
LITERATURVERZEICHNIS

7 LITERATURVERZEICHNIS

1. Forth W, Henschler D, Rummel W, Starke K.: *Allgemeine und spezielle Pharmakologie und Toxikologie*, Spektrum Akademischer Verlag, Heidelberg-Berlin-Oxford, 7. Aufl. (1996).
2. Schneemann H.: *Angewandte Arzneimitteltherapie, Klinisch-pharmazeutische Betreuung in Fallbeispielen*, Springer Verlag, Berlin-Heidelberg (2001).
3. Statistisches Bundesamt Deutschland: <http://www.destatis.de/basis/d/gesu/gesutab20.php> (2005).
4. Laurent D., Bolene-Williams C., Williams F.L., Katz L.N.: Effects of heart rate on coronary flow and cardiac oxygen consumption. *Am. J. Physiol.* **185**: 355-364 (1956).
5. Sarnoff S.J., Braunwald E., Welch G.H., Jr., Case R.B., Stainsby W.N., Macruz R.: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am. J. Physiol.* **192**: 148-156 (1958).
6. Sonnenblick E.H., Ross J., Jr., Braunwald E.: Oxygen consumption of the heart. Newer concepts of its multifactorial determination. *Am. J. Cardiol.* **22**: 328-336 (1968).
7. Braunwald E.: Control of myocardial oxygen consumption: physiologic and clinical considerations. *Am. J. Cardiol.* **27**: 416-432 (1971).
8. Rietbrock N, Staib AH, Loew D.: *Klinische Pharmakologie, Ein Leitfaden für die Praxis*, Dr. Dietrich Steinkopff Verlag, Darmstadt (1991).
9. Frishman W.H.: Multifactorial actions of beta-adrenergic blocking drugs in ischemic heart disease: current concepts. *Circulation* **67**: I11-I18 (1983).
10. Frishman W.H.: Beta-adrenergic blockade for the treatment of angina pectoris. In: Weiner DA, Frishman WH (Hrsg.), *Therapy of Angina pectoris. A Comprehensive Guide for the Clinicians*, Marcel Dekker Inc., New York, 83-144 (1986).
11. Guth B.D., Seitelberger R., Lee J.D., Katayama K., Miller M., Ross J., Jr.: Mechanism of increased ischemia during exercise: deleterious effect without drug-induced bradycardia. *J. Am. Coll. Cardiol.* **7**: 54A (1986).
12. Kjekshus J.K.: Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am. J. Cardiol.* **57**: 43F-49F (1986).
13. Guth B.D., Heusch G., Seitelberger R., Ross J., Jr.: Mechanism of beneficial effect of beta-adrenergic blockade on exercise-induced myocardial ischemia in conscious dogs. *Circ. Res.* **60**: 738-746 (1987).
14. Kjekshus J.: Heart rate reduction--a mechanism of benefit? *Eur. Heart J.* **8 Suppl L**: 115-122 (1987).
15. Frishman W.H., Sonnenblick E.H.: Calcium-channel blockers. In: Schlant RC, Alexander RW (Hrsg.), *The Heart*, McGraw Hill, New York, 1291-1308 (1994).
16. Dammgen J.W., Lampert K.A., Gross G.J.: Actions of two new bradycardic agents, AQ-AH 208 and UL-FS 49, on ischemic myocardial perfusion and function. *J. Cardiovasc. Pharmacol.* **7**: 71-79 (1985).
17. Schulz R., Rose J., Skyschally A., Heusch G.: Bradycardic agent UL-FS 49 attenuates ischemic regional myocardial dysfunction and reduces infarct size in swine: comparison with the beta-blocker atenolol. *J. Cardiovasc. Pharmacol.* **25**: 216-228 (1995).
18. Kannel W.B., Kannel C., Paffenbarger R.S., Jr., Cupples L.A.: Heart rate and cardiovascular mortality: the Framingham Study. *Am. Heart J.* **113**: 1489-1494 (1987).
19. Gillum R.F.: The epidemiology of resting heart rate in a national sample of men and women: associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. *Am. Heart J.* **116**: 163-174 (1988).
20. Hjalmarson A., Gilpin E.A., Kjekshus J., Schieman G., Nicod P., Henning H., Ross J., Jr.: Influence of heart rate on mortality after acute myocardial infarction. *Am. J. Cardiol.* **65**: 547-553 (1990).
