Target controlled infusion pump occlusion alarm response times and their clinical implications: A bench-top and simulation study

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Abstract

Background: There is a time-delay between obstruction of the infusion apparatus and the onset of the occlusion alarm on both the Alaris PK and Braun Perfusor Space target controlled infusion (TCI) pumps. Depending on the extent of this time-delay, it is possible that drug effect-site concentrations could decrement below minimally effective levels during this period, potentially exposing patients to the risk of accidental awareness under general anaesthesia.

Methods: In a bench-top experiment, we recorded the alarm response time of both devices after intentional obstruction using a standardised protocol. We then computer-simulated a series of clinically relevant TCIs to determine if the effect-site concentration of propofol or remifentanyl could decrement below 2 $\mu\text{g.mL}^{-1}$ or 3 ng.mL^{-1} before the alarm was predicted to sound.

Results: The alarm response time of both devices was longer at higher alarm level settings and slower infusion rates, but different between brands at equivalent alarm level settings ($p < 0.0001$ for all comparisons). The simulations revealed that the drug effect-site concentrations of propofol and remifentanyl could decrement below minimally effective levels within the alarm response time of either device, when Schnider or Minto effect kinetics utilising slow infusion rates were combined with high alarm level settings.

Conclusions: Our study suggests that, under certain conditions of use, the design and performance of the occlusion alarm on the Alaris PK and Braun Perfusor Space TCI pumps can potentially permit inadequate drug delivery during TCI anaesthesia. We believe our findings should serve as a warning to clinicians to be wary of utilising slow infusion rates in combination with high alarm level settings and propose that clinicians mitigate against this risk by choosing alarm level settings based upon the baseline alarm performance in order to minimise any redundancy in the alarm response time.

Keywords: Infusion Pumps, Patient Safety, Anaesthetics i.v., Propofol

Background

Total intravenous anaesthesia is used in ~8 % of general anaesthetics in the UK and, in the majority of cases, administered via a target controlled infusion (TCI) pump [1]. A principle concern with TCI anaesthesia is that patients may experience accidental awareness if intravenous drug delivery stops unintentionally, for example by obstruction of the infusion apparatus [2]. Consequently, the Alaris PK and Braun Perfusor Space TCI pumps have an adjustable occlusion alarm to alert the user should this happen [3, 4]. The clinician selects an alarm level, which corresponds to a pressure-limit, and the alarm sounds if the pressure in the infusion apparatus exceeds this limit. As a result of this design, there is a time-delay between obstruction of the infusion apparatus and the onset of the occlusion alarm because the pressure needs to build up before the alarm is triggered. It is possible that drug effect-site concentrations could decrement below minimally effective levels during this period, potentially exposing patients to accidental awareness under general anaesthesia. This study aimed to measure the alarm response time of both

devices after intentional obstruction using a standardised protocol, and computer simulate a number of common TCI scenarios to determine if the effect-site concentration of propofol or remifentanyl could decrement below minimally effective levels within the alarm response time.

Methods

Bench top experiment

All equipment was used according to the manufacturers' instructions and a standardised protocol. First, a 50 mL syringe (Omnifix Luer Lock Solo, B Braun, Melsungen, Germany) was filled with 50 mL 0.9 % saline (Macoflex, Macopharma, Tourcoing, France). Then a 3-way TIVA set (3.0 metre, Medipius, High Wycombe, UK) was connected to the syringe. Next, a 3-way tap (BD Connecta, Becton, Dickinson and Company, New Jersey, USA) was attached to the TIVA set, flushed and turned to an open position. Finally, the assembled infusion system (syringe, TIVA set and 3-way tap) was loaded into either an Alaris PK (BD Connecta, Becton, Dickinson and Company, New Jersey, USA) or a Braun Perfusor Space (B Braun, Melsungen, Germany) TCI pump. The alarm on the TCI pump was set at level one and the infusion started at an infusion rate of 10 mL.hr⁻¹. After a period of 30 seconds, the 3-way tap was switched to a closed position in order to obstruct the infusion and the time for the alarm to sound recorded. This process was repeated through each sequential alarm setting for each TCI pump. The apparent volume change (VD) at each alarm setting was calculated by multiplying the infusion rate by the alarm response time. Three pumps were used for each brand, allowing mean values to be reported. This process was repeated at infusion rates of 20 and 30 mL.hr⁻¹ respectively. A new infusion system was used for each pump at each infusion rate. The 3-way TIVA set was chosen because this is the standard issue device at our hospital and prepared so that the intravenous infusion port and redundant Siamese tube was filled with saline and clamped as close to the common infusion point as possible. Statistical analysis was performed using GraphPad Prism (version 5.0 GraphPad Software). Linear regression was used to compare the alarm response times at different infusion rates and between brands; a p value < 0.05 was considered significant.

