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In vitro delivery accuracy of Computer Controlled Infusion Pump software linked to an Alaris® GH syringe pump for propofol target-controlled infusion in dogs

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Summary

We calculated the in vitro delivery accuracy of a computer software (CCIP) linked to an Alaris® GH syringe pump to deliver propofol by target-controlled infusion in dogs. This was studied by simulating an infusion of propofol at two target concentrations (2 and 6 µg ml^{-1}) in a 6 and 22 kg dog, each for 10, 60 and 240 minutes in a crossover design. Each infusion was replicated three times (36 infusions). The total volume of propofol delivered at the end of each infusion was measured using a high precision scales and compared with the volume predicted by the software and that displayed by the syringe driver. Median prediction error (MDPE), median absolute performance error (MDAPE), divergence and intraclass correlation coefficient (ICC) were calculated as indexes of bias, accuracy, time-related changes in accuracy and reliability, respectively. The ranges of MDPA and MDAPE for all the infusions were –2.08-4.28% and 1.85-4.28%, respectively and the median (95% CI) was –1.75% (–1.84-1.02%) and 2.18% (2.23-4.13%), respectively. The divergence was 0.010 ± 0.004% h^{-1}. The ICC was 1.00% (0.99-1.00%; P < 0.0001). The volume of propofol infused by the CCIP linked to an Alaris® GH syringe pump is accurate and has a small tendency to overestimate the real volume delivered. The prediction error fell in the ± 5% range of delivery performance considered clinically acceptable. The performance of the CCIP ameliorates with time and the error will decrease for long infusions, reducing the risk of administering an excessive dose of propofol and increasing the safety of CCIP. The CCIP had also an excellent index of reliability for all the targets, animal body weight and length of infusions tested. In conclusion, CCIP linked to an Alaris® GH syringe pump is precise, reliable and suitable for clinical practice.

Keywords: delivery accuracy, target-controlled infusion, propofol, CCIP, dog

Target controlled infusion (TCI) is a technique that administers drugs intravenously using a syringe driver controlled by a computer. The system requires use of software which incorporates previously established pharmacokinetic data, and it is based on the principle that steady-state plasma concentrations are reached over different times and rates, according to the pharmacokinetics of the drug (27). Since the 1980s, TCI has been routinely used to infuse anaesthetic agents. Instead of setting a fixed infusion rate, the anaesthetist sets a desired (target) plasma concentration on the computer and titrates this by observing the clinical effects on the patient. This is very similar to the technique that is applied when altering the vaporiser setting to deliver an appropriate alveolar concentration of anaesthetic vapour for a given patient in response to anaesthetic depth (5). The TCI software, by using an algorithm, calculates the rate of drug infusion and ensures that target plasma concentrations are maintained at a steady-state over time, and that any variations are attained rapidly. To do this, the software controls the syringe driver's motor and, using the pre-selected pharmacokinetic parameters, rates are frequently readjusted by the computer to maintain constant plasma concentrations

(20). The advantage of the TCI method in comparison to continuous infusions is that steady-state plasma concentrations are better maintained (6, 11). However, as with volatile anaesthesia, there will be variability between subjects, and the expected plasma level will need to be altered based on the pharmacodynamic responses of each patient (18). Another, but not irrelevant drawback of TCIs, is the requirement of a dedicated syringe pump that incorporates TCI software or alternatively, of a computer incorporating the TCI software and connected to a syringe driver through a standardised serial port interface cable (RS232) (9).

In 1996, Zeneca Ltd developed the first commercial TCI software, Diprifusor® for propofol administration in human medicine using the pharmacokinetic model published by Marsh et al. (11). This TCI module was specifically designed to infuse Diprivan (propofol 1%, AstraZeneca) and it was incorporated into syringe drivers of different manufactures. By having the TCI module incorporated in their pumps, the manufacturers had to perform an *in vitro* study to prove that the delivery performance of the integrated pumps met criteria required by the drug company. Thus, Diprifusor® was the first standardized TCI system approved by Regulatory Medicine Authorities in Europe for accurate delivery of both volume infused and predicted plasma concentrations (7).

Once Diprifusor® patents expired in 2002, the so-called 'open TCI systems' were developed. Open TCI systems allow the infusion of both generic preparations of propofol and other anaesthetic and analgesic drugs, using multiple pharmacokinetic models (21). Many open TCI systems meet the requirements for commercial medical devices in Europe (EU Regulation 2017/745; Annex I) regarding their design, manufacture and quality assurance.

