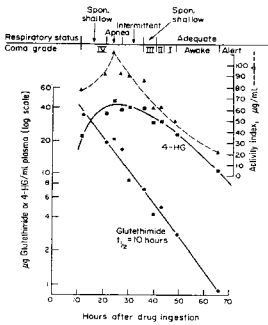


METABOLITE KINETICS

I. SIGNIFICANCE OF DRUG METABOLITES



Reproduced from: Houston JB. Drug metabolite kinetics. *Pharmac Ther* 15:521-552, 1982

CONSEQUENCES OF BIOTRANSFORMATION

Active Drug to Inactive Metabolite

Phenobarbital $\xrightarrow{\text{hydroxylation}}$ Hydroxyphenobarbital

Active Drug to Active Metabolite

Procainamide $\xrightarrow{\text{acetylation}}$ N-acetylprocainamide

Inactive Drug to Active Metabolite

Codeine $\xrightarrow{\text{demethylation}}$ Morphine

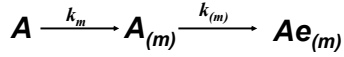
Active Drug to Reactive Metabolite

Acetaminophen \longrightarrow Reactive metabolite

Examples of Therapeutically Important Drugs That Give Rise to Active Metabolites

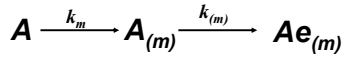
DRUG	METABOLITE	DRUG	METABOLITE
Acetylsalicylic acid	Salicylic acid	Isosorbide dinitrate	Isosorbide 5-mononitrate
Amitriptyline	Nortriptyline	Merperidine	Normeperidine
Carbamazepine	Carbamazepine-10,11-epoxide	Morphine	Morphine-6-glucuronide
Chlordiazepoxide	Desmethyldiazepam	Prazepam	Desmethyldiazepam
Codeine	Morphine	Prednisone	Prednisolone
Diazepam	Desmethyldiazepam	Primidone	Phenobarbital
Enalapril	Enalaprilat	Procainamide	N-acetylprocainamide
Encainide	O-desmethylencaïnide	Sulindac	Sulindac sulfide
Fluoxetine	Norfluoxetine	Verapamil	norverapamil
Imipramine	Desipramine	Zidovudine	Zidovudine triphosphate

II. SINGLE DOSE ADMINISTRATION
A. Importance of Rate-Limiting Step



A – amount of xenobiotic in body
A_(m) – amount of metabolite in body
Ae_(m) – amount of metabolite eliminated
k_m – first-order rate constant for drug to metabolite
k_(m) – first-order elimination rate constant for metabolite

II. SINGLE DOSE ADMINISTRATION
A. Importance of Rate-Limiting Step



$$\frac{dA_{(m)}}{dt} = k_m \times A - k_{(m)} \times A_{(m)}$$

When $k_m < k_{(m)}$, metabolite is said to be **formation rate-limited** in its disposition.

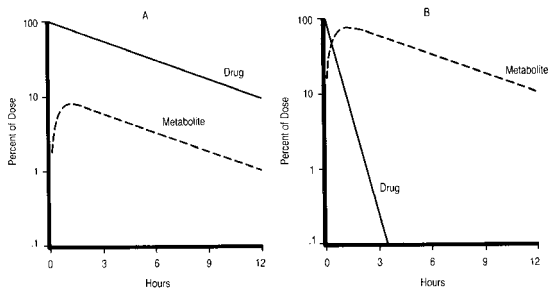


Fig. 21-1. Consequences of a rate limitation. When the elimination rate constant of the drug is smaller than that of the metabolite, the metabolite declines in parallel with the drug (A). Conversely, when the elimination rate constant of the metabolite is smaller than that of the drug, the metabolite declines more slowly than the drug (B). In the former case (A), the half-life of the metabolite decline is rate-limited by the elimination of the drug and, in the latter case (B), by the elimination of the metabolite. The graphs were simulated using k and $k_{(m)}$ values of 0.2 and 2 hour⁻¹ in the former case, and 2 and 0.2 hour⁻¹ in the latter.

