

tor of total intubation difficulty available to date. As such, it is anticipated that best uses will be to influence patient care and as a research tool to discern significant differences in clinical variables and care. It is very probable that the innovative IDS will inspire further research that is concerned with developing the best IDS and the best use of the IDS.

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Drug Distribution

Less Passive, More Active?

DRUG effects are largely determined by the concentration of drug at the site of action. During the past few years we have come to recognize that there is considerable variation among individuals in their response to similar doses of drug. Some of that interindividual variability is a result of differences in drug sensitivity (pharmacodynamic variability), but a large amount of interindividual variability seen in drug response is a result of variability in drug concentration at the receptor site (pharmacokinetic variability).

In most therapeutic situations and in some anesthetic settings, drugs are administered in multiple doses, most often by the oral route. With such chronic dosing, the important determinant of mean plasma (and hence receptor site) concentration is the drug's clearance, or elimination, from the body. Hence we see the familiar

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Reference

1. Adnet F, Borron SW, Racine SX, Clemessy J, Fournier, Plaisance P, Lapandry C: The Intubation Difficulty Scale (IDS): Proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *ANESTHESIOLOGY* 1997; 87:1290-7

relationship of Cp_{ss} = rate of administration/clearance (where Cp_{ss} is the mean steady state concentration). Thus at steady state, mean plasma drug concentration depends only on the dose (rate of administration) and the drug's clearance. As dose is defined, interindividual variability in steady state plasma drug concentration depends solely on drug clearance. The recognition of the importance of drug clearance as a determinant of plasma drug concentration has led to considerable effort being devoted to defining the factors responsible for interindividual variability in drug clearance. For most lipid-soluble drugs, the principal route by which a drug is eliminated from the body is *via* metabolism by the cytochrome P450 system in the liver. For water-soluble drugs such as digoxin, elimination occurs principally through glomerular filtration. The effects of drug interactions, disease states, and pharmacogenetic factors, and so on on these processes of elimination have been well defined. Inhalational anesthetics themselves inhibit drug metabolism and result in higher drug concentrations, *e.g.*, during halothane anesthesia.¹

However, anesthesiologists frequently do not administer drugs for long enough to reach steady state. On the contrary, they often administer single doses of drugs to produce rapid effects (*e.g.*, induction agents) that dissipate quickly. The principal determinant of drug effect after such a single (usually intravenous) dose is not drug elimination but drug distribution, and drug effect is terminated when drug concentration at the

site of action decreases, not as a result of irreversible elimination from the body as occurs in drug clearance, but because of redistribution from its site of action to other tissues. Thus an understanding of drug distribution and the factors influencing such distribution is of great importance to anesthesiologists.

The fundamental import of the processes of distribution and redistribution were well recognized with highly lipid-soluble induction agents such as thiopental, whose initial, relatively rapid, onset of action is a result of its rapid entry into highly perfused tissues such as the brain, into which, because of its high-lipid solubility, it diffuses rapidly. However other tissues, although more poorly perfused, have a high capacity for drug, and therefore drug will distribute out of the vessel-rich tissues to the more poorly perfused but high-capacity tissues, resulting in termination of drug action.

An understanding of the variables affecting the rapid changes that occur in plasma drug concentrations, and hence concentrations at the effect site, is important for anesthesiologists who seek to understand interindividual variability in response to single bolus injections of the drugs that they use daily in their practice. The paper by Avram² in this issue highlights the interaction of the physiologic effects of halothane on drug distribution. The techniques that the authors use are not new; the three markers used—indocyanine green to measure intravascular space and blood flow, inulin to measure extracellular space and free water diffusion, and antipyrine to measure total body water and tissue perfusion—have been used for these purposes for decades. Although antipyrine became best known to pharmacologists as an index of drug metabolism, its original use was to measure total body water. The authors set out to focus not on the late phase of drug elimination but on the processes that occur very early after drug administration and that determine drug delivery to the vessel-rich tissues such as the heart and central nervous system. It is these very early processes that are important to the clinical anesthesiologist. These processes include mixing, flow, and diffusion. The pharmacokinetic model used by the authors allowed them to quantify the effects of increasing doses of halothane on these processes and to quantify the well-recognized cardiovascular effects of halothane on these distributive processes. The authors have developed a physiologic and pharmacokinetic model to relate pharmacokinetic