A number of other non-approved open TCI software systems exist e.g. Computer Control Infusion Pump (CCIP), RUGLOOP, STANPUMP, STELPUMP. The main reason why they are not approved for use in humans is because the delivery performance for a specific drug has not been verified, however their use in veterinary patients is not regulated. These TCI systems can be directly downloaded from the internet onto a laptop, and used to drive a computer compatible syringe pump. When used in this way they are classified as medical devices, and fall under medical device legislation. However, non-approved systems are considered experimental programmes and have to be used under the responsibility of the institution following local ethics committee approval (21). Currently, there are no equivalent EU directives for veterinary medical devices and, to the author's knowledge, there are no immediate plans at a European level to implement veterinary-specific legislation in this area.

As Diprifusor® incorporates only the pharmacokinetics of propofol published by Marsh et al. (11) in humans and as the pharmacokinetic constants of a drug measured in one species cannot be translated to another, this TCI model is not suitable for dogs. In veterinary medicine the pharmacokinetics of propofol in dogs has been studied (4, 8, 13, 15) and the pharmacokinetic values have been used to develop a TCI model in a population of mixed breed dogs and Greyhounds during dental surgery (2). In this study by Beths et al (2) propofol was infused using a prototype computer-driven TCI system incorporated into a Graseby® 3400 syringe driver. The performance of the system was validated in the same study and showed that the calculated plasma concentrations were under-predicted compared to the measured plasma concentrations in mixed breed dogs by 1.56%, and over-predicted by 12.47% in Greyhounds. Overall, the bias less than 20% and the performance of the system was considered clinically acceptable. The authors concluded that their results make this TCI model suitable for infusions in clinical practice (2).

The pharmacokinetic model described by Beths and co-workers for dogs (2) can also be used to programme other non-approved TCI software e.g. CCIP. This is a free software that can be downloaded from the internet and can support the use of both Alaris® and Graseby® syringe drivers. It has been previously used to infuse a TCI of propofol in dogs (23). When using any novel combination of TCI software and syringe driver, the delivery accuracy of the syringe driver should be measured before use in order to confirm the suitability of the integrated devices in clinical practice.

In this study we used the open TCI software CCIP, linked an Alaris® GH syringe pump via a RS323 cable and applied the three-compartment pharmacokinetic model published in dogs (2) to infuse and measure propofol.

Our hypothesis was that the delivery accuracy of this system would be clinically acceptable (i.e. within 5% of the predicted volume) and would not be affected by the set target plasma concentration, the weight of the animal or the length of infusion. Acceptance of the null hypothesis would indicate that the TCI software CCIP linked to an Alaris® GH syringe pump could be safely used to infuse a known volume of propofol in dogs in a clinical setting.

Material and methods

Study design. Two infusions were set at a target plasma concentration of 2 and 6 $\mu g\ ml^{-1}$, and each was simulated in real-time mode in a 9 and 22 kg dog, in a cross-over study design. For each of the four groups (group 2 $\mu g\ ml^{-1} \times 9$ kg; group 6 $\mu g\ ml^{-1} \times 9$ kg; group 2 $\mu g\ ml^{-1} \times 22$ kg; group 6 $\mu g\ ml^{-1} \times 22$ kg) the infusion was delivered for 10, 60 and 240 minutes. The procedure was repeated three times for each combination, resulting in 36 infusions in total.

Computer settings. The CCIP version 3 (https://www.cuhk.edu.hk/med/ans/softwares.htm) software was down-

loaded and installed in a laptop (Asus Eee PC X101H, Intel, Windows 7) and connected via an RS323 cable to an Alaris® GH syringe pump (CareFusion, Italy). The three-compartment pharmacokinetic model of propofol (2) was inserted into the drug dialogue box (Vd = 0.78 L kg^{-1}; k10 = 0.07 min; k12 = 0.0356 min; k21 = 0.0312 min; k13 = 0.0049 min; k31 = 0.0011 min, where Vd, k10, k12, k21, k13 and k31 were the volume of distribution, clearance and transfer rate constant between compartment 1 and 2, 2 and 1, 1 and 3, 3 and 1, respectively). The pump actions 'infusion' and 'bolus' were limited to administer a 4 mg kg^{-1} bolus over one minute. The weight was entered in the patient information dialogue box.

Syringe driver settings. A disposable 50 ml syringe which was specified in the Alaris® GH list of approved syringes (BBraun Omnifix, Germany) was filled with propofol 1% (Vetofol, Norbrook, Northern Ireland), avoiding formation of air bubbles, and connected to a rigid, non-expandable infusion line of 200 cm length (Lectro-cath, Vygon, France) and to a 23G 16 mm needle (Henry Schein Inc., USA). All the assembled set was pre-filled with propofol prior to positioning in the Alaris® GH syringe pump. The pump occlusion pressure level was adjusted to its maximum to avoid occlusion during the infusion. The software P.E.C. (Pump Error Correction) setting was activated to allow the programme check the volume within the pump and correct it if it was different.