II. SINGLE DOSE ADMINISTRATION
A. Importance of Rate-Limiting Step
B. Drug-Metabolite Plasma Concentration Relationships

$$\frac{dA_{(m)}}{dt} = CL_m \times C - CL_{(m)} \times C_{(m)}$$

CL_m – formation clearance of metabolite (CL_f)
 $CL_{(m)}$ – elimination clearance of metabolite
 $C_{(m)}$ – concentration of metabolite

Integrating the above relationship yields:

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$$\frac{AUC_{(m)}}{AUC} = \frac{CL_m}{CL_{(m)}}$$

since $CL_m = f_m \times CL$

$$\frac{AUC_{(m)}}{AUC} = f_m \times \frac{CL}{CL_{(m)}}$$

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Drug $\xrightarrow{k_m}$ **Metabolite** $\xrightarrow{k_{(m)}}$ **Metabolite in urine**

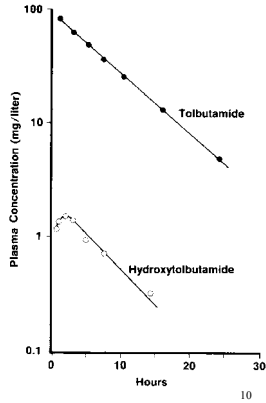
$$f_m = \frac{Ae_m}{Dose} \quad \text{assuming } F = 1$$

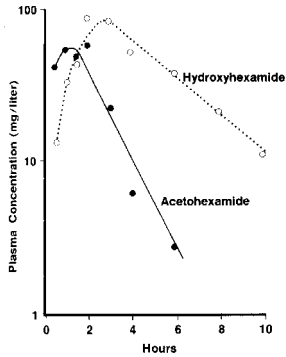
$$CL_m = f_m \times CL$$

$$\frac{AUC_{(m)}}{AUC} = f_m \frac{CL}{CL_{(m)}}$$

9

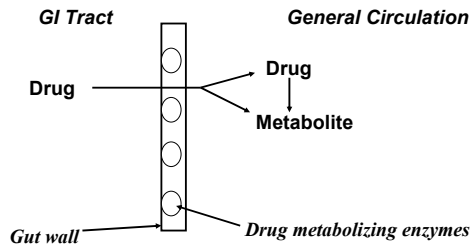
Plasma concentrations of tolbutamide and hydroxytolbutamide after an i.v. bolus dose of 1 g. Note the concentrations of tolbutamide and its metabolite decline in parallel. The volume of distribution of tolbutamide and hydroxy-tolbutamide are similar. From: Matin SB, Rowland M. Determination of tolbutamide and its metabolites in biological fluids. *Anal Letters* 6:865-876, 1973.





Plasma concentrations of acetohehexamide and its metabolite after administration of an oral 1 g dose of acetohehexamide. Note that the metabolite displays elimination rate-limited kinetics and will accumulate. From: Galloway JA, et al. Metabolism, blood levels, and rate of excretion of acetohehexamide in human subjects. *Diabetes* 16:118-123, 1967.

II. SINGLE DOSE ADMINISTRATION
A. Importance of Rate-Limiting Step
B. Drug-Metabolite Plasma Concentration Relationships
C. Impact of First-pass Metabolism



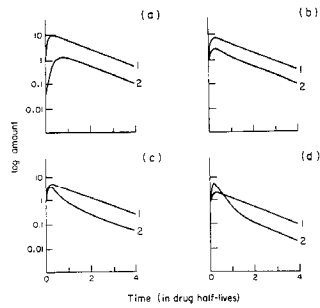


FIG. 7. Drug and metabolite-time profiles simulated according to the model for first pass metabolite kinetics following oral administration of drug in Scheme 4. Curves 1 refer to parent drug and Curves 2 to metabolite. $D = 10$, $k_a = 2$, $k = 0.1$, $k_{12} = 0.5$, $F_p(m) = 0.99$ (Panel a), 0.75 (Panel b), 0.5 (Panel c) and 0.25 (Panel d).

Reproduced from: Houston JB. Ibid.

