Population pharmacokinetics of sevoflurane in conjunction with the AnaConDa® Towards target controlled infusion of volatiles into semiopen breathing systems.

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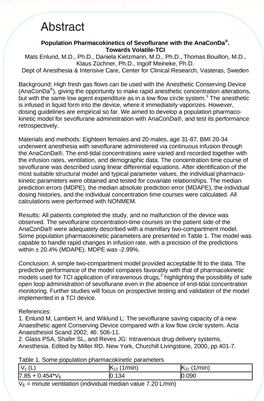
Background

The Anesthetic Conserving Device (AnaConDa) (Fig 1) combines low anesthetic expenditure with the opportunity to make rapid anesthetic concentration alterations (1). The anesthetic is infused in liquid form into the device, where it immediately vaporizes. However, dosing guidelines are empirical so far.

We aimed to develop a population pharmacokinetic model for sevoflurane administration with AnaConDa, test its performance retrospectively and provide target controlled infusion (TCI) simulations.

Fig 1. AnaConDa®



Abstract

Population Pharmacokinetics of Sevoflurane with the AnaConDa®, Towards Volatile-TCI

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Background: High fresh gas flows can be used with the Anesthetic Conserving Device (AnaConDa®), giving the opportunity to make rapid anesthetic concentration alterations, but with the same low agent expenditure as in a low flow circle system.[2] The anesthetic is infused in liquid form into the device, where it immediately vaporizes. However, dosing guidelines are empirical so far. We aimed to develop a population pharmacokinetic model for sevoflurane administration with AnaConDa®, and test its performance retrospectively.

Materials and methods: Eighteen females and 20 males, age 31-87, BMI 20-34 underwent anesthesia with sevoflurane administered via continuous infusion through the AnaConDa®. The end-tidal concentrations were varied and recorded together with the infusion rates, ventilation, and demographic data. The concentration time course of sevoflurane was described using linear differential equations. After identification of the most suitable structural model and typical parameter values, the individual pharmacokinetic parameters were obtained and tested for covariate relationships. The median prediction errors (MDPE), the median absolute prediction error (MDAPE), the individual dosing histories, and the individual concentration time courses were calculated. All calculations were performed with NONMEM.

Results: All patients completed the study, and no malfunction of the device was observed. The sevoflurane concentration-time courses on the patient side of the AnaConDa® were adequately described with a mamillary two-compartment model. Some population pharmacokinetic parameters are presented in Table 1. The model was capable to handle rapid changes in infusion rate, with a precision of the predictions within ± 20.4% (MDAPE). MDPE was -2.99%.

Conclusion: A simple two-compartment model provided acceptable fit to the data. The predictive performance of the model compares favorably with that of pharmacokinetic models used for TCI application of intravenous drugs,[1] highlighting the possibility of safe open loop administration of sevoflurane even in the absence of end-tidal concentration monitoring. Further studies will focus on prospective testing and validation of the model implemented in a TCI device.

References:
1. Enlund M, Lambert H, Wiklund L: The sevoflurane saving capacity of a new Anaesthetic agent Conserving Device compared with a low flow circle system. Acta Anaesthesiol Scand 2002; 46: 506-11.
2. Glass PSA, Shafer SL, and Reves JG: Intravenous drug delivery systems. Anesthesia. Edited by Miller RD. New York, Churchill Livingstone, 2000, pp 401-7.

Table 1. Some population pharmacokinetic parameters

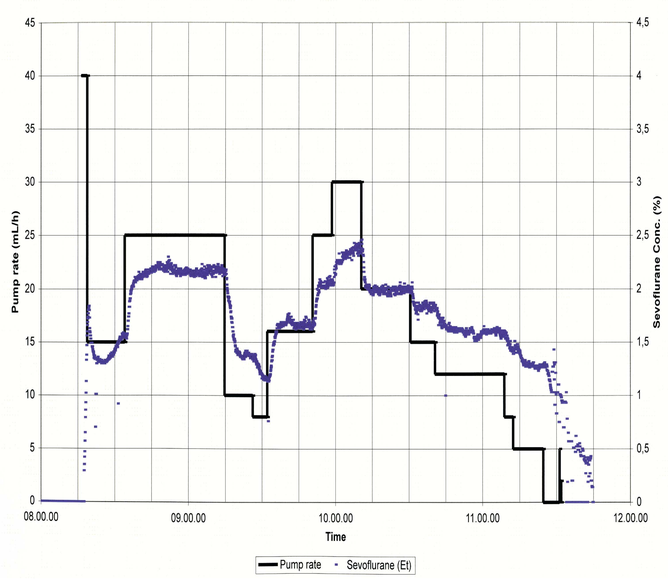
V_c (L)	K_{10} (1/min)	K_{21} (1/min)
7.85 + 0.454*V_E	0.134	0.090

