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# Editorial Views

## *Whither Drug Distribution?*

VOLUMES OF DISTRIBUTION exemplify the mathematical precision and physiologic ambiguity of pharmacokinetics. Complex physicochemical and physiologic processes determine the rates and sites of distribution of exogenous substances within the living organism. Characterization and understanding of these processes has always been a difficult undertaking, since tissue concentrations of drugs are not conveniently accessible to repeated measurement. Consequently, our understanding of drug distribution is largely theoretical, being based upon changes in blood, serum, or plasma concentrations over time, rather than actual measurement of quantities of drug in living tissues.

The mathematical theory of drug distribution focuses upon "compartments"—imaginary spaces having fictitious volumes.[1–3] Upon entering such a compartment, a drug is assumed to be very rapidly and homogeneously distributed within it. The most widely applicable pharmacokinetic models assume the body to consist of one, two, or three compartments. A particular drug's "total apparent volume of distribution" ($V_d$) is the sum of the volumes of the individual compartments.

$V_d$ is usually determined from the time-course of blood concentrations following rapid injection of a drug into the vascular system. At least three methods can be used to calculate $V_d$, of which the most appropriate is widely debated at cocktail parties and in the pharmacokinetic literature.[1–5] In fact, all methods of calculation of $V_d$ are mathematically rigorous and viable, and give similar or identical numerical results. On the other hand, no matter how calculated, $V_d$ corresponds to no real anatomic entity, and elucidates none of the processes that determine drug distribution.

Although morphine has been in clinical use for many decades, a sensitive and reliable method for quantitation of nonradioactive morphine in body fluids has only recently been developed.[6–8] The availability of this radioimmunoassay technique has generated interest in the clinical pharmacokinetics of morphine, including its distribution characteristics. Studies of intravenous morphine in man indicate that distribution is very rapid and moderately extensive.[9–11] Yet the limitations of pharmacokinetics leave important questions unanswered: where does morphine distribute? how does morphine distribution relate to its pharmacologic action?

Tempting though it is to base anatomic and physiologic conclusions upon mathematical volumes of distribution, the temptation must be resisted. Physiologic interpretation of volumes of distribution may be not only irrelevant to reality, but in some cases downright wrong. The study of Finck and associates,[12] reported elsewhere in this issue, clearly demonstrates this pitfall. Morphine is a weak organic base having a $p$K of about 7.9. According to classic physicochemical theory, the proportion of unionized ("free" or "lipid-soluble") morphine present in a solution at $p$H 7.4 is greater than that in a solution at $p$H 7.1 to 7.2. Since only the unionized fraction of the total morphine concentration can cross lipoidal biological membranes with ease, the value of $V_d$ for morphine at physiologic $p$H, not surprisingly, is larger than when systemic acidosis exists. Although one can surmise that the overall "extent of tissue distribution" of morphine is therefore decreased by systemic acidosis, no further anatomic or physiologic conclusions are warranted. The decrease in the mathematical value of $V_d$ by no means implies that morphine concentrations are equally decreased in all

tissues, any more than $V_d$ by itself implies a particular pattern of distribution. On the contrary, actual measurement of morphine concentrations in brain—presumably its principal site of analgesic action—revealed an increase rather than a decrease in brain concentrations during acidosis. The "paradoxical" result is probably explained by an increase in cerebral blood flow during hypercarbia that more than offsets the decrease in morphine's lipid solubility.

Volumes of distribution are useful numbers provided their limitations are clearly recognized. They can estimate the proportion of the total amount of a drug that is present in "peripheral" or "tissue" compartments. But volumes of distribution as such do *not* tell us precisely where the drug is and what the individual tissue concentrations are. Only direct analysis of organs and tissues can provide this information.

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## Obstetric Anesthesia

**EPIDURAL ANALGESIA AND TWINS** In this study the effects on mothers and infants of epidural analgesia for labor and delivery of twins were examined. Fourteen women with twins received lumbar epidural analgesia. Maternal radial-artery and umbilical vessel blood-gas and acid–base measurements together with Apgar scores were determined. Resulting values were compared with those of women receiving epidural analgesia for labor and delivery of one infant. Apgar scores and blood-gas values for first twins were virtually the same as those for singleton controls. This small series confirms the problem of second-twin compromise, but this was minimal and was more pronounced in nonvertex presentations, as would be expected. Lumbar epidural analgesia for labor and delivery of twins is recommended, and it appears to be a safe form of analgesia for this situation. (*James FM III, and others: Lumbar epidural analgesia for labor and delivery of twins, Am J Obstet Gynecol 127:176–180, 1977.*)