REPORTS OF SCIENTIFIC MEETINGS

James C. Eisenach, M.D., Editor

Workshop on Safe Feedback Control of Anesthetic Drug Delivery. Schloss Reinhartshausen, Germany. June 29, 1998.

This international workshop was organized by Helmut Schwilden, M.D., Ph.D., and Jürgen Schüttler, M.D., of the University of Erlangen, Germany, and by J. B. (Iain) Glen, Ph.D., of Zeneca Pharmaceuticals, Macclesfield, United Kingdom. The aim of the organizing committee was to provide a forum to discuss current progress in the area of feedback-controlled administration of anesthetic drugs and to examine future prospects and the steps required before such systems may become commercially available.

Methods of Feedback Control

Dwayne Westenskow, Ph.D. (Salt Lake City, Utah) reviewed features of proportional-integral-derivative (PID) and model-based control techniques. A patient model is not required for PID controllers, which act on the error signal (*e.g.*, target blood pressure − measured blood pressure) as an input and adjust the output (*e.g.*, drug infusion rate) to achieve the desired target. To achieve a reasonably rapid "rise time" to a desired effect, such systems are generally tuned to provide an initial overshoot of 25%, following which the system closes in on the target. Patient variability in response may generate oscillation and the need to adjust the gain of the control system to the sensitivity of an individual patient.

Model-based systems require an accurate pharmacokinetic-pharmacodynamic model of a particular drug or patient. The drug delivery rate depends on the pharmacokinetic parameters in the model, and ideally these parameters should be adapted, based on the response achieved in an individual patient (adaptive control). Model-based systems act best during the transition toward a target, whereas PID control may be more effective once a steady state has been achieved.

Alex Zbinden, M.D., of Bern, Switzerland, reviewed the aims and features of control systems for anesthesia. To be worthwhile, such systems should reduce the anesthetist's workload, decrease anesthetic gas or drug consumption, and increase patient safety.

Christian Frei, M.S.S.E., of Zurich, Switzerland, described knowledge- and rule-based approaches to feedback control. Fuzzy logic has the advantage that it uses linguistic rules based on expert knowledge and the requirements of the user. Prototypes can be developed rapidly, and appropriate rules can be used to handle nonlinearity. Disadvantages relate to the difficulty in obtaining a good mathematical model of the system to allow testing by simulation. Under restrictive conditions (patient type, drug delivery, fresh gas flow), good results have been obtained using fuzzy logic control of blood pressure during anesthesia. More problems were encountered when an attempt was made to use this controller in different patient types and operating conditions. More sophisticated systems, incorporating linear models for the combined effects of surgical stimulation and volatile anesthetics on mean arterial pressure, derived from experimental data, are being developed. An adaptive controller uses off-line precomputation of controller parameters and provides continuous on-line application. All controllers can be adapted, and a realistic approach may be the use of multiple-model PID systems with subsequent adaptation.

Biologic Signals for Feedback Control

Cedric Prys-Roberts, M.D., of Bristol, United Kingdom, and Jürgen Schüttler, M.D., chaired the session on clinical experience of feedback control in anesthesia with different biologic signals. This began with a review by Helmut Schwilden of the methods that have been used to assess depth of anesthesia. Several indices derived from electroencephalographic (EEG) monitoring are proving useful as indicators of the level of hypnosis or sedation. These include the median frequency of the EEG power spectrum, spectral edge frequency, auditory evoked potentials (AEP), and bispectral analysis (BIS). The relative merits of the different indices continue to be debated and further work is needed to demonstrate a correlation between surrogate indices (*e.g.*, derived from AEP) and other EEG parameters indicative of drug-induced central nervous system depression. No consensus on clinical and EEG–AEP relations could be achieved during the discussion phase of this presentation.

Klaus Olkkola, M.D., of Helsinki, Finland, discussed the input signals that can be used to monitor and control neuromuscular blockade and referred to a useful consensus document on methods for pharmacodynamic studies in this area (Acta Anaesth Scand 1996; 40:59). For many years, mechanomyography has been the standard method for precise quantification of neuromuscular block. However, for feedback control, electromyography is the preferred technique. There is less need for immobilization, but a stable skin temperature must be maintained to avoid baseline drift.

For feedback control of propofol anesthesia, Gavin Kenny, M.D., of Glasgow, United Kingdom, described a system that uses an AEP index derived from the EEG as the control input. In a comparative study (Br J Anaesth 1997; 78:180), the AEP index provided a more reliable prediction of the transition between asleep and awake states than did the BIS monitor, whereas the BIS index revealed a better correlation with calculated blood propofol concentrations. Studies suggest that the AEP index may reflect an overall level of arousal and may be influenced by the balance between the degree of surgical stimulation and the amount of hypnotic or analgesic provided.

Michel Struys, M.D., of Ghent, Belgium, described his experience with a prototype feedback control system incorporating a commercial BIS monitor (Aspect Medical, Natick, MA) and an adaptive pharmacokinetic-pharmacodynamic model for propofol. The system is set to achieve an initial target propofol effect site concentration of 2 μg/ml and, when this target is increased at intervals, titration to a desired level of effect in an individual patient is achieved. Once consciousness is lost, the BIS value at that time is used as the target for closed-loop control. This system has been used successfully in patients breathing spontaneously.

