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

H. Ihmsen1*,‡, K. Naguib2‡, G. Schneider2, H. Schwilden1, J. Schüttler1 and E. Kochs2

1Department of Anaesthesiology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. 2Department of Anaesthesiology, Klinikum rechts der Isar, Technische Universität München, München, Germany

*E-mail: harald.ihmsen@kfa.imed.uni-erlangen.de

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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‡These two authors contributed equally to this work.
power spectrum, the Bispectral index (BIS®, Aspect Medical Systems Inc., Newton, MA, USA), or auditory evoked potentials 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.

**EEG recording and processing**

The patient's EEG (one channel: Fp1-Fz) was recorded with silver/silver chloride pregelled 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. 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 kₜ₀ of 0.30 min⁻¹. A three-compartment model with a multi-exponential disposition function: \( c(t) = \sum_{i=1}^{3} A_i \cdot e^{-\lambda_i \cdot t} \) 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:

\[
E = E_0 - E_{\text{max}} \cdot \frac{\left(\frac{C_E}{EC_{50}}\right)^5}{1 + \left(\frac{C_E}{EC_{50}}\right)^5}
\]

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.

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Fig 1 Set-up of the teletherapeutic system.
applied a default propofol target concentration. The infusion rate, as determined from the target concentration and the pharmacokinetic model, was sent from the control site computer to the patient site computer. Every 8 s, the delivery rate of the infusion pump was updated by the control site computer. The actual infusion rate of the infusion pump, which was sent back to the control site computer was used for the prediction of the propofol concentration. If the computer at the patient site did not receive an infusion rate from the remote computer at the control site, the infusion was continued as local TCI, controlled by the patient site computer and using the last valid target concentration. At any time, the anaesthesiologist at the patient site was able to stop the automatic control of propofol and continue the propofol administration by manual dosing.

**Patients, anaesthesia**

After approval from the institutional ethics committee (Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany), written informed consent was obtained from 11 patients, American Society of Anaesthesiologists physical status I and II, aged 18–60 yr, who were scheduled for general surgery at the Klinikum rechts der Isar in Munich. Exclusion criteria included neurological disorder and use of psychoactive medication. All patients received a premedication of midazolam 7.5 mg orally 1 h before surgery. As there was no internet access in the induction room, anaesthesia was introduced manually with a bolus of propofol 2 mg kg\(^{-1}\), sufentanil 0.2 µg kg\(^{-1}\), and atracurium 0.5 mg kg\(^{-1}\). After intubation, anaesthesia was continued with additional doses of propofol 1.5 to 2.0 mg kg\(^{-1}\) (3 patients), or with sevoflurane 1.5 to 2.0 vol.% (5 patients), or with desflurane 6.0 vol.% (3 patients), respectively. After arrival in the operation theatre, the EEG electrodes were placed and the impedances were checked, the computer at the patient site was started, and the internet connection with the computer at the control site in Erlangen was established. Propofol was started as TCI, taking the previously administered propofol doses into account, and sevoflurane or desflurane was stopped. After skin incision, propofol administration was switched from TCI to closed-loop control with a set point of 1.5 or 2 Hz MEF. Approximately 20 min before end of the surgery, propofol was again administered as TCI with decreasing target concentrations, and propofol was stopped at the end of skin closure. During TCI phases, the propofol target concentration was set by the supervisor at the remote site in accord with the anaesthesiologist at the patient site. During surgery, analgesia was realized with repetitive doses of sufentanil 10 to 20 µg at the discretion of the anaesthesiologist in charge according to clinical assessment. For neuromuscular block, repetitive doses of atracurium 0.1 mg kg\(^{-1}\) were administered if necessary. Systolic and diastolic arterial blood pressure, heart rate, oxygen saturation, and end-tidal carbon dioxide were recorded every 5 to 10 min.

