinician changes the infusion flow rate (ml/h) of the pharmaceutical solution in a certain concentration (mg/ml). A dose was therefore defined as the amount (ml) delivered after a certain time interval (the area under the curve of the flow rate). The relative dosing error was defined as the deviation (%) of the administered dose (ml) from the set point value (i.e. intended dose). A Dosing Error (DE) can thus be described using Eq. (1)

$$\text{Dosing Error} = \frac{\textit{Administered Dose}}{\textit{Intended Dose}} - 1\ [\%] \tag{1}$$

where the administered dose is the measured value and the intended dose is the set point value.

It was anticipated that dosing errors may occur in the pumps where flow rate changes were initiated, as well as the parallel pumps combined on the same central line and catheter. From each measurement the standard deviation σ (sigma) between the measured values and set point in steady state was calculated in order to distinguish dosing errors from the random error. The implications this has for the statistical significance of the data is further explained in the Data analysis section. The following endpoints related to dosing errors were investigated (see Fig. 3 for a full explanation):

1) **Total** Dosing Error: dosing error (%) during the total time $T = t_1 - t_2 = 0$–8 h for each pump.

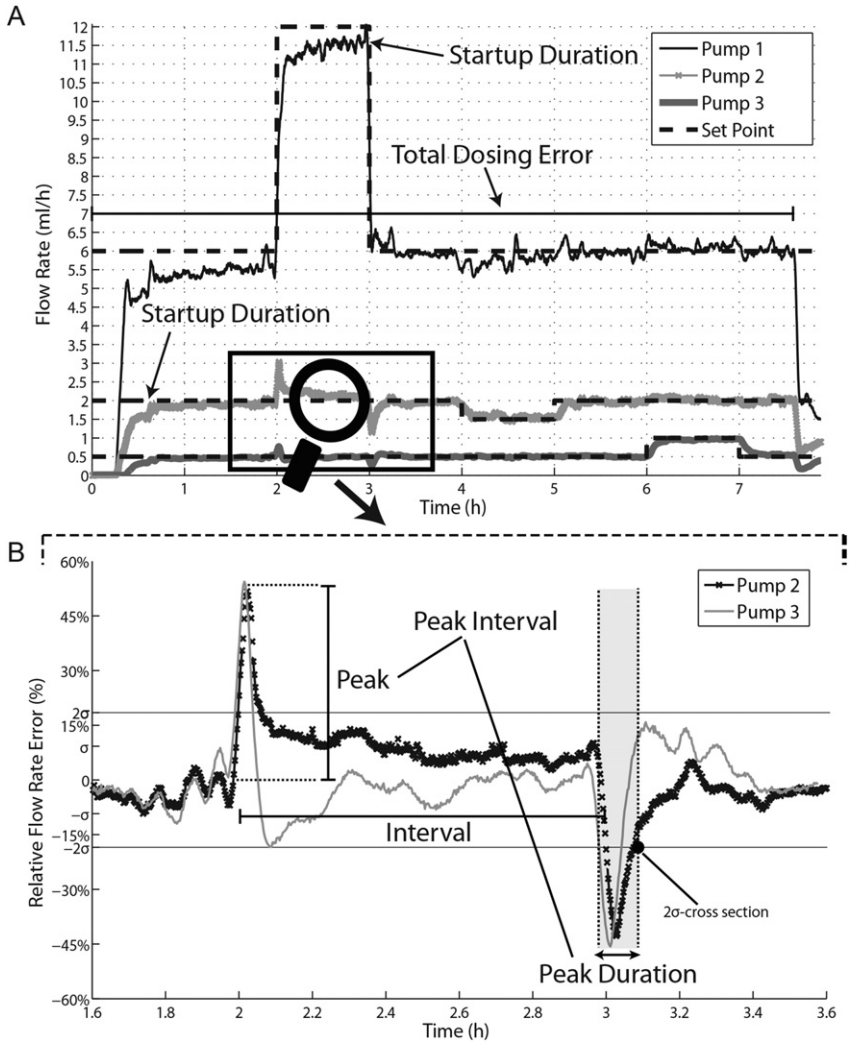

Fig. 3. Measurement of flow rates after carrying out the medication scheduled (A). Measurement of dosing errors between approximately t = 2 and 3 h in the parallel pumps. Standard deviations (σ) are indicated as well (B). The endpoints of Startup, Interval, Peak interval and Total dosing errors are illustrated in the plots, the values will be given in the results.

