TARGETING THE EFFECT SITE WITH A
COMPUTER CONTROLLED INFUSION PUMP

Steven L. Shafer
Department of Anesthesia
Stanford University School of Medicine
and
Palo Alto Veterans Administration Medical Center

ABSTRACT

Over the last decade computer controlled infusions have been used to rapidly achieve and maintain constant plasma drug concentrations for drugs having pharmacokinetics characterized by polyexponential disposition functions. For most drugs the plasma is not the site of drug effect. Thus, targeting the plasma drug concentration may not be a rational approach to optimal drug therapy. Drawing on previously described effect site models, an algorithm is developed for computer controlled infusion pumps to target the apparent concentration at the site of drug effect, rather than the concentration in the plasma. Simulations are based on the pharmacokinetics and plasma-effect site equilibration delay that have been reported for fentanyl, an intravenous opioid commonly used in anesthetic practice.

INTRODUCTION

The pharmacokinetics of many intravenous drugs used in anesthesia are described by a three compartment mammillary model, as shown in Fig. 1. Drug is administered into and eliminated from the central compartment. The central compartment is also the site of blood sampling. Drug is also transferred from the central compartment into rapid and slow distributional compartments. Based on preliminary work by Krüger-Thiemer [1], Schwilden described a general method of rapidly reaching and maintaining a constant plasma drugs concentration for drug described by multicomartment mammillary models [2]. Many research groups have incorporated this linear model into computer controlled infusion pumps (CCIP) using a variety of algorithms to maintain steady plasma drug concentrations [3,4,5,6,7].

Figure 2 shows a simulated anesthetic course using a computer controlled infusion of fentanyl, a synthetic opioid, based on the pharmacokinetic parameters reported by Scott and Stanski [8]. Following induction of anesthesia with an intravenous hypnotic (e.g., thiopental), the desired fentanyl concentration to be maintained by the CCIP is set by the anesthesiologist at 6 ng/ml for endotracheal intubation, which is the most stimulating part of the anesthetic. Following intubation, the target concentration is decreased to 3 ng/ml, and then to 2.5 ng/ml. The target concentration is increased to 4 ng/ml immediately prior to incision in anticipation of
the increased stimulation. Over the course of the surgery the target plasma fentanyl concentration is titrated downwards, based on patient responsiveness, to a concentration of 2 ng/ml. With the increased stimulation of skin closure, the fentanyl concentration is briefly increased to 2.5 ng/ml. Following skin closure, the infusion is terminated and the patient awakens from anesthesia.

Titrating an infusion to the plasma concentration, as shown in Fig. 2, is irrational for most of the drugs used in anesthesia because the plasma is not the site of drug effect. Sheiner et al. [9] and Hull et al. [10] independently proposed that the three compartment model be modified for drugs whose site of action is not the plasma by the addition of an effect compartment, as shown in Fig. 3. The effect compartment is postulated to have negligible volume, so it does not influence the pharmacokinetic model. The effect compartment model allows parametric characterization of the hysteresis between drug administration and drug effect. This hysteresis has been measured for many intravenous anesthetics. For fentanyl, the half-time of equilibration between the plasma and the site of drug effect is about 6 minutes [11]. Since the concentration at the site of drug effect cannot be measured directly, the concentration at the site of drug effect is expressed as the apparent concentration, which is the plasma concentration at steady state which would produce the same degree of drug effect.

Figure 4 shows the apparent fentanyl concentration at the site of drug effect produced by the dosing regimen from Fig. 2. The precise increases and decreases in

---

**Fig. 1.** Three compartment (i.e., triexponential) mammillary pharmacokinetic model.

**Fig. 2.** Simulated plasma fentanyl concentration over time produced by a CCIP for a brief surgical procedure.