GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

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Table A–II–1

PHARMACOKINETIC DATA (*Continued*)

DIAZEPAM[a] (Chapters 17, 19)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
Oral: 100 ± 14 Rectal: 90	<1	98.7 ± 0.2 ↓ RD, Cirr, NS, Preg, Neo, Alb, Burn, Aged ⟷ HTh	0.38 ± 0.06[a,b] ↑ Alb ↓ Cirr ⟷ Aged, Smk, HTh	1.1 ± 0.3 ↑ Cirr, Aged, Alb ⟷ RD, HTh	43 ± 13[a,b] ↑ Aged, Cirr ⟷ HTh	Oral: 1.3 ± 0.2[c] Rectal: 1.5[c]	IV: 400–500 ng/ml[c] Oral: 317 ± 27 ng/ml[c] Rectal: ~400 ng/ml[c]

[a]Active metabolites, desmethyldiazepam and oxazepam, formed by CYP2C19 (polymorphic) and CYP3A.
[b]*CL* increased and $t_{1/2}$ decreased by administration of other drugs that induce metabolic enzymes.
[c]Range of data following a single 5–10-mg IV dose (15- to 30-second bolus) or mean data following a single 10-mg oral or 15-mg rectal dose given to healthy adults. A concentration of 300 to 400 ng/ml provides anxiolytic effect, and >600 ng/ml provides control of seizures.

References: Friedman, H., Greenblatt, D.J., Peters, G.R., Metzler, C.M., Charlton, M.D., Harmatz, J.S., Antal, E.J., Sanborn, E.C., and Francom, S.F. Pharmacokinetics and pharmacodynamics of oral diazepam: effect of dose, plasma concentration, and time. *Clin. Pharmacol. Ther.,* **1992,** *52*:139–150.
Greenblatt, D.J., Allen, M.D., Harmatz, J.S., and Shader, R.I. Diazepam disposition determinants. *Clin. Pharmacol. Ther.,* **1980,** *27*:301–312.
Physicians' Desk Reference, 54th ed. Medical Economics Co., Montvale, NJ, **2000,** p. 1012.

DICLOFENAC (Chapter 27)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
54 ± 2	<1	>99.5	4.2 ± 0.9[a] ↓ Aged ⟷ RD, Cirr, RA	0.17 ± 0.11[b] ↑ RA	1.1 ± 0.2 ⟷ RA	EC: 2.5 (1.0–4.5)[c] SR: 5.3 ± 1.5[c]	EC: 2.0 (1.4–3.0) μg/ml[c] SR: 0.42 ± 0.17 μg/ml[c]

[a]Cleared primarily by CYP2C9-catalyzed 4′-hydroxylation; urine and biliary metabolites account for 30% and 10% to 20% of dose, respectively.
[b]V_{area} reported.
[c]Mean (range) following a single 50-mg enteric-coated tablet (EC) or 100-mg of sustained-release tablet (SR), given to healthy adults.

References: Tracy, T. Nonsteroidal antiinflammatory drugs. In, *Metabolic Drug Interactions.* (Levy, R.H., Thummel, K.T., Trager, W.F., Hansten, P.D., and Eichelbaum, M., eds.) Lippincott Williams & Wilkins, Philadelphia, **2000,** pp. 457–468.
Willis, J.V., Kendall, M.J., Flinn, R.M., Thornhill, D.P., and Welling, P.G. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur. J. Clin. Pharmacol.,* **1979,** *16*:405–410.

DICLOXACILLIN (Chapter 45)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
50–85	60 ± 7	95.8 ± 0.2 ↓ RD, Aged, Cirr ⟷ CF	1.6 ± 0.3[a,b] ↓ RD ↑ CF[c]	0.086 ± 0.017[a] ↑ RD, CF	0.70 ± 0.07 ↑ RD ⟷ CF	0.5–1.6[d]	47–91 μg/ml[d]

[a]Calculated assuming a 70-kg body weight.
[b]Possible saturation of renal clearance at doses of 1 to 2 g.
[c]Concomitant increase in clearance of both dicloxacillin and creatinine.
[d]Estimated range of data following a single 2-g oral dose given to healthy (fasted) adults.