2) **Interval** Dosing Error: dosing error (%) during the pre-defined one hour intervals $T = t_1 - t_2 = 2–3, 4–5, 6–7$ h (Fig. 2), i.e. between each initiated flow rate increase and flow rate decrease.
3) **Peak Interval** Dosing Error: average dosing error (%) during the area under the curve of the peak after each flow rate change. The beginning and ending of the peak were defined by the moments that the flow rate crossed the set point $\pm 2\sigma$. The average dosing error was the area under the curve of the peak divided by the peak duration (defined later). Since some dosing errors in the parallel pumps were expected to be temporary, the durations of these dosing errors were also measured. This end point was analyzed for the parallel pumps only.
4) **Startup Duration**: the duration in minutes until steady state has been reached after starting or changing the flow rate of the pumps. The startup period lasts until the set point $\pm 2\sigma$ was crossed.
5) **Peak Duration**: the duration in minutes of a peak dosing error. Peak errors were recorded after T = 2, 3, 4, 5, 6 and 7 h, i.e. after each initiated flow rate increase and flow rate decrease. The peak duration was defined by the moment that the flow rate crossed the set point $\pm 2\sigma$. This end point was analyzed for the parallel pumps only.

2.4. Data analysis

The data were analyzed using linear regression calibration which was described earlier (Dinç and Özdemir, 2005). The method was able to acquire the concentration of each laser dye that flows through the flowcell individually in μg/h. The magnitude of the absorption peaks was related to the magnitude of the dilution of each dye. This, in turn, is proportional to the ratio of the flow rates between the pumps. Because the total volume is registered by the balance (ml), a flow rate can be obtained in [ml/h] for each pump. An additional fourth-degree Savitzky-Golay filter was used to remove a portion of the noise present in the balance data. All results are presented as averages of the three measurements.

A dosing error peak larger than 2σ ($p < 0.05$) compared to the random error was considered significant. Peak errors that were not statistically significant were discarded. Furthermore, only relative errors were investigated and presented. To analyze the spectrometric and balance data using the methods described, a program was written in Matlab 2009a 7.8.0.347 32 bits. An extensive physical and mathematical description of the method is given in Appendix A.

3. Results

Statistically significant dosing errors were found as a result of flow rate variability in the simulation of IV multi-infusion therapy on the NICU (Table 1). The **total** dosing errors (−5.5 to −7.9%), measured over the entire medication schedule (Fig. 2), and the **interval** dosing errors, measured over a one-hour period after the flow rate changes at t = 2 h, t = 4 h and t = 6 h, (−7.1% to 11.1%) were relatively small and not statistically significant.

Significant **peak** dosing errors were found in the parallel pumps, i.e. the pumps in which no flow rate change was initiated. The highest peak dosing error in the parallel pumps found was +48.2% ± 23.3% at t = 2 h, with a peak duration of approximately 6 min before the set point value and steady state was reached again. A similar peak of −32.5% ± 18.6% at t = 3 h was found lasting approximately 4 min before the set point value and steady state was reached again. Although the peak dosing errors at t = 2 h and t = 3 h in the parallel pumps were found to be significant, the peak errors at t = 4 h, t = 5 h, t = 6 h and t = 7 h were not significant for the parallel pumps.

Startup durations of up to 43 min were found when starting the pumps at t = 0 h from a flow rate of zero ml/h. Pump 1 (set point 6 ml/h) was shown to reach the desired flow rate set point significantly faster than pump 2 and 3 (set point 2 resp. 0.5 ml/h). When flow rates were changed at t = 2 h–t = 7 h, the duration until the set point was reached was up to 8.4 min. Similar to the startup at t = 0 h, the faster

Table 1
Dosing errors results of investigated endpoint.