Data collection and measurements. The infused propofol was collected in a glass beaker positioned at the same level as the syringe driver and sealed with a paraffin self-sealing film (ParaFilm "M", American National Can, USA) to avoid evaporation. An appropriate high precision scale (Ohaus Adventurer Pro AS64, 65 g ± 0.1 µg or Ohaus Adventurer Pro AS 153, 150 g ± 1 µg; USA) was used to weigh the mass of propofol infused at the end of each infusion. The volume of propofol was derived using a density of 0.9945 g ml^{-1}. The density of propofol was calculated by weighing 1 ml propofol. The volumes of propofol displayed by the software (CCIP) interface and by the screen of the Alaris® GH syringe pump were manually recorded every minute for the 10-minute infusion and every 10 minutes for the 60- and 240-minute infusions. These volumes were then compared to the calculated volume derived from the mass of propofol during the same laboratory set. The same operator (BC) set up and conducted all infusions and performed all measurements. The experiment was performed at sea level (estimated atmospheric pressure 101.3 kPa) and at room temperature (20 ± 1°C).

Calculation of delivery accuracy. Percentage performance error (PE) and absolute PE ($|PE|$) of the total volume of propofol calculated by the software (PE_{CCIP} and $|PE_{CCIP}|$) and delivered by the pump ($PE_{Alaris\ GH}$ and $|PE_{Alaris\ GH}|$) were used as indexes of accuracy as previously described by Varvel et al. (24). At the end of each infusion, these indexes were calculated for each sample as follows:

$$PE_{CCIP} = \frac{\text{measured volume} - \text{calculated volume}}{\text{calculated volume}} \times 100$$

$$PE_{Alaris\ GH} = \frac{\text{measured volume} - \text{calculated volume}}{\text{calculated volume}} \times 100$$

$$|PE_{CCIP}| = \left|\frac{\text{measured volume} - \text{calculated volume}}{\text{calculated volume}} \times 100\right|$$

$$|PE_{Alaris\ GH}| = \left|\frac{\text{measured volume} - \text{calculated volume}}{\text{calculated volume}} \times 100\right|$$

Both the PE and $|PE|$ were calculated for each group and for pooled groups (combined measurements for all groups) and the latter was used to determine the overall accuracy of the system.

The median prediction error (MDPE) and the median absolute performance error (MDAPE) of the CCIP ($MDPE_{CCIP}$ and $MDAPE_{CCIP}$) were calculated using the median value derived from PE and $|PE|$, respectively:

$$MDPE = \text{median } \{PE_{ij}, j = 1, ..., N_i\}$$

$$MDAPE = \text{median } \{|PE_{ij}|, j = 1, ..., N_i\}$$

where N_i is the number of the performance errors in the i^{th} individual. Both the within group and pooled MDPE and MDAPE were calculated. The time-related changes in accuracy was calculated by the divergence, characterized by the slope of the linear regression obtained by plotting $|PE|$ against time.

Statistical analysis. Due to the low number of replicates, no normality tests were performed and non-Gaussian distribution was assumed. Data are presented as median and 95% lower/upper confidence intervals (CI).

In order to assess the reliability of the CCIP software and the Alaris® GH syringe pump separately, the intraclass correlation coefficient (ICC) was used to compare the predicted volume delivered by CCIP or the syringe pump with that weighed by the electronic scales. The ICC and its 95% confidence intervals were calculated using SPSS statistical package version 22.0 (SPSS Inc, Chicago, IL) based on a single measurement, absolute-agreement, two-way mixed effect. Linear regression analysis was used to assess the relationship between $|PE_{CCIP}|$ over time, where the slope is a measurement of the divergence. Significance was accepted for $P < 0.05$.

Results and discussion

The median (95% CI) volumes (ml) of propofol calculated by the CCIP and measured by the electronic balance at the end of each infusion are summarised in Tab. 1. The PE_{CCIP}, $PE_{Alaris\ GH}$, $|PE_{CCIP}|$ and $|PE_{Alaris\ GH}|$ of the different groups and of pooled data at the end of the 10, 60 and 240 minute of infusions are summarised in Tab. 2 and 3. The highest PE and $|PE|$ values were recorded during the 10 minutes infusion.

