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TECHNICAL REPORT

On-line determination of serum propofol concentrations by expired air analysis

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Abstract Propofol (2,6-diisopropylphenol)—an intravenous anaesthetic—can be identified and quantified in expired air directly. For the first time, a β-radiation ion mobility spectrometer operated in the positive mode and coupled to a multi-capillary column for rapid (seconds–minutes) pre-separation (MCC/IMS) was used for the quantification of Propofol in expired air. The comparison of the concentrations in exhaled air (300 ppt_V–5 ppb_V) and in serum (0.3–5 μg/mL) showed satisfying agreement affirmed by a correlation coefficient of 0.73. Therefore, MCC/IMS is an adequate method to determine Propofol concentrations in exhaled air and may be applied for the prediction of venous concentrations or for automatic anaesthesia control.

Keywords Propofol · 2,6-diisopropylphenol · Anaesthesia · Serum · TIVA · Breath analysis · Ion mobility spectrometry · GC/MS · GC/IMS

Introduction

The monitoring of volatile anaesthetics in end-tidal breath is a standard procedure to improve safety of the patient and to adjust anaesthetic depth. Presently, this is not easy to perform for intravenous anaesthetics such as Propofol. Complex and time consuming off-line analyses of blood samples are required. Therefore, an on-line method for the determination of the serum anaesthetics concentration is desirable to improve safety and adjust anaesthetic depth or the level of sedation in intensive care units (ICU).

The on-line measurement of Propofol in exhaled air has already been demonstrated using different techniques like proton transfer reaction mass spectrometry (PTR-MS) [1, 2], thermal desorption gas chromatography [3] and ion molecule reaction-mass spectrometry (IMR-MS) [4]. Those investigations showed close relations of Propofol concentrations in exhaled air and in blood [2–4]. However, those instruments are expensive and in general not commercially available as validated medical instrumentation.

For the present study, an ion mobility spectrometer in combination with a multi-capillary column (MCC/IMS) was applied for the quantification of Propofol in exhaled air for the first time as presented in [5] for the medical community, in particular with regard to the possible routine application. Here, the technical aspects will come to the fore. The results were compared to serum concentrations of Propofol determined by GC/MS. The MCC/IMS has already been applied successfully for medical purpose [6–8]. It is a suitable tool to analyse human breath as it provides high sensitivity (down to ppt_V) and selectivity combined with high-speed data acquisition (single spectra 0.1 s / complete breath analysis ~5 min) and relatively low technical expenditure.

Experimental

The bi-directional β-radiation MCC/IMS operated with synthetic air under ambient pressure and temperature used

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for the study was custom designed at ISAS and has been described in detail in literature as well as the software used for data acquisition and evaluation [6–8]. For pre-separation, a 20 cm un-polar multi-capillary chromatographic column (OV-5, MULTICHROM, Novosibirsk, Russia) was operated isothermal at 40 °C. Sampling was controlled by a CO_2 sensor (IRMA, Fa. PhaseIn, Danderyd, Sweden), which was used to flush the sample loop (8 mL volume) only if carbon dioxide exceeded 25 mmHg, thus sampling only end-tidal breath. The volume of the sample loop was then introduced directly into the MCC without any pre-treatment of the sample.

Propofol (2,6-diisopropylphenol) is characterised by a molecular mass of 178 u and a phenolic chemical structure. Propofol and Thymol (used as internal standard) for calibration were obtained from Sigma–Aldrich (Seelze, Germany). A calibration gas generator (HovaCAL 3834SC VOC, Inspire Analytical Systems GmbH, Frankfurt am Main, Germany, see [9]) was used for calibration of MCC/IMS. The generator provided Propofol concentrations (1, 3, 5, 7, 9 and 10 ppb_v) in humid air (100% relative humidity at 37 °C). The calibration results (correlation coefficient of 0.984, n=24) are presented in Fig. 1. The Propofol concentration could be determined by the MCC/IMS in breath with a mean standard deviation of 2.5% and by GC/MS in serum with 12.2%.

