PHARMACOKINETICS OF POPS: SIMPLE MODELS WITH DIFFERENT IMPLICATIONS FOR HALFLIVES AND STEADY STATE LEVELS

Webster TF
Dept Environmental Health, Boston University School of Public Health, 715 Albany St, Boston MA 02118 USA

Introduction

The effect of body composition and weight change on the pharmacokinetics of persistent, lipophilic compounds remains a topic of interest. For example, body weight loss increased concentrations of organochlorine pesticides and PCBs.[1] While obese individuals are often assumed to have decreased concentrations of POPs, this does not always occur.[2] Steady-state concentrations of POPs are frequently estimated assuming a first order pharmacokinetic model with elimination proportional to the amount of adipose tissue:

$$\hat{C}_F = \frac{aI}{k_e V_F} \tag{1}$$

where $\hat{C}_F$ is the steady-state concentration in lipid, a is the fraction absorbed, I is the exposure rate, k_e is the first order elimination rate constant and V_F is the mass ("volume") of lipid. The aim of this paper is to suggest some reasonable alternative models.

Methods/Results

Model 1: First order model in lipid with constant volume: Suppose that the pharmacokinetics of a lipophilic compound is adequately described by a single lipid compartment with first order elimination:

$$\frac{dA_F}{dt} = \dot{A}_F = aI - k_e A_F \tag{2}$$

where $A_F = C_F V_F$ is the mass of the compound in the lipid compartment. Suppose V_F is constant:

$$\dot{C}_F = \frac{\dot{A}_F}{V_F} = \frac{aI}{V_F} - k_e C_F \tag{3}$$

For a, I and k_e constant, C_F rises until it reaches the steady state given by (1). If exposure stops (I=0), exponential decay occurs. The halflife, $t_h = \ln(2)/k_e$, does not depend on V_F while $\hat{C}_F$ is inversely related to V_F.

Model 2: Simple PBPK model: The simple physiologically-based pharmacokinetic (PBPK) model of Figure 1 uses three compartments relevant to modeling POPs: fat, liver and the rest of the body. The model includes blood sub-compartments (allowing limitation by exchange between subcompartments and tissues), but ignores binding by protein in the liver, inducible elimination, etc.[3] It assumes absorbed oral exposure (I_a) via the liver, and elimination proportional to the amount of the compound in the liver (with rate constant k_e):

$$\begin{aligned}
\dot{A}_R &= P_R(C_{Rb} - C_R / R_R) \\
\dot{A}_{Rb} &= Q_R(C_b - C_{Rb}) + P_R(C_R / R_R - C_{Rb}) \\
\dot{A}_F &= P_F(C_{Fb} - C_F / R_F) \\
\dot{A}_{Fb} &= Q_F(C_b - C_{Fb}) + P_F(C_F / R_F - C_{Fb}) \\
\dot{A}_L &= P_L(C_{Lb} - C_L / R_L) - k_e C_L V_L \\
\dot{A}_{Lb} &= Q_L(C_b - C_{Lb}) + P_L(C_L / R_L - C_{Lb}) + I_a
\end{aligned} \tag{4}$$

where A_i is the mass in main compartment i, P_i parameterizes the rate of transfer between the main compartment and its blood sub-compartment, and R_i is the partition constant between the two. Q_i is the flow of blood to each compartment. C_b is the concentration in blood, mixed according to the flow from each compartment. Setting each derivative to zero, the steady state concentration in fat (the main compartment for lipophilic compounds) is

$$\hat{C}_F = \frac{I_a}{k_e V_L}\left(\frac{R_F}{R_L}\right) \tag{5}$$

The PBPK model predicts that concentrations in fat are inversely proportional to the weight of the liver, not the weight of adipose tissue as is equation 1 (This conclusion is not affected by R_L/R_F, the ratio of concentrations in

fat to liver). If inter-compartment flows (including sub-compartments) are fast compared to elimination, and concentrations are proportional to lipid concentrations, a modification of the methods of van der Molen[4] shows that the overall elimination constant (k') and halflife (t_h) are

$$k' = -k_e\left(\frac{V_L R_L}{V_R R_R + V_F R_F + V_L R_L + V_{Rb} + V_{Fb} + V_{Lb}}\right) \approx -k_e\left(\frac{V_L R_L}{V_F R_F}\right) \quad (6)$$

$$t_h = \frac{\ln(2)}{k_e}\left(\frac{V_F R_F}{V_L R_L}\right) \quad (7)$$

where the approximation assumes that fat dominates storage of the compound. Contrary to model 1, the halflife is directly proportional to the size of the fat compartment V_F (assuming volumes are constant).

Model 3: First order model in lipid with weight change: PBPK models are very useful, but sometimes harder to interpret than simpler models. For non-constant tissue volumes, one can solve (2) (or 4) numerically and then compute concentration. However, another approach provides more insight. Using simple calculus, we note that

$$\dot{A}_F = V_F \dot{C}_F + \dot{V}_F C_F \quad (8)$$

Substituting into (2) and rearranging, we obtain:

$$V_F \dot{C}_F = aI - k_e V_F C_F - \dot{V}_F C_F$$

$$\dot{C}_F = \frac{aI}{V_F} - \left(k_e + \frac{\dot{V}_F}{V_F}\right) C_F = \frac{aI}{V_F} - k' C_F \quad (9)$$

Equation (9) is a one compartment model with apparent first order rate constant k' equal to the original elimination constant k_e plus a term k_v due to change in lipid volume:

$$k_v = \frac{\dot{V}_F}{V_F} \quad (10)$$

k_v describes the fractional (or %) rate of change of lipid volume. Suppose the system was at steady state and then undergoes a period of constant weight change. The effect is easiest to see if there is no input (I=0):

$$C_F(t) = C_0 e^{-(k_e + k_v)t} \quad (11)$$

where C_0 is the concentration at the time input ceases. Equations 10-11 show that concentration can decrease, remain constant or even increase (Table 1). This approach can be also be applied to model 2.[4]

