HIGHLIGHTS

Effect of Infusion Rate on Thiopental Dose-Response Relationships: Assessment of a Pharmacokinetic-Pharmacodynamic Model

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CRITICS claim that pharmacokinetic and pharmacodynamic studies are clinically meaningless. Usually, they are correct. Traditional pharmacokinetic-pharmacodynamic studies conclude with two sets of mathematical equations: one set relating dose to plasma concentration and the other relating plasma concentration to drug effect. The mathematical model sits at the terminus of the manuscript like an ancient glyph on a stone altar: mystic, unfathomable, and of no practical use.

In the last few years, investigators and clinicians have used computers to crack the glyphs. Pharmacokinetic-pharmacodynamic models are now used by computer-controlled infusion pumps to instantaneously achieve, and then maintain, any desired drug effect. Computer simulations using pharmacokinetic-pharmacodynamic models are used to construct specific dosing guidelines and to help clinicians understand the clinical relevance of pharmacokinetic-pharmacodynamic concepts.

In this issue of ANESTHESIOLOGY, Gentry *et al.* (page 316) use a pharmacokinetic-pharmacodynamic model to investigate the relationship between thiopental infusion rate, thiopental dose requirement, and a clinical endpoint (loss of consciousness). The authors demonstrate that two different pharmacokinetic-pharmacodynamic models, constructed from very different data, predict with remarkable accuracy the total dose required to induce unconsciousness. In doing so, the authors show how a simple "dose to effect" study is absolutely uninterpretable without pharmacokinetic-pharmacodynamic models, because the thiopental dose required to induce unconsciousness depends on the infusion rate. At either very rapid or very slow infusion rates, the thiopental dose to induce unconsciousness rises toward infinity. At intermediate infusion rates, the dose required to induce unconsciousness agrees with the doses used in clinical practice.

The message is that pharmacokinetic-pharmacodynamic models work. Two models that might superficially have been considered irreconcilably different produced nearly identical clinical predictions, and those predictions have been verified. The two pharmacokinetic-pharmacodynamic models for thiopental revealed an inherent but masked similarity. The authors' analyses show how small differences in study design (*e.g.,* infusion rate) may produce big differences in the apparent dose *versus* response relationship in "dose to effect" studies. The models even help explain why an intravenous technique that always works for one clinician may fail in the hands of another.

Thus, the work by Gentry *et al.* represents another milestone in the evolution of pharmacokinetic-pharmacodynamic research, as we move from an endpoint of cryptic glyphs to a new goal of using pharmacokinetic-pharmacodynamic models to develop practical insights into the clinical pharmacology of anesthetic drugs.

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A Prospective, Randomized, Double-blind Comparison of Epidural and Intravenous Sufentanil Infusions

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WHETHER there is any clinical benefit to epidural *versus* intravenous administration of lipid-soluble opioids remains controversial. To examine this issue, Miguel *et al.* (page 346) infused sufentanil epidurally or intravenously, with placebo control by the other route, in postoperative patients. They avoided having to make assumptions as to the relative potency of sufentanil by these two routes by giving the *same* infusion rate by either route and comparing the amount of patient-controlled intravenous morphine used by the patient to

determine whether epidural administration was more effective than intravenous administration. As might be expected with this design, they found identical plasma concentrations of sufentanil regardless of route of injection, because the same dose was being infused by either route, and they found identical pain scores regardless of route of injection, because the sufentanil infusion rates were low, and patients used patient-controlled intravenous morphine to achieve the same degree of analgesia. The groups did not differ in a meaningful way in morphine use, sedation, or nausea, although more patients were withdrawn in the intravenous sufentanil group because of excessive sedation. The authors properly conclude that, using this design, there is no clinical benefit to administering sufentanil epidurally *versus* intravenously.

This study highlights two factors important in the growing number of studies examining the relative efficacy of lipophilic opioids by the epidural route. *First,* it adds to the preponderance of literature suggesting that differences in efficacy and side effects between epidural and intravenous administration of lipophilic opioids are small in magnitude. Meaningful additions to our understanding of this controversy therefore will require examination of a large number of patients, with proper power analysis during study design to determine appropriate sample size. *Second,* this well designed study demonstrates a basic design factor that should be included in future investigations of this controversy: Either full-dose responses should be obtained with drug by each route, their precise equivalent potencies by each route known in advance, or equivalent doses should be administered by each route, with alternative, "rescue" medication administered as a primary endpoint.

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