Blood Propofol Concentrations: On Demand for Pharmacokinetic/Pharmacodynamics Models and New Measurement Automatic Technologies

S. Campos[1], A. Silva[1], P. G. de Pinho[2] and L. Antunes[1]

[1]Veterinary Sciences Department, Universidade de Trás-os-Montes e Alto Douro
Quinta de Prados, Apartado 1013, 5001-801 Vila Real, Portugal
[2]Laboratory of Toxicology, Department of Biological Sciences, Faculty Pharmacy
Universidade do Porto, Porto, Portugal

Abstract. Propofol is a widespread anaesthetic agent in human medicine. It allows the practice of total intravenous anaesthesia through the use of sophisticated delivery systems due to its pharmacokinetic/ pharmacodynamics properties.
Three New Zealand White rabbits were anaesthetized with three different infusion rates (70, 100, 130 $mg.kg^{-1}.h^{-1}$) in a random order, during thirty minutes each. Clinical parameters as well as arterial blood samples were collected at specific time points. Rugloop II Vet software was used to storage all data and to predict the propofol concentrations during the anaesthetic period. A correlation analysis was done between real and predicted propofol concentrations, in each infusion rate.
It was only observed a significant correlation between concentrations during the lower infusion rate (70 $mg.kg^{-1}.h^{-1}$).
There is a lack of automatic devices and pharmacokinetic/pharmacodynamics models that allow a real-time or predicted measurement of the propofol concentrations in the patient, for veterinary medicine.

1 Introduction

During the last decades, the growing knowledge about the pharmacokinetic properties of propofol allowed a continuous remodeling of pooled data, describing together information of clinical trials and adequate modeling for the specie in which it is used [6]; [7]. These characteristics are very well documented in humans and, in veterinary medicine some research groups have already reported pharmacokinetic data for propofol, especially in the dog and the cat [3]; [5]; [1]; [7].

From a pharmacokinetic point of view, propofol remains the best controllable intravenous hypnotic, since it has a huge body uptake and a fast elimination due to a large apparent volume of distribution and a high clearance [6].

Drug delivery systems, based on pharmacokinetic and pharmacodynamic properties of propofol, were developed allowing a reasonable real-time estimation of its plasma concentrations, during the anaesthetic period [6]; [9]. This can be equated with the continuous measurement of end-tidal volatile anaesthetic agent concentration

Campos S., Silva A., G. de Pinho P. and Antunes L..
Blood Propofol Concentrations: On Demand for Pharmacokinetic/Pharmacodynamics Models and New Measurement Automatic Technologies.
DOI: 10.5220/0003880900180023
In *Proceedings of the International Workshop on Veterinary Biosignals and Biodevices* (VBB-2012), pages 18-23
ISBN: 978-989-8425-94-2

that led to the concept of MAC (Minimum Alveolar Concentration) and provides the best available method to monitor continuous brain concentration, nowadays.

Pharmacodynamic properties of propofol depend on its therapeutic plasma concentrations. The knowledge of pharmacokinetic models allows a more accurately prediction of the optimal dosage [9]. The required plasma concentration varies with the desired pharmacological effect (sedation, induction or maintenance of anaesthesia), the simultaneous use of other drugs (opioids, muscle relaxants), the type of operation and the patient's sensitivity to the drug (age, weight and pre-existing diseases) [9]. So, the use of propofol demands a continuous titration of the drug infusion rate to the desired pharmacological end point, however there is an absence of a clinically useful method for measuring blood propofol concentrations.

In this study, an analysis over real propofol concentrations together with predicted concentrations was performed using a rabbit model.

2 Methodology

2.1 Animals

All procedures were carried out under personal and project licenses approved by the national regulatory office (Direcção Geral de Veterinária – DGV). Three healthy male New Zealand White rabbits, approximately 2 months old, were used.