**Assessment of the performance of the closed-loop control**

The closed-loop system was characterized by several performance measures as proposed by Varvel and colleagues\(^1\) for the evaluation of TCI systems. The performance error (PE) was determined as relative deviation from the set point:

\[
\text{PE}_{ij} = \frac{\text{MEF}_{ij} - \text{setpoint}}{\text{setpoint}}
\]

where MEF\(_{ij}\) is the \(j\)th measured MEF in the \(i\)th patient. As a quantitative measure of bias, we determined in each patient the median performance error, MDPE\(_i\) = median \{PE\(_{ij}\), \(j=1, \ldots, N_i\}\}, and as a quantitative measure of accuracy the median absolute performance error, MDAPE\(_i\) = median \{|PE\(_{ij}\)|, \(j=1, \ldots, N_i\}\}, where \(N_i\) is the number of performance measurements in the \(i\)th patient. Furthermore, linear regression of |PE\(_{ij}\)| vs time yielded the divergence \(D_i\) as the slope of the regression line which is a measure for a time-related trend of the performance. The wobble \(W_i\) = median \{|PE\(_{ij}\) − MDPE\(_i\)|, \(j=1, \ldots, N_i\}\} was calculated as a measure for the intrindividual variability of the performance error. As the processed EEG parameters from the Aspect monitor were also transmitted, we were able to compare the intrindividual variation of the BIS and the MEF by calculating the wobble of these parameters:

\[
\text{WBIS}_i = \text{median}\left\{\left|\frac{\text{BIS}_{ij} - \text{MDBIS}_i}{\text{MDBIS}_i}\right|, \, j=1, \ldots, N_i\right\}
\]

and

\[
\text{WMEF}_i = \text{median}\left\{\left|\frac{\text{MEF}_{ij} - \text{MDMEF}_i}{\text{MDMEF}_i}\right|, \, j=1, \ldots, N_i\right\}
\]

where BIS\(_{ij}\) and MEF\(_{ij}\) are the \(j\)th measured value of BIS and MEF in the \(i\)th patient and MDBIS\(_i\) and MDMEF\(_i\) are the median values of these parameters in the \(i\)th subject. All performance parameters were determined for those phases where propofol was closed-loop controlled. Loss of data by the internet transfer was assessed by comparing the data stored on the patient site computer and the control site computer, respectively. Data are presented as mean (SD) unless otherwise stated.

**Results**

The patient characteristics are shown in Table 1. Teletherapeutic drug control, either as remote TCI or as remote closed-loop control, could be performed in all 11 subjects and lasted at least 49 min in the shortest case with 85 min duration of anaesthesia (Table 2). In one subject, the teletherapeutic drug control was stopped after 2 h and
the propofol administration was continued manually because the VPN connection was interrupted. In two other subjects, the teletherapeutic drug control was terminated prematurely after 1 h because of a software error which could be fixed in the following patients. Apart from these interruptions, it was not necessary in any case to stop the remote propofol control and continue with manual dosing. There were no signs of inadequate anaesthesia. For data analysis, we used those time periods of all 11 patients where closed-loop administration could be performed, which was possible in approximately 65% of the time of teletherapeutic drug control. In the remaining time, which included the beginning and the end of anaesthesia and the phases with EEG disturbance by electrocautery, propofol was administered as remote TCI, where the infusion rate was determined at the control site and sent to the patient site computer. The time for the transfer of one EEG package of 1664 bytes (containing the data of 1 s EEG, including derived parameters) from Munich to Erlangen was 8 ms. From a total number of 10 905 EEG epochs in all patients, there were only five epochs lost (0.05%), with no further consequences for the control. The mean values of MEF and BIS during closed-loop control were 1.8 (0.2) Hz and 42 (2), with a wobble of 18.8 (5.9)% and 6.2 (3.5)%, respectively (Figures 2 and 3). The performance of the closed-loop control is summarized in Table 3. The total delivered propofol amount for anaesthesia was 5.9 (1.4) mg kg$^{-1}$ h$^{-1}$. The predicted propofol effect site concentration increased during the first 30 min of closed-loop control and stayed thereafter between 3 and 4 µg ml$^{-1}$ (Figure 4). Blood pressure and heart rate were stable (Figure 5). The oxygen saturation did not decrease below 97%, with a mean value of 98.9 (0.4)%. The end tidal carbon dioxide stayed between 30 and 40 mm Hg, with a mean value of 32.9 ± 0.8 mm Hg.