changes to changes in cardiac output and halothane concentrations and advanced our understanding of the acute effects of halothane on pharmacokinetics. They have shown that halothane-induced changes in flow affect the early phases of drug distribution and hence drug effect. Thus, during anesthesia induction, when multiple drugs are being administered intravenously in the presence of a volatile agent, the anesthesiologist should expect higher drug concentrations compared with during the awake state.

Readers should not be left with the impression that all drug entry into tissue is a passive process, dependent solely on diffusion or blood flow. Recently, it has become clear that active transporters are responsible for transport of many drugs out of cells. The particular importance to anesthesiologists of the phenomenon is that such transporters may limit drug access to the brain, by pumping drug out of the central nervous system. Perhaps the best studied of these transporters is P-glycoprotein (P-gp), the product of the MDR1 gene.³ Overexpression of P-gp in cancer cells is now recognized as a major cause of the development of resistance to chemotherapy during anticancer treatment. P-gp is a transmembrane glycoprotein that pumps drugs and other toxins out of cells and is but one of a large super family of ATP-binding cassette transport proteins whose ability to pump drugs out of cells and hence control drug entry into tissues and drug distribution is only now being recognized. The importance of P-gp of anesthesiologists may lie in its presence in endothelial cells of the blood-brain barrier and gastrointestinal tract. Inhibition of this transport system occurs with specifically targeted P-gp inhibitors³ and many commonly used drugs such as quinidine and verapamil.³ The P-gp inhibitor will decrease the effectiveness of the P-gp pump, resulting in increased tissue (*e.g.*, brain) concentrations of drug. Are these transporters involved in the transport of anesthetic agents such as intravenous opioids? We do not yet know the answer to this. However one titillating suggestion that they might comes from studies in the MDR knock-out mouse in which the mouse MDR1A gene has been disrupted so that P-gp is not expressed. In such knock-out mice, the oral administration of the antidiarrheal opioid loperamide (Imodium) results in potent opioid central nervous system effects, demonstrating that the usual lack of central nervous system effects of loperamide is a result of P-gp preventing its access to the brain.⁴ Other opioids also appear to be transported by these transporters.⁵ Domperidone and ondansetron are effective antiemetic agents whose lack of major central

nervous system effects also appears to be a result of their being P-gp substrates and hence having limited access to the brain. Thus I predict that improved understanding of the role of drug transporters in controlling drug access to their sites of action (particularly the central nervous system) will be of considerable importance in facilitating rational dosage choice for the non volatile agents used by anesthesiologists during the next few years.

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References

1. Reilly CS, Wood AJJ, Koshajii RP, Wood M: The effect of halothane on drug disposition: Contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. *ANESTHESIOLOGY* 1985; 63:70-6
2. Avram MJ, Krejcie TC, Niemann CU, Klein C, Brooks Gentry W, Shanks CA, Henthorn TK: The effect of halothane on the recirculatory pharmacokinetics of physiological markers. *ANESTHESIOLOGY* 1997; 87:1381-93
3. Pinedo HM, Giaccone G: P-glycoprotein—A marker of cancer-cell behavior [Editorial]. *N Engl J Med* 1995; 333:1417-9
4. Schinkel AH, Wagenaar E, Moi CAAM, van Deemter L: P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. *J Clin Invest* 1996; 7:2517-24
5. Callaghan R, Riordan JR: Synthetic and natural opiates interact with P-glycoprotein in multidrug-resistant cells. *J Biol Chem* 1993; 268:16059-64