Initiated flow rate change (ml/h)	Parallel pumps (no change)	Dosing errors (%)						Duration (min)	
		Total	p value	Interval	p value	Peak interval[a]	p value	Startup	Peak Duration[a]
Pump 1 (0–6)		−7.40	0.48	–	–	–	–	22.8	–
Pump 2 (0–0.5)		−5.45	0.60	–	–	–	–	30.6	–
Pump 3 (0–2)		−7.94	0.44	–	–	–	–	42.6	–
Pump 1 (6–12)		–	–	−7.05	0.50	–	–	2.20	–
	Pump 2	–	–	11.1	0.29	39.1	4.22E−6[‡]	–	5.70
	Pump 3	–	–	2.48	0.81	39.7	1.23E−4[†]	–	3.30
Pump 1 (12–6)		–	–	–	–	–	–	3.00	–
	Pump 2	–	–	–	–	−31.2	0.0021[**]	–	3.80
	Pump 3	–	–	–	–	−35.5	0.0019[**]	–	3.60
Pump 2 (2–1.5)		–	–	7.65	0.46	–	–	4.10	–
	Pump 1	–	–	−3.74	0.72	N/A	N/A	–	N/A
	Pump 3	–	–	−0.83	0.94	N/A	N/A	–	N/A
Pump 2 (1.5–2)		–	–	–	–	–	–	3.48	–
	Pump 1	–	–	–	–	N/A	N/A	–	N/A
	Pump 3	–	–	–	–	N/A	N/A	–	N/A
Pump 3 (0.5–1)		–	–	−7.10	0.50	–	–	7.32	–
	Pump 1	–	–	−2.03	0.85	N/A	N/A	–	N/A
	Pump 2	–	–	4.24	0.68	N/A	N/A	–	N/A
Pump 3 (1–0.5)		–	–	–	–	–	–	8.40	–
	Pump 1	–	–	–	–	N/A	N/A	–	N/A
	Pump 2	–	–	–	–	N/A	N/A	–	N/A

The flow rates in pumps 1–3 were changed three times and, subsequently, changed back another three times, resulting in a total of six changes. During these changes the interval dosing errors were registered as well as the total dosing errors during the entire measurement. The changes resulted in dosing errors in the parallel pumps and the pumps in which the flow rate was initiated. The peaks of these dosing errors are listed. All the errors were temporary. The startup duration denotes the delay before the set point is reached for the pumps in which the flow rate changes were initiated. The Peak Duration states the time delay until the peak dosing errors in the parallel pumps reached the set point. The p values of all dosing errors are listed. Non-significant peak intervals could not be distinguished from noise in the data.

** $p < 0.01$.
† $p < 0.001$.
‡ $p < 0.0001$.
[a] N/A = peak was not observed.

pumps consistently reached the desired set point values earlier than the slower pumps.

The initial startup contributed 91.8%, 83.7% and 74.1% to the total dosing errors for pumps 1–3, respectively. Excluding the initial startup, pumps 2 and 3 contributed resp. 66.2% and 26.5% to the total dosing error as parallel pumps, at t = 2 h and t = 3 h. The contributions to the total dosing error due to startup delays were 33.8% and 73.5%, resp. for pumps 2–3 at t = 4 h and t = 5 h and t = 6 h and t = 7 h in this case. In terms of peak and startup duration, 56% and 31% were resp. due to the dosing errors in the parallel pumps for pumps 2 and 3, at t = 1 h and 2 h (initial startup excluded).

4. Discussion

The results indicate that - after changing the flow rate in one pump - clinicians should consider the possibility of an unintended short-term over- or under-dosing of medication in pumps combined on the same central line or catheter as the pump that was changed. The largest part of the total dosing errors were caused by the initial startup. Furthermore, the results show that, if the flow rate changes are larger, the contribution of the parallel pumps to the total dosing error of those flow rate changes is larger. Besides the dosing errors in de parallel pumps, clinicians should be aware of substantial startup durations after the pumps are started or the flow rates are deliberately changed. These long startup delays typically occur in the pumps containing critical medications such as inotropics, which are often required by extremely and very preterm neonates with hypotension immediately.

4.1. Underlying physics and consequences for disposables

We previously explained three physical effects: dead volume, compliance and resistance. These effects were also found in biomedical literature (Décaudin et al., 2009; Lovich et al., 2005; Snijder et al., 2015).