2.2 Anaesthetic Protocol

Anaesthesia was induced with a dose of 20 $mg.kg^{-1}$ propofol (Propofol Lipuro®, B. Braun Melsungen, Germany) intravenously, using a syringe pump (Asena GH, Alaris Medical Systems) controlled by the Rugloop II software (developed by Tom DeSmet (Demed Engineering, Gent, Belgium)) at an infusion rate of 200 $ml.h^{-1}$. Following blind orotracheal intubation with a cuffed endotracheal tube with 2.5 mm in internal diameter, propofol started to be administered according to an infusion scheme in which three infusion rates were used in every animal: each infusion (70, 100 and 130 $mg.kg^{-1}.h^{-1}$) was maintained during thirty minutes. The order of the administration rates chosen for each animal was random.

Monitoring of anaesthesia included cardio-respiratory parameters (heart rate (HR), mean arterial blood pressure (MABP), arterial blood oxygen (SpO_2) and respiratory rate (RR)), temperature (T), clinical evaluation of depth of anaesthesia (DoA) and the Index of Consciousness (IoC).

Anaesthetic monitoring included cardio-respiratory monitoring provided by a Datex S/5 Anaesthetic station (Datex Ohmeda, Helsinki, Finland) which included: pulse-oxymetry and pulse rate monitored with the probe placed in the ear, invasive mean arterial blood pressure (MBAP), inspired and end-tidal concentrations of oxygen and carbon dioxide. The animals were under mechanical ventilation with 100% oxygen, with ventilation parameters set to maintain the end-tidal CO_2 ($ETCO_2$) between 35 and 45 mmHg. At the end of the infusion scheme fresh gas flow rate was

increased to 5 L.min^{-1} of 100% oxygen until the rabbits regained swallowing reflexes and at this point extubation was performed. Animals were considered recovered from anaesthesia when they exhibited an alert stance and had regained ambulation and limbs coordination.

2.3 Data Acquisition

Data were stored using the Rugloop II Vet software that was also used as software to predict the propofol concentrations at the different time points. This software uses the Beths' pharmacokinetic/ pharmacodynamics parameters for propofol in order to predict its concentration in blood.

2.4 Blood Sampling

Arterial blood samples were collected before the beginning of anaesthesia and at three time points in each infusion rate (20, 25 and 30 minutes after the start of the infusion rate) and in the totally recovered animals (Figure 1). This infusion scheme was designed to achieve a steady-state, based on pharmacokinetic data of clearance from Cockshott et al. [3].

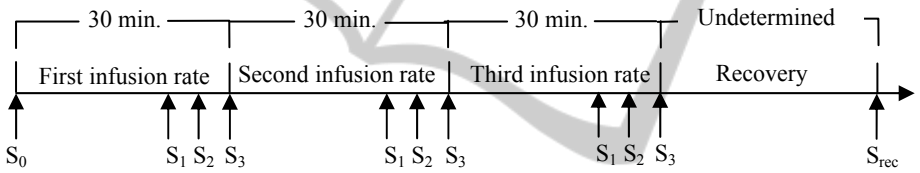

Fig. 1. Schematic representation of blood samples (S) collection. S_0 represents the baseline sample; S_1, S_2 and S_3 represent the blood sample collection of each infusion rate. S_1 is collected 20 minutes after the beginning of each infusion rate; S_2 is collected 5 minutes after S_1 and S_3 is collected 5 minutes after S_2. S_{rec} is the blood sample collection from recovered animals.

2.5 Propofol Quantification in Blood Serum

Propofol concentrations were determined by Gas Chromatography/ Ion Trap - Mass Spectrometry (GC/IT-MS) in rabbit serum. This method was adapted from that previously described by Guitton et al. 1995, used to quantify propofol in human blood [4].

2.6 Statistical Analysis

Statistical analyses were performed by using Excel® and GraphPad Prism® (GraphPad Prism, version 5.00 for Windows, GraphPad Software, San Diego, California, USA, and www.graphpad.com). A Kolmogorov-Smirnov test [8] was used to test data for normality.

Pearson and Spearman Rank correlation analysis were used to study the correlation between real propofol concentrations and the propofol concentrations calculated by Rugloop II.

3 Results and Discussion

In this study, three rabbits weighing 2.79±0.25 Kg were successfully anaesthetized with three different propofol infusion rates (70, 100 and 130 $mg.kg^{-1}.h^{-1}$) in a randomized order, during thirty minutes.