21. Shaper A.G., Wannamethee G., Macfarlane P.W., Walker M.: Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. *Br. Heart J.* **70**: 49-55 (1993).
22. Goldberg R.J., Larson M., Levy D.: Factors associated with survival to 75 years of age in middle-aged men and women. The Framingham Study. *Arch. Intern. Med.* **156**: 505-509 (1996).
23. Mensink G.B., Hoffmeister H.: The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. *Eur. Heart J.* **18**: 1404-1410 (1997).
24. Indolfi C., Ross J., Jr.: The role of heart rate in myocardial ischemia and infarction: implications of myocardial perfusion-contraction matching. *Prog. Cardiovasc. Dis.* **36**: 61-74 (1993).

25. Kobinger W.: Specific bradycardic agents, a new approach to therapy in angina pectoris? *Prog. Pharmacol.* 89-100 (1985).
26. Krumpl G., Schneider W., Raberger G.: Can exercise-induced regional contractile dysfunction be prevented by selective bradycardic agents? *Naunyn Schmiedebergs Arch. Pharmacol.* **334**: 540-543 (1986).
27. Franke H., Su C.A., Schumacher K., Seiberling M.: Clinical pharmacology of two specific bradycardiac agents. *Eur. Heart J.* **8**: 91-98 (1987).
28. Kobinger W., Lillie C.: Specific bradycardic agents--a novel pharmacological class? *Eur. Heart J.* **8**: 7-15 (1987).
29. Raberger G., Krumpl G., Schneider W.: Effects of the bradycardic agent UL-FS 49 on exercise-induced regional contractile dysfunction in dogs. *Int. J. Cardiol.* **14**: 343-354 (1987).
30. van Bogaert P.P., Goethals M.: Pharmacological influence of specific bradycardic agents on the pacemaker current of sheep cardiac Purkinje fibres. A comparison between three different molecules. *Eur. Heart J.* **8**: 35-42 (1987).
31. Kobinger W., Lillie C.: Falipamil (AQ-A 39) and UL-FS 49. *Cardiovasc. Drug Rev.* **6**: 35-43 (1988).
32. Krumpl G., Winkler M., Schneider W., Raberger G.: Comparison of the haemodynamic effects of the selective bradycardic agent UL-FS 49, with those of propranolol during treadmill exercise in dogs. *Br. J. Pharmacol.* **94**: 55-64 (1988).
33. Reiffen M., Eberlein W., Muller P., Psiorz M., Noll K., Heider J., Lillie C., Kobinger W., Luger P.: Specific bradycardic agents. 1. Chemistry, pharmacology, and structure-activity relationships of substituted benzazepinones, a-new class of compounds exerting antiischemic properties. *J. Med. Chem.* **33**: 1496-1504 (1990).
34. van Woerkens L.J., van der Giessen W.J., Verdouw P.D.: The selective bradycardic effects of zatebradine (UL-FS 49) do not adversely affect left ventricular function in conscious pigs with chronic coronary artery occlusion. *Cardiovasc. Drugs Ther.* **6**: 59-65 (1992).
35. Breall J.A., Watanabe J., Grossman W.: Effect of zatebradine on contractility, relaxation and coronary blood flow. *J. Am. Coll. Cardiol.* **21**: 471-477 (1993).
36. Fain G.L., Quandt F.N., Bastian B.L., Gerschenfeld H.M.: Contribution of a caesium-sensitive conductance increase to the rod photoresponse. *Nature* **272**: 466-469 (1978).
37. Brown H.F., DiFrancesco D., Noble S.J.: How does adrenaline accelerate the heart? *Nature* **280**: 235-236 (1979).
38. Yanagihara K., Irisawa H.: Inward current activated during hyperpolarization in the rabbit sinoatrial node cell. *Pflugers Arch.* **385**: 11-19 (1980).
39. Attwell D., Wilson M.: Behaviour of the rod network in the tiger salamander retina mediated by membrane properties of individual rods. *J. Physiol.* **309**: 287-315 (1980).
40. DiFrancesco D.: A new interpretation of the pace-maker current in calf Purkinje fibres. *J. Physiol.* **314**: 359-376 (1981).