Dead volume is the volume between the mixing point and the patient at the catheter or infusion needle tip. The dead volume causes a temporary mass flow rate change in the parallel pumps, due to the 'push-out' effect (Timmerman et al., 2015). Due to this effect, a temporary overdose or underdose occurs in the parallel pumps after a flow rate increase or decrease, respectively. When the dead volume of a central infusion line is smaller, it is expected that the dosing errors shown in this study will be smaller as well. It is therefore advised to use disposables with small internal volumes (Lannoy et al., 2012). Inside the dead volume mixing effects are of interest. With the flow rates and infusion lines used in this study, a laminar flow is expected, with no relevant diffusion in the axial, i.e. longitudinal, direction. However, full diffusion in radial direction should occur before entering the patient. Moreover, because the viscosity is close to water, the friction that the infusion line wall is exerting on the fluid is expected to cause an additional concentration gradient as the drug solution moves along the length of the infusion line (Hutton and Thornberry, 1986; Lovich et al., 2005; Taylor, 1953). Dosing errors resulting from dead volume and the cessation of one pump in high flow rate pumps were demonstrated before (Lannoy et al., 2010; Lovich et al., 2005). Dosing errors were quantified in a two-pump low flow rate setup (Tsao et al., 2013). In this study it was demonstrated that dosing errors in a three-pump setup, using a NICU medication schedule and disposables are plausible.

The second effect, compliance, is responsible for the slow onset of the flow rates, even if the infusion lines are pre-filled. Compliance is caused by the elasticity of the infusion disposables, most notably syringes and infusion lines (Snijder et al., 2015; Weiss et al., 2000a, 2000b). If the flow differences are big, it is even possible for backflow to occur due to compliance. For example, TPN has a higher flow rate and may flow back into the slower infusion line of the slower infusion pump, e.g. the dopamine pump with a flow rate of 0.5 ml/h. This may cause a substantial additional delay for the critical drug to reach the patient again. Anti-reflux valves might prevent or mitigate this effect (Lannoy et al., 2010), although it has been shown that anti-reflux valves, in turn, produce other problems such as longer startup times (Van Der Eijk et al., 2014). Most NICU's use specific disposables with a minimal dead volume and anti-reflux valves. The infusion line used in this study is an infusion line specifically designed for neonatal infusion therapy. However, it was shown that clinicians should be aware that dosing errors still occur.

4.2. Clinical implications

The dosing errors found may result in unintended and unexpected clinically relevant adverse events, depending on the pharmaceutical used. Therefore, the blood concentration changes were investigated for these dosing errors.

Blood concentration change (Fig. 4) can be calculated using dosing errors and the duration of the dosing errors (i.e. peak durations) from Table 1 (see Appendix B), and half-lives of the pharmaceuticals used (Table 2) as input (Steenhoek, 1983).

All the peak durations were in the order of 2–10 min after a peak dosing error had occurred. Even during this short duration and with the small half-lives of inotropic agents (Table 2) this still accounts for a possible blood concentration overdosing of 35% ± 17 and −28% ± 10 underdosing. It can be assumed that a 25% blood concentration change is clinically significant. Therefore, it is expected that these blood concentrations may cause adverse events for neonates. Moreover, these errors are found in the pumps of 0.5 and 2.0 ml/h, these flow rates are commonly used for high-risk pharmaceuticals such as inotropics.

For anesthetic drugs, the change in blood concentrations will be less. This might, however, still have influence on the effects of common pharmaceuticals such as propofol, especially in the neonatal population which was found to be subject to considerable variability in pharmacokinetics (Vanderhaegen et al., 2010; Wang et al., 2014). For analgesic drugs such as opioids, with half-lives longer than 1 h, the blood concentration changes were small and therefore improbable to be clinically significant for the dosing errors described in this study.

There are several adverse events associated with dosing errors in the delivery of medications such as inotropics, especially for (preterm) neonates. For example, overdosing of inotropics can cause fluctuations of blood pressure and even life-threatening hypertension (Panna et al., 1996), which may result in conditions such as peri-intraventricular hemorrhages (Alderliesten et al., 2013; Dempsey, 2015; Plomgaard et al., 2015). Hypotension is a very common medical condition in preterm neonates, which may lead to insufficient perfusion of critical tissue, such as cerebral brain tissue (Alderliesten et al., 2013; Plomgaard et al., 2015). Hypotension will not be treated sufficiently in case of an underdose or when the delivery is delayed. The experiments show

