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Half-time or Half-life

What Matters for Recovery from Intravenous Anesthesia?

Peter S. A. Glass, M.B., Ch.B., F.F.A.(S.A.)*

Context-sensitive Half-time in Multicompartment Pharmacokinetic Models for Intravenous Anesthetic Drugs. By Michael A. Hughes, Peter S. A. Glass, and James R. Jacobs. ANESTHESIOLOGY 1992; 76:334–41. Reprinted with permission.

Abstract: Elimination half-life is the pharmacokinetic parameter used most commonly to describe duration of pharmacologic action, including that expected of intravenous anesthetic drugs administered by continuous infusion. Little consideration has been given, however, to the relevance of elimination half-life in describing plasma (central compartment) drug concentrations in the context of relevant infusion durations. Therefore, simulations were performed with multicompartment pharmacokinetic models for six intravenous anesthetic drugs. These models had elimination half-lives ranging from 111 to 577 min. The input in each simulation was in infusion regimen designed to maintain a constant plasma drug concentration for durations ranging from 1 min to 8 h and until steady state. The time required for the plasma drug concentration to decrease by 50% after terminating each infusion in each of the models was determined and was designated the "context-sensitive half-time," where "context" refers to infusion duration. The context-sensitive half-times were markedly different from their respective elimination half-lives and ranged from 1 to 306 min. The half-times were explained by posing each pharmacokinetic model in the form of a hydraulic model. These simulations demonstrate that elimination half-life is of no value in characterizing disposition of intravenous anesthetic drugs during dosing periods relevant to anesthesia. We propose that context-sensitive half-times are a useful descriptor of postinfusion central compartment kinetics.

DETERMINING the implication of the interplay between various pharmacokinetic components to explain the offset of drug effect as opposed to the much held assumption that this was related only to elimination half-life lead our group at Duke University (Durham, North Carolina) to coin the term context-sensitive half-time.[1] Developing a simple understanding of the implications of pharmacokinetics became an important goal of my research when I teamed up

* Professor of Anesthesiology, Department of Anesthesia, State University of New York, Stony Brook, New York.

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Address correspondence to Dr. Glass: Department of Anesthesia, Level 4, Room 060, Health Sciences Center, SUNY, Stony Brook, New York 11794-8480. peter.glass@stonybrook.edu.

Fig. 1. The present computer-assisted continuous infusion system used at Duke University Medical Center. It consists of a laptop computer electronically linked to an infusion pump. The desired drug plasma or effect-site concentration is entered using the keyboard. Reprinted with permission from Glass PSA, Shafer SL, Jacobs JR, Reves JG: Intravenous drug delivery systems, Anesthesia, 4th edition. Edited by Miller R. New York, Churchill Livingstone Publishers, 1994, pp 389–416.

with Dr. Jerry Reves, M.D. (Professor and Chair, Department of Anesthesia, Duke University), and his postgraduate student, James R. Jacobs (B.Sc.).

On first arriving at Duke in 1984, I had indicated to the then Chairman, David Watkins, M.D., Ph.D., my interest in clinical research. At this time, alfentanil had just been released and Johnson & Johnson (New Brunswick, NJ) was undertaking, as part of their launch of the compound, a series of phase 4 studies. Dr. Watkins was kind enough to pass on an invitation to participate in these studies. These postmarketing studies consisted of a variety of protocols, one of which was the maintenance of anesthesia by alfentanil as part of a nitrous narcotic technique.[2] Dr. Reves had started at Duke just a few weeks before me. He heard that I had attended the investigator meeting for the use of alfentanil and began to discuss with me the value of using a device he and Michael J. Alvis (a bioengineering student at the University of Alabama, Birmingham, Alabama) had developed, computer-assisted continuous infusion (fig. 1), to administer an Intravenous drug to a desired concentration, rather than by dose. Dr. Reves had been exposed to a similar device developed by Schuttler *et al.*[3–5] on a visit to their department in Bonn, Germany. Fascinated by the logic of such a device, he worked with Mike Alvis as part of his graduate studies to develop a similar device.[6,7] On moving from the University of Alabama-Birmingham to Duke, Dr. Reves had brought with him a bioengineer, James R. Jacobs, Ph.D., who had worked with Mike Alvis and was doing his postgraduate thesis at Duke. Soon after arriving at Duke, the first use of computer-assisted continuous infusion by Dr. Reves' group at Alabama was published.[6,7] It was soon discovered that there had been a programming error in the device. Jim Jacobs was asked by Dr. Reves to rewrite the program so as to fix the error. As I was to use the device for the alfentanil protocol, I was introduced to Jim, and this started a wonderful collaboration between Jim, Jerry, and myself.