V_E = minute ventilation (individual median value 7.20 L/min)

Material and Methods

Eighteen females and 20 males, age 31-87, BMI 20-34 underwent anesthesia with sevoflurane administered via continuous infusion through the AnaConDa. The end-tidal concentrations were varied and recorded together with the infusion rates, and ventilation- and demographic data (Fig 2).
The concentration-time course of sevoflurane was described using linear differential equotions. After identification of the most suitable structural model and typical parameter values, the individual pharmacokinetic parameters were obtained and tested for covariate relationships. MDPE, MDAPE, the individual dosing histories and the individual concentration time courses were calculated. All calculations were performed in NONMEM.

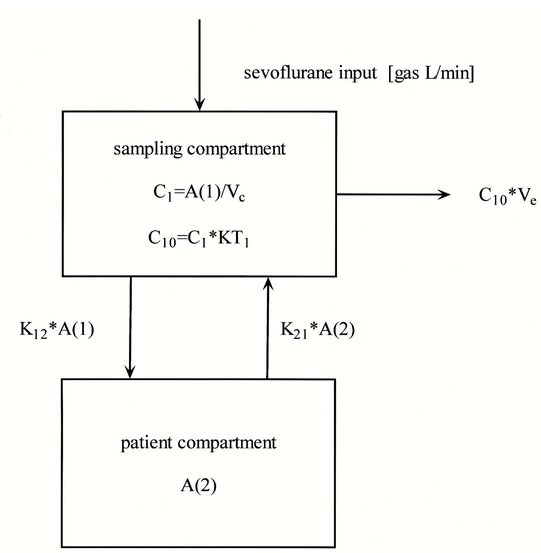
Fig 2. An example of variations in pump rate and the resulting end-tidal sevoflurane concentration.



Results

No malfunction of the device was observed. The sevoflurane concentration-time courses on the patient side of the AnaConDa were adequately described with a two-compartment model (Fig 3). The model was capable to handle rapid changes in infusion rate (Fig 4), with a precision of the predictions within +/-20% (MDAPE) and a bias of -3% (MDPE).

Fig 3. The two-compartment model.
KT_1 = concentration gradient in AnaConDa.



Conclusion

A simple two-compartment model provided acceptable fit to the data. The predictive performance of the model compares favorably with that of pharmacokinetic models used for TCI application of intravenous drugs, highlighting the possibility of safe open loop administration of sevoflurane even in the absence of end-tidal monitoring. Further studies will focus on prospective testing and validation of the model implemented in a TCI device.

Reference

1. Enlund M, Lambert H, Wiklund L. Acta Anaesthesiol Scand 2002;46:506-11.

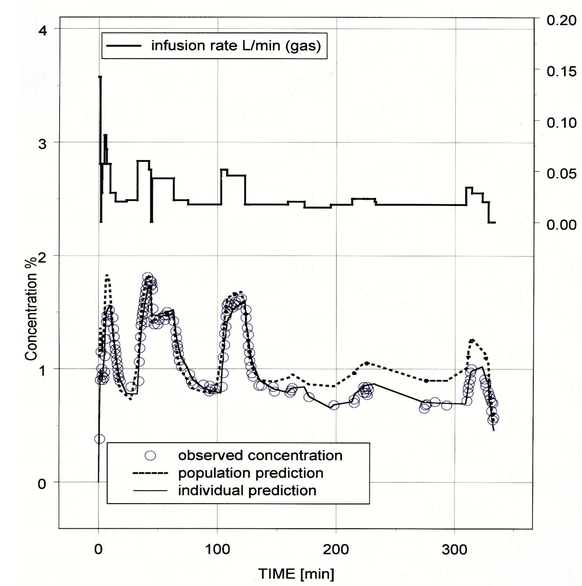



Fig 4. The prediction of the model in a single study patient.