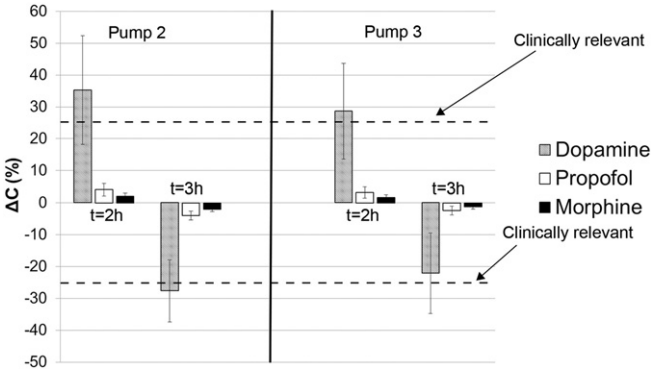

Fig. 4. Blood plasma concentration change (ΔC) of Peak Dosing Errors at t = 2 h and 3 h for the parallel pumps 2 and 3. Illustrative medications with different half-lives, dopamine, propofol and morphine are shown. Note that the half-life may vary with gestational age (GA) and propofol is typically given as a bolus on the NICU. The dashed line at 25% indicates that the dosing errors are possibly clinically relevant.

Table 2
Half-lives of common pharmaceuticals.

Type	Common pharmaceutical	Half-life ($t_{1/2}$)
Inotrope	Dopamine	1–2 min
	Dobutamine	1–2 min
	Noradrenaline	1–2 min
Anesthetic	Propofol	30–60 min
Analgesic	Morphine	2–3 h

that the startup duration can be around 45 min, this is undesirable (Lovich et al., 2006). The startup duration in the fastest pump was significantly shorter. However, high flow rates are not preferred in neonates as fluid delivery should be minimized.

The faster pump typically contains total parenteral nutrition (TPN), which is combined on the same central line and catheter as the pumps containing inotropics. Clinicians have to perform flow rate changes to anticipate on vital signs or to follow a regimen. Consequently, the flow rate of the TPN pump is regularly adjusted. As the results show, this may result in potential clinically relevant effects in the slower parallel pumps containing inotropics. It is therefore advised to avoid combining high-risk medications, such as inotropics, on a single central line or catheter-lumen with other pumps. However, vascular access is very limited and challenging, especially in neonates, therefore combining multiple pumps on the same lumen cannot be avoided in many cases. It should be noted that the results are applicable to situations where the pumps may represent other combinations of medications.

From the results it can be seen that the significant dosing errors are short, while the longer interval dosing errors of 1 h and the total dosing errors of 8 h are not statistically significant. Therefore, the results do not show a systematic under- or over-dosing for any medication. The results do show that, for short half-life medication such as inotropics, blood concentrations are altered with possible clinical consequences. Moreover, the startup delays will cause a delayed onset of any medication, especially when lower flow rates are used.

4.3. Strengths and limitations of the study

No actual pharmaceuticals nor realistic concentrations were used. Laser dyes were used because pharmaceuticals do not usually produce well-defined absorption peaks. Conversely, laser dyes produce absorption peaks that can be measured and analyzed using a spectrophotometric method. Laser dye solution had to be prepared manually. A dye quantity was measured with the precision balance (Fig. 1A) and diluted using a pipette with an accuracy of 1 ml. A realistic concentration for an inotropic agent in the syringe is in the order of 1–5 mg/ml, which typically produces properties similar to water in terms of viscosity and density (Batista et al., 2015). The dye concentrations were lower and can be considered equal the properties of water as well, hence it can be assumed there is linear relation between dye absorption and the mass flow rate of each pump. Nevertheless, the viscosity of TPN and glucose is typically different from water. This may impact delay times with relation to the compliance and resistance of the infusion system, these may increase. Moreover, TPN may be administered using a gravity-driven pump. However, the results presented in this study were mainly due to the dead volume effect, therefore the experiment is still applicable and the dosing errors are still expected to occur.

The standard deviations of the regression coefficients are relatively small, therefore the calibration method is relatively strong. However, the steady state flow rate error standard deviation was around 10% for measurement 1–3, respectively. This is a considerable error, which made it impossible to analyze the more subtle dosing errors and should therefore be considered a weak point of this study. The reason for this large standard deviation was that the balance registered a relative large amount of noise. The causes mentioned above are likely to be the reason why the initiated flow rate changes of T = 4–5 h and T = 6–7 h were not found to produce significant dosing errors in the parallel pumps in the measurements.