Jürgen Schüttler described the use of the median frequency of the EEG power spectrum between 0.5 and 32 Hz as the control variable in a model-based, adaptive, feedback controller. Certain parameters of the pharmacokinetic model are adapted to maintain a desired effect (*e.g.*, a median frequency of 2 or 3 Hz). In clinical settings, this system has been used for feedback control of propofol anesthesia in combination with alfentanil. In patients in the intensive care unit who require sedation, this feedback system, with median frequency targets of 1 or 2 Hz, has been used successfully to control the administration of propofol for 72 h; in nontrauma patients, a circadian rhythm in propofol requirements has been seen.

Donald Stanski, M.D., of Stanford University, Stanford, California,

and Iain Glen, Ph.D., chaired the plenary session in which the views of five separate syndicate groups were discussed, as follows:

1. Pros and Cons of Closed-loop Control
   This group, led by Frederick Camu, M.D., Brussels, Belgium, highlighted potential benefits of an improved ability to account for interpatient pharmacokinetic and pharmacodynamic variability and obtain a targeted effect more precisely. The avoidance of overdosage should reduce drug consumption and could possibly improve perioperative outcomes. Although surrogate indices of the depth of anesthesia such as AEP, BIS, and median frequency have been used successfully in prototype feedback control systems, it is likely that additional direct monitors, such as for blood pressure, will need to be incorporated to ensure patient safety in a fully automated system.
2. Clinical Applications Most Suitable for the Introduction of This Approach
   In presenting the conclusions of her group, Frederique Servin, M.D., Paris, France, indicated that feedback control of inhalational anesthesia using the end-tidal concentration as the control variable was technically feasible and clinically attractive. To ensure safety, closed-loop systems for hypnotic agents, using an EEG index of effect as the input, will need to consider hemodynamic variables, and multiple input-multiple output systems probably will be required. The effect of analgesic agents on any index of hypnotic effect also will need to be considered. Developments in this area should provide intelligent advisory systems that could improve the standard of care and would be most useful in special patient groups.
3. Performance Specification for Feedback Control Systems in Anesthesia
   No defined criteria exist to evaluate and compare different prototype systems. A group discussion on this topic, led by Steven Shafer, M.D., of Stanford University, Stanford, California, proposed several performance indices. Criteria for such systems will depend on the drugs used, the patient population studied, and the particular clinical scenario involved. The effect measured may be direct (*e.g.*, blood pressure or ventilation), or in the case of hypnosis, processed EEG signals may be used as a surrogate drug effect.

   Given the nonlinear nature of most concentration-*versus*-response curves, it will be important to define criteria relevant to target effect levels at different points on this curve (*e.g.*, 5%, 20%, 50%, 80%, and 95% of the maximum effect) and to select those that are clinically acceptable. To describe the onset data achieved at a particular effect target, the following indices were proposed: (1) Rise time, or the time required to move from 20% to 80% of steady state of the drug effect; (2) onset time, or the time required to achieve 80% of eventual steady state; and (3) overshoot, or the maximum value achieved, expressed as a percentage above the steady state value.

   It is proposed that *steady state* should be defined in terms of the level of effect achieved after a given number of multiples (*e.g.*, 10) of the half-time for equilibration between the blood and effect site concentrations of the drug being infused, in the absence of a change in target setting.

   To describe steady state conditions, error can be expressed as the absolute difference above or below the target or as a percentage of the target value. Consideration could be given to cumulative error over time (average error) or squared error over time. Both will depend on the set point; the former is insensitive to outliers, whereas the latter is sensitive to outliers but may provide results that are more difficult to interpret. Data from individual patients will need to be combined to describe performance in a population.
4. Clinical Studies Required To Gain Regulatory Approval
   This group, led by Wolfgang Friesdorf, M.D., Berlin, Germany, indicated that within Europe, procedures to evaluate and approve new medical devices are discussed in a European Directive (93/42/EEC). Certain essential requirements in relation to safety and performance are specified, and compliance with these requirements is assessed by approved Notified Bodies. Within the United States, medical devices are evaluated by the Food and Drug Administration's Center for Devices and Radiological Health. The clinical studies required will depend on the claims made for the system. Studies will need to show that the system meets designated performance criteria and is fit for the purpose claimed. Risk analysis and simulation of hypothetical situations should evaluate the consequences of failure of any component of the system, ensure that the system is fail-safe, and provide guidance to users in the event of any particular failure.
5. Formats Envisaged for Commercial Systems
   Gavin Kenny and his group considered that the development of commercial systems would require that pharmaceutical, monitoring, and pump companies work together with control algorithm designers. Some form of partnership will probably be necessary. Considerations of format will need to balance the cost benefits of integrating existing units (*e.g.*, approved monitors, pumps, and so forth) with the potential safety benefits of a discrete stand-alone system.

What Are the Next Steps?

Applications that could be considered now are feedback control of neuromuscular blockade, blood pressure, and end-tidal concentrations of inhalational agents. The future may bring an opportunity for systems that can control depth of anesthesia and sedation, but further validation of EEG indices of depth of anesthesia and sedation, and the influence on these of analgesic drugs, will be necessary. A more detailed system-ergonomic analysis would be useful to identify those clinical situations in which feedback control could be of real benefit.

J. B. (Iain) Glen, Ph.D.
Clinical Specialist
Zeneca Pharmaceuticals
Alderley Park, Macclesfield
United Kingdom
Helmut Schwilden, M.D., Ph.D.
Professor of Experimental Anesthesiology
University of Erlangen-Nurnberg
Erlangen, Germany
Donald R. Stanski, M.D.
Professor of Anesthesia and Medicine (Clinical Pharmacology)
Stanford University School of Medicine
Stanford, California

(Accepted for publication April 29, 1999.)