Median prediction error (MDPE). The CCIP software had the tendency to over-predict the volume delivered as demonstrated by the negative value of the MDPE (Tab. 4). However, there was a tendency to under-predict the volume delivered in the 6 µg ml^{-1} × 22 kg group, i.e. when the volume of infusion was

Tab. 1. Volume of propofol (ml) calculated by the Computer Control Infusion Pump (CCIP) software and measured by electronic balance at the end of 10, 60 and 240 minute infusions at two simulated target plasma concentrations (2 and 6 µg ml^{-1}) and in two simulated weights (9 and 22 kg) of dog. Results are expressed as median (95% lower/upper CI)

Group	Median (95% CI) volume of propofol calculated by CCIP (ml); n = 3			Median (95% CI) volume of propofol measured by electronic balance (ml); n = 3		
	10 min	60 min	240 min	10 min	60 min	240 min
2 µg ml^{-1} × 9 kg	2.9 (2.9/2.9)	9.1 (9.1/9.1)	28.2 (28.1/28.5)	2.7 (2.5/2.9)	9.0 (8.7/9.0)	27.7 (27.2/28.0)
2 µg ml^{-1} × 22 kg	7.1 (7.1/7.1)	22.2 (22.2/22.2)	69.3 (69.0/69.5)	7.1 (6.9/7.2)	21.7 (21.5/21.8)	68.0 (67.3/68.1)
6 µg ml^{-1} × 9 kg	8.4 (8.4/8.4)	27.1 (27.1/27.2)	85.5 (84.8/85.6)	9.0 (8.5/9.1)	26.4 (26.4/26.8)	83.2 (82.7/83.7)
6 µg ml^{-1} × 22 kg	20.6 (20.6/20.7)	67.5 (67.5/68.2)	211 (211/211)	21.9 (21.6/22.4)	70.4 (68.4/71.8)	212.8 (207.2/213.4)

Tab. 2. Performance error (PE%) calculated by the Computer Control Infusion Pump software (PE_{CCIP}) and by the Alaris® GH syringe pump ($PE_{Alaris\ GH}$) at the end of 10, 60 and 240 minute infusions at two simulated target plasma concentrations (2 and 6 µg ml^{-1}) and in two simulated weights (9 and 22 kg) of dog. Pooled data represents combined measurements for all groups. Results are expressed as median (95% lower/upper CI)

Group	PE_{CCIP} (%) Median (95% CI) Time			$PE_{Alaris\ GH}$ (%) Median (95% CI) Time		
	10 min	60 min	240 min	10 min	60 min	240 min
2 µg ml^{-1} × 9 kg (n = 3)	–6.3 (–13.0/–0.4)	–0.7 (–4.4/–0.6)	–1.9 (–3.1/–1.8)	–6.3 (–21.1/12.4)	0.4 (–6.2/4.6)	–1.5 (–3.8/–0.03)
2 µg ml^{-1} × 22 kg (n = 3)	–0.3 (–2.1/1.1)	–2.4 (–3.1/–2.0)	–2.1 (–2.4/–1.7)	–0.3 (–4.4/3.6)	–2.0 (–2.8/–1.0)	–2.1 (–2.8/–1.3)
6 µg ml^{-1} × 9 kg (n = 3)	7.3 (1.2/8.3)	–2.5 (–2.6/–1.6)	–2.2 (–3.3/–1.9)	8.3 (–4.4/16.5)	–2.2 (–2.9/–1.2)	–2.1 (–4.2/–0.7)
6 µg ml^{-1} × 22 kg (n = 3)	6.1 (4.3/8.8)	4.3 (0.3/6.4)	0.8 (–1.8/1.1)	5.6 (1.0/11.1)	4.4 (–3.9/11.4)	0.8 (–3.9/4.0)
Pooled (n = 12)	1.2 (–2.1/7.3)	–1.8 (–2.6/0.3)	–1.9 (–2.4/–1.7)	2.2 (–1.9/5.5)	–1.6 (–2.1/1.6)	–1.8 (–2.4/–0.8)

Tab. 3. Absolute performance error (|PE|%) calculated by the Computer Control Infusion Pump software ($|PE_{CCIP}|$) and by the Alaris® GH syringe pump ($|PE_{Alaris\ GH}|$) at the end of 10, 60 and 240 minute infusions at two simulated target plasma concentrations (2 and 6 µg ml^{-1}) and in two simulated weights (9 and 22 kg) of dog. Pooled data represents combined measurements for all groups. Results are expressed as median (95% lower/upper CI)

Group	$\|PE_{CCIP}\|$ (%) Median (95% CI) Time			$\|PE_{Alaris\ GH}\|$ (%) Median (95% CI) Time		
	10 min	60 min	240 min	10 min	60 min	240 min
2 µg ml^{-1} × 9 kg (n = 3)	6.3 (0.4/13.0)	0.7 (0.6/4.4)	1.9 (1.8/3.1)	6.3 (–1.9/14.7)	0.5 (–2.7/5.5)	1.5 (0.04/3.8)
2 µg ml^{-1} × 22 kg (n = 3)	1.1 (0.3/2.1)	2.4 (2.0/3.1)	2.1 (1.7/2.4)	1.1 (–1.0/3.4)	2.0 (1.0/2.8)	2.1 (1.3/2.8)
6 µg ml^{-1} × 9 kg (n = 3)	7.3 (1.2/8.3)	2.5 (1.6/2.6)	2.2 (1.9/3.3)	8.3 (–4.4/16.5)	2.2 (1.2/2.9)	2.1 (0.7/4.2)
6 µg ml^{-1} × 22 kg (n = 3)	6.1 (4.5/8.8)	4.3 (0.3/6.4)	1.1 (0.8/1.8)	5.6 (1.0/11.1)	4.4 (–3.9/11.4)	0.8 (–3.9/4.0)
Pooled (n = 12)	5.2 (1.1/8.3)	2.5 (0.7/4.3)	1.9 (1.7/2.4)	4.9 (2.8/7.1)	2.1 (1.1/3.4)	1.8 (1.5/2.3)

higher. Overall CCIP over-estimated the volume of infusion by 1.74%.

