AMERICAN COLLEGE OF CLINICAL PHARMACOLOGY

The Journal of Clinical Pharmacology

Inadequate Pain Management: A Suicidogen (Dr. Jack Kevorkian: Friend or Foe?)

Toxicology Evaluation and Single Intravenous Dose Studies in Human Subjects

β-Blocker Use in Systolic Heart Failure and Dilated Cardiomyopathy

The Eleventh International Conference on AIDS: Cautious Celebration in Vancouver

Safety and Tolerance of Methylnaltrexone in Healthy Humans: A Randomized, Placebo-Controlled, Intravenous, Ascending-Dose, Pharmacokinetic Study

Bioavailability of Sublingual Buprenorphine

A Dose-Ranging Study of Azathioprine Pharmacokinetics After Single-Dose Administration of a Delayed-Release Oral Formulation

Perindopril/Hydrochlorothiazide Dose Combinations for the Treatment of Hypertension: A Multicenter Study

Safety and Efficacy of Monotherapy with Fantofarone, a Novel Calcium Channel Antagonist, in Patients with Chronic Stable Angina Pectoris

Temporal Variation in the Effects of Ophthalmic Timolol on Cardiovascular and Respiratory Functions in Healthy Men

Alterations in Pharmacodynamics of Anxiolytics in Abstinent Alcoholic Men: Subjective Responses, Abuse Liability, and Electroencephalographic Effects of Alprazolam, Diazepam, and Buspirone

COMPLETE CONTENTS INSIDE

January 1997
Vol. 37 No. 1

Official Publication of the American College of Clinical Pharmacology

This journal is indexed in *Index Medicus, Excerpta Medica, Current Contents,* and *Index Internacional de Cardiología*

For submission of manuscripts only: Deborah L. Keefe, MD, MPH, Editor, Journal of Clinical Pharmacology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021. Editorial office will accept inquiries by fax at (212) 717–3370. For **permission requests** contact Marie Wayne, Lippincott–Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106-3780; fax 215-238-4419. For **subscription information,** see below.

LIPPINCOTT–RAVEN PUBLISHERS

Publishing Staff
Publisher
MARCIA E. SEREPY
Production Editor
DARA L. COAN

Managing Editor
ELISA C. SCHULZ
Assistant Production Manager
PHYLLIS DAVIDSON

Advertising Sales Department
Lippincott–Raven Publishers
East Washington Square
Philadelphia, PA 19105
(215) 238-4273

The JOURNAL OF CLINICAL PHARMACOLOGY (ISSN 0091-2700) is published monthly by the American College of Clinical Pharmacology through Lippincott–Raven Publishers at 12107 Insurance Way, Hagerstown, MD 21740. Business offices are located at 227 East Washington Square, Philadelphia, PA 19106. Printed in the U.S.A.
Address for subscription information, orders, or changes of address (except Japan): Journal Fulfillment Department, Journal of Clinical Pharmacology, 12107 Insurance Way, Hagerstown, MD 21740, or call 1-800-638-3030. In Japan, contact Igaku-Shoin, Ltd, 1-28-36 Hongo, Bunkyo-ku, Tokyo 113, Japan.
Annual subscription rates: U.S.: $220.00 individual; $265.00 institution; special resident/student rate, $60.00. Canada and Mexico: $275.00 individual; $320.00 institution. The Canadian GST tax of 7% will be added to the subscription price of all orders shipped to Canada. Lippincott–Raven Publishers' GST identification number is 130876246. All other countries (except Japan): $288.00 individual; $333.00 institution (prices include $13.00 air freight delivery; air freight delivery occurs within 7–21 days worldwide). International subscriptions must be prepaid. Single copies $28.00. (Rates are subject to change.) In Japan, contact Igaku-Shoin, Ltd., 1-28-36 Hongo, Bunkyo-ku, Tokyo 113, Japan. Copies will be replaced without charge if the publisher receives a request within 90 days of the mailing date, both in the U.S. and worldwide.
POSTMASTER: Send address changes to JOURNAL OF CLINICAL PHARMACOLOGY, P.O. Box 1550, Hagerstown, MD 21741.
Articles are indexed in *Current Contents, Index Medicus, Social Sciences Citation Index, Biological Abstracts,* and *Chemical Abstracts.*

♾ Text printed on acid-free paper.

CONTENTS

Editorial	**Inadequate Pain Management: A Suicidogen (Dr. Jack Kevorkian: Friend or Foe?)** *Frederick J. Goldstein, PhD, FCP*	**1**
Commentary	**Toxicology Evaluation and Single Intravenous Dose Studies in Human Subjects** *Wayne A. Colburn, PhD, FCP*	**4**
Therapeutic Review	**β-Blocker Use in Systolic Heart Failure and Dilated Cardiomyopathy** *Thomas W. Hash II* *L. Michael Prisant, MD, FACC, FCP*	**7**
Current Issues in Clinical Pharmacology	**The Eleventh International Conference on AIDS: Cautious Celebration in Vancouver** *Milo Gibaldi, PhD*	**20**
Pharmacokinetics	**Safety and Tolerance of Methylnaltrexone in Healthy Humans: A Randomized, Placebo-Controlled, Intravenous, Ascending-Dose, Pharmacokinetic Study** *Joseph F. Foss, MD* *Michael Murphy, MD* *Michael F. O'Connor, MD* *Jonathan Moss, MD, PhD* *Chun-Su Yuan, MD, PhD* *