The administration of Intravenous drugs using a target-controlled infusion (TCI) system at this time was limited. The obvious question in proceeding with the alfentanil protocol was what plasma concentrations (rather than dose) would be appropriate. Fortunately, the therapeutic plasma concentrations for alfentanil had been published but not for the majority of Intravenous drugs used for anesthesia. Thus, my interest was piqued in trying to determine appropriate concentrations for fentanyl during anesthesia. Soon after the alfentanil protocol, a protocol was initiated using fentanyl.[8] The original computer-assisted continuous infusion device contained a graphic of the estimated concentration in each

compartment (central and theoretical peripheral compartments). While doing these two protocols, I began to observe that for both drugs, there was an initial rapid decrease in the central compartment concentration and then this would slow down. The initial decrease was more prominent with fentanyl than with alfentanil, especially for shorter cases. It also became obvious to me that the actual time taken for the concentration to decrease by 50% was different to the elimination half-life. This began a review of the literature and a discussion within our group on the implications of these observations. Dr. Reves pointed out the classic article by Riegelman *et al.*[9] showing how patients recover from a single dose of thiopental much more rapidly than would be predicted by their elimination half-life and that redistribution plays an important role in enabling this to occur. In fact, as we described in the original article, elimination half-life only represents drug offset in a one-compartment model. All the Intravenous drugs used for anesthesia have multicompartmental models, thus negating the clinical value of the elimination half-life as a measure of the offset of drug concentration. In fact, these concepts of the role of redistribution and elimination in drug offset were well recognized in classic pharmacology texts, but their clinical implication had not been emphasized, probably because the use of infusions in clinical medicine at the time was rare, drug offset was not observed or of clinical importance. This clearly contrasts with the administration of Intravenous anesthetics.

Soon after the first publication of computer-assisted continuous infusion,[6,7] we became aware that Steven Shafer, M.D., who was working in the laboratory of Donald Stanski, M.D., Ph.D., at Stanford University (Palo Alto, California) had developed his own TCI device that he called Stanpump.[10] In fact, both groups on the east and west coast were starting to do similar work: optimizing software programming for such devices, inclusion of an effect compartment into the models, and defining optimal pharmacokinetic models for drugs that could be used in a TCI device. These common interests led to the groups agreeing to meet at Stanford University in 1991 to develop common nomenclature and share ideas. During this meeting, among many other topics, the observation that a decrease of 50% in drug concentration was not solely related to the elimination half-life of the drug was discussed. Dr. Shafer had already begun to lecture on the differences between alfentanil, sufentanil, and fentanyl, pointing out their relative onset and offset times, with alfentanil having the fastest onset but not necessarily the fastest offset, although it had the shortest elimination half-life.[11] Rather, sufentanil had the shortest duration of effect especially for shorter procedures. The concept that offset of drug effect, as well as a decrease in drug concentration, was not only due to the elimination half-life of the drug had already been pointed out by Schwilden *et al.*[5] in one of their first descriptions of their TCI device and by Fisher and Rosen[12] to explain the phenomena of cumulative effect of neuromuscular blockers. However, our group believed that

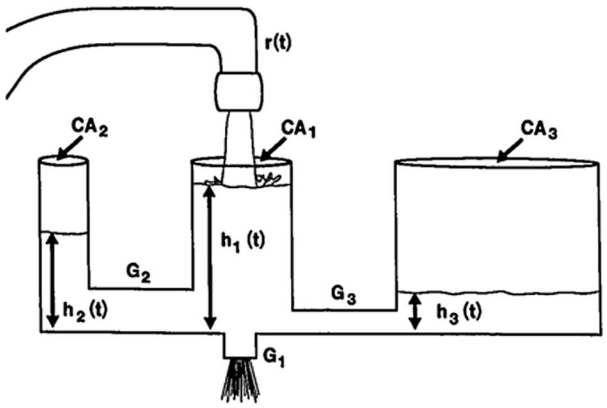

Fig. 2. Hydraulic model analogy to three-compartment pharmacokinetic model. The height, $h_1(5)$, of the water level in the ith bucket is analogous to the drug concentration in the ith compartment. Each bucket is characterized by a cylindrical area, CA_1, and the pipes connecting the buckets with each other or the outside world are characterized by a conductance, G_1. Water enters bucket 1 at the rate r(t) and leaks irreversibly through G_1. Reprinted with persmission from Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. ANESTHESIOLOGY 1992; 76:334–41.

no article had clearly explained why elimination half-life and offset were not the same.