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DRUG

- Alprenolol
- Amitriptyline
- Codeine
- Dextropropoxyphene
- Doxepin
- Imipramine
- Meperidine
- Metoprolol
- Propranolol
- Quinidine
- Verpamil

METABOLITE

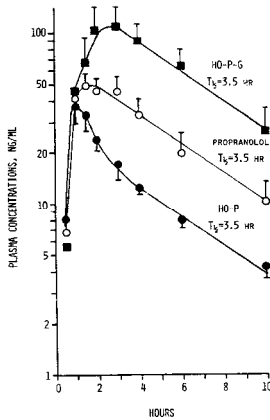
- 4-hydroxylprenolol
- nortriptyline
- morphine
- norpropoxyphene
- desmethyldoxepin
- desipramine
- normeperidine
- hydroxymetoprolol
- 4-hydroxypropranolol
- 3-hydroxyquinidine
- norverpamil

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Plasma concentration of propranolol, hydroxypropranolol and hydroxypropranolol glucuronide in 6 normal subjects after an 80 mg oral dose of propranolol.

From: Walle T, et al. *Clinical Pharmacology & Therapeutics* 27:22-31, 1980.



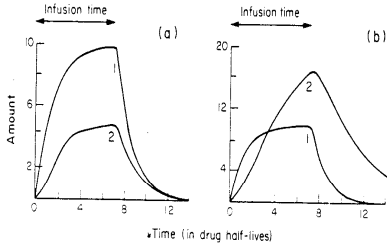


Fig. 13. Drug and metabolite-time profiles during and after drug infusion. Curve 1 refers to parent drug and Curve 2 to metabolite for the FRL case (Panel a) and the ERL case (Panel b). For this simulation the general model in Scheme 1 was used where drug is infused over a time period equivalent to 7 drug half-lives at a rate of 7 units per half-life, $k = 1$ and $k(m) = 2$ (Panel a) and 0.5 (Panel b).

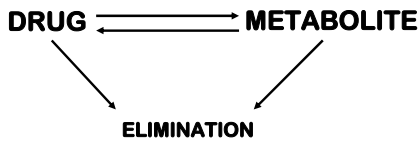
Reproduced from: Houston JB. Ibid.

The amount or concentration of metabolite at steady-state can be expressed as:

$$A_{m_{ss}} = \frac{f_m \times K_o}{k_{(m)}}$$

$$C_{(m)_{ss}} = \frac{f_m \times K_o}{CL_{(m)}}$$

IV. METABOLIC INTERCONVERSION



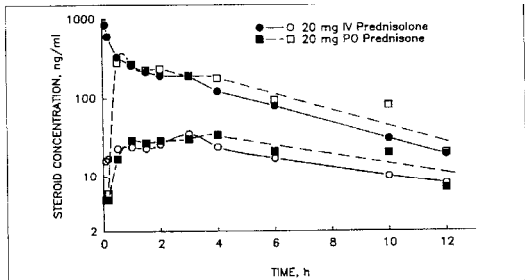


Figure 27-2. Plasma prednisolone (upper curves) and prednisone (lower curves) concentrations observed after a single oral dose of 20 mg prednisone (■—□) and an intravenous dose of 20 mg prednisolone phosphate (●—○) to a healthy male volunteer.

Reproduced from: Jusko WJ, Ludwig EA. Corticosteroids, In: *Applied Pharmacokinetic - Principles of Therapeutic Drug Monitoring*, 3rd edition, 1992, p. 27-4.

DRUG	METABOLITE	COMPOUND THAT PREDOMINATES AT EQUILIBRIUM	COMMENT
Canrenone	Canrenoate	Canrenone	Canrenoate is inactive
Clofibric acid	Glucuronide	Clofibric acid	In renal impairment glucuronide elimination is reduced
Cortisol	Cortisone	Cortisol	Cortisone is inactive
Dapsone	Monoacetyl-dapsone	Dapsone	Acetylation shows genetic polymorphism; acetylated metabolite is less active
Haloperidol	Reduced haloperidol	Haloperidol	Haloperidol is reduced by carbonyl reductase
Sulindac	Sulindac sulfide		Sulindac is prodrug
Vitamin K	Vitamin K epoxide	Vitamin K	Epoxide is inactive; oral anticoagulants act by preventing conversion of epoxide back to vitamin K