41. Halliwell J.V., Adams P.R.: Voltage-clamp analysis of muscarinic excitation in hippocampal neurons. *Brain Res.* **250**: 71-92 (1982).
42. Bader C.R., Bertrand D.: Effect of changes in intra- and extracellular sodium on the inward (anomalous) rectification in salamander photoreceptors. *J. Physiol.* **347**: 611-631 (1984).
43. Barnes S., Hille B.: Ionic channels of the inner segment of tiger salamander cone photoreceptors. *J. Gen. Physiol.* **94**: 719-43 (1989).
44. Schmidt RF, Thews G. *Physiologie des Menschen*, Springer Verlag, 26. Aufl. (1995).
45. Edman A., Gestrelus S., Grampp W.: Current activation by membrane hyperpolarization in the slowly adapting lobster stretch receptor neurone. *J. Physiol.* **384**: 671-690 (1987).
46. Hestrin S.: The properties and function of inward rectification in rod photoreceptors of the tiger salamander. *J. Physiol.* **390**: 319-333 (1987).
47. Maricq A.V., Korenbrot J.I.: Inward rectification in the inner segment of single retinal cone photoreceptors. *J. Neurophysiol.* **64**: 1917-1928 (1990).
48. Solomon J.S., Nerbonne J.M.: Hyperpolarization-activated currents in isolated superior colliculus-projecting neurons from rat visual cortex. *J. Physiol.* **462**: 393-420 (1993).
49. DiFrancesco D., Tortora P.: Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. *Nature* **351**: 145-147 (1991).

50. DiFrancesco D.: Characterization of single pacemaker channels in cardiac sino-atrial node cells. *Nature* **324**: 470-473 (1986).
51. DiFrancesco D., Ducouret P., Robinson R.B.: Muscarinic modulation of cardiac rate at low acetylcholine concentrations. *Science* **243**: 669-671 (1989).
52. DiFrancesco D.: The pacemaker current (I_f) plays an important role in regulating SA node pacemaker activity. *Cardiovasc. Res.* **30**: 307-308 (1995).
53. Moosmang S., Biel M., Hofmann F., Ludwig A.: Differential distribution of four hyperpolarization-activated cation channels in mouse brain. *Biol. Chem.* **380**: 975-980 (1999).
54. Monteggia L.M., Eisch A.J., Tang M.D., Kaczmarek L.K., Nestler E.J.: Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. *Brain Res. Mol. Brain Res.* **81**: 129-139 (2000).
55. Santoro B., Chen S., Luthi A., Pavlidis P., Shumyatsky G.P., Tibbs G.R., Siegelbaum S.A.: Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS. *J. Neurosci.* **20**: 5264-5275 (2000).
56. Pape H.C.: Queer current and pacemaker: the hyperpolarization-activated cation current in neurons. *Annu. Rev. Physiol.* **58**: 299-327 (1996).
57. Luthi A., McCormick D.A.: H-current: properties of a neuronal and network pacemaker. *Neuron* **21**: 9-12 (1998).
58. Wollmuth L.P., Hille B.: Ionic selectivity of I_h channels of rod photoreceptors in tiger salamanders. *J. Gen. Physiol.* **100**: 749-765 (1992).
59. Satoh T.O., Yamada M.: Multiple inhibitory effects of zatebradine (UL-FS 49) on the electrophysiological properties of retinal rod photoreceptors. *Pflugers Arch.* **443**: 532-40 (2002).
60. Ludwig A., Zong X., Jeglitsch M., Hofmann F., Biel M.: A family of hyperpolarization-activated mammalian cation channels. *Nature* **393**: 587-591 (1998).
61. Ishii T.M., Takano M., Xie L.H., Noma A., Ohmori H.: Molecular characterization of the hyperpolarization-activated cation channel in rabbit heart sinoatrial node. *J. Biol. Chem.* **274**: 12835-12839 (1999).
62. Seifert R., Scholten A., Gauss R., Mincheva A., Lichter P., Kaupp U.B.: Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis. *Proc. Natl. Acad. Sci. U. S. A.* **96**: 9391-9396 (1999).
63. Shi W., Wymore R., Yu H., Wu J., Wymore R.T., Pan Z., Robinson R.B., Dixon J.E., McKinnon D., Cohen I.S.: Distribution and prevalence of hyperpolarization-activated cation channel (HCN) mRNA expression in cardiac tissues. *Circ. Res.* **85**: 1-6 (1999).
