BLEED-TO-PLASMA

CONCENTRATION RATIO

The inter-relationships among extraction ratio, blood flow, and blood clearance of drugs require measurement of drug concentration in whole blood. Because plasma is the usual site of measurement, knowledge of how blood concentration and plasma concentration are related can be useful.

At equilibrium the ratio of blood-to-plasma concentrations depends on plasma protein binding, partitioning into blood cells, and the volume occupied by blood cells. This dependence is, perhaps, most readily appreciated from mass balance considerations, as follows:

\[ C_b \cdot V_b = C \cdot V_p + C_{bc} \cdot V_{bc} \]

Amount in blood \quad Amount in plasma
\quad Amount in blood cells

where:
- \( C_b \) = blood concentration of drug
- \( V_b \) = blood volume
- \( C \) = plasma concentration of drug
- \( V_p \) = plasma volume
- \( C_{bc} \) = blood cell concentration of drug
- \( V_{bc} \) = volume occupied by blood cells

The ratio of concentration in blood cells to that unbound in plasma, \( C_u \), is a measure of the affinity of blood cells for drug. Using \( \rho \) for this ratio and since \( C_u = f_u \cdot C \),

\[ C_{bc} = \rho \cdot C_u = \rho \cdot f_u \cdot C \]

The volume occupied by blood cells is a function of hematocrit, \( H \), and blood volume, i.e.,

\[ V_{bc} = H \cdot V_b \]

The plasma volume is related to hematocrit by

\[ V_p = (1 - H) V_b \]

Substituting Eqs. 2 to 4 in Eq. 1
\[ C_b \cdot V_b = (1 - H) \cdot V_b \cdot C + f_u \cdot \rho \cdot H \cdot V_b \cdot C \]

Finally, dividing by \( V_b \cdot C \), and simplifying,

\[ \frac{C_b}{C} = 1 + H[f_u \cdot \rho - 1] \]

This relationship clearly shows how the ratio of concentrations, blood/plasma, varies with hematocrit, plasma protein binding, and affinity of drug for blood cells. The ratio can be calculated if these parameters are known. If hematocrit and affinity are constant, a plot of the ratio against \( f_u \) gives a straight line with an intercept of \( 1 - H \) and a slope of \( H \cdot \rho \). This correlation is useful in situations in which plasma protein binding is variable, such as for certain drugs in uremia, in hypo- and hyperalbuminemic states, and in displacement interactions. In situations in which the plot is not linear, affinity of the blood cells or hematocrit is also changing.

If Eq. 6 is rearranged to solve for \( \rho \), a useful means of determining affinity of blood cells for the drug is obtained, namely,

\[ \rho = \frac{H - 1 + (C_b/C)}{f_u \cdot H} \]

Determination of \( \rho \) requires measurement of hematocrit, concentration ratio, and fraction of drug in plasma unbound to proteins.

**STUDY PROBLEM**

The ratio of concentration of a drug in blood to that in plasma usually averages about 2.35 in a typical patient who has a hematocrit of 0.45 and a fraction unbound in plasma of 0.1.

a. Calculate the ratio of concentration in blood cells to that unbound in plasma (\( \rho \)).

b. In an anemic patient hematocrit is decreased to 0.27, but serum concentration of albumin, the protein to which this drug binds, remains normal, 4.3 g/dL. Calculate the expected ratio of drug concentrations in blood and plasma in this patient.

c. Predict the ratio of plasma and blood clearances in a patient with the nephrotic syndrome in whom the hematocrit is normal but the fraction unbound in plasma is increased to 0.32, a secondary consequence of the loss of plasma proteins into urine.

Answers to Study Problems are in Appendix II, p. 583.