Reference: Nauta, E.H., and Mattie, H. Dicloxacillin and cloxacillin: pharmacokinetics in healthy and hemodialysis subjects. *Clin. Pharmacol. Ther.,* **1976,** *20*:98–108.

DIDANOSINE (Chapter 51)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
38 ± 15 ↓ Child, Food	36 ± 9	<5	16 ± 7 ⟷ Child, ↓ RD	1.0 ± 0.2	1.4 ± 0.3	B: 0.75[a] M: 0.50[a]	B: 2.1 ± 0.6 μg/ml[a] M: 2.1 ± 0.5 μg/ml[a]

[a]Mean C_{max} and median T_{max} following a single 375-mg oral dose of didanosine formulated as a citrate-phosphate buffered (B) solution or as a mixture with MAALOX suspension (M), taken after a fast by patients with HIV infection.

References: Knupp, C.A., Shyu, W.C., Dolin, R., Valentine, F.T., McLaren, C., Martin, R.R., Pittman, K.A., and Barbhaiya, R.H. Pharmacokinetics of didanosine in patients with acquired immunodeficiency syndrome or acquired immunodeficiency syndrome-related complex. *Clin. Pharmacol. Ther.,* **1991,** [illegible]
[illegible]

Table A–II–1
PHARMACOKINETIC DATA (*Continued*)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
CLAVULANATE[a] (Chapter 45)							
75 ± 21	43 ± 14	22	3.6 ± 1.0[b] ↓ RD ⟷ Child	0.21 ± 0.05[b] ⟷ RD, Child	0.9 ± 0.1 ↑ Neo, RD ⟷ Child	1.3[c]	2.8 μg/ml[c]

[a]Kinetic parameters do not change appreciably when given with amoxicillin or ticarcillin.
[b]Calculated assuming a 70-kg body weight.
[c]Mean data following a single 125-mg oral dose, administered with penicillin to healthy adults. No accumulation with multiple dosing.

Reference: Watson, I.D., Stewart, M.J., and Platt, D.J. Clinical pharmacokinetics of enzyme inhibitors in antimicrobial chemotherapy. *Clin. Pharmacokinet.*, **1988,** *15*:133–164.

CLINDAMYCIN (Chapter 47)							
~87[a] Topical: 2	13	93.6 ± 0.2	4.7 ± 1.3 ⟷ Child	1.1 ± 0.3[b] ⟷ RD, Child	2.9 ± 0.7 ⟷ Child, RD, Preg ↑ Prem	—	IV: 17.2 ± 3.5 μg/ml[c] Oral: 2.5 μg/ml[d]

[a]Clindamycin hydrochloride given orally.
[b]V_{area} reported.
[c]Following a 1200-mg IV dose (30-min infusion) of clindamycin phosphate (prodrug), given twice a day to steady state in healthy male adults.
[d]Following a single 150-mg oral dose of clindamycin hydrochloride to adults.

References: Physicians' Desk Reference, 54th ed. Medical Economics Co., Montvale, NJ, **2000,** p. 2421.
Plaisance, K.I., Drusano, G.L., Forrest, A., Townsend, R.J., and Standiford, H.C. Pharmacokinetic evaluation of two dosage regimens of clindamycin phosphate. *Antimicrob. Agents Chemother.,* **1989,** *33*:618–620.

