
H. Gerhard Vogel (Ed.)

Franz Jakob Hock

Jochen Maas

Dieter Mayer

(Co-Editors)

Drug Discovery and Evaluation

Safety and Pharmacokinetic Assays

With 131 Figures and 125 Tables

 Springer

Dr. Reddy's Labs. v. Indivior UK Ltd, IPR2016-01113

Hans Gerhard Vogel
Bohl Str. 28
73430 Aalen
Germany
ProfGerhardVogel@aol.com

Q1
74
D
2

ISBN-10: 3-540-25638-5
ISBN-13: 978-3-540-25638-0

This publication is available also as:
Electronic publication under ISBN 3-540-29804-5 and
Print and electronic bundle under ISBN 3-540-33442-4

Library of Congress Control Number: 2006928067

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in other ways, and storage in data banks. Duplication of this publication or parts thereof is only permitted under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer-Verlag. Violations are liable for prosecution under the German Copyright Law.

Springer is part of Springer Science+Business Media
springer.com

© Springer-Verlag Berlin Heidelberg New York 2006
Printed in Germany

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publishers cannot guarantee the accuracy of any information about the application of operative techniques and medications contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Editor: Thomas Mager, Heidelberg
Development Editor: Andrew Spencer, Heidelberg
Production Editor: Frank Krabbes, Heidelberg
Cover Design: Frido Steinen-Broo, Spain

Printed on acid-free paper

SPIN: 10981627 2109 - 5 4 3 2 1 0

Contents

Section I Safety Pharmacology

Chapter I.A		
Introduction to Safety Pharmacology		3
Chapter I.B		
Status of Safety Pharmacology and Present Guidelines		5
I.B.1	Origins of Safety Pharmacology	5
I.B.2	Practice of Safety Pharmacology (ICH S7A)	9
I.B.3	Institutional Strategies	10
I.B.4	Future of Safety Pharmacology	10
Chapter I.C		
Central Nervous System (CNS) Safety Pharmacology Studies		15
I.C.1	General Considerations	15
I.C.2	Core Battery CNS Studies	18
I.C.2.1	Irwin Test	18
I.C.2.2	Activity Meter Test	22
I.C.2.3	Rotarod Test	24
I.C.2.4	Convulsive Threshold Tests	25
I.C.2.5	Barbital Interaction Test	27
I.C.2.6	Hot Plate Test	29
I.C.3	Supplementary CNS Studies	30
I.C.3.1	Cognitive Processes	30
I.C.3.1.1	Passive Avoidance Test	30
I.C.3.1.2	Morris Maze Test	32
I.C.3.1.3	Radial Maze Test	35
I.C.3.1.4	Social Recognition Test	37
I.C.3.1.5	Delayed Alternation Test	39
I.C.3.2	EEG Studies	42
I.C.3.2.1	QEEG	42
I.C.3.2.2	Sleep/Wake Cycle	45
I.C.3.3	Drug Dependence and Abuse	48
I.C.3.3.1	Drug Dependence	49
I.C.3.3.1.1	Non-Precipitated Withdrawal Test	49
I.C.3.3.2	Drug Abuse	51

