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EDITORIAL VIEWS

Alfentanil—A Kinetically Predictable Narcotic Analgesic

ALFENTANIL is a new fentanyl analog with a distinctly shorter duration of action than fentanyl. In this issue, Bovill *et al.*[1] describe the pharmacokinetics of alfentanil and provide a basis for understanding some of the differences between alfentanil and fentanyl. Let us explore these differences along with their implications for the use of this new narcotic analgesic in anesthesia.

The more important pharmacokinetic and physiochemical properties of fentanyl and alfentanil are shown in table 1. Fentanyl is eliminated from the body almost exclusively by hepatic metabolism.[2] The liver is relatively efficient at metabolizing fentanyl since 60–80% of the fentanyl is removed from the blood passing through the liver. Fentanyl's extensive hepatic extraction results in a clearance of 10–15 $ml \cdot kg^{-1} \cdot min^{-1}$ that approaches hepatic blood flow (18–21 $ml \cdot kg^{-1} \cdot min^{-1}$). (The high clearance of fentanyl is similar to that of other narcotic analgesics.[3,4]) Because the terminal elimination half-life of a drug is directly proportional to the volume of distribution and inversely proportional to clearance, fentanyl's relatively long terminal elimination half-life is secondary to its large volume of distribution, which results in low blood concentrations that limit the amount of fentanyl in the body delivered to and removed by the liver per unit time.

Because fentanyl has a relatively long terminal elimination half-life, its short duration of narcotic effect after a single dose cannot be due only to its elimination from the body. Fentanyl is highly lipid soluble and readily traverses the blood-brain barrier. High brain concentrations occur soon after a single intravenous dose and then decrease rapidly due to the redistribution of fentanyl to muscle and fat, analogous to thiopental.[5] After very large doses or multiple smaller doses of fentanyl, the redistribution mechanism becomes less effective in lowering the brain and plasma concentrations below the threshold for analgesia and respiratory depression.[2,6,7] Under these circumstances, the duration of fentanyl's narcotic effect is no longer short because the decline of blood and brain concentrations is dependent upon the slow elimination half-life. As the fentanyl dose is increased, the duration of narcotic effect will also increase; thus, it becomes more difficult for the anesthesiologist to judge the duration of fentanyl's effect.

If the main mechanism of terminating the action of a drug is its elimination from the body instead of redistribution, it is possible to obtain greater predictability between the administered dose and duration of effect. An example is the short and generally predictable duration of paralysis produced by succinylcholine which has an elimination half-life of 4.5 min.[8] Given a high clearance drug like fentanyl, the only mechanism to shorten the terminal elimination half-life is to decrease the volume of distribution. A smaller volume of distribution results in higher plasma concentrations making more of the drug in the body available to the liver for elimination. In this issue of the Journal Bovill *et al.*[1] have shown that distribution volume of alfentanil is approximately four times smaller, and its clearance is two times smaller than that of fentanyl. The greater decrease of alfentanil's distribution volume relative to the decrease in its clearance results in a significantly shorter terminal elimination half-life. The lower lipid solubility of alfentanil limits its penetration into cells (*e.g.*, red blood cells, see table 1) and tissues such as muscle and fat; this probably explains its smaller volume of distribution. Decreased lipid solubility also will limit its penetration of the blood-brain barrier. Tissue distribution studies in animals revealed that brain concentrations of fentanyl exceeded those in plasma by a factor of 3 to

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TABLE 1. Pharmacokinetic and Physiocochemical Properties of Fentanyl and Alfentanil

Property	Fentanyl[2]	Alfentanil[1]
Elimination half-life (h)	3.7 ± 0.4†	1.6 ± 0.3†
Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	11.6 ± 2.6	6.4 ± 4.6
Vdss* (l/kg)	4.2 ± 0.6	0.86 ± 0.62
Per cent of dose in urine		
Unchanged drug	6.5	1% in dogs and rats‡
Metabolites	69	75% in dogs and rats‡
Free fraction in plasma (%)[16]	16	8
pK_a[16]	8.4	6.5
Per cent unionized at *p*H 7.4	9	89
Octanol: Water partition coefficient at *p*H 7.4[16]	860	130
Red blood cell/plasma concentration ratio[16]	0.92	0.12

* Vdss = Volume of distribution at steady state.

† Means ± SD.

‡ Personal communication: Schuermans V, Heykants J: Absorption, distribution, metabolism and excretion of alfentanil in animals. Preclinical Research Report, R 39 209/27, Janssen Pharmaceutica, Beerse, Belgium, March 1982.

