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Pharmacokinetic and Pharmacodynamic Modeling for Optimizing Analgesic and Anesthetic Delivery (3-Dec-2002)

S. Kern

University of Utah, Salt Lake City, UT, USA.

My research is centered in pharmacokinetic and pharmacodynamic analysis, with specific application to analgesic and anesthetic agents. This focus is motivated by the clinical need to optimize drug delivery so that effective doses of these agents are administered and side-effects from overdosage are minimized. My current research compares the kinetics and dynamics of agents during normal and pathophysiologic conditions and also in clinical situations where coadministration with other agents can alter the kinetics and dynamics of each drug.

A primary tool used in my research is a pharmacokinetic-based computer controlled drug delivery systems that maintain a targeted concentration of drug in plasma or at the biophase during an experiment. These systems, considered open loop because no feedback from the subject is available, can rapidly achieve a target concentration of drug in a subject and maintain that concentration for the duration desired. This provides a way to concentration "clamp" an experiment in either humans or animals, which can be critical for determining pharmacodynamic relationships.

By adding a pharmacodynamic (PD) model to a computer controlled drug delivery system, a means to maintain a specified level of drug effect has been developed. The system uses small bolus doses of drug to maintain the level of drug effect within a user specified range. It adjusts the magnitude of the bolus dose and the interval between doses by both pharmacokinetic and pharmacodynamic characteristics of the particular drug. In essence, it creates an approximation to an exponentially changing continuous infusion by combining multiple small bolus doses together. An advantage to this approach is that it creates a simple means to provide PK/PD based drug delivery. It also provides a means to input a repeated perturbation into the pharmacological system, which can aid in parameter adaptation for closed loop drug delivery applications. Using measured drug effect as feedback, this PD model-based method has been incorporated into a closed-loop system for administering muscle relaxants during surgery. While there has been interest in applying this method towards the delivery of analgesics, its use is complicated by the lack of a specific physiologic indicator to adapt a model and titrate analgesics during anesthesia and surgical procedures. We are investigating the role, if any, that the electroencephalogram can be used to monitor changing levels of anesthetic and analgesic agents administered during anesthesia.

A challenge to using the electroencephalogram for indicating analgesic or anesthetic effect is that there are non-unique changes that occur with this signal in response to increasing amounts of either of these agents. As well, analgesics have their effects throughout the CNS and spinal cord thus monitoring only the terminal end of this system (the brain) presents a challenge to "see" the effects of analgesia present at the level of the spinal cord. We are exploring the use of non-linear entropy methods to extract additional information from the EEG during changes in analgesic and anesthetic levels. These entropy measures compare changes in the time series of raw EEG data to determine qualities about the system which is generating the data. As such, they have potential to impart information about changes in CNS state from a baseline condition. We evaluated EEG data that was gathered in a study to assess the impact of a 10 minute infusion of remifentanil in swine. When this data was analyzed using approximate entropy (ApEn), all animals evaluated showed a significant decrease in EEG ApEn levels which followed increasing concentrations of both the analgesic remifentanil and the anesthetic propofol.

In studies with human volunteers, our group has quantified the interaction between the opioid analgesic remifentanil and intravenous anesthetic propofol over the complete clinical dosing range of these two compounds. In this research, computer-controlled infusions of the anesthetic and the analgesic were administered to volunteers to create pseudo steady-state plateaus of drug concentration. At each plateau, the subjects were administered a series of surrogate stimuli whose intensities correlate

with intraoperative stimuli ranging from loss of consciousness to laryngoscopy. Using this study paradigm, characterization of the complete pharmacodynamic interaction surface can be done for these agents in a manner that could not be achieved easily in the operating room. Response surface maps for anesthetics and analgesics have been determined that define the degree of synergism present from their interaction. The surfaces can be used to optimize drug combination for a variety of outcomes of interest and to investigate the relationship between the interaction surface shapes and mechanism of drug interaction.

Pharmacodynamic models are typically defined by functions that do not vary with time. The exception to this is the series of indirect effect models that have been defined by Jusko and colleagues for pharmacodynamic relationships that alter an endogenous compound. Our lab group is investigating the use of a pharmacokinetic model of a drug and its metabolite formation that is linked to an interaction pharmacodynamic model to describe the kinetics and dynamics of morphine. Morphine, like many opioid analgesics, is metabolized to a pharmacologically active and an inactive metabolite which can both compete with the parent drug for opioid receptor binding. Formation of the metabolite varies among individuals and how much the metabolite variation contributes to variability in pain relief due to synergism or antagonism has not been explored in detail. Using a preliminary set of data from four different groups of elderly volunteer subjects who show different levels of metabolite formation for the same dose of morphine, we are beginning to investigate this question using a linked kinetic and interaction dynamic model. It is anticipated that this model will be applicable to many other pharmacologic agents and can be helpful in characterizing drug interactions that occur for pharmacokinetic reasons (e.g. altered P450 enzymes, protein binding) from those that occur due to pharmacodynamic reasons (e.g. different agents producing the same effect).

The long-term plan for this research is to integrate understanding of biological chemistry, molecular biology, pharmaceutical chemistry and pathophysiology into the structure of pharmacokinetic and pharmacodynamic models. The current model systems my group is investigating represent first steps in expanding the complexity and, hopefully, applicability of linked pharmacokinetic and pharmacodynamic models towards this longer-term goal.

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