Dr. Reddy's Labs. v. Indivior UK Ltd, IPR2016-01113

INDIVIOR EX 2023 - 3/20

I.C.3.3.2.1	Conditioned Place Preference Test	52
I.C.3.3.2.2	Drug Discrimination	54
I.C.3.3.2.3	Self-Administration	57
Chapter I.D		
Methods in Cardiovascular Safety Pharmacology		61
I.D.1	Background	61
I.D.1.1	General Considerations	62
I.D.2	In vivo Experimental Models for Cardiovascular Safety Pharmacology	65
I.D.2.1	Cardiovascular Safety Studies in Conscious Dogs and Other Species	65
I.D.2.2	Cardiovascular Safety Pharmacology Studies in Anesthetized Dogs and Other Species	68
I.D.2.3	Cardiovascular General Pharmacology Studies in Conscious Rats	70
I.D.3	In vitro Cardiovascular Safety Pharmacology Models	72
I.D.3.1	“High throughput”hERG Assays	72
I.D.3.1.1	Binding Competition Assays	72
I.D.3.1.2	Rubidium Flux Assays	73
I.D.3.1.3	Fluorescence Ion Channels Assays Using Voltage-Sensitive Dyes	73
I.D.3.1.4	Automated Patch Clamp Systems	74
I.D.3.2	Voltage Clamp Studies on Potassium Channels	74
I.D.3.2.1	General Characteristics of the Voltage Clamp Technique	74
I.D.3.2.2	Voltage Clamp Studies on Potassium Channels	75
I.D.3.2.3	Voltage Clamp Studies on hERG Potassium Channels in Heterologous Cell Systems	76
I.D.3.2.4	Studies on Potassium Channels in Isolated Ventricular Myocytes	78
I.D.3.3	Myocardial Action Potential Configuration	79
I.D.3.3.1	Studies in Isolated Purkinje Fibers	80
I.D.3.3.2	Studies in Isolated Guinea Pig Papillary Muscles	82
I.D.3.3.3	Arterially Perfused Wedge of Canine Left Ventricle	84
I.D.4	Models for Proarrhythmic Potential	84
I.D.4.1	Studies of Arrhythmogenic Effects in Isolated Heart Preparations	85
I.D.4.2	Langendorff Rabbit Heart (Screenit System)	86
I.D.4.3	Methoxamine-Induced Arrhythmia in Rabbits	87
I.D.4.4	Drug-Induced Proarrhythmic Effects in Dogs with Chronic AV Ablation	87
I.D.5	Supplemental and/or Follow-Up Studies	89
I.D.5.1	In-Depth Hemodynamic Analysis in Anesthetized Dogs	89
I.D.5.2	Measurement of Heart Dimensions in Anesthetized Dogs	90
I.D.5.3	Baroreceptor Reflexes	91
I.D.5.3.1	Influence on Orthostatic Hypotension	91
I.D.5.3.2	Bezold–Jarisch Reflex	92
I.D.5.4	Measurement of Cardiac Output and Regional Blood Flow with Microspheres	93

Chapter I.E		
Safety Pharmacology of Drugs for the Urinary Tract		95
I.E.1	General Functional Assessments	96
I.E.1.1	In vitro and in situ Assessments	96
I.E.1.1.1	Carbonic Anhydrase Inhibition in vitro	96
I.E.1.1.2	Inhibition of Xanthine Oxidase in vitro Indicating Hypouricemic Activity	97
I.E.1.1.3	Urate Uptake in Brush Border Membrane Vesicles	97
I.E.1.1.4	Patch Clamp Technique in Kidney Cells	98
I.E.1.1.5	Perfusion of Isolated Kidney Tubules	99
I.E.1.1.6	Isolated Perfused Kidney	102
I.E.1.1.7	Micropuncture Techniques in the Rat	103
I.E.1.1.8	Stop Flow Techniques	104
I.E.1.2	In vivo Techniques	104
I.E.1.2.1	Diuretic Activity in Rats (LIPSCHITZ Test)	104
I.E.1.2.2	Saluretic Activity in Rats	105
I.E.1.2.3	Diuretic and Saluretic Activity in Dogs	106
I.E.1.2.4	Evaluation of Renal Concentrating Ability	107
I.E.1.2.5	Clearance Methods	108
I.E.1.2.6	Fractional Excretion Methods	110
I.E.1.2.7	Diuretic and Uricosuric Activity in Mice	112
I.E.1.2.8	Inhibition of Allantoxanamide-Induced Hyperuricemia in Rats	113
I.E.1.2.9	Phenol Red Excretion in Rats	113
I.E.1.2.10	Uricosuric Activity in Relevant Animal Models	114
I.E.2	Assessment of Renal Injury	115
I.E.2.1	Assessment of Renal Injury by Serum Chemistry	115
I.E.2.2	Assessment of Renal Injury by Urinalysis	117
I.E.2.3	Assessment of Renal Injury by Urine Proteins	119
I.E.2.4	Assessment of Renal Injury by Urine Enzymes	121
I.E.3	Experimental Models of Renal Failure	124
I.E.3.1	Chronic Renal Failure in the Rat	124
I.E.3.2	Chronic Renal Failure after Subtotal (Five-Sixths) Nephrectomy in Rats	125
I.E.3.3	Experimental (Immune-Mediated) Glomerulonephritis	128
I.E.3.4	Toxicant-Induced Renal Injury	131
I.E.4	Assessment of the Lower Urinary Tract	133
I.E.4.1	In vivo Studies	133
I.E.4.1.1	Micturition Studies	133
I.E.4.2	Studies in Isolated Organs	135
I.E.4.2.1	Studies on Renal Pelvis	135
I.E.4.2.2	Studies on the Urinary Bladder and Internal Urethral Sphincter	137
I.E.4.2.3	Effects on the External Urethral Sphincter	139
I.E.4.2.4	Propagation of Impulses in the Guinea Pig Ureter	140
Chapter I.F		
Respiratory Function Assays in Safety Pharmacology		141
I.F.1	Respiratory Function Assays – General Approach	141
I.F.2	Respiratory Function in Conscious Rats	143
I.F.3	Respiratory Function in Monkeys and Dogs	145

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.