CLOFIBRATE[a] (Chapter 36)							
95 ± 10	10.8 ± 2.7[b]	97.2 ± 0.9[c] ↓ NS, Cirr, RD ⟷ AVH	0.10 ± 0.03[b] ↑ NS ↓ RD[d] ⟷ AVH, Cirr	0.14 ± 0.02[b] ↑ Cirr, RD	18 ± 4.3 ↑ RD	3.5–4[e]	109 ± 32 μg/ml[e]

[a]Clofibrate is the ethyl ester of *p*-chlorophenoxyisobutyric acid (CPIB). All values are for CPIB, since clofibrate is rapidly de-esterified upon absorption.
[b]Oral dose; *CL/F* and V_{area}/F are reported. *CL/F* calculated assuming 70-kg body weight.
[c]Binding may decrease at high concentrations of CPIB (>200 μg/ml).
[d]Due to accumulation of glucuronide metabolite of CPIB, which is hydrolyzed back to parent drug.
[e]Mean steady-state concentration following a 1-g oral dose, given twice a day to patients with hypercholesterolemia or cholestasis for 2 to 416 weeks.

References: Gugler, R., Kurten, J.W., Jensen, C.J., Klehr, U., and Hartlapp, J. Clofibrate disposition in renal failure and acute and chronic liver disease. *Eur. J. Clin. Pharmacol.*, **1979,** *15*:341–347.
Sedaghat, A., and Ahrens, E.H. Lack of effect of cholestyramine on the pharmacokinetics of clofibrate in man. *Eur. J. Clin. Invest.*, **1975,** *5*:177–185.

CLONAZEPAM (Chapters 17, 19)							
98 ± 31	<1	86 ± 0.5 ↓ Neo	1.55 ± 0.28[a,b]	3.2 ± 1.1	23 ± 5	Oral: 2.5 ± 1.3[c]	IV: 3–29 ng/ml[c] Oral: 17 ± 5.4 ng/ml[c]

[a]*CL/F* reported; this value is consistent for a number of studies, but is higher than the clearance determined in a single study of IV administration.
[b]Metabolized by CYP3A.
[c]Range of C_{max} values following a single 2-mg IV dose (model-fitted for bolus dose) or mean following a 2-mg oral dose (tablet), given to healthy adults. Most patients, including children, whose seizures are controlled by clonazepam have steady-state concentrations in the range of 5 to 70 ng/ml. However, patients who do not respond and those with side effects achieve similar levels.

References: Berlin, A., and Dahlstrom, H. Pharmacokinetics of the anticonvulsant drug clonazepam evaluated from single oral and intravenous doses and by repeated oral administration. *Eur. J. Clin. Pharmacol.*, **1975,** *9*:155–159.

MIDAZOLAM (Chapters 14, 17)

44 ± 17[a] ↑ Cirr	<1%	98 ↓ Aged, RD ⟷ Smk, Cirr	6.6 ± 1.8[b] ↑ RD[c] ↓ Cirr, Neo ⟷ Obes, Smk, Child	1.1 ± 0.6 ↑ Obes ⟷ Cirr ↓ Neo	1.9 ± 0.6 ↑ Aged, Obes, Cirr ⟷ Smk	Oral: 0.67 ± 0.45[d]	IV: 113 ± 16 ng/ml[d] Oral: 78 ± 27 ng/ml[d]

[a]Bioavailability appears to be dose-dependent; 35% to 67% at 15 mg, 28% to 36% at 7.5 mg, and 12% to 47% at 2-mg oral dose, possibly due to saturable first-pass intestinal metabolism.
[b]Undergoes extensive first-pass metabolism by intestinal and hepatic CYP3A. Metabolically cleared exclusively by CYP3A.
[c]Increased clearance due to increased plasma free fraction; unbound clearance is unchanged.
[d]Following a single 5-mg IV bolus dose or 10-mg oral dose.

References: Garzone, P.D., and Kroboth, P.D. Pharmacokinetics of the newer benzodiazepines. *Clin. Pharmacokinet.*, **1989,** *16*:337–364.

Thummel, K.E., O'Shea, D., Paine, M.F., Shen, D.D., Kunze, K.L., Perkins, J.D., and Wilkinson, G.R. Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin. Pharmacol. Ther.*, **1996,** *59*:491–502.