5.[5] The opposite was true for alfentanil; the brain concentrations were seven to nine times *lower* than in plasma.* Another factor that may limit the entry of alfentanil into the brain is its higher degree of protein binding relative to fentanyl. Although lower than that of fentanyl, the lipid solubility of alfentanil is still sufficiently high for the unionized form that predominates in plasma (table 1) to permit a rapid onset of action.

The combination of a short terminal elimination half-life and moderate lipid solubility suggest two mechanisms for the termination of alfentanil's narcotic effect. Redistribution of alfentanil from the brain to other tissues most likely occurs. Redistribution to muscle tissue is probably more important than fat given alfentanil's limited ability to enter the latter tissue.* The redistribution mechanism will be most important for a single small dose. The elimination half-life will determine the duration of narcotic effects after a large single bolus dose, multiple small bolus doses, or a continuous infusion. Figures 1 and 2 demonstrate these two mechanisms for fentanyl and alfentanyl. To interpret these figures it is necessary to indicate what *therapeutic* narcotic plasma concentrations are needed for adequate analgesia during anesthesia (with supplemental inhalational anesthetics, usually nitrous oxide) and what *threshold* concentrations are associated with adequate spontaneous ventilation. Presently, there is a very limited amount of information available on therapeutic and threshold narcotic analgesic concentrations, so we have chosen values available from the literature and our own personal experience. Obviously, definitive research will be necessary to accurately define these values.

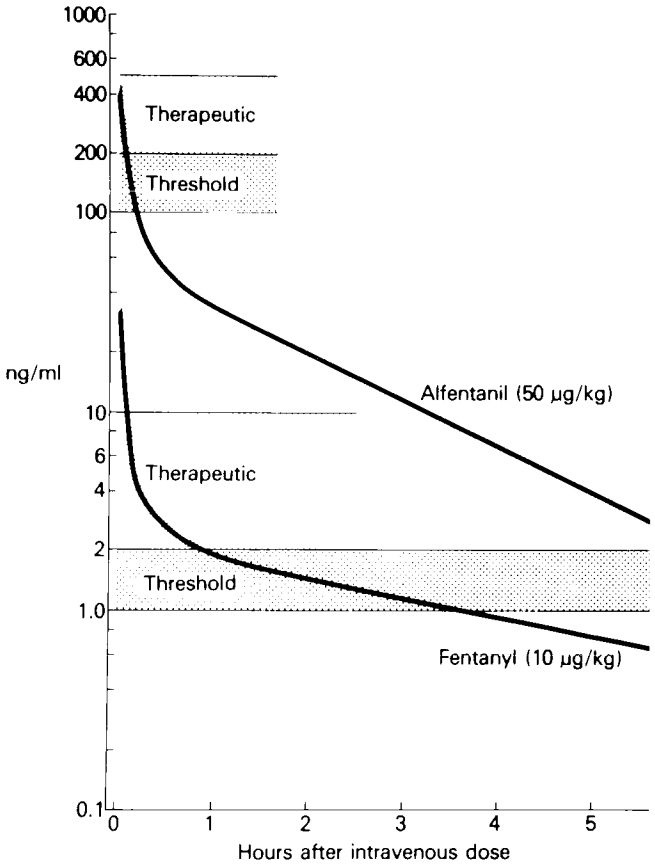

FIG. 1. A comparison of the plasma decay curves of a single iv bolus dose of fentanyl and alfentanil. The solid line is the predicted plasma concentration in a single patient with representative pharmacokinetics. While the equivalent alfentanil dose is five times that of fentanyl, during the first 2 h after injection the alfentanil plasma concentrations are 14 to 25 times higher. This is due in part to the smaller volume of distribution of alfentanil.

The decay of alfentanil and fentanyl concentrations in plasma is depicted in figure 1 for humans given a single intravenous bolus dose approximately one-third of that required to *induce* (not necessarily to maintain) unconsciousness in premedicated surgical patients.[9,10] It is evident that alfentanil concentrations rapidly decline below those that are useful in supplementing inhalational anesthetics for surgical operations (200–500 ng/ml).[1]† It is also evident that alfentanil concentra-

* Personal communication: Michaels M, Hendriks R, Michielsen L, Heykants J, Lenaerts F: Plasma levels and tissue distribution of alfentanil (R39209) in the male Wistar rat after a single intravenous dose of 0.16 mg/kg. Preclinical Research Report R39 209/13, Janssen Pharmaceutica, Beerse, Belgium, January 1981.

† Ausems M, Hug CC Jr, de Lange S: Unpublished observations.