Study population

Thirteen patients scheduled for an elective ear–nose–throat surgery procedure (nine male, four female, all classified as American Society of Anaesthetist physical status I or II, see [10]) were involved in the study. In the mean, patients were 45 years of age and their body-mass-index (BMI) was 24.6 (Table 1). The study was approved by the ethics committee of the University of Göttingen, Germany (protocol No. 01/07/08). All patients gave written informed consent to participate in the investigation.

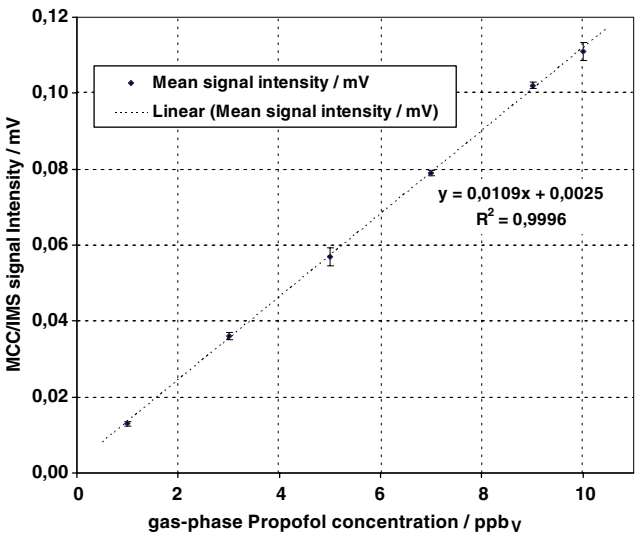

Fig. 1 Calibration of the MCC/IMS to gas-phase Propofol in humid air

Anaesthesia and sample acquisition

The patients received a standard total intravenous anaesthesia (TIVA) with Propofol (Disoprivan 1%; Astra Zeneca, Wedel, Germany) as hypnotic agent, Remifentanil for analgesia and optional Rocuronium as muscle relaxant. Anaesthesia was induced with intravenous application of 2.1 (±0.7) mg/kg Propofol bolus and 30 μg/kg/h Remifentanil. After tracheal intubation, the lung was ventilated with a standard anaesthesia respirator (Cato, Dräger, Lübeck, Germany). Propofol (3.9 (±1.8) mg/kg/h) and Remifentanil (30 μg/kg/h) were applied continuously to maintain anaesthesia adjusted to clinical parameters. Sampling was performed as described above and in Total Intravenous Anaesthesia in analogy to Schubert et al. [11] measuring CO_2 in breath with mainstream capnography (IRMA, Fa. PhaseIn, Danderyd, Sweden). Breath samples were drawn when the CO_2 level exceeded 25 mmHg and venous blood samples were obtained via a separate venous access at the opposite site of the drug infusion simultaneously. All samples were collected at steady state conditions (achieved by administration of Propofol and Remifentanil for 15 min). Depending on the duration of surgery, one or two sample pairs of breath and serum were taken per patient.

Determination of propofol concentrations by GC/MS

Breath samples have been adsorbed on Tenax tubes (1 L of breath, controlled by the sampling control of the MCC/IMS) and were thermally desorbed and analysed just as the blood samples (injected in one bolus at 250 °C) using a GC/MS with EI-ionisation (70 eV) by Agilent Technologies 6,890 N GC-system connected to an Agilent Technologies 5,973 mass selective detector (MSD; Gerstel, Mülheim, Germany). The operating parameters were: SSL-injector 180 °C; column DB-5: 30 m; 0,25 mm ID; 0,25 μm FD; 1 mL/min He const.; T-program 40 °C/5 °C/min–100 °C/

Table 1 Demographics of the study population: Median (Min. Max.)

