Pharmacokinetic-Based Minibolus Delivery as an Alternative to Continuous Infusion for Drugs That Exhibit a Biophase Lag

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The presence of a biophase compartment in a pharmacokinetic model indicates that the response to an administered dose of drug is damped such that the time to peak effect occurs after the peak concentration in the bloodstream. This phenomenon, which is common to most intravenous anesthetic agents, can be exploited by a drug delivery method that administers minibolus doses of drug rather than a continuous infusion. Through analysis of the frequency response behavior of the biophase compartment, a bolus magnitude and dose frequency or interval (1/frequency) can be chosen such that the oscillation in drug effect is minimized even though the plasma concentration may be changing significantly with each supplemental dose. A pharmacokinetic and pharmacodynamic based method for calculating the bolus dose size and dosing interval is presented. The trade-off between dose interval and change in drug effect is exemplified through computer simulation of this strategy applied to delivery of the neuromuscular blocking agent pancuronium. The method provides a repetitive perturbation to the pharmacokinetic and pharmacodynamic system that can aid in model parameter identification during closed loop applications.

KEY WORDS: pharmacokinetics; pharmacodynamics; frequency response; biophase models; infusion pumps.

INTRODUCTION

Pharmacokinetic-based computer-controlled infusion pumps are popular clinical research tools used for administering intravenous agents during anesthesia. These systems use a multicompartiment model of the drug's distribution and elimination to determine an infusion profile that maintains a constant concentration of drug in the bloodstream or at the site of drug effect. Published studies have documented the ability of this technique to

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maintain relatively constant concentrations of drugs during intraoperative procedures even though often the maintained concentration level differs from the target value (1,2). This difference is due to interpatient variability in the pharmacokinetic (PK) parameters but may also be affected by variability in pump delivery and drug assay technique.

Many intravenous agents do not act primarily in the bloodstream but instead exhibit behavior characteristic of a distinct biophase. After an administered dose, these agents show a delay between the occurrence of the peak concentration of drug in the bloodstream and the time to peak effect achieved from that dose. Due to this delay, the change in drug concentration that occurs in the biophase is damped with respect to the change in concentration that occurs in the bloodstream with each dose. This damping can be exploited to create a simplified drug administration strategy that uses small bolus doses rather than continuous infusions to produce a delivery profile based on the pharmacokinetics and pharmacodynamics of the agent being given. In essence, this bolus delivery profile becomes a discrete approximation to the continuous infusion profile necessary to maintain the desired PK goal.

For many intravenous agents, the pharmacologic consequence of giving small bolus doses instead of a continuous infusion are minimal. Depending on the pharmacokinetic characteristics of the particular agent, relatively small changes in biophase concentration occur for significantly larger changes in plasma concentration. In addition, creating a delivery profile with small boluses instead of a frequently changing infusion rate may decrease error in drug delivery by the computer-controlled infusion pump. The delivery profile necessary to maintain a constant concentration of drug in the plasma may require changing the pump infusion rate at frequent intervals (4–10 times per min). This can present a problem for certain types of infusion pumps if they exhibit a delay before the pump delivery equals the desired rate. When the pump rate is changed frequently relative to this delay (called the rise time), the delivery from the pump can underdose with respect to the desired delivery profile. Over time, this can accumulate to produce a significant underinfusion error during computer control if the pump does not report this volumetric error to the computer (3).

In this article, a minibolus strategy is developed for a computer-controlled delivery method that uses a pharmacokinetic and pharmacodynamic model to estimate the drug concentration in the biophase and, consequently, the theoretical drug effect. The strategy establishes a minimum level of drug effect and then determines minibolus doses necessary to keep the drug effect within an allowable range above the minimum. This range determines how much the drug effect can change with each minibolus dose and consequently determines the magnitude and frequency at which the minibolus doses are delivered.