BJA Advance Access published July 10, 2014

doi:10.1093/bja/aeu193

BJA

Gas chromatograph–surface acoustic wave for quick real-time assessment of blood/exhaled gas ratio of propofol in humans

X. Chen[1], X. L. Zhang[1], L. Liu[2], Y. Chen[2,3], M. Y. Piao[2], F. J. Zhang[2], W. D. Wu[2], Y. B. Zhong[2], K. Sun[2], Y. C. Zou[1], X. Zhang[1], D. Wang[1], P. Wang[1] and M. Yan[2]*

[1] Department of Biomedical Engineering, Key Laboratory of Biomedical Engineering of Ministry of Education of China, Zhejiang University, Hangzhou, Zhejiang, China
[2] Department of Anaesthesia, The Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China
[3] Department of Anaesthesia, The First People Hospital of Hangzhou, Hangzhou, Zhejiang, China

* Corresponding author. E-mail: yanminnina@hotmail.com

Editor's key points

- Propofol concentrations can be measured in exhaled breath, but the relationship to plasma concentrations is not known.
- This study describes a new system to measure blood and exhaled propofol concentrations simultaneously.
- There was close correlation between blood and exhaled values, allowing rapid calculation of blood/expired partial pressure ratio (R_{BE}).
- This system may enable the determination of the factors affecting R_{BE} in different patients.

Background. Although pilot studies have reported that exhaled propofol concentrations can reflect intraoperative plasma propofol concentrations in an individual, the blood/exhaled partial pressure ratio R_{BE} varies between patients, and the relevant factors have not yet been clearly addressed. No efficient method has been reported for the quick evaluation of R_{BE} and its association with inter-individual variables.

Methods. We proposed a novel method that uses a surface acoustic wave (SAW) sensor combined with a fast gas chromatograph (GC) to simultaneously detect propofol concentrations in blood and exhaled gas in 28 patients who were receiving propofol i.v. A two-compartment pharmacokinetic (PK) model was established to simulate propofol concentrations in exhaled gas and blood after a bolus injection. Simulated propofol concentrations for exhaled gas and blood were used in a linear regression model to evaluate R_{BE}.

Results. The fast GC–SAW system showed reliability and efficiency for simultaneous quantitative determination of propofol in blood (correlation coefficient $R^2=0.994$, $P<0.01$) and exhaled gas ($R^2=0.991$, $P<0.01$). The evaluation of R_{BE} takes <50 min for a patient. The distribution of R_{BE} in 28 patients showed inter-individual differences in R_{BE} (median 1.27; inter-quartile range 1.07–1.59).

Conclusions. Fast GC–SAW, which analyses samples in seconds, can perform both rapid monitoring of exhaled propofol concentrations and fast analysis of blood propofol concentrations. The proposed method allows early determination of the coefficient R_{BE} in individuals. Further studies are required to quantify the distribution of R_{BE} in a larger cohort and assess the effect of other potential factors.

Clinical trial registration. ChiCTR-ONC-13003291.

Keywords: anaesthetics i.v., propofol; chromatography, gas; monitoring; surface acoustic wave sensor

Accepted for publication: 21 February 2014

Propofol has largely replaced sodium thiopental (Pentothal) for the induction of anaesthesia and is increasingly used for the maintenance of total i.v. anaesthesia and sedation. However, i.v. propofol can be associated with risks of haemodynamic instability awareness at low dosage.[1] In particular, the online monitoring of blood or plasma propofol concentrations during anaesthesia or sedation is advantageous for specific patients, such as obese patients and those undergoing liver transplantation.

Although pilot studies[2 3] have reported that exhaled propofol concentrations reflect intraoperative plasma propofol levels in individuals, the blood/exhaled coefficient (R_{BE}), which is the ratio of propofol partial pressure in the 'headspace (HS)' of blood to that in exhaled gas, varied from one person to another. The partial pressures of propofol in the HS, which refers to the mixed gases above the blood, have been shown to be proportional to the concentrations in the blood.[4] It is not yet possible to monitor blood propofol concentrations by a real-time detection of exhaled propofol concentrations,[5] largely because the correlation between concentrations in exhaled gas and blood has not yet been determined.

A solution to this is to develop a model incorporating several relevant factors, such as age, gender, tidal volume, ventilatory frequency, disease state-based pulmonary diffusion, and functional residual capacity, to predict R_{BE}. This would

require data from a large cohort. However, no efficient and easy-to-operate detection system for a rapid evaluation of the ratio R_{BE} currently exists. This is probably the most significant reason why the application of breath monitoring of propofol is limited.