**Discussion**

It was the aim of this pilot study to investigate whether computer-controlled drug delivery in general, and closed-loop control in particular, can be performed over long distances using common internet connections. Two issues are important for successful teletherapy: the time needed for transmission of the signals and the stability of the connection. As modern internet connections allow a transfer with more than 1 Mbit s$^{-1}$, the online transfer of an EEG signal with a sample rate of 128 Hz should be no problem. In our study, the measured transfer time for a EEG package of 1 s was indeed about 8 ms, so that the EEG processing at the control-site was approximately in real time. Whereas the data loss of 0.05% by the internet transfer was negligible and had no consequences for the automatic drug control, the interruption of the internet connection in one patient shows the possible problems with this type of data transfer. Another general problem with EEG-controlled drug delivery is the disturbance of the EEG by artifacts, which are mainly caused by electrocaugulation. If this occurs, the administration of the drug must be controlled either by the user at the patient site or the supervisor at the control site, or it may be continued

### Table 1  Patient characteristics. Data are shown as mean (SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>11</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 (10)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>5/6</td>
</tr>
</tbody>
</table>

### Table 2  Clinical data. Data are shown as median and range

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>185 (85–630)</td>
</tr>
<tr>
<td>Duration of teletherapeutic drug control (min)</td>
<td>133 (49–338)</td>
</tr>
<tr>
<td>Duration of closed-loop control (min)</td>
<td>80 (16–196)</td>
</tr>
<tr>
<td>Recovery until extubation (min)</td>
<td>7.5 (5–10)</td>
</tr>
</tbody>
</table>
Teletherapeutic closed-loop control of propofol

by holding automatically a defined target concentration, which can be predefined by the user or can be derived from the previous infusion history.

The general principles of long distance closed-loop control are, of course, not different from the commonly realized ‘local’ closed-loop control where the control computer is situated next to the patient. Previous versions of the closed-loop software Ivmfeed were used in interaction studies\(^\text{12, 13}\) and in animal studies.\(^\text{14, 15}\) The adaptation of the pharmacokinetic–pharmacodynamic model during the control by estimating the ratios \(A_i/EC_{50}\) was also developed earlier\(^\text{10}\) and is similar to the recently introduced adaptation of \(EC_{50}\) by Struys and colleagues.\(^\text{7}\) A controller where the infusion rate is controlled by a simple proportional-integral-derivative control algorithm as used by Sakai and colleagues\(^\text{16}\) seems not to be very suitable, because the concentration–effect relationship for propofol is non-linear and because the relationship between the applied infusion rate and the resulting concentration varies with time until the steady-state is reached. Therefore, other investigators used TCI combined with a proportional-integral controller for the adaptation of the target concentration.\(^\text{8, 17, 18}\) This approach should work well in the concentration range around the half-maximum concentration \(EC_{50}\) where the concentration–effect relationship is approximately linear. However, as the concentrations of propofol during anaesthesia are usually closer to the non-linear part of the concentration–effect curve where ceiling occurs, a model based controller as realized in the presented system, where the target concentration is derived using a pharmacodynamic model may be more suitable. This approach for closed-loop control was also used by other investigators.\(^\text{7, 19, 20}\)

The performance of a closed-loop system is usually characterized by the deviation of the actually measured effect from the targeted set point, that is, the performance error and derived parameters as MDPE, MDAPE, divergence, and wobble. The negative value of the MDPE in the present study means that the system tended to slightly overdose propofol achieving a deeper concentration of sedation than targeted. This was, however, a consequence of the control algorithm where a deviation of the EEG MEF towards higher values was immediately answered by a higher propofol target concentration in order to avoid the risk of awareness. In addition, if the MEF is too low, the system can only stop the infusion and has to wait until the drug concentration has decreased, whereas a too light level of sedation can be easily answered by an increase of the infusion rate or a bolus dose. Because of this asymmetry, closed-loop systems of drugs where the effect can be reduced only by elimination and distribution may always tend to overshoot the targeted effect. This is confirmed by the results of other studies on closed-loop control of propofol which also revealed negative median prediction errors in the range of \(-1\) to \(-7\%\);\(^\text{7, 17, 19–21}\) only one investigator found a positive MDPE of \(2.2\%\).\(^\text{18}\) Whereas the MDPE of \(-4.6\%\) in the present study is in fair agreement with other studies, the values of the median absolute prediction error (19%) and the wobble (17%) were significantly higher in this study compared with other investigations which reported MDAPE and wobble of 6 to 8%;\(^\text{7, 17, 18, 20, 21}\) However, this may be partially explained by the choice of the control variable. Whereas we used the EEG MEF as control parameter, the cited investigators used the bispectral index (BIS). As the BIS is calculated