Computer simulation experiment

The simulations were performed over a four-hour period using TIVAtainer9 (www.eurosiva.eu). Computer-generated obstruction was imitated by reducing the drug target to zero at five time points (30, 60, 120, 180 and 240 minutes). It is possible to record the calculated effect-site concentration predicted by both the Marsh and Schnider pharmacokinetic models in the simulation software, and so the propofol TCIs were programmed to target effect-site concentrations between 3 - 6 ug.mL⁻¹. The following anthropometric data was entered: Marsh model: male; age 40 years; height 180 cm; and weight 60 or 100 kg. Schnider model: male or female; age 40 years; height 180 cm; and weight 60 or 100 kg. Similarly, the remifentanyl TCIs were programmed to target effect-site concentrations between 5 - 8 ng.mL⁻¹. The following anthropometric data was entered: Minto model: male or female; age 20 or 80 years; height 180 cm; and weight 80 kg. Results were generated for a 2 % propofol solution and a 0.05 mg.mL⁻¹

remifentanyl solution because these are the drug concentrations are frequently used at our institution. The time (T_1) for the drug effect-site concentration to decrement below 2 ug.mL^{-1} for propofol and 3 ng.mL^{-1} for remifentanyl was reported in the computer program. The predicted time (T_2) for the alarm to sound was calculated by dividing mean VD at the relevant alarm level setting from the bench top experiment by the infusion rate at the time of obstruction from the simulation experiment. The duration of time (T_3) that the drug effect-site concentration was predicted to be below minimally effective levels prior to the alarm sounding was derived: $T_3 = T_2 - T_1$.

Results

Bench-top experiment

The results from the bench-top experiment are shown graphically in Figure 1. As expected, the alarm response time of both devices was longer at slower infusion rates ($p < 0.0001$ for all comparisons). In addition, and somewhat counter-intuitively, the alarm response time was different between brands at equivalent alarm level settings ($p < 0.0001$ for all comparisons).

Computer simulation experiment

Propofol effect-site concentrations were only predicted to decrement below 2 ug.mL^{-1} before the alarm sounded when using a Schnider pharmacokinetic model and targeting an effect-site concentration of 3 ug.mL^{-1} in combination with high alarm level settings (Table 1). The risk and duration of inadequate drug delivery also depended on the pump brand, patient sex and weight as well as the duration of the infusion. The duration of time that the drug effect-site concentration was $< 2 \text{ ug.mL}^{-1}$ varied between 1 – 49 seconds and occurred at infusion rates ranging from $18.39 - 34.20 \text{ mL.hr}^{-1}$ and decrement times between 134 – 215 seconds (Tables S1 and S2). The Marsh model was not associated with inadequate drug delivery despite forecasting infusion rates as low as 16.93 mL.hr^{-1} because the corresponding decrement times were predicted to be longer.