64. Moosmang S., Stieber J., Zong X., Biel M., Hofmann F., Ludwig A.: Cellular expression and functional characterization of four hyperpolarization-activated pacemaker channels in cardiac and neuronal tissues. *Eur. J. Biochem.* **268**: 1646-1652 (2001).
65. Herrmann S., Stieber J., Feil S., Feil R., Biel M., Hofmann F., Ludwig A.: Pacemaker channel HCN4 is required for normal cardiac function in the mouse embryo. *Naunyn Schmiedebergs Arch. Pharmacol.* **367**: R91 (2003).
66. Ludwig A., Budde T., Stieber J., Moosmang S., Wahl C., Holthoff K., Langebartels A., Wotjak C., Munsch T., Zong X., Feil S., Feil R., Lancel M., Chien K.R., Konnerth A., Pape H.C., Biel M., Hofmann F.: Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. *EMBO J.* **22**: 216-224 (2003).
67. DiFrancesco D.: Some properties of the UL-FS 49 block of the hyperpolarization-activated current (I_f) in sino-atrial node myocytes. *Pflugers Arch.* **427**: 64-70 (1994).
68. van Bogaert P.P., Pittoors F.: Use-dependent blockade of cardiac pacemaker current (I_f) by cilobradine and zatebradine. *Eur. J. Pharmacol.* **478**: 161-71 (2003).
69. van Bogaert P.P., Goethals M., Simoens C.: Use- and frequency-dependent blockade by UL-FS 49 of the I_f pacemaker current in sheep cardiac Purkinje fibres. *Eur. J. Pharmacol.* **187**: 241-256 (1990).
70. Goethals M., Raes A., van Bogaert P.P.: Use-dependent block of the pacemaker current I_f in rabbit sinoatrial node cells by zatebradine (UL-FS 49). On the mode of action of sinus node inhibitors. *Circulation* **88**: 2389-2401 (1993).
71. Pape H.C.: Specific bradycardic agents block the hyperpolarization-activated cation current in central neurons. *Neuroscience* **59**: 363-373 (1994).

72. Bois P., Bescond J., Renaudon B., Lenfant J.: Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. *Br. J. Pharmacol.* **118**: 1051-7 (1996).
73. Raes A., Van de Vijver G., Goethals M., van Bogaert P.P.: Use-dependent block of I_h in mouse dorsal root ganglion neurons by sinus node inhibitors. *Br. J. Pharmacol.* **125**: 741-750 (1998).
74. Bucchi A., Baruscotti M., DiFrancesco D.: Current-dependent block of rabbit sino-atrial node I(f) channels by ivabradine. *J. Gen. Physiol.* **120**: 1-13 (2002).
75. Harris N.C., Constanti A.: Mechanism of block by ZD 7288 of the hyperpolarization-activated inward rectifying current in guinea pig substantia nigra neurons in vitro. *J. Neurophysiol.* **74**: 2366-2378 (1995).
76. Shin H., Rothberg B.S., Yellen G.: Blocker state dependence and trapping hyperpolarization-activated cation channels: evidence for an intracellular activation gate. *J. Gen. Physiol.* **117**: 91-102 (2001).
77. Kobinger W., Lillie C.: Cardiovascular characterization of UL-FS 49, 1,3,4,5-tetrahydro-7,8-dimethoxy-3-[3-][2-(3,4-dimethoxyphenyl)ethyl]methylimino]propyl]-2H-3-benzazepin-2-on hydrochloride, a new "specific bradycardic agent". *Eur. J. Pharmacol.* **104**: 9-18 (1984).
78. Kedem J., Acad B.A., Weiss H.R.: Pacing during reperfusion elevates regional myocardial oxygen consumption. *Am. J. Physiol.* **259**: H872-H878 (1990).
79. Kobinger W., Lillie C., Pichler L.: Cardiovascular actions of N-allyl-clonidine (ST 567), a substance with specific bradycardic action. *Eur. J. Pharmacol.* **58**: 141-150 (1979).
80. Dammgen J., Kadatz R., Diederer W.: Cardiovascular actions of 5,6-dimethoxy-2-(3-[(alpha-(3,4-dimethoxy)-phenylethyl)-methylamino]-propyl)-phthalimidine (AQ-A 39), a specific bradycardic agent. *Arzneimittelforschung*. **31**: 666-670 (1981).