MINOCYCLINE (Chapter 47)

95–100	11 ± 2	76	1.0 ± 0.3 ↓ HL	1.3 ± 0.2[a] ↓ HL	16 ± 2 ⟷ Cirr, HL RD[b]	Oral: 2–4[c]	IV: 3.5 μg/ml[c] Oral: 2.3–3.5 μg/ml[c]

[a]V_{area} reported.
[b]In patients with reduced CL_{cr}, there is a tendency for half-life to increase. However, there is no accumulation of drug beyond that seen in normal subjects during repeated administration of minocycline to patients with CL_{cr} = 18–45 ml/min.
[c]Mean value following a single 200-mg IV infusion (1 hour) or range of values following a 100-mg oral dose given twice a day to steady state.

Reference: Saivin, S., and Houin, G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin. Pharmacokinet.*, **1988,** *15*:355–366.

MIRTAZAPINE[a] (Chapter 19)

50 ± 10	—	85	9.12 ± 1.14[b] ↓ LD,[d] RD[e]	4.5 ± 1.7	16.3 ± 4.6[b,c] ↑ LD,[d] RD[e]	1.5 ± 0.7[f]	41.8 ± 7.7 ng/ml[f]

[a]Data from healthy adult subjects. Metabolized by CYP2D6 and CYP1A2 (8-hydroxy) and CYP3A (*N*-desmethyl, *N*-oxide).
[b]Women of all ages exhibit lower *CL/F* and longer $t_{1/2}$ than men.
[c]The $t_{1/2}$ of the (−)-enantiomer is approximately twice as long as the (+)-antipode; ~threefold higher blood concentrations (+ *vs.* −) are achieved.
[d]*CL/F* reduced, hepatic impairment.
[e]*CL/F* reduced, moderate to severe renal impairment.
[f]Following a 15-mg oral dose, once daily, to steady state.

References: Fawcett, J., and Barkin, R.L. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J. Affect. Disord.*, **1998,** *51*:267–285.

Physicians' Desk Reference, 54th ed. Medical Economics Co., Montvale, NJ, **2000,** p. 2109.

Key: Unless otherwise indicated by a specific footnote, the data are presented for the study population as a mean value ± 1 standard deviation, a mean and range (lowest–highest in parenthesis) of values, a range of the lowest–highest values, or a single mean value.

ADH = alcohol dehydrogenase; Aged = aged; AIDS = acquired immunodeficiency syndrome; Alb = hypoalbuminemia; Atr Fib = atrial fibrillation; AVH = acute viral hepatitis; Burn = burn patients; C_{max} = peak concentration; CAD = coronary artery disease; Celiac = celiac disease; CF = cystic fibrosis; CHF = congestive heart failure; Child = children; Cirr = hepatic cirrhosis; COPD = chronic obstructive pulmonary disease; CP = cor pulmonale; CPBS = cardiopulmonary bypass surgery; CRI = chronic respiratory insufficiency; Crohn = Crohn's disease; Cush = Cushing's syndrome; CYP = cytochrome P450; Fem = female; Hep = hepatitis; HIV = human immunodeficiency virus; HL = hyperlipoproteinemia; HTh = hyperthyroid; IM = intramuscular; Inflam = inflammation; IV = intravenous; LD = liver disease; LTh = hypothyroid; MAO = monoamine oxidase; MI = myocardial infarction; NAT = *N*-acetyltransferase; Neo = neonate; NIDDM = non–insulin-dependent diabetes mellitus; NS = nephrotic syndrome; Obes = obese; Pneu = pneumonia; Preg = pregnant; Prem = premature; RA = rheumatoid arthritis; RD = renal disease (including uremia); SC = subcutaneous; Smk = smoking; ST = sulfotransferase; T_{max} = peak time; Tach = ventricular tachycardia; UGT = UDP-glucuronosyl transferase; Ulcer = ulcer patients. Other abbreviations are defined in the text section of this appendix.

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