Soon after the Stanford meeting, ANESTHESIOLOGY published the article "Pharmacokinetics, Pharmacodynamics, and Rational Opioid Selection" by Shafer and Varvel.[11] This manuscript explained the differences between these drugs based on their pharmacokinetics and began to explain the relative roles of distribution and elimination in determining offset of drug effect. Before publication of this article, Michael Hughes, a bioengineering student, had begun working with Jim Jacobs. Mike had been given the task of modeling the decrease in drug concentration for all the Intravenous anesthetic drugs that we had appropriate pharmacokinetics for. What I wanted to show was that the rate of decrease changed over time as peripheral compartments filled, and the decrease in the central compartment concentration slowed as it became more dependent on elimination. Or stated in reverse, central compartment (blood or plasma) concentrations decrease more rapidly after brief periods of administration primarily because of redistribution and then decrease more slowly as the peripheral compartments fill, and any decrease becomes more and more dependent on the elimination half-life. Jim Jacobs coined the term "context-sensitive half-time." The term "context sensitive" was becoming popular in computer verbiage, and we wanted to distinguish this concept from elimination half-life by calling it "half-time." The concept (fig. 2) and graphs illustrating this (fig. 3) were originally presented at a small seminar at Duke. It was apparent that what was presented helped individuals better understand the importance of modeling each drug to determine offset *versus* elimination half-life. The article, when completed, was shared with Dr. Reves who helped to further refine it. Steve Shafer was a reviewer who also played an important role in the final publication. In addition, he and

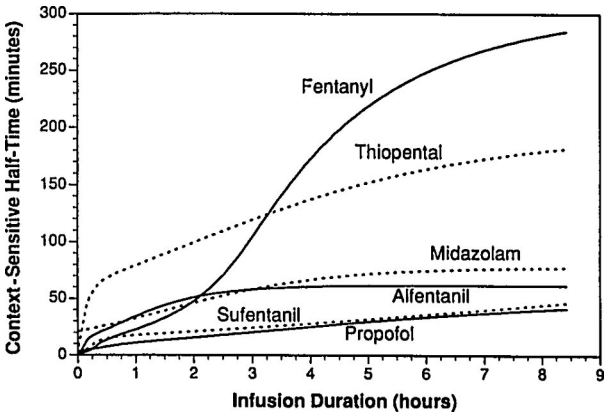

Fig. 3. Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. *Solid* and *dashed line* patterns are used only to permit overlapping lines to be distinguished. Reprinted with permission from Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. ANESTHESIOLOGY 1992; 76: 334–41.

Dr. Stanski published an accompanying editorial in which they further clarified the importance of computer modeling in predicting drug effect using the drug duzital.[13] In essence, the concept of context-sensitive half-time allowed the practicing anesthesia provider to gain a much better understanding of the effect of time and dosing with an Intravenous drug infusion on the time required for recovery (wake up) when the infusion was stopped.

The acceptance of the terminology context-sensitive half-time and its importance in understanding Intravenous drug delivery grew rapidly. The Food and Drug Administration incorporated this nomenclature in the package insert for propofol soon after our article was published. Virtually, all new Intravenous hypnotics or analgesics now define their context-sensitive half-time early on in development, thereby improving the understanding of how the drug can be used as a continuous infusion. The concept presented in our article facilitated the understanding of an important principle of Intravenous anesthesia for the every day anesthesiologist and probably helped to popularize the use of total Intravenous anesthesia as a standard anesthetic technique.

This was an exciting time in the development of Intravenous anesthesia. Several groups were working on or developing concepts such as the biophase, effect compartment modeling, time-to-peak effect, the evolution of TCI anesthesia, the evaluation of pharmacokinetics and dynamics of each drug, drug interactions in providing anesthesia, and the ability to actually measure the hypnotic component of the anesthetic state. It was truly a privilege to be part of such a vibrant group of investigators who contributed to ultimately making Intravenous anesthesia part of the daily routine of clinical anesthesia practice.

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