81. Kobinger W., Lillie C., Pichler L.: N-Allyl-derivative of clonidine, a substance with specific bradycardic action at a cardiac site. *Naunyn Schmiedebergs Arch. Pharmacol.* **306**: 255-262 (1979).
82. Kobinger W., Lillie C.: AQ-A 39 (5,6-dimethoxy-2-[3[[alpha-(3,4-dimethoxy)-phenylethyl]methylamino]propyl]phthalimidine), a specific bradycardic agent with direct action on the heart. *Eur. J. Pharmacol.* **72**: 153-164 (1981).
83. Shanks R.G.: The clinical pharmacology of alnidine and its side-effects. *Eur. Heart J.* **8** Suppl L: 83-90 (1987).
84. Frishman W.H., Pepine C.J., Weiss R.J., Baiker W.M.: Addition of zatebradine, a direct sinus node inhibitor, provides no greater exercise tolerance benefit in patients with angina taking extended-release nifedipine: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The Zatebradine Study Group. *J. Am. Coll. Cardiol.* **26**: 305-312 (1995).
85. Glasser S.P., Michie D.D., Thadani U., Baiker W.M.: Effects of zatebradine (ULFS 49 CL), a sinus node inhibitor, on heart rate and exercise duration in chronic stable angina pectoris. Zatebradine Investigators. *Am. J. Cardiol.* **79**: 1401-1405 (1997).
86. Borer J.S., Fox K., Jaillon P., Lerebours G.: Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* **107**: 817-823 (2003).
87. Tardif J.C.F.I., Tendera M., Fox K.F.: Anti-anginal and anti-ischemic effects of the If current inhibitor ivabradine versus atenolol in stable angina. A 4-month randomised, double-blind, multicenter trial. *Eur. Heart J.* **24**: 20 (2003).
88. Mulder P., Barbier S., Chagraoui A., Richard V., Henry J.P., Lallemand F., Renet S., Lerebours G., Mahlberg-Gaudin F., Thuillez C.: Long-term heart rate reduction induced by the selective I(f) current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. *Circulation* **109**: 1674-1679 (2004).
89. Granetzny A., Schwanke U., Schmitz C., Arnold G., Schafer D., Schulte H.D., Gams E., Schipke J.D.: Pharmacologic heart rate reduction: effect of a novel, specific bradycardic agent on the heart. *Thorac. Cardiovasc. Surg.* **46**: 63-69 (1998).
90. Aarons L.: Population pharmacokinetics: theory and practice. *Br. J. Clin. Pharmacol.* **32**: 669-670 (1991).
91. Ludden T.M.: Population pharmacokinetics. *J. Clin. Pharmacol.* **28**: 1059-1063 (1988).
92. Sheiner L.B., Rosenberg B., Marathe V.V.: Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J. Pharmacokinet. Biopharm.* **5**: 445-479 (1977).
93. Reynolds J.E.F.: *Martindale - The Extra Pharmacopoeia*, The Pharmaceutical Press London (1993).
94. Sheiner L.B., Rosenberg B., Melmon K.L.: Modelling of individual pharmacokinetics for computer-aided drug dosage. *Comput. Biomed. Res.* **5**: 411-459 (1972).

95. Sheiner L.B.: Analysis of pharmacokinetic data using parametric models--1: Regression models. *J. Pharmacokinet. Biopharm.* **12**: 93-117 (1984).
96. Vozeh S., Katz G., Steiner V., Follath F.: Population pharmacokinetic parameters in patients treated with oral mexiletine. *Eur. J. Clin. Pharmacol.* **23**: 445-451 (1982).
97. Sheiner L.B., Beal S.L.: Evaluation of methods for estimating population pharmacokinetics parameters. I. Michaelis-Menten model: routine clinical pharmacokinetic data. *J. Pharmacokinet. Biopharm.* **8**: 553-571 (1980).
98. Sheiner L.B., Beal S.L.: Some suggestions for measuring predictive performance. *J. Pharmacokinet. Biopharm.* **9**: 503-512 (1981).