Sex (male/female)	9/4
Age [years]	45 (18 69)
Weight [kg]	76 (58 107)
Height [cm]	173 (160 183)
BMI	25 (19.6 38.8)

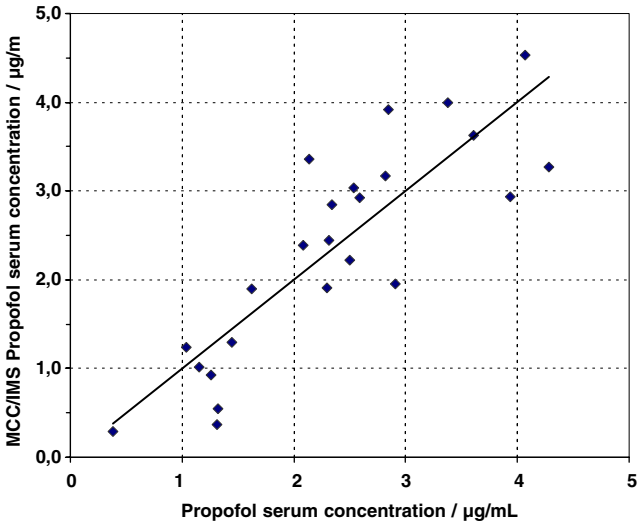

Fig. 2 Propofol concentrations in exhaled air determined by MCC/IMS and converted into serum concentrations versus Propofol serum concentrations determined by GC/MS. The *solid line* indicates a linaer regression with a correlation coefficient of 0.73

20 °C/min–200 °C (5 min). Integrated signals from the internal standard Thymol (*m*/*z* 135,150) and from Propofol (*m*/*z* 163,178) were evaluated by AMDIS/NIST (Automated Mass Spectral Deconvolution and Identification System; version 2.62, 2005; NIST version 2.0, 2005).

Simultaneously to breath sampling, venous blood was from the arm that was not used for the infusion. All samples were collected under steady-state conditions (Achieved by administration of Propofol and Remifentanil for 15 min). Depending on the duration of surgery, 1–2 samples were obtained from each patient.

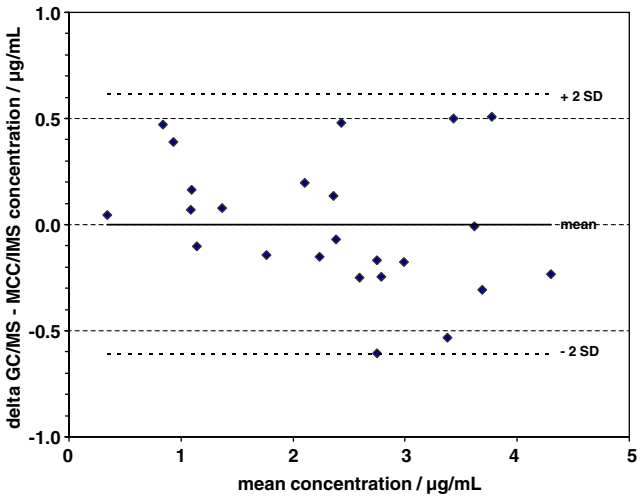

Fig. 3 Deviation of the MCC/IMS concentration from the mean concentration determined by both MCC/IMS and GC/MS. The *dotted lines* indicate twice the standard deviation

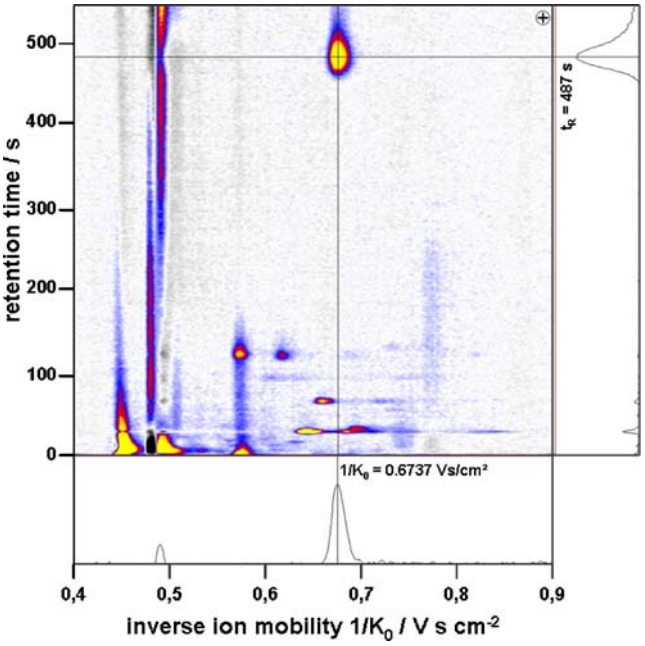

Fig. 4 MCC/IMS chromatogram of Propofol with pre-separation operated at 40 °C. The Propofol signal is indicated by the cross line and the single spectra (*bottom*) and chromatogram (*right*) are displayed in the extra figures