Anaesthetic induction was smooth in all animals, without any excitatory movements and was achieved with a propofol bolus of 20 $mg.kg^{-1}$. Due to the randomization of the infusion schemes, the same infusions and its duration did not produce the same propofol plasma concentrations.

The duration of the infusions was stipulated based on pharmacokinetic data of propofol in rabbits from Cockshott et al. [3]. A ten minute steady-state at the end of each infusion rate was produced, according to data from these authors. Table 1 shows the infusion schemes that were made for each rabbit.

Table 1. Propofol infusion schemes order and respective rabbit.

Rabbit(s)	Infusion scheme ($mg.kg^{-1}.h^{-1}$)
1 and 2	70→130→100
3	100→70→130

As it can be observed in the graphs, the propofol concentrations predicted by the software are underestimated when compared with the real propofol concentrations, particularly at high infusion rates. This is especially important due to the dose-dependent effects of anaesthetics that should be precisely measured in the blood and automatically adjusted to the desired level of anaesthetic depth and hemodynamic answers of the animal. Besides, it was only observed a very significant correlation (r=0,833; P=0,0083) between real propofol concentrations and predicted concentrations during the lowest infusion rate (70 $mg.kg^{-1}.h^{-1}$). The other two infusion rates did not show significant correlations. This indicates that the pharmacokinetic/ pharmacodynamic parameters incorpored in VET Rugloop II are not adequate for estimation of propofol concentrations when infusion rates above 70 $mg.kg^{-1}.h^{-1}$ are used, in rabbits. This can be justified because the pharmacokinetic/ pharmacodynamics parameters from the VET Rugloop II are based on the Beths model for dogs, which are suited for other species [2].

Despite many advantages over traditional volatile anaesthetic techniques, propofol total intravenous anaesthesia makes up a small percentage of general anaesthetics administered. One of the reasons for this is the absence of a clinically useful method for measuring blood propofol concentrations.

The knowledge of the real propofol plasma concentration achieved at each study moment may allow a more precise analysis of the effects of propofol on clinical signs