Median absolute performance error (MDAPE). The absolute performance errors of the different groups are summarised in Tab. 4. The highest MDAPE was 4.28% (group 6 µg ml^{-1} × 22 kg). Overall the inaccuracy of the CCIP was 2.18%.

Divergence. The slope of the linear regression analysis of $|PE_{CCIP}|$ against time was negative giving a divergence of the CCIP of –0.010 ± 0.004% h^{-1} (Fig. 1).

Intraclass correlation coefficient (ICC). The ICC of the CCIP software and of the Alaris GH syringe pump were 1.00 (0.99-1.00; $P < 0.0001$) and 1.00 (1.00-1.00; $P < 0.0001$), respectively (Fig. 2).

In this study we measured the delivery accuracy of the TCI software CCIP, linked an Alaris® GH syringe pump via a RS323 cable during a simulation of propofol infusion in dogs. The two target concentrations (2 and 6 µg ml^{-1}) were chosen as they represent plasma concentrations used in clinical practice to maintain anaesthesia in dogs (2). Two different weights (6 and 22 kg) were also chosen because the body weight represents the

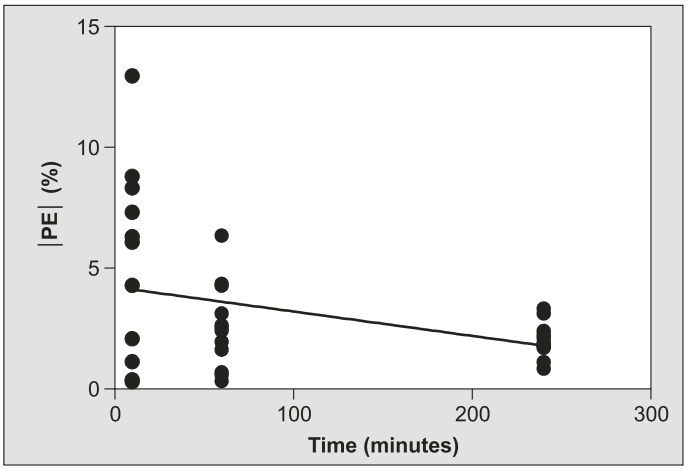

Fig. 1. Absolute performance error (%) of Computer Control Infusion Pump (CCIP) software plotted against time (minutes). The slope of the linear regression represents divergence (–0.010 ± 0.004% h^{-1})

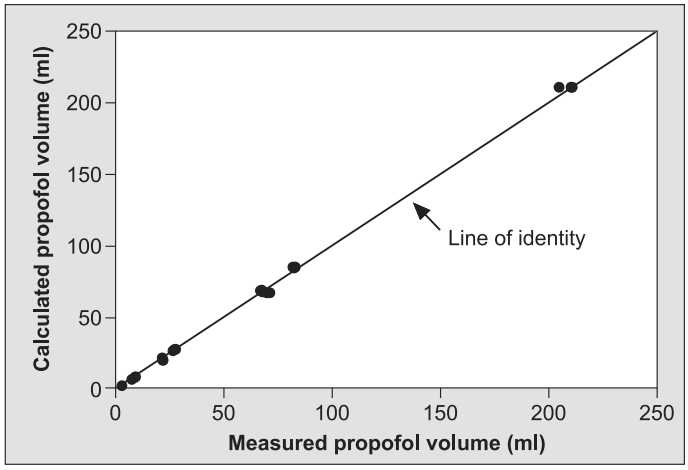

Fig. 2. Scatter plots of reliability data taken from volume of propofol calculated by Computer Control Infusion Pump (CCIP) software (y axis) plotted against propofol measured by electronic balance (x axis). The line of identity represents the perfect performance

Tab. 4. Median prediction error (MDPE%) and median absolute performance error (MDAPE%) calculated by the Computer Control Infusion Pump (CCIP) software at two simulated target plasma concentrations (2 and 6 µg ml^{-1}) and in two simulated weights (9 and 22 kg) of dog following 10, 60 and 240 minute infusions. Results are expressed as median (95% lower/upper CI)