Results and discussion

In total 24 measurements were carried out during anaesthesia of the study population. The Propofol signal in the MCC/IMS spectra was identified via parallel Tenax samples of breath and TD-GC/MS analysis earlier from a different study population. The Propofol concentration in exhaled air was determined by MCC/IMS and converted into serum concentrations. The related serum Propofol concentration was determined by GC/MS using the reference analyte for quantification. The comparison of both measurements is presented in Fig. 2. A correlation

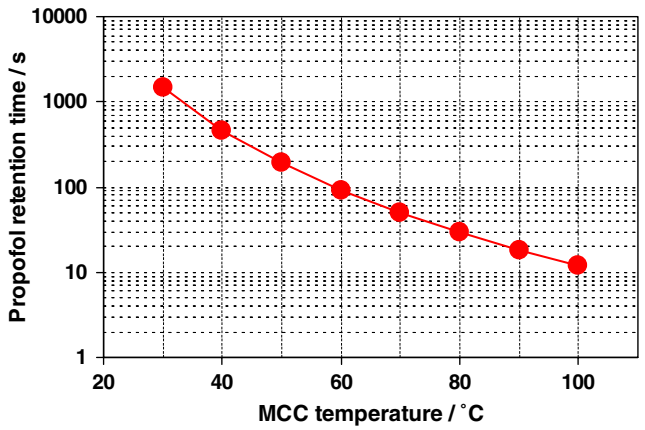

Fig. 5 From calibration measurements, a decrease of the Propofol retention time described by the formula $t_R(T) = 11^{8} * T^{-3.98}$ was determined

coefficient of 0.73 was obtained. In contrast to Miekisch et al. [12] but conformable to Grossherr et al. [3] a correlation between venous serum and exhaled air Propofol concentration was observed.

To provide more general information about the reliability of the serum Propofol concentration determined via breath analysis, the MCC/IMS concentrations were compared to the mean concentration as determined by both MCC/IMS and GC/MS (see Fig. 3). The standard deviation of the MCC/IMS compared to this normalised mean value was with 12.3% in the same range as found when other techniques are used [2–4].

For the present study, the pre-separation of the MCC/IMS was operated at 40 °C. With this experimental setup, the Propofol signal was detected with a mean retention time of 474.5 s and a mean inverse reduced ion mobility $1/K_0$ of 0.6737 Vs/cm² (see Fig. 4). However, as the signal occurs in general separated from others, the pre-separation temperature may be increased to reduce retention time and analysis time respectively.

Calibration measurements at different MCC temperatures showed, that retention time follows an almost logarithmic decrease with increasing MCC temperature. For Propofol, the correlation can be described by the formula $t_R(T) = 1.1*10^{8}*T^{-3.98}$ (see Fig. 5). Exceeding 70 °C, retention time is already <1 min and at 100 °C only 10 s. The very isolation location of the Propofol signal in the breath spectra would furthermore enable to use a 10 cm MCC instead of 20 cm, which will halve the retention time. Therefore, at 100 °C, the retention time of Propofol concentration can be determined after about 5 s.

Conclusion

The correlation between exhaled air concentrations and serum concentrations of Propofol was described for the first time using a MCC/IMS. The system obtains a point of care measurement with non-invasive sampling and reliable prediction of venous Propofol concentrations without pre-concentration. The on-line determination (5–10 s after sample acquisition) of serum Propofol concentrations via breath analysis with regard to safety factors is feasible for infusion control at ICU and for Total Intravenous Anaesthesia (TIVA).

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