99. Sheiner L.B., Beal S.L.: Evaluation of methods for estimating population pharmacokinetic parameters. III. Monoexponential model: routine clinical pharmacokinetic data. *J. Pharmacokinet. Biopharm.* **11**: 303-319 (1983).
100. Steimer J.L., Mallet A., Golmard J.L., Boisvieux J.F.: Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the nonlinear mixed-effect model. *Drug Metab. Rev.* **15**: 265-292 (1984).
101. Sheiner L.B., Beal S., Rosenberg B., Marathe V.V.: Forecasting individual pharmacokinetics. *Clin. Pharmacol. Ther.* **26**: 294-305 (1979).
102. Beal S.L., Sheiner L.B.: *NONMEM users guide*, NONMEM project group, University of California, San Francisco, CA (1992).
103. Sheiner L.B., Beal S.L.: Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. *J. Pharm. Sci.* **71**: 1344-1348 (1982).
104. Karlsson M.O., Thomson A.H., McGovern E.M., Chow P., Evans T.J., Kelman A.W.: Population pharmacokinetics of rectal theophylline in neonates. *Ther. Drug Monit.* **13**: 195-200 (1991).
105. Maire P., Barbaut X., Girard P., Mallet A., Jelliffe R.W., Berod T.: Preliminary results of three methods for population pharmacokinetic analysis (NONMEM, NPML, NPEM) of amikacin in geriatric and general medicine patients. *Int. J. Biomed. Comput.* **36**: 139-141 (1994).
106. Bruno R., Vivler N., Vergniol J.C., De Phillips S.L., Montay G., Sheiner L.B.: A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. *J. Pharmacokinet. Biopharm.* **24**: 153-172 (1996).
107. Thomson A.H., Whiting B.: Bayesian parameter estimation and population pharmacokinetics. *Clin. Pharmacokinet.* **22**: 447-467 (1992).
108. Vozeh S., Muir K.T., Sheiner L.B., Follath F.: Predicting individual phenytoin dosage. *J. Pharmacokinet. Biopharm.* **9**: 131-146 (1981).
109. Center for Drug Evaluation and Research C.D.E.R.: Population pharmacokinetics. FDA (Hrsg.), *Guidance for Industry*, Rockville (1999).
110. Shah V.P., Midha K.K., Dighe S.: Conference report. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. *Pharm. Res.* **9**: 588-592 (1992).
111. Gibaldi M., Perrier D.: *Pharmacokinetics*, Marcel Dekker Inc., New York, 2. Aufl. (1982).
112. Derendorf H., Gramatte T., Schaefer H.G.: *Pharmakokinetik. Einführung in die Theorie und Relevanz für die Arzneimitteltherapie*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 2. Aufl. (2002).
113. Wagner J.G.: *Pharmacokinetics for the Pharmaceutical Scientist*, Technomic Publishing Company Inc., Lancaster, Basel (1993).
114. Roth W., Bauer E., Heinzel G., Cornelissen P.J., van Tol R.G., Jonkman J.H., Zuiderwijk P.B.: Zatebradine: pharmacokinetics of a novel heart-rate-lowering agent after intravenous infusion and oral administration to healthy subjects. *J. Pharm. Sci.* **82**: 99-106 (1993).
115. Ragueneau I., Laveille C., Jochemsen R., Resplandy G., Funck-Brentano C., Jaillon P.: Pharmacokinetic-pharmacodynamic modeling of the effects of ivabradine, a direct sinus node inhibitor, on heart rate in healthy volunteers. *Clin. Pharmacol. Ther.* **64**: 192-203 (1998).
116. Duffull S.B., Chabaud S., Nony P., Laveille C., Girard P., Aarons L.: A pharmacokinetic simulation model for ivabradine in healthy volunteers. *Eur. J. Pharm. Sci.* **10**: 285-94 (2000).
117. Maitre P.O., Buhrer M., Thomson D., Stanski D.R.: A three-step approach combining Bayesian regression and NONMEM population analysis: application to midazolam. *J. Pharmacokinet. Biopharm.* **19**: 377-384 (1991).
118. StatSci: *S-Plus guide to statistical and mathematical analysis*, a division of Mathesoft, Inc, Seattle (1995).

119. Mandema J.W., Verotta D., Sheiner L.B.: Building population pharmacokinetic--pharmacodynamic models. I. Models for covariate effects. *J. Pharmacokinet. Biopharm.* **20**: 511-528 (1992).
