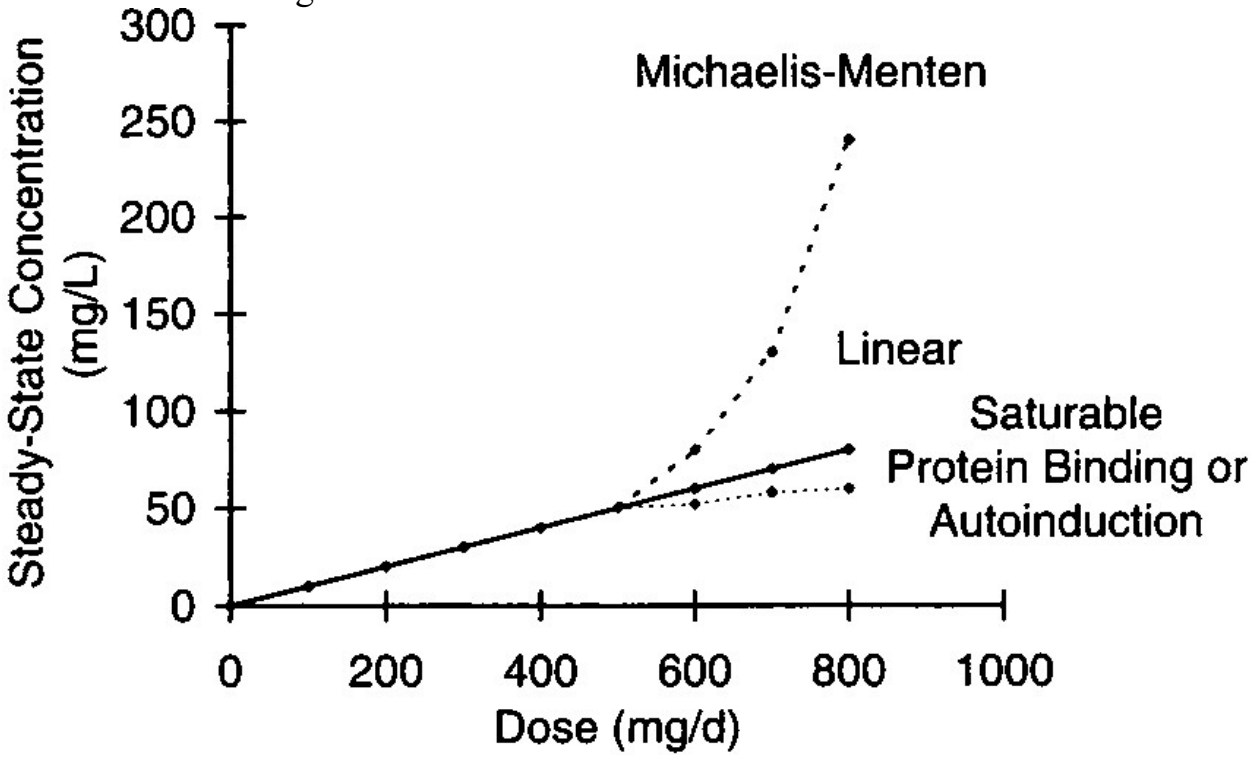
MICHAELIS-MENTEN OR SATURABLE PHARMACOKINETICS

Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug.2,3 When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase.



In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems:

$$\text{rate of metabolism} = (V_{max} \cdot C) / (Km + C)$$

Where:
Vmax is the maximum rate of metabolism,
C is the substrate concentration,
Km is the substrate concentration where the rate of metabolism = Vmax/2.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent. As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions:

$$Cl = V_{max}/(Km + C)$$

The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T):

$$V = V_B + \frac{f_B}{f_T} V_T$$

Also, half-life (t1/2) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics:

$$t_{1/2} = (0.693 \cdot V)/Cl$$

As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug:

$$\uparrow t_{1/2} = (0.693 \cdot V)/\downarrow Cl$$

The clinical implication of this finding is that the time to steady state (3–5 t1/2) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.

Under steady-state conditions the rate of drug administration equals the rate of drug removal. Therefore, for a drug that is solely removed by metabolism via one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{V_{max} \cdot Css}{Km + Css}$$