Variable	Group (n = 12)	Median	CI	
			95% Lower	95% Upper
MDPE (%)	2 µg ml^{-1} × 9 kg	–1.85	–6.31	–0.60
	2 µg ml^{-1} × 22 kg	–2.08	–2.42	–0.31
	6 µg ml^{-1} × 9 kg	–1.92	–2.64	7.32
	6 µg ml^{-1} × 22 kg	4.28	0.33	6.36
	Pooled	–1.75	–2.12	0.33
MDAPE (%)	2 µg ml^{-1} × 9 kg	1.85	0.60	6.31
	2 µg ml^{-1} × 22 kg	2.08	1.13	2.42
	6 µg ml^{-1} × 9 kg	2.54	1.63	7.32
	6 µg ml^{-1} × 22 kg	4.28	0.84	6.36
	Pooled	2.18	1.78	3.13

covariate used by the algorithm of the CCIP for the calculation of the rate of infusions.

The highest PE and |PE| values of both CCIP and Alaris® GH syringe pump were recorded at the end of the 10 minute infusions, indicating that the performance was worse during the first few minutes of infusion and then ameliorated over time as previously demonstrated in other studies (1). This finding was also supported by a negative value of the divergence (–0.010 ± 0.004 h^{-1}). The divergence measures how the accuracy changes over time. This parameter is clinically important, as it reflects how the volume calculated by the system can diverge for prolonged infusions (hours or days). This is particularly important for propofol, because the drug can be infused for several hours (or days) to sedate patients, for example in an intensive care unit setting. Our data demonstrated that the performance of the CCIP is not negatively affected by time, but, on the contrary, it improves with it. Thus the error will decrease for long infusions, reducing the risk of administering an excessive dose of drugs and increasing the safety of CCIP.

The MDPE is a measurement of the bias of the predictions and indicates whether the CCIP systematically under- (positive value) or over-estimates (negative value) the volume calculated from the CCIP compared to the actual volume infused. The closer the bias is to zero, the more precise are the calculations. Overall, the bias ranged from –2.08% to 4.28% within the groups and, when the infusions are pooled, the CCIP has a tendency to overestimate by 1.75% the real volume of propofol infused. For both the weights and target concentrations selected in this experiment, the MDPE was within the limits considered acceptable (MDPE < 10-20%) in studies comparing the predicted plasma concentrations delivered by TCI systems to the measured plasma concentrations (22, 24). There are no specific limits published for infusion devices.

This small imprecision could have been caused by several factors. The plastic syringe and the tubing are characterised by their intrinsic compliance and they could have expanded under the pressure generated by the stepper motor of the syringe driver. The plastic material expands with any increase in pressure leading to an increase in volume (16). Thus, at the beginning of the infusion, when the syringe driver delivers a bolus to reach the target plasma concentration selected, the volume of propofol will not immediately reach the glass beaker due to the expansion of the plastic syringe (26), causing a delay of the infusion and, as a consequence, a reduced volume delivered in comparison to the one calculated. It is less likely that the inaccuracy was caused by the tubing, as a rigid and non-compliant infusion line was chosen for this experiment. Another cause that could have increased the percentage of bias

is the presence of iatrogenic compressible air bubbles trapped into the propofol solution. Attention was paid while filling the syringe with propofol to avoid the formation of air bubbles; however it is impossible to completely avoid and detect the presence of micro air bubbles. Furthermore, before starting the infusion, an initial resistance of the syringe barrel in contact with its plunger might exist and be responsible for the delay in drug delivery (14). In order to overcome this problem, Neff et al. (12) suggested starting a bolus at ambient pressure. In the Alaris® GH syringe driver this can be obtained by selecting the function 'priming', which delivers a volume of 2 ml. This can also minimise the internal mechanical slack of the syringe pump, which is another cause of delay. Unfortunately, this was not carried out in our study.

We also tried to reduce the source of errors by placing the syringe driver at the same level as the beaker glass; this will prevent siphoning which can occur with a difference in height. If the syringe driver is placed more than 50 cm above the level of the patient, the syringe will empty itself driven by hydrostatic pressure. In a clinical setting, this will be enhanced by the spontaneous breathing of the patient, as the negative intrathoracic pressure increases the pressure gradient. On the other hand, if the syringe driver is placed below the level of the patient, blood will flow back into the infusion line and towards the syringe (24).

The absolute performance error (MDAPE) is an index of inaccuracy of the system and measures how different the calculated volume is compared to the measured volume in the various groups. A higher MDAPE indicates greater inaccuracy. In this study MDAPE ranged between 1.85% (group 2 $\mu g\ ml^{-1} \times 9$ kg) and 4.28% (group 6 $\mu g\ ml^{-1} \times 22$ kg). Overall, in the pooled groups, MDAPE was 2.18%. This means that half of the CCIP-calculated volume would be within 2.18% or closer to the measured volume, and half would be outside this range.