120. Jonsson E.N., Karlsson M.O.: Xpose-an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput. Methods Programs Biomed.* **58**: 51-64 (1999).
121. Akaike H.: Canonical correlation analysis of time series and the use of an information criterion. In: Mehra, R.K.; Lainiotis, D.G. (Hrsg.), *System identification: Advances and case studies*, Academic Press, New York, 27-96 (1976).
122. Jonsson E.N., Karlsson M.O.: Automated covariate model building within NONMEM. *Pharm. Res.* **15**: 1463-1468 (1998).
123. Aarons L.: Software for population pharmacokinetics and pharmacodynamics. *Clin. Pharmacokinet.* **36**: 255-264 (1999).
124. Beal S.L.: Population pharmacokinetic data and parameter estimation based on their first two statistical moments. *Drug Metab. Rev.* **15**: 173-193 (1984).
125. Karlsson M.O., Jonsson E.N., Wiltse C.G., Wade J.R.: Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. *J. Pharmacokinet. Biopharm.* **26**: 207-246 (1998).
126. Yano Y., Beal S.L., Sheiner L.B.: Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check. *J. Pharmacokinet. Pharmacodyn.* **28**: 171-92 (2001).
127. Vozeh S., Steimer J.L., Rowland M., Morselli P., Mentre F., Balant L.P., Aarons L.: The use of population pharmacokinetics in drug development. *Clin. Pharmacokinet.* **30**: 81-93 (1996).
128. Sachs L.: *Angewandte Statistik*, Springer Verlag, New York (1992).
129. Hamann S.R., Blouin R.A., McAllister R.G., Jr.: Clinical pharmacokinetics of verapamil. *Clin. Pharmacokinet.* **9**: 26-41 (1984).
130. Amidon G.L., Lennernas H., Shah V.P., Crison J.R.: A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* **12**: 413-420 (1995).
131. Lalka D., Griffith R.K., Cronenberger C.L.: The hepatic first-pass metabolism of problematic drugs. *J Clin. Pharmacol* **33**: 657-669 (1993).
132. Kunta J.R., Lee S.H., Perry B.A., Lee Y.H., Sinko P.J.: Differentiation of gut and hepatic first-pass loss of verapamil in intestinal and vascular access-ported (IVAP) rabbits. *Drug Metab Dispos.* **32**: 1293-1298 (2004).
133. Greenblatt D.J., Arendt R.M., Abernethy D.R., Giles H.G., Sellers E.M., Shader R.I.: In vitro quantitation of benzodiazepine lipophilicity: relation to in vivo distribution. *Br. J. Anaesth.* **55**: 985-989 (1983).
134. Mannhold R.: The impact of lipophilicity in drug research: a case report on beta-blockers. *Mini. Rev. Med. Chem.* **5**: 197-205 (2005).
135. Schunack W., Mayer K., Haake M.: *Arzneistoffe*, Vieweg, Braunschweig; Wiesbaden; 2. Aufl. (1983).
136. van Bogaert P.P., Goethals M.: Blockade of the pacemaker current by intracellular application of UL-FS 49 and UL-AH 99 in sheep cardiac Purkinje fibers. *Eur J Pharmacol* **229**: 55-62 (1992).
137. Schomerus M., Spiegelhaider B., Stieren B., Eichelbaum M.: Physiologic disposition of Verapamil in man. *Cardiovasc. Res.* **10**: 605-612 (1976).
138. Koike Y., Shimamura K., Shudo I., Saito H.: Pharmacokinetics of verapamil in man. *Res. Commun. Chem. Pathol. Pharmacol.* **24**: 37-47 (1979).
139. Woodcock B.G., Rietbrock I., Vohringer H.F., Rietbrock N.: Verapamil disposition in liver disease and intensive-care patients: kinetics, clearance, and apparent blood flow relationships. *Clin. Pharmacol. Ther.* **29**: 27-34 (1981).
140. Eichelbaum M., Somogyi A., von Unruh G.E., Dengler H.J.: Simultaneous determination of the intravenous and oral pharmacokinetic parameters of D,L-verapamil using stable isotope-labelled verapamil. *Eur. J. Clin. Pharmacol.* **19**: 133-137 (1981).