Model 4: Metabolism in the liver: Model 1 assumes that elimination is proportional to the mass of the compound in lipid. Suppose instead that elimination takes place through metabolism in the liver as in model 2. Further assume that metabolism is the rate-limiting step in elimination, i.e., considerably slower than compartmental transfers; this might be realistic for compounds with long halflives. On a long enough time scale, the concentration in liver is in a quasi-steady state relative to lipid:

$$\frac{C_F}{R_F} = \frac{C_L}{R_L} \quad (12)$$

Modify equation (2) so that elimination is proportional to the amount of compound in the liver:

$$\begin{aligned} \dot{A}_F &= aI - k_e C_L V_L \\ &= aI - k_e C_F \left(\frac{R_L}{R_F}\right) V_L \end{aligned} \quad (13)$$

Assuming that the amount of lipid (V_F) is constant:

$$\begin{aligned} \dot{C} &= \frac{aI}{V_F} - \frac{k_e V_L R_L}{V_F R_F} C_F \\ &= \frac{aI}{V_F} - k'' C_F \end{aligned} \quad (14)$$

$$k'' = k_e \frac{V_L R_L}{V_F R_F} \quad (15)$$

As in model 2, the halflife is directly proportional to the lipid content V_F of the body. See equation (7). As in model 2, the steady state concentration in lipid is independent of the lipid content of the body (equation 5). More formally, we can derive these results from a two compartment model consisting of liver and fat, focusing on the smaller eigenvalue (which dominates long-run behavior) and approximating the latter via Taylor series in k_e:

$$\lambda \approx -k_e\left(\frac{R_L V_L}{R_L V_L + R_F V_F}\right) \approx -k_e\left(\frac{R_L V_L}{R_F V_F}\right) \tag{16}$$

where the second approximation holds when $R_F V_F >> R_L V_L$.

Model 5: Excretion via the gut: Instead of excretion via the liver, lipophilic compounds might be excreted via partitioning between lipids across the gut.[5] Figure 2 provides a very simple two-compartment model: a lipid compartment with direct partitioning to the gut contents (assuming blood flows are rapid compared with these processes), and elimination rate equal to the concentration in feces C_G times the feces excretion rate q:

$$\begin{aligned} V_F \dot{C}_F &= P_G\left(\frac{C_G}{R_G} - \frac{C_F}{R_F}\right) \\ V_G \dot{C}_G &= P_G\left(\frac{C_F}{R_F} - \frac{C_G}{R_G}\right) + I - qC_G \end{aligned} \tag{17}$$

The steady-state concentration in fat and halflife (approximating the smaller eigenvalue) are:

$$\begin{aligned} \hat{C}_F &= \frac{I}{q}\left(\frac{R_F}{R_G}\right) \\ t_h &= \ln(2) V_F\left(\frac{1}{q} + \frac{1}{P_G}\right) \end{aligned} \tag{18}$$

where the rate limiting step in elimination could be fecal excretion or partitioning into the gut. $\hat{C}_F$ is inversely proportional to fecal excretion (or fecal excretion of lipid); half-life is directly proportional to V_F.

Discussion

The simple first order model for lipid (model 1) makes two predictions: steady state concentrations are inversely related to lipid mass and halflife is independent of lipid mass (assuming body weight is constant; change in lipid mass, model 3, can lead to increases or decreases in concentration). Alternative models involving elimination via metabolism in the liver (models 2 and 4) or partitioning into the gut (model 5) make different predictions: steady state concentrations depend on other parameters and halflives are directly proportional to the amount of fat. Information regarding the elimination process is useful is modeling the pharmacokinetics of persistent lipophilic compounds.

References

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Figure 1. Simple PBPK Model

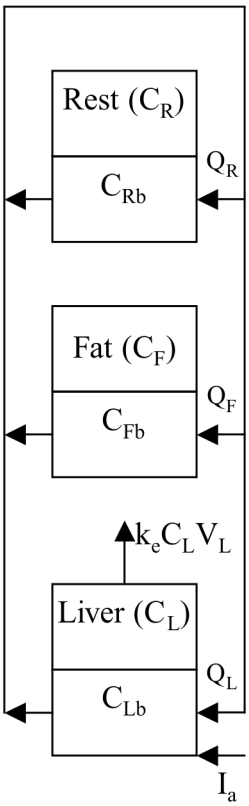

Figure 2. Excretion via the gut

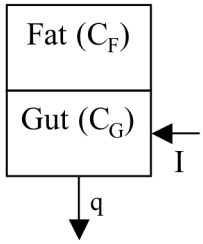

Table 1. Effect of change in lipid compartment volume on concentration and halflife

case	case	overall rate constant	concentration at time t	apparent halflife relative to the reference case
$\frac{\dot{V}}{V} = 0$	constant lipid (reference case)	$k' = k > 0$	decreases (reference case)	reference case
$\frac{\dot{V}}{V} > 0$	weight gain	$k' > k > 0$	decrease larger than the reference case ("dilution")	decreased
$-k_e < \frac{\dot{V}}{V} < 0$	small weight loss	$k' > 0$	decrease slower than reference case	increased
$-k_e = \frac{\dot{V}}{V} < 0$	weight loss balances elimination	$k' = 0$	no change	infinite
$\frac{\dot{V}}{V} < -k_e < 0$	larger weight loss	$k' < 0$	increase	not applicable