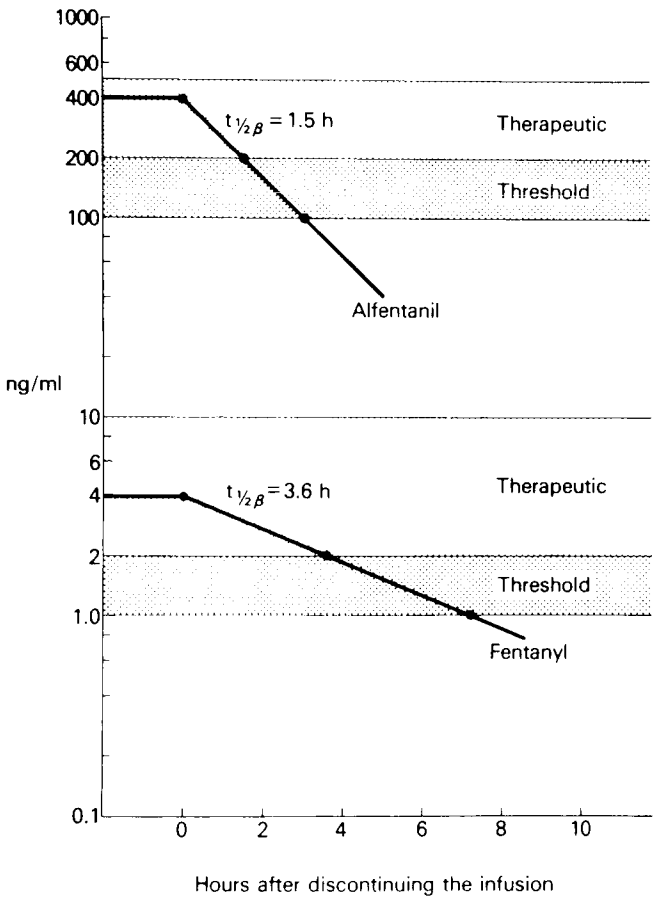

FIG. 2. Assuming that a steady-state plasma level of the narcotic analgesic has been maintained in the effective range (see text), the rate of decline of drug concentrations will be determined by the elimination half-life. In this example, concentrations compatible with satisfactory spontaneous ventilation will be reached in two half-lives: 3 hours for alfentanil and 7.2 hours for fentanyl.

tions compatible with the recovery of spontaneous ventilation (approximately 100–200 ng/ml) are reached within 10 to 20 minutes after its injection. In contrast, fentanyl concentrations useful in supplementing inhalational anesthetics (2–10 ng/ml)[11–13] are maintained for about 1 hour, and their decline to threshold levels for ventilatory depression in unstimulated volunteers (approximately 1–2 ng/ml) can be expected to occur 2 or more hours after the injection.[2]

Alfentanil's pharmacokinetic properties should allow it to be used efficiently in anesthesia for brief surgical procedures as well as for long operations. As suggested by Bovill *et al.*[1] and others,[14] a continuous infusion of alfentanil would be a rational approach to administer the drug. A constant plasma concentration of alfentanil would be expected to produce a stable degree of effect and to minimize the "peak and valley" fluctuations of repeated bolus injections. Termination of the alfentanil infusion should be followed by a rapid dissipation of the effects (providing excessive plasma concentrations have not been produced). Alfentanil's unique pharmacokinetic profile may cause anesthesiologists to develop more rational and efficient methods of administering narcotic analgesics for anesthesia and for the control of postoperative pain.[15]

Numerous questions remain to be answered about the pharmacokinetics and pharmacodynamics of alfentanil. In pharmacokinetic terms, what are the effects of age and various disease states on the distribution and elimination of alfentanil? Does the presence of other drugs and anesthetics alter the pharmacokinetics of alfentanil? Will analytical methods be developed to allow the measurement of alfentanil concentrations rapidly in the operating room and thereby enable the anesthesiologist to monitor and to individualize the administration of this narcotic analgesic?

In regard to pharmacodynamics, what is the nature of the plasma concentration *vs.* response relationship? Most importantly, how does it vary among patients and what factors influence their sensitivity to alfentanil? It can be anticipated that some, if not all, of the factors affecting the MAC of inhalational anesthetics will also influence the concentration requirements of intravenous drugs such as alfentanil. Future research will have to be directed towards these questions.

DONALD R. STANSKI, M.D.
Assistant Professor of Anesthesia and Medicine (Clinical Pharmacology)
Stanford University School of Medicine
Stanford, California 94305
and
CARL C. HUG JR., M.D., PH.D.
Professor of Anesthesiology and Pharmacology
Department of Anesthesiology
Emory University School of Medicine
Atlanta, Georgia 30322
and
Visiting Research Professor
Department of Anesthesiology
University of Leiden
The Netherlands

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