In human studies, when comparing predicted and actual plasma concentrations of a drug infused, it has been proposed by Schüttler et al. that the performance of a TCI system can be considered clinically acceptable when the MDPE is not greater than 10% to 20% and the MDAPE is between 20% and 30% (17). In this study, both the MDPE and the MDAPE fell well below these ranges, however we were not measuring plasma concentration. There is not full agreement on an acceptable range regarding the performance error of a TCI model interfaced with a computer-compatible syringe driver. In 1998 Glen (7) proposed a delivery performance of ± 5%, which reflects the delivery accuracy of an anaesthetic vaporiser according to the International Standard Organization (ISO) standard. Similar acceptable errors were proposed by Schafer in a study that tested infusion pumps by simulation, without measuring the delivered volumes (20). In a study where three different commercial syringe drivers incorporating the Diprifusor® module were tested for delivery accuracy, the Alaris® TIVA TCI was characterised by a higher performance error (maximum 4.2%) compared to the other pumps (Graseby 3500® and Fresenius Vial Master TCI®) and there was a tendency to over-predict the real volume delivered (16). The syringe driver used in our study was of the same brand and we have found similar results. The performance error that we calculated was lower than the proposed ± 5% and thus the CCIP can be considered an accurate software for the delivery of propofol TCI in clinical settings.

The intraclass correlation coefficient (ICC) is a measure of reliability and reflects both the degree of correlation and agreement between the volume of propofol calculated by the CCIP and the Alaris® GH syringe pump. Values less than 0.4, between 0.4 and 0.59, between 0.60 and 0.74 and greater than 0.75 are indicative of poor, fair, good and excellent reliability, respectively (3). In this study we aimed to assess if the CCIP software was reliable in terms of delivery accuracy when compared to a 'gold standard' method (weighing with an electronic balance). The measurement of ICC answered two questions: "is the CCIP software accurate?" and "are there significant median deviations between the volumes of propofol calculated with the CCIP and measured with the electronic balance?". The CCIP software had an excellent agreement with the measurement taken with the electronic balance (ICC = 1.00; 0.99-1.00 CI), thus it represents a reliable method to infuse propofol; moreover, the Alaris® GH had also an excellent agreement with the electronic balance (ICC = 1.00; 1.00-1.00 CI), so there were no confounding factors related to the instrument used.

The CCIP is an free online software and one of its purposes is to infuse drugs through a TCI technique. This can be achieved by loading the pharmacokinetic constants of a drug (e.g. propofol) described in the published literature into a dialogue box and selecting the desired target plasma concentration. According to the patient's weight and the distribution and elimination of the drug, an algorithm calculates the amount of drug to be administered in order to achieve and maintain the target concentration. This algorithm calculates the rate at which the syringe driver should infuse the drug. In comparison with the human authorised TCI infusion system (Diprifusor®), the CCIP system lacks a second microprocessor, which, using information from the pump motor encoder, independently checks the calculations, thus providing an additional safety feature. This means that the Diprifusor® has been validated and standardised, so that all devices incorporating Diprifusor® will deliver propofol in a standard manner and meet the medical device safety requirement of EU Regulation 2017/745. Medical devices for veterinary use are not required to meet these standards.

This study had a few limitations. Firstly, the CCIP performance was only assessed with one syringe driver and with one brand of syringes. Different results may be obtained using other devices and consumables. Secondly, within the Alaris® syringe driver's brand, the results can be applied only to the GH model, which unfortunately is no longer available and has been replaced by a newer model (GH Plus). The software of the latter has been locked and does not allow communication with external devices. Finally, as discussed previously, 'priming' was not carried out before starting the experiment. Priming has been demonstrated to decrease the inaccuracy of TCI, particularly at the beginning of the infusion, by reducing the start-up time (i.e. delay between starting an infusion pump and the delivery of drugs at the set rate); this is a result of engagement of gears in the mechanical compliance and drive of the syringe (10). This could partially account for the greater inaccuracy following the short (10 minute) infusion.

In conclusion, we have demonstrated that the delivery accuracy of CCIP software linked to an Alaris® GH syringe pump via an RS323 cable to infuse propofol in TCI mode is precise and reliable and its error was similar to that required for the validation and legal requirements of software intended for TCI infusions. The error is neither affected by the weight of the animal nor the target plasma concentration selected and has a tendency to decrease over time. The CCIP software is suitable for clinical studies using propofol target controlled infusion in dogs.