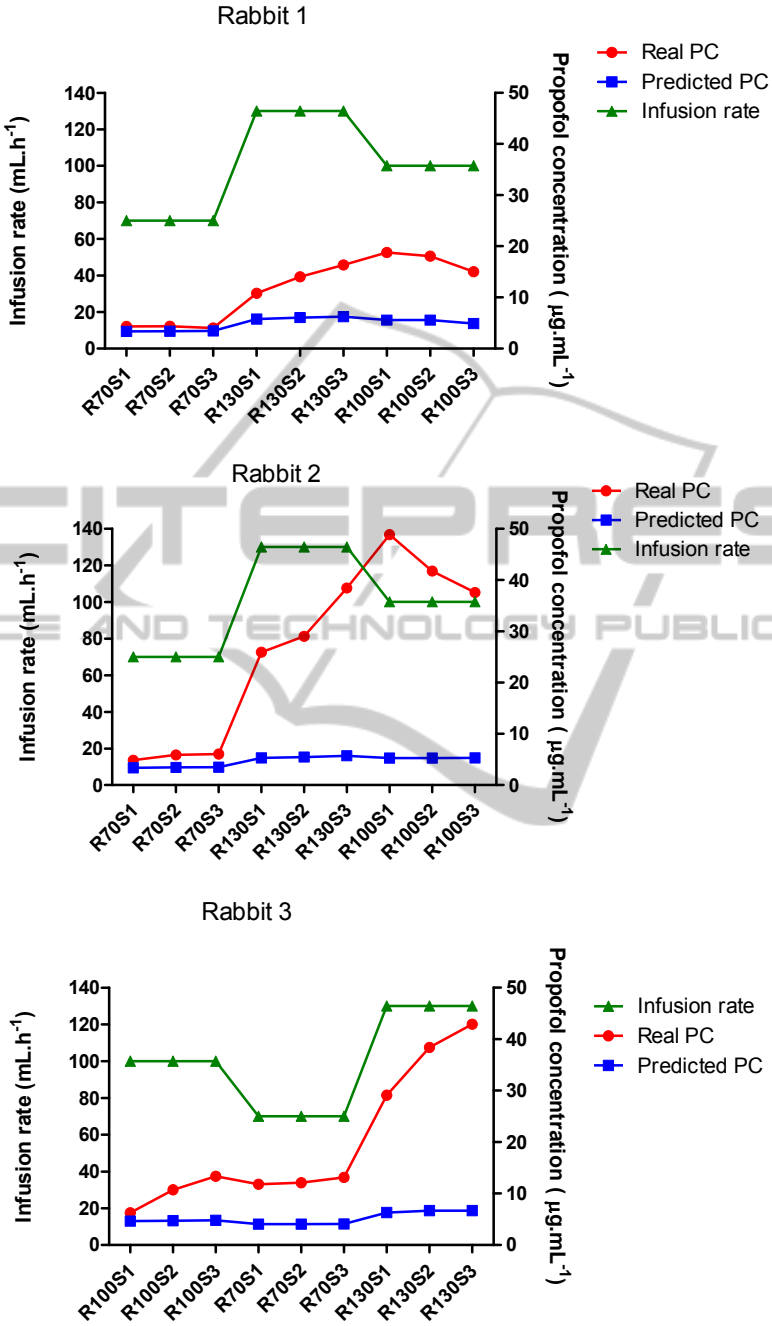

Fig. 2. Graphic representations of real propofol plasma concentration, predicted propofol concentration and for infusion rate to rabbit 1, 2 and 3. In the x-axis is represented each blood sample collection (S1- sample 1; S2 – sample 2 and S3 – sample 3) for each propofol infusion

rate (R70 – infusion rate of 70 $mg.Kg^{-1}.h^{-1}$; R130 – infusion rate of 130 $mg.Kg^{-1}.h^{-1}$ and R100 – infusion rate of 100 $mg.Kg^{-1}.h^{-1}$).

of the anaesthetized animals. This is particular important attending to the different animal species that demand the development of pharmacokinetic/pharmacodynamic models for each one of them, in order to respond to the individual variance between species.

In conclusion, regarding the intravenous anaesthesia in the veterinary medicine there is a huge lack in the offer of devices and pharmacokinetic/pharmacodynamics models that allow an accurate and real-time measurement (predicted or real) of the intravenous anaesthetics in the animal, for immediate adjustment of the anaesthetic plane.

Acknowledgements

This investigation was supported by FEDER funds through the COMPETE Program, and by national funds from Portuguese Foundation for Science and Technology, under the project COMPETE: FCOMP-01-0124-FEDER-009497 PTDC/CVT/ 099022/2008).and personal grant from FCT: SFRH/BD/72360/2010.

References

1. Beths, T., J. B. Glen, et al. (2001). "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 148(7): 198-203.
2. Bras, S., N. Bressan, et al. (2009). "A step towards effect-site target-controlled infusion with propofol in dogs: a k(e0) for propofol." J Vet Pharmacol Ther 32(2): 182-8.
3. Cockshott, I. D., E. J. Douglas, et al. (1992). "The pharmacokinetics of propofol in laboratory animals." Xenobiotica 22(3): 369-75.
4. Guitton, J., M. Desage, et al. (1995). "Quantitation of propofol in whole blood by gas chromatography-mass spectrometry." J Chromatogr B Biomed Appl 669(2): 358-65.
5. Hall, L. W., E. Lagerweij, et al. (1994). "Effect of medetomidine on the pharmacokinetics of propofol in dogs." Am J Vet Res 55(1): 116-20.
6. Schuttler, J. and H. Ihmsen (2000). "Population pharmacokinetics of propofol: a multicenter study." Anesthesiology 92(3): 727-38.
7. Sneyd, J. R. (2004). "Recent advances in intravenous anaesthesia." Br J Anaesth 93(5): 725-36.
8. Sokal, R. S. and F. J. Rohlf (1995). Biometry. The Principles and Practice of Statistic in Biological Reasherch. New York, Freeman: 716-21.
9. White, P. F. (2005). "Intravenous (non-opioid) anesthesia." Seminars in Anesthesia, Perioperative Medicine and Pain 24: 101-107.