### Table 3 Performance of control. MDPE, median performance error; MDAPE, median absolute performance error. The performance error was defined as the percentage deviation of the measured EEG MEF from the setpoint. Divergence is a measure for a time related trend of the absolute performance error, and wobble is a measure for the intraindividual variability of the performance error. Data are shown as mean (SD).

| MDPE (%) | –4.6 (4.4) |
| MDAPE (%) | 18.8 (5.7) |
| Divergence (%) h\(^{-1}\) | –4.2 (8.6) |
| Wobble (%) | 16.9 (5.1) |

\(Ai/EC_{50}\) was also derived by the choice of the control variable. Whereas we used the EEG MEF as control parameter, the cited investigators used the bispectral index (BIS). As the BIS is calculated

### Fig 4 Time course of the predicted propofol effect site concentration during closed-loop control. The black line shows the mean of all 11 patients, the grey lines the 95% confidence interval. Time is given in minutes since the start of closed-loop control.

### Fig 5 Time course of mean arterial pressure (MAP) and heart rate (HR). Data are presented as mean and 95% confidence interval. Time is given in minutes since the start of closed-loop control.
from epochs longer than 8 s, it may be inherently smoother than MEF which was derived from epochs of 8 s. This is obvious in the present study where the time course of BIS was as stable as the time course of the MEF (Figure 3) but with a markedly smaller intrapatient variation, as expressed by a wobble of 6% compared with 18% for the MEF. The question, however, whether the smoother time course of BIS is paid by a delayed reaction of this parameter if sudden changes of the anaesthetic state occur, remains open.22

The presented closed-loop control over a long distance has obviously some limitations. Because of technical reasons we were not able to perform closed-loop infusion during the induction of anaesthesia. EEG-controlled closed-loop administration may be suitable to improve the induction as shown in the study of Struys and colleagues,2 where closed-loop control did not speed up the induction but reduced the overshoot, when compared with manual control. However, the high incidence of movement artifacts in the EEG during induction can be a problem for automated infusion. During the maintenance of anaesthesia, the feasibility of closed-loop control depends on the incidence of electric artifacts. In the present study, the system was in closed-loop control only in 65% of time, because of EEG artifacts and as we started and ended with TCI for safety reasons. If one began earlier with closed-loop control and performed it until the end of anaesthesia, it would be possible to achieve a higher percentage of closed-loop control during anaesthesia.

Teletherapeutic closed-loop control will probably not become clinical routine, as until now even local closed-loop control has been realized only in experimental set-up because of the regulatory and legal issues with automated drug delivery.7 Moreover, the control of the hypnotic drug is only one part of anaesthesia. For ‘teleanaesthesia’ it would be also necessary to control the analgesic drug and to transfer additional data such as vital parameters and a video signal, as the information about the ongoing surgery is mandatory, for example, for the dosing of the analgesic drug. There does not exist any monitoring that reliably predicts awareness in advance; therefore, automated control is yet always reactive and not anticipating. A simpler application would be telementoring, clinic-wide, or even over long distance. The presented system could function as a model for a server-based monitoring system, where the EEG is recorded and digitized by a small analogue–digital converter (client), sent to a control computer (server) where it is analysed, and the derived EEG parameters are sent back to the client where only a small presenting monitor like a palmtop computer would be needed additionally. With this approach, one server would be able to analyse EEG data from numerous different clients, thereby reducing the costs of EEG monitoring.

In conclusion, this first realization of teletherapeutic drug administration in anaesthesia demonstrates that automated teletherapeutic drug delivery can be performed even over a longer distance under complex and time critical circumstances. Even if teleanaesthesia will probably not become routine in typical clinical settings, the presented system may serve as a model for remote drug therapy under special circumstances. Further studies have to investigate the safety and efficacy of teletherapeutic drug treatment.

References

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