It can be seen that disposables yield substantial variance in drug delivery. From experience it was recognized that especially the syringe shows considerable variance in compliance and reliability for, amongst other effects, the startup durations, this is also supported by the literature (Neff et al., 2001b). The use of actual disposables enhanced the realistic representation of the clinical practice in this study, it is therefore considered a strength.

5. Conclusions

Significant flow rate variability was found as a result of using multi-infusion, resulting in dosing errors with potential clinical relevance for medications which are fast acting. These errors are both unwanted and unexpected during multi-infusion therapy on the NICU. This study reinforces that especially inotropics are likely to cause clinically relevant adverse events as a result of the small therapeutic ranges. Sudden changes from hypo- to hypertension are known to cause peri-intraventricular hemorrhages, which in turn may be caused by the dosing errors found in this study. Especially preterm infants, suffering from hypo- or medication-induced hypertension are at risk. It is advised to combine high risk medications delivered with comparable flow rates on one catheter lumen and to avoid doing the same with medications delivered at higher flow rates, e.g. TPN. This may not always be possible in clinical practice. Therefore, it is important that the clinician is aware of the effects shown in this study.

Conflict of interest

None.

Acknowledgements

The authors would like to thank L.A.F. van Rossum for his assistance in producing the artwork.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejps.2016.07.019.

References

Alderliesten, T., Lemmers, P.M.A., Smarius, J.J.M., Van De Vosse, R.E., Baerts, W., Van Bel, F., 2013. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. J. Pediatr. 162, 698–704. http://dx.doi.org/10.1016/j.jpeds.2012.09.038.

Bartels, K., Moss, D.R., Peterfreund, R.A., 2009. An analysis of drug delivery dynamics via a pediatric central venous infusion system: quantification of delays in achieving intended doses. Anesth. Analg. 109, 1156–1161. http://dx.doi.org/10.1213/ane.0b013e3181b220c9.

Batista, E., Almeida, N., Furtado, A., Filipe, E., Souse, L., Rui, M., Peter, L., Petter, H.T., Snijder, R., Timmerman, A., Sousa, L., Martins, R., Lucas, P., Petter, H.T., Snijder, R., Timmerman, A., 2015. Assessment of drug delivery devices. Biomed. Tech. 347–357 http://dx.doi.org/10.1515/bmt-2014-0138.

Caicedo, A., De Smet, D., Naulaers, G., Ameye, L., Vanderhaegen, J., Lemmers, P., Van Bel, F., Van Huffel, S., 2011. Cerebral tissue oxygenation and regional oxygen saturation can be used to study cerebral autoregulation in prematurely born infants. Pediatr. Res. 69, 548–553. http://dx.doi.org/10.1203/PDR.0b013e3182176d85.

Décaudin, B., Dewulf, S., Lannoy, D., Simon, N., Secq, A., Barthélémy, C., Debaene, B., Odou, P., 2009. Impact of multiaccess infusion devices on in vitro drug delivery during multi-infusion therapy. Anesth. Analg. 109, 1147–1155. http://dx.doi.org/10.1213/ane.0b013e3181ae06e3.

Dempsey, E.M., 2015. Under pressure to treat? Arch. Dis. Child. Fetal Neonatal Ed. 100, F380–F381. http://dx.doi.org/10.1136/archdischild-2015-308667.

Dinç, E., Özdemir, A., 2005. Linear regression analysis and its application to multivariate chromatographic calibration for the quantitative analysis of two-component mixtures. Farmaco 60, 591–597. http://dx.doi.org/10.1016/j.farmac.2005.04.008.

Bell, E.F., Acarregui, M.J., 2014. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. In: Bell, E.F. (Ed.), Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, Chichester, UK, pp. 1–9. http://dx.doi.org/10.1002/14651858.CD000503.pub3.

Hall, J.M., Roberts, F.L., 2005. An investigation into the reduction in flow rate of intravenous fluid by antireflux valves. Anaesthesia 60, 797–800. http://dx.doi.org/10.1111/j.1365-2044.2005.04239.x.

Husch, M., Sullivan, C., Rooney, D., Barnard, C., Fotis, M., Clarke, J., Noskin, G., 2005. Insights from the sharp end of intravenous medication errors: implications for infusion pump technology. Qual. Saf. Health Care 14, 80–86. http://dx.doi.org/10.1136/qshc.2004.011957.