141. Ma M.K., Woo M.H., McLeod H.L.: Genetic basis of drug metabolism. *Am. J. Health Syst. Pharm.* **59**: 2061-2069 (2002).
142. Funaki T., Furuta S., Kaneniwa N.: Effect of metoclopramide on the absorption of cimetidine in rats. *J. Pharmacobiodyn.* **9**: 811-818 (1986).

143. Letendre L., Scott M., Dobson G., Hidalgo I., Aungst B.: Evaluating barriers to bioavailability in vivo: validation of a technique for separately assessing gastrointestinal absorption and hepatic extraction. *Pharm. Res.* **21**: 1457-1462 (2004).
144. Lindberg-Freijls A., Karlsson M.O.: Dose dependent absorption and linear disposition of cyclosporin A in rat. *Biopharm. Drug Dispos.* **15**: 75-86 (1994).
145. Colom H., Prunonosa J., Peraire C., Domenech J., Azcona O., Torrent J., Obach R.: Absolute bioavailability and absorption profile of cyanamide in man. *J. Pharmacokinet. Biopharm.* **27**: 421-36 (1999).
146. Chulavatnatol S., Charles B.G.: Determination of dose-dependent absorption of amoxycillin from urinary excretion data in healthy subjects. *Br. J. Clin. Pharmacol.* **38**: 274-277 (1994).
147. Murata K., Noda K., Kohno K., Samejima M.: Pharmacokinetic analysis of concentration data of drugs with irregular absorption profiles using multi-fraction absorption models. *J. Pharm. Sci.* **76**: 109-113 (1987).
148. Savic R., Jonker D.M., Kerbusch T., Karlsson M.O.: Evaluation of a transit compartment model versus lag time model for describing drug absorption delay, *13th Population Approach Group Europe Meeting*, Uppsala, Schweden, Abstr. 513 (2004).
149. Sun H., Fadiran E.O., Jones C.D., Lesko L., Huang S.M., Higgins K., Hu C., Machado S., Maldonado S., Williams R., Hossain M., Ette E.I.: Population pharmacokinetics. A regulatory perspective. *Clin. Pharmacokinet.* **37**: 41-58 (1999).
150. Aarons L., Karlsson M.O., Mentre F., Rombout F., Steimer J.L., Van Peer A.: Role of modelling and simulation in Phase I drug development. *Eur. J. Pharm. Sci.* **13**: 115-122 (2001).
151. Steimer J.L., Vozeh S., Racine-Poon A.: The Population Approach: Rationale, Methods, and Applications in Clinical Pharmacology and Drug Development. In: Welling PG, Balant LP (Hrsg.), *Pharmacokinetics of Drugs (Handbook of Experimental Pharmacology)*, Springer Verlag, Berlin, Heidelberg, 404-451 (1994).
152. Gieschke R., Steimer J.L.: Pharmacometrics: modelling and simulation tools to improve decision making in clinical drug development. *Eur. J. Drug Metab. Pharmacokinet.* **25**: 49-58 (2000).
153. Duffull S.B., Aarons L.: Development of a sequential linked pharmacokinetic and pharmacodynamic simulation model for ivabradine in healthy volunteers. *Eur. J. Pharm. Sci.* **10**: 275-284 (2000).
154. Holford N.H., Sheiner L.B.: Pharmacokinetic and pharmacodynamic modeling in vivo. *CRC Crit. Rev. Bioeng.* **5**: 273-322 (1981).
155. Dingemanse J., Haussler J., Hering W., Ihmsen H., Albrecht S., Zell M., Schwilden H., Schuttler J.: Pharmacokinetic-pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects. *Br. J. Anaesth.* **79**: 567-574 (1997).
156. Manz M., Reuter M., Lauck G., Omran H., Jung W.: A single intravenous dose of ivabradine, a novel I(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology* **100**: 149-155 (2003).
157. Kaneko A., Tachibana M.: A voltage-clamp analysis of membrane currents in solitary bipolar cells dissociated from Carassius auratus. *J. Physiol.* **358**: 131-152 (1985).
158. Demontis G.C., Longoni B., Barcaro U., Cervetto L.: Properties and functional roles of hyperpolarization-gated currents in guinea-pig retinal rods. *J. Physiol.* **515** (Pt 3): 813-828 (1999).