Remifentanyl effect-site concentrations were also predicted to decrement below minimally effective levels within the alarm response time at high alarm level settings. When targeting an effect-site concentration of 5 ng.mL^{-1} , the duration that the drug effect-site concentration was $< 3 \text{ ng.mL}^{-1}$ varied between 1 – 149 seconds, and occurred at infusion rates ranging from $11.92 - 18.78 \text{ mL.hr}^{-1}$ and decrement times between 175 – 332 seconds (Tables S3 and S4). The risk and duration of inadequate drug delivery was also influenced by patient age and sex as well as pump brand. In the case of an 80 year old female patient and using a Braun Perfusor Space TCI pump set at alarm level 9, it was even possible for the remifentanyl effect-site concentration to fall below threshold when targeting a drug effect-site concentration of 6 ng mL^{-1} . Under these latter conditions, the duration of inadequate drug delivery extended between 7 - 9 seconds throughout the 4-hour study period.

Discussion

Our bench top study quantifies the time-delay between obstruction of the infusion apparatus and the onset of the occlusion alarm on the Alaris PK and Braun Perfusor Space TCI pumps. Uniquely, our simulation study contextualises these findings in a series of clinically relevant TCIs, integrating actual infusion rates and predicted decrement times encountered in everyday practice. We show that predicted propofol and remifentanyl effect-site concentrations can decrement below minimally effective levels within the alarm response time of either device when Schnider or Minto effect kinetics utilising slow infusion rates are combined with high alarm level settings. Taken together, our work suggests that, under certain conditions of use, the design and performance of the occlusion alarm on these devices could potentially permit inadequate drug delivery during TCI anaesthesia. Whilst this is an *in vitro* study only, we believe our findings should serve as a warning to clinicians to be wary of utilising slow infusion rates in combination with high alarm level settings and demonstrates the importance of choosing appropriate alarm level settings during TCI anaesthesia.

A simple approach to minimise the occlusion alarm response time would be to set the occlusion alarm at a low setting (i.e., level 3). However, alarm level selection is a balance between the alarm's sensitivity to detect an occlusion and specificity so that it triggers appropriately. The alarm level needed for each case is variable and depends on a number of factors including the type and characteristics of the syringe, anti-siphon valve and infusion line tubing, the speed and viscosity of the fluids being administered and the type and positioning of the cannula to the extent that we don't believe one rule will suit all occasions. Consequently, we propose that clinicians choose alarm settings for each case based upon the baseline alarm performance as follows. Start the TCI infusion at the lowest alarm level and escalate through sequential alarm settings until the baseline alarm level required for forward flow in the infusion apparatus is established. Thereafter, set the alarm level two settings higher than baseline. This empirical approach will minimise redundancy in the time-delay before the occlusion alarm sounds and also account for any differences in the alarm specifications between TCI pump brands. When utilising the highest two alarm level settings, the drug concentration could instead be diluted so that there is a corresponding decrease in the alarm response time. For example, if the remifentanyl concentration is reduced from 0.05 to 0.02 mg.mL⁻¹, the alarm response time will also shorten by 60% because an increased infusion rate is needed to maintain the desired drug effect-site concentration.

We defined inadequate drug delivery as a drug effect-site concentration of < 2 ug.mL⁻¹ for propofol and < 3 ng.mL⁻¹ of remifentanyl because these values were recently suggested as suitable minimum drug effect-site concentrations [5]. However, caution should be applied to the specific values used and reported in our study because there is known to be variation between the *actual* drug concentration in the patients and the *theoretical* drug concentration predicted by pharmacokinetic models as well as the *actual* drug concentration needed for adequate anaesthesia [6, 7]. Nonetheless, this experiment represents a proof of principle and the steps outlined above can be easily and safely used to mitigate against the risk of accidental awareness under general anaesthesia.

Co-infusions of propofol and remifentanyl have been shown to markedly reduce the amount of propofol required to maintain anaesthesia [8]. At the highest remifentanyl dose reported, 8 ng.mL⁻¹, the plasma propofol concentration needed for anaesthesia varied between 2.20 - 3.38 ug.mL⁻¹. Our analysis suggests that the propofol effect-site concentration could decrement below 2 ug.mL⁻¹ should the infusion become obstructed for much of this therapeutic range because there would be a compound-effect from a slower infusion rate, prolonging the time delay before the alarm sounds, as well as a faster decrement time (both on account of a lower propofol effect-site concentration). In clinical practice, this tendency for drug effect-site concentration to decrement below 2 ug.mL⁻¹ may be counter-balanced by additional pressures in the infusion apparatus should the obstruction occur at/after the common mixing point as well as the combined effect of both drugs on awakening.