Hutton, P., Thornberry, E.A., 1986. Factors affecting delivery of drug through extension tubing. Br. J. Anaesth. 58, 1141–1148.

Lannoy, D., Décaudin, B., Dewulf, S., Simon, N., Secq, A., Barthélémy, C., Debaene, B., Odou, P., 2010. Infusion set characteristics such as antireflux valve and dead-space volume affect drug delivery: an experimental study designed to enhance infusion sets. Anesth. Analg. 111, 1427–1431. http://dx.doi.org/10.1213/ANE.0b013e3181f66ee3.

Lannoy, D., Decaudin, B., Simon, N., Barthelemy, C., Debaene, B., Odou, P., 2012. The impact on drug mass flow rate of interrupting and resuming carrier fluid flow: an in vitro study on a very low dead-space volume infusion set. Anesth. Analg. 114, 328–332. http://dx.doi.org/10.1213/ANE.0b013e3182373a27.

Levi, D.S., Peterson, N., Shah, S.D., Rakholia, B., Haught, A., Carman, G., 2010. Connecting multiple low-flow intravenous infusions in the newborn: problems and possible solutions. Pediatr. Crit. Care Med. 11, 275–281. http://dx.doi.org/10.1097/PCC.0b013e3181cead7f.

Lovich, M.A., Doles, J., Peterfreund, R.A., 2005. The impact of carrier flow rate and infusion set dead-volume on the dynamics of intravenous drug delivery. Anesth. Analg. 100, 1048–1055. http://dx.doi.org/10.1213/01.ANE.0000146942.51020.88.

Lovich, M.A., Kinnealley, M.E., Sims, N.M., Peterfreund, R.A., 2006. The delivery of drugs to patients by continuous intravenous infusion: modeling predicts potential dose fluctuations depending on flow rates and infusion system dead volume. Anesth. Analg. 102, 1147–1153. http://dx.doi.org/10.1213/01.ane.0000198670.02481.6b.

Lovich, M.A., Wakim, M.G., Wei, A., Parker, M.J., Maslov, M.Y., Pezone, M.J., Tsukada, H., Peterfreund, R.A., 2013. Drug infusion system manifold dead-volume impacts the delivery response time to changes in infused medication doses in vitro and also in vivo in anesthetized swine. Anesth. Analg. 117, 1313–1318. http://dx.doi.org/10.1213/ANE.0b013e3182a76f3b.

Medlicott, N.J., Reith, D.M., McCaffrey, F., Krittaphol, W., Broadbent, R.S., 2013. Delayed delivery of intravenous gentamicin in neonates: impact of infusion variables. J. Pharm. Pharmacol. 65, 370–378. http://dx.doi.org/10.1111/jphp.12000.

Murphy, R.S., Wilcox, S.J., 2010. The link between intravenous multiple pump flow errors and infusion system mechanical compliance. Anesth. Analg. 110, 1297–1302. http://dx.doi.org/10.1213/ANE.0b013e3181d56758.

Neal, D., Lin, J.A., 2009. The effect of syringe size on reliability and safety of low-flow infusions. Pediatr. Crit. Care Med. 10, 592–596. http://dx.doi.org/10.1097/PCC.0b013e3181a0e2e9.

Neff, T.A., Fischer, J.E., Schulz, G., Baenziger, O., Weiss, M., 2001a. Infusion pump performance with vertical displacement: effect of syringe pump and assembly type. Intensive Care Med. 27, 287–291. http://dx.doi.org/10.1007/s001340000784.

Neff, T., Fischer, J., Fehr, S., Baenziger, O., Weiss, M., 2001b. Start-up delays of infusion syringe pumps. Paediatr. Anaesth. 11, 561–565. http://dx.doi.org/10.1046/j.1460-9592.2001.00730.x.

Panna, C., Arvind, B., Krishan, C., Siddharth, R., 1996. Principles of Pediatric and Neonatal Emergencies. Jaypee Brothers Medical Publishers Pvt. Ltd., New Delhi.