References

1. *Adapa R. M., Axell R. G., Mangat J. S., Carpenter T. A., Absalom A. R.*: Safety and performance of TCI pumps in a magnetic resonance imaging environment. Anaesthesia 2012, 67, 33-39.
2. *Beths T., Glen J. B., Reid J., Monteiro A. M., Nolan A. M.*: Evaluation and optimisation of a target-controlled infusion system for administering propofol to dogs as part of a total intravenous anaesthetic technique during dental surgery. Vet. Rec. 2001, 148, 198-203.
3. *Cicchetti D. V.*: Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol. Assess. 1994, 6, 284-290.
4. *Cockshott I. D., Douglas E. J., Plummer G. F., Simons P. J.*: The pharmacokinetics of propofol in laboratory animals. Xenobiotica 1992, 22, 369-375.
5. *Egan T. D.*: Target-Controlled Drug Delivery Progress toward an Intravenous "Vaporizer" and Automated Anesthetic Administration. Anesthesiology 2003, 99, 1214-1219.
6. *Gepts E., Camu F., Cockshott I. D., Douglas E. J.*: Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth. Analg. 1987, 66, 1256-1263.
7. *Glen J. B.*: The development of 'Diprifusor': a TCI system for propofol. Anaesthesia 1998, 53, 13-21.
8. *Hughes J. M., Nolan A. M.*: Total Intravenous Anesthesia in Greyhounds: Pharmacokinetics of Propofol and Fentanyl – A Preliminary Study. Vet. Surg. 1999, 28, 513-524.
9. *Kenny G. N., White M.*: A portable target controlled propofol infusion system. Int. J. Clin. Monit. Comput. 1992, 9, 179.
10. *Kim J. Y., Moon B. K., Lee J. H., Jo Y. Y., Min S. K.*: Impact of priming the infusion system on the performance of target-controlled infusion of remifentanil. Korean J. Anesthesiol. 2013, 64, 407-413.
11. *Marsh B. M. W. M. N., White M., Morton N., Kenny G. N. C.*: Pharmacokinetic model driven infusion of propofol in children. Br. J. Anaesth. 1991, 67, 41-48.
12. *Neff T., Fischer J., Fehr S., Baenziger O., Weiss M.*: Start-up delays of infusion syringe pumps. Pediat. Anesth. 2001, 11, 561-565.
13. *Nolan A. M., Reid J.*: Pharmacokinetics of propofol administered by infusion in dogs undergoing surgery. Br. J. Anaesth. 1993, 70, 546-551.
14. *O'Kelly S. W., Edwards J. C.*: A comparison of the performance of two types of infusion device. Anaesthesia 1992, 47, 1070-1072.
15. *Reid J., Nolan A. M.*: Pharmacokinetics of propofol as an induction agent in geriatric dogs. Res. Vet. Sci. 1996, 61, 169-171.
16. *Schraag S., Flaschar J.*: Delivery performance of commercial target-controlled infusion devices with Diprifusor® module. Eur. J. Anaesthesiol. 2002, 19, 357-360.
17. *Schüttler J., Kloos S., Schwilden H., Stoeckel H.*: Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 1988, 43, 2-7.
18. *Shafer A., Doze V. A., Shafer S. L., White P. F.*: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 1988, 69, 348-356.
19. *Shafer S. L., Gregg K. M.*: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J. Pharmacokinet. Biopharm. 1992, 20, 147-169.
20. *Shafer S. L., Siegel L. C., Cooke J. E., Scott J. C.*: Testing computer-controlled infusion pumps by simulation. Anesthesiology 1988, 68, 261-266.
21. *Struys M. M., De Smet T., Glen J. I. B., Vereecke H. E., Absalom A. R., Schnider T. W.*: The history of target-controlled infusion. Anesth. Analg. 2016, 122, 56-69.
22. *Swinhoe C. F., Peacock J. E., Glen J. B., Reilly C. S.*: Evaluation of the predictive performance of a 'Diprifusor' TCI system. Anaesthesia 1998, 53, 61-67.
23. *Tseng C. T., Sakai D. M., Libin M., Mostowy M., Cheetham J., Campoy L., Gleed R. D., Martin-Flores M.*: Partial neuromuscular block impairs arytenoid abduction during hypercarbic challenge in anesthetized dogs. Vet. Anaesth. Analg. 2017, 44, 1049-1056.
24. *Vanelderen P. J., Soetens F. M., Soetens M. A., Janssen H. J., De Wolf A. M.*: Hypoglycemia caused by siphoning of an insulin infusion. J. Clin. Anesth. 2007, 19, 251-255.
25. *Varvel J. R., Donoho D. L., Shafer S. L.*: Measuring the predictive performance of computer-controlled infusion pumps. J. Pharmacokinet. Biopharm. 1992, 20, 63-94.
26. *Weiss M., Hug M. I., Neff T., Fischer J.*: Syringe size and flow rate affect drug delivery from syringe pumps. Can. J. Anesth. 2000, 47, 1031-1035.
27. *White M., Kenny G. N. C.*: Intravenous propofol anaesthesia using a computerised infusion system. Anaesthesia 1990, 45, 204-209.

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