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Pharmacokinetics and Pharmacodynamics
During Cardiac Surgery and Cardiopulmonary Bypass
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Introduction

The physiologic trespasses produced by cardiac surgery and cardiopulmonary bypass (CPB) profoundly affect the concentrations of drugs within the body and its ultimate response to these agents. The application of systemic hypothermia precipitates significant changes in regional blood flow and the eventual metabolism and elimination of these compounds. The effects of hypothermia and CPB on drug levels and receptor dynamics will be examined in this chapter, as well as the effects of bypass on individual compounds. To fully grasp the changes produced during cardiac surgery, however, a basic understanding of the principles of pharmacokinetics and pharmacodynamics is imperative.

Basic Principles of Pharmacokinetics and Pharmacodynamics

Drugs introduced into the body must be absorbed and delivered to a target site in order to exert their effect. The study of the way in which the body processes a particular drug, including its eventual metabolism and excretion, is termed pharmacokinetics. Once available at the cellular level, drugs interact with specific membrane receptor sites to initiate a sequence of intracellular events leading to a pharmacologic effect. The study of how an individual drug interacts with a cell to produce this effect is termed pharmacodynamics. Related classes of drugs, such as inotropic agents, share common pharmacokinetic and pharmacodynamic properties. We shall first examine the pharmacokinetic forces that determine the plasma concentration of drug available in the body at a given time.

Determinants of Drug Concentration in Plasma

Measurement of Drug Concentration in Plasma

The study of pharmacokinetics depends upon the precise quantification of drug levels within the body. Levels are usually reported as the concentration of unaltered drug in the plasma or whole blood. This value, however, may be composed of the concentrations of up to three different forms of a compound. A large percentage of drug may be bound to carrier plasma proteins, such as albumin or α-1-acid glycoprotein. The protein-bound fraction of the drug is generally inactive, but is measured as part of the total plasma concentration. The drug may exist in its free, unbound state, which generally accounts for the active fraction of the drug. If drug levels in whole blood are measured, a portion may also be sequestered by the red blood cells. The free concentration may be determined by measuring the amount of drug in a protein-free ultrafiltrate of plasma, using techniques of ultrafiltration or equilibrium dialysis.

The metabolic products of a drug (which may frequently produce pharmacodynamic effects) are generally not reported as a component of the measured drug concentration. The analytical procedure employed for measurement of a drug must thus be specific for active drug and not its metabolites.

Single IV Dose

The majority of medications given during cardiac surgery are administered as single IV bolus injections. Following an IV bolus of a drug, a number of processes occur that ultimately determine the concentration of drug to be found in plasma over time. Following a rapid injection, the drug will be diluted in the blood, achieving its peak concentration within 1 to 2 minutes after administration.
Drug within the bloodstream will then be delivered to and taken up by tissues within the body, a process known as distribution. The drug concentration in plasma rapidly equilibrates with a group of highly perfused tissues, known as the vessel-rich group, during this initial distribution phase. Uptake of drug by the brain, heart, lungs, liver, and kidneys results in a rapid decline in blood levels measured shortly after administration, especially for those drugs that are highly lipid soluble. Drug concentrations in plasma are reduced further by a gradual uptake into less well-perfused tissues, such as muscle and fat, which serve as a large peripheral compartment where the drug may accumulate. Elimination by biotransformation and excretion ultimately removes the drug from the blood and the tissue reservoirs in the body. Elimination of most drugs follows first-order kinetics, whereby a constant fraction of the drug remaining in the body is eliminated per each unit of time.

A two-compartment model may be constructed to describe the distribution of a drug within a central compartment (blood) and peripheral compartment(s) (tissues), and the ultimate biotransformation of drug and its elimination from the body (Figure 4.1). The rate of transfer between the blood, tissues, and elimination sites can be described by a series of rate constants:

- \( K_{10} \) or \( K_{12} \): elimination rate constant representing the sum of all first-order elimination processes (such as biotransformation and excretion) that occur from the central compartment.
- \( K_{12} \): first-order rate constant for diffusion or transfer of drug from the central to peripheral compartment.
- \( K_{21} \): first-order rate constant for transfer of drug from the peripheral compartment back to the central compartment.

Measurement of drug levels in plasma after a single IV dose allows the construction of a concentration versus time curve depicting the respective contributions of the distribution and elimination processes to the logarithmic decline in plasma drug concentrations (Figure 4.2). Pharmacokinetic models may then be constructed based on the mathematical equations describing this log concentration versus time curve. The concentration of the drug in plasma \( (C_p) \) at any time may be calculated from the equation:

\[
C_p = Ae^{-at} + Be^{-\beta t}
\]

where:
- \( C_p \) = concentration of drug in plasma
- \( A \) = constant determined from the Y-axis intercept (time = 0) of the distribution portion of the log concentration versus time curve, derived by subtracting the contribution of the (constant, first-order) elimination phase of the curve
- \( a \) = slope of the log concentration versus time curve of the distribution phase, derived by subtracting the contribution due to elimination
- \( B \) = constant determined from the Y-axis intercept (time = 0) of the elimination phase of the log concentration versus time curve
- \( \beta \) = slope of the log concentration versus time curve of the elimination phase

A three-compartment model incorporates two phases of distribution (fast, to highly perfused tissues, and slow, to less highly perfused tissues), as well as an elimination phase.

The plasma concentration versus time curve for the three-compartment model is described by the equation:

\[
C_p = Pe^{-pt} + A\epsilon^{-at} + Be^{-\beta t}
\]

where \( A, B, a, \) and \( \beta \) are the same as for a two-compartment model, and:

- \( P \) = Y-axis intercept (time = 0) for the log concentration versus time curve derived after subtracting the contributions of the slow distribution and elimination phases
- \( p \) = slope of the log concentration versus time curve for the rapid distribution phase

Other models may be constructed, but two- and three-compartment models are sufficient for the vast majority of drugs.

The concentration of a drug in plasma may be predicted once an estimation of the volume of distribution \( (V_d) \) into which the dose will be introduced can be made. This theoretical volume does not correspond directly to actual tissue compartments within the body (such as blood, brain, extracellular fluid, etc.) but is useful in predicting drug