Plomgaard, A.M., Hagmann, C., Alderliesten, T., Austin, T., van Bel, F., Claris, O., Dempsey, E., Franz, A., Fumagalli, M., Gluud, C., Greisen, G., Hyttel-Sorensen, S., Lemmers, P., Pellicer, A., Pichler, G., Benders, M., 2015. Brain injury in the international multicentre randomised SafeBoosC phase II feasibility trial: cranial ultrasound and magnetic resonance imaging assessments. Pediatr. Res. 79, 466–472. http://dx.doi.org/10.1038/pr.2015.239.

Sherwin, C.T., Medlicott, N.J., Reith, D.M., Broadbent, R.S., 2014. Intravenous drug delivery in neonates: lessons learnt. Arch. Dis. Child. 99, 590–594. http://dx.doi.org/10.1136/archdischild-2013-304887.

Snijder, R.A., Konings, M.K., Lucas, P., Egberts, T.C., Timmerman, A.D., 2015. Flow variability and its physical causes in infusion technology: a systematic review of in vitro measurement and modeling studies. Biomed. Tech. 60, 277–300. http://dx.doi.org/10.1515/bmt-2014-0148.

Snijders, C., van Lingen, R.A., van der Schaaf, T.W., Fetter, W.P.F., Molendijk, A., 2010. Multi-Centre Sampling and Analysis of High-Risk, Low-Fequency Incidents: Lessons from 114 Inotrope-Related Incident Reports in Neonatal Intensive Care.

Steenhoek, A., 1983. Drugs Given by Intravenous Infusion. University of Groningen.

Stowe, C.D., Storgion, S.A., Lee, K.R., Phelps, S.J., 1996. Hemodynamic response to intentionally altered flow continuity of dobutamine and dopamine by an infusion pump in infants. Pharmacotherapy 16, 1018–1023.

Taylor, G., 1953. Dispersion of soluble matter in solvent flowing slowly through a tube. Proc. R. Soc. A Math. Phys. Eng. Sci. http://dx.doi.org/10.1098/rspa.1953.0139.

Timmerman, A.M., Snijder, R.A., Lucas, P., Lagerweij, M.C., Radermacher, J.H., Konings, M.K., 2015. How physical infusion system parameters cause clinically relevant dose deviations after setpoint changes. Biomed. Tech. 60, 365–376. http://dx.doi.org/10.1515/bmt-2014-0139.

Tsao, A.C., Lovich, M.A., Parker, M.J., Zheng, H., Peterfreund, R.A., 2013. Delivery interaction between co-infused medications: an in vitro modeling study of microinfusion. Paediatr. Anaesth. 23, 33–39. http://dx.doi.org/10.1111/j.1460-9592.2012.03898.x.

Van Der Eijk, A.C., Van Rens, R.M.F.P.T., Dankelman, J., Smit, B.J., 2013. A literature review on flow-rate variability in neonatal IV therapy. Paediatr. Anaesth. 23, 9–21. http://dx.doi.org/10.1111/pan.12039.

Van Der Eijk, A.C., Van Der Plas, A.J., Van Der Palen, C.J.N.M., Dankelman, J., Smit, B.J., 2014. In vitro measurement of flow rate variability in neonatal IV therapy with and without the use of check valves. J. Neonatal-Perinatal Med. 7, 55–64. http://dx.doi.org/10.3233/NPM-1475213.

Vanderhaegen, J., Naulaers, G., Van Huffel, S., Vanhole, C., Allegaert, K., 2010. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. Neonatology 98, 57–63. http://dx.doi.org/10.1159/000271224.

Wang, C., Allegaert, K., Peeters, M.Y.M., Tibboel, D., Danhof, M., Knibbe, C.A.J., 2014. The allometric exponent for scaling clearance varies with age: a study on seven propofol datasets ranging from preterm neonates to adults. Br. J. Clin. Pharmacol. 77, 149–159. http://dx.doi.org/10.1111/bcp.12180.

Weiss, M., Fischer, J., Neff, T., Baenziger, O., 2000a. The effects of syringe plunger design on drug delivery during vertical displacement of syringe pumps. Anaesthesia 55, 1094–1098. http://dx.doi.org/10.1046/j.1365-2044.2000.01550.x.

Weiss, M., Hug, M.I., Neff, T., Fischer, J., 2000b. Syringe size and flow rate affect drug delivery from syringe pumps. Can. J. Anaesth. 47, 1031–1035. http://dx.doi.org/10.1007/BF03024878.