Our study design was influenced by previous work that has shown that TCI pumps have a number of physical performance limitations, including start-up loss, a time delay between the start of the pump and the movement of the infusion fluid, and update loss, a time delay as the pump switches between infusion rates [9, 10]. These limitations can be influenced by a variety of equipment factors including the infusion rate, the syringe as well as the presence of water or lubricant on the syringe. Consequently, in our bench top study, the infusion system was primed and run for a period of 30 seconds prior to obstruction to minimise the effect of start-up loss. Thereafter, all experiments were conducted at fixed infusion rates and so update loss would not affect our results. In addition, a new syringe was used for each pump at each flow rate to control for variable wetness, lubricant and use on the syringe. Similarly, the Marsh, Schnider and Minto pharmacokinetic models predict distinct infusion rates and decrement times during a TCI based upon the internal parameters of their pharmacokinetic calculations, which affected our study design and results [11]. Gender does not influence the Marsh model and so was not incorporated in our analysis, whereas it does affect the Schnider and Minto models and so was assessed. Age is an important covariate the Minto model and so we included a wide age gap in our remifentanyl simulations [12, 13]. Separately, there may be some small differences between the values reported in the simulations for the Schnider model and the values predicted by the Alaris PK in practice because our simulations utilised a fixed K_{e0} method (as implemented in the Braun Perfusor space) to calculate the effect-site concentration, whereas the Alaris PK pump incorporates a variable K_{e0} approach [14]. We decided against using two different versions of the Schnider model in our experiment so that we could compare the effect of the occlusion alarm from each brand on the predicted drug concentrations in isolation rather than introducing an additional variable.

A potential weakness of our study is that only two types of TCI pump and a limited number of components of the infusion system were examined. However, the Alaris PK and Braun Perfusor space are widely used and therefore the results are of interest. Any TCI pump fitted with an occlusion alarm that has an analogous pressure-sensing mechanism would be expected to exhibit similar behaviour. Given the large number of TCI pumps, syringes, giving sets, cannulae and possible configurations available, a comprehensive review of all equipment options was beyond the scope of this exploratory study. Future work comparing the resistance and compliance of a broad range of giving sets is warranted to assess if

the materials used influence the occlusion alarm response time. In addition, the presence and strength of a magnetic field has previously been shown to interfere with the occlusion alarm and so the interaction between the magnetic field and the occlusion alarm, and its effect on predicted drug concentrations should be assessed in TCI pumps that are used during magnetic resonance imaging [15]. There is also an opportunity to engineer solutions to the potential risk we have identified by altering the design of the occlusion alarm from a pressure-sensing to a flow-sensing mechanism. Standardising the alarm pressure limits at each alarm level setting across TCI pump brands would also assist informed practice.

Conclusions

This study suggests that, under certain conditions of use, the design and performance of the occlusion alarm on the Alaris PK and Braun Perfusor Space TCI pumps can potentially permit inadequate drug delivery during TCI anaesthesia. We believe our findings should serve as a warning to clinicians to be wary of utilising slow infusion rates in combination with high alarm level settings and demonstrate the importance of choosing appropriate alarm level settings during TCI anaesthesia.

Abbreviations

TCI: Target controlled infusion

VD: Apparent volume change

T_1 : The time for the drug effect-site concentration to decrement below threshold.

T_2 : The predicted time for the alarm to sound.

T_3 : The duration of time that the drug effect-site concentration was below threshold before the alarm sounded.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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and interpretation of data. Critically revised the article and gives final approval for the manuscript to be published. Agrees to be accountable for all aspects of the work. PSS: Substantial contribution to acquisition of data. Critically revised the article and gives final approval for the manuscript to be published. Agrees to be accountable for all aspects of the work. SQ: Substantial contribution to conception and design. Critically revised the article and gives final approval for the manuscript to be published. Agrees to be accountable for all aspects of the work. PT: Substantial contribution to analysis and interpretation of data. Critically revised the article and gives final approval for the manuscript to be published. Agrees to be accountable for all aspects of the work. AH: Substantial contribution to conception and design and interpretation of data. Critically revised the article and gives final approval for the manuscript to be published. Agrees to be accountable for all aspects of the work.

