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CLINICAL PRACTICE

Teletherapeutic drug administration by long distance closed-loop control of propofol†

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Background. The objective of this pilot study was to investigate the feasibility of an EEG-controlled closed-loop administration of propofol over a long distance of about 200 km.

Methods. We performed a teletherapeutic propofol infusion during total intravenous anaesthesia with propofol in 11 patients undergoing general surgery. The teletherapeutic system consisted of a computer at the patient site in Munich and a computer at the control site in Erlangen, which were connected via the internet through a virtual private network. The patient's EEG signal was sent to the control site computer, where the median frequency (MEF) of the EEG power spectrum was calculated. The propofol infusion, determined by a model-based adaptive feedback algorithm to maintain a MEF of 1.5 to 2 Hz, was sent to the patient site computer connected to the infusion pump. The quality of the control was assessed by the performance error defined as the percentage deviation of the measured MEF from the set point and the necessity of interventions by the anaesthetist at the patient site.

Results. During closed-loop administration of propofol [83 (52) min] the median performance error of the system was −4.6 (4.4)% and the median absolute performance error was 18.8 (5.7)%. From a total number of 10 905 transmitted EEG epochs, there were five epochs with transmission errors, without further consequences for drug control. In one patient, teletherapy was stopped because the internet connection was interrupted.

Conclusions. Teletherapeutic drug administration could be realized over a longer distance. Further studies have to investigate the practicability and safety of teletherapeutic drug control in anaesthesia.

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With the rapid development of telecommunication in the last few years, telemedicine has become more interesting with the perspective of medical support even over long distances and in case of restricted access, as, for example, in the maritime environment or in space missions.[1] Whereas remote control of robot-assisted surgery (telesurgery) has been successfully realized in recent years,[2–4] teleanaesthesia has not yet been performed. The control of drug administration and the monitoring of the electroencephalogram (EEG) are two components of anaesthesia which are well suited to test the concept of teletherapy in anaesthesia. These two components can be combined to a closed-loop system where drug administration is automatically controlled to maintain a defined set point of the EEG effect as therapeutic target. EEG-controlled closed-loop systems were developed for the first time about 50 yr ago,[5] and during the last 20 yr different approaches using the median frequency (MEF) of the EEG

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power spectrum,[6] the Bispectral index (BIS®, Aspect Medical Systems Inc., Newton, MA, USA),[7] or auditory evoked potentials[8] were realized. In the present pilot study, we investigated the feasibility of a real-time EEG-controlled closed-loop administration of propofol during surgery over a long distance of about 200 km as a model for remote drug therapy under special circumstances.

Methods

System specifications

The teletherapeutic system consisted of an EEG monitor (A1000, Aspect Medical Systems Inc., Newton, MA, USA), an infusion pump (Perfusor fm, B. Braun Melsungen AG, Melsungen, Germany), and two computers, one at the patient site in Munich, Germany and the other at the control site in Erlangen, 200 km north of Munich (Fig. 1). Whereas the patient site computer was responsible for signal acquisition and control of the infusion pump, the control site computer performed the signal analysis and the algorithms to determine the infusion rate. Additional information, for example, haemodynamic parameters, the status of the surgery and comments were also transferred as free text in a message box between the attending anaesthetist at the patient site and the supervisor at the remote site. Both computer systems were connected via a virtual private network (VPN) through the internet with high speed terrestrial optical-fibre connection of up to 1000 Mbits s^{-1}. Data were transmitted using the User Datagram Protocol. The computer software for EEG recording, data analysis, data transfer, and infusion control (IvFeed, Department of Anaesthesiology, Erlangen, written in Visual Basic 6.0) was developed by two of the authors (H. I. and H. S.). All devices of the teletherapeutic system including the computers had the CE mark. The power supplies of the notebook computer at the patient site, of the EEG monitor and of the infusion pump were buffered by batteries. As the control program IvFeed was used on the patient site computer and on the control site computer, the drug infusion could be continued by the patient site computer if the connection with the control computer was disturbed.

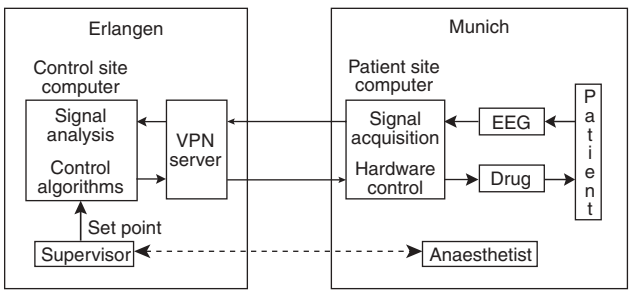

Fig 1 Set-up of the teletherapeutic system.

EEG recording and processing

The patient's EEG (one channel: Fp1-Fz) was recorded with silver/silver chloride pre-gelled electrodes (Medicotest Blue Sensor N-00, AMBU Germany, Bad Nauheim, Germany) and the following monitor settings: 0.25 Hz high pass, 35 Hz low pass, 50 Hz line filter. The digitized signal (sampling rate: 128 Hz) and the processed parameters (version 3.31) were obtained from the serial port of the A1000 monitor. Every second, a package of 1664 bytes containing the EEG data was sent from the patient site computer to the control site computer, where the EEG was analysed and the MEF of the EEG power spectrum (0.5–32 Hz) was calculated from epochs of 8 s length. Artifacts were rejected by automatic artifact detection and the MEF was smoothed by applying a moving average of eight epochs, including only epochs free of artifacts.

Infusion control

The system IvFeed allows drug control by target controlled infusion (TCI) or by closed-loop control. In case of TCI, the target concentration is set either by the user at the patient site or by the supervisor at the control site. In case of closed-loop control, the target concentration is determined by a model-based adaptive feedback algorithm, based on the difference between the targeted MEF (set point) and the actually measured MEF.[6] As propofol shows a distinct hysteresis between plasma and effect site concentration, the targeted concentration was the effect site concentration, assuming a transfer rate constant k_{e0} of 0.30 min^{-1}. A three-compartment model with a multi-exponential disposition function: $c(t) = \Sigma_{i=1}^{3} A_i \cdot e^{-\lambda_i \cdot t}$ and the pharmacokinetic parameters for adults as reported by Marsh[9] (which are also implemented in commercial TCI systems) were used for the pharmacokinetic part of the model. The propofol target concentration was changed based on the pharmacodynamic model:[6]

$$E = E_0 - E_{max} \frac{(C_E/EC_{50})^{\gamma}}{1 + (C_E/EC_{50})^{\gamma}}$$

From the measured MEF and the infusion history, the pharmacokinetic–pharmacodynamic model was adapted to the individual patient. If no measured plasma concentrations are available, it is impossible to determine the coefficients A_i of the pharmacokinetic disposition function and the half-maximum concentration EC_{50}. However, as the effect depends only on the ratio C_E/EC_{50}, the ratios A_i/EC_{50} can be estimated from the measured effect and the dosing history.[10] This parameter adaptation was performed throughout the closed-loop control. If no EEG signal was available or if the EEG was disturbed by artifacts as, for example, caused by electro coagulation, the user could either switch from closed-loop control mode to TCI mode and enter the propofol target concentration or maintain the closed-loop control mode and the system