In this study, we proposed a novel method that uses a surface acoustic wave (SAW) sensor combined with a fast gas chromatograph (GC)[6–8] to determine the concentration (or partial pressure) of propofol in exhaled gas, and also that in blood samples by exactly the same procedure in the analysis. Calibrations by standard gas-phase propofol and standard blood samples show reliability and efficiency of GC–SAW for the simultaneous determination of propofol concentrations in human blood and exhaled gas (see our calibration results). The ratio R_{BE} in individuals could thus be derived from a direct comparison of the responses with propofol partial pressures in blood and those in exhaled gas. Fast GC–SAW, which analyses samples in seconds, can perform not only an online monitoring of propofol concentrations in gas exhaled by patients but also an on-site fast analysis of propofol concentrations in blood. The proposed method takes about 50 min to evaluate R_{BE} for one patient. It accelerates the determination of the coefficient R_{BE} in individuals, the distribution of which could then be observed in a larger cohort, to allow examination of its association with other variables. This study aimed to provide a method for a quick evaluation of R_{BE} in individuals, to increase understanding of inter-individual differences, with the subsequent aim of modelling or even predicting R_{BE}. This would aid the development of non-invasive real-time monitoring of blood propofol concentrations for use in clinical practice.

Methods

Patients and anaesthetic management

The clinical study was approved by the Office of Human Research Protections at Zhejiang University with institutional review board (ref.: IRB-SAHZU-2013 No. 14) and registered with ChiCTR (ref.: ChiCTR-ONC-13003291). Written informed consent was obtained from all the 28 patients. All the patients who participated had been evaluated with ASA physical status I or II.

After pre-oxygenation of the lungs via a facemask for 5 min, anaesthesia was induced using i.v. routine doses of midazolam, rocuronium, sufentanil, and etomidate. Tracheal intubation was performed after 3–5 min, and patients' lungs were ventilated [tidal volume 8 ml kg^{-1}, respiratory rate 12 bpm, inspiratory-to-expiratory ratio of 1:2 with oxygen–air mixture (fraction of inspired oxygen 50%)]. A central venous catheter was inserted into the right internal jugular vein for blood sampling. For all the patients, adequate analgesia was achieved by continuous infusion of remifentanil and inhalation of sevoflurane, and further increments of rocuronium as necessary.

After a bolus i.v. injection of propofol, at a dose of 2 mg kg^{-1} body weight, we continuously recorded exhaled propofol concentrations using the fast GC–SAW detection system (Fig. 1). Blood sampling started 2 min after the injection. One millilitre of blood was sampled every 2 min in the first 10 min after the injection and a further five samples were collected in the next 20 min, at each decline of 100 Hz response (from the SAW sensor) of propofol concentration in exhaled gas. A total of 10 ml of venous whole blood were separately collected from each patient and successively stored into 10 vacuum blood collection tubes (1 ml for each tube, sorted by the time at sampling) containing trisodium citrate for anticoagulation. It usually takes 20 min to analyse 10 blood samples.

Fast GC–SAW detection system

The detection system included a micro-thermal adsorption/desorption pre-concentration sampler, a 3 m long DB-5 capillary column (cut from an Agilent® column of 10 m × 0.1 mm × 0.33 μm) with a direct resistive heating component (manufactured by Ningbo Oulaike Metal Capillary Technology Co., Ltd, Ningbo, China), and a 36° *Y*–*X* quartz-based SAW sensor (manufactured by HuaYing Electronics, Wukang, China) with a central frequency of 500 MHz (Fig. 1). All the components, including the helium container, were assembled into a designed shell of a portable size (40 × 30 × 20 cm). The outer

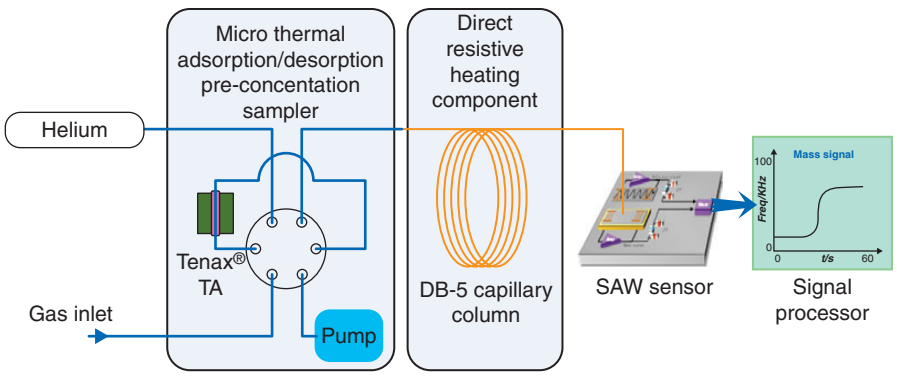

Fig 1 Structure of the fast GC–SAW detection system.