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Tables

Table 1.

Device	Sex	Weight (kg)	Alarm level	30 minutes	60 minutes	120 minutes	180 minutes	240 minutes
Alaris PK								
	Female	60	9	-	-	-	-	-
		100	9	-	-	-	-	-
	Female	60	10	-	-	-	-	-
		100	10	-	-	-	-	-
	Male	60	9	-	-	-	-	-
		100	9	-	-	-	-	-
	Male	60	10	1 s	2 s	1 s	-	-
		100	10	-	-	-	-	-
Braun Perfusor Space								
	Female	60	8	5 s	6 s	5 s	5 s	4 s
		100	8	-	-	-	-	-
	Female	60	9	31 s	34 s	36 s	37 s	37 s
		100	9	8 s	10 s	11 s	11 s	11 s
	Male	60	8	12 s	14 s	14 s	13 s	12 s
		100	8	-	-	-	-	-
	Male	60	9	41 s	45 s	48 s	49 s	49 s
		100	9	23 s	25 s	26 s	27 s	27 s

Potential duration of inadequate drug delivery in seconds (s) at five timepoints during propofol simulations using a 2% solution, Schnider pharmacokinetic model, target effect-site

concentration of 3 ug mL⁻¹ with high alarm level settings on the Alaris PK or Braun Perfusor space target controlled infusion pump. – symbolizes no risk of inadequate drug delivery.

Table 2.

Device	Sex	Age (years)	Alarm level	30 minutes	60 minutes	120 minutes	180 minutes	240 minutes
Alaris PK								
	Female	20	8	-	-	-	-	-
			9	18 s	18 s	19 s	18 s	18 s
			10	42 s	42 s	43 s	42 s	42 s
	Female	80	8	-	-	-	-	-
			9	33 s	33 s	33 s	33 s	34 s
			10	68 s	69 s	70 s	70 s	70 s
	Male	20	8	-	-	-	-	-
			9	9 s	10 s	9 s	9 s	9 s
			10	32 s	33 s	32 s	33 s	33 s
	Male	80	8	-	-	-	-	-
			9	14 s	14 s	14 s	15 s	14 s
			10	47 s	48 s	48 s	49 s	48 s
Braun Perfusor Space								
	Female	20	7	24 s	24 s	25 s	24 s	24 s
			8	56 s	56 s	57 s	56 s	57 s
			9	94 s	95 s	96 s	95 s	95 s
	Female	80	7	42 s	42 s	43 s	43 s	43 s
			8	89 s	90 s	91 s	91 s	91 s
			9	146 s	147 s	148 s	148 s	149 s
	Male	20	7	15 s	15 s	15 s	15 s	15 s
			8	45 s	46 s	46 s	46 s	46 s
			9	82 s	83 s	83 s	83 s	84 s
	Male	80	7	22 s	23 s	22 s	23 s	23 s
			8	67 s	68 s	68 s	69 s	68 s
			9	120 s	121 s	122 s	123 s	122 s

Potential duration of inadequate drug delivery in seconds (s) at five timepoints during remifentanil simulations using a 0.05 mg.mL⁻¹ solution, Minto pharmacokinetic model and target effect-site concentration of 5 ng.mL⁻¹ with high alarm level settings on the Alaris PK or Braun Perfusor space target controlled infusion pump. – symbolizes no risk of inadequate drug delivery.

Figures

Figure 1

Alarm response time at each level setting for the Alaris PK (solid) and Braun Perfusor Space (dashed) target controlled infusion pumps at 10 (red), 20 (green) and 30 mL.hr⁻¹ (blue). The alarm response times were longer at slower infusion rates ($p < 0.0001$) and different between brands at equivalent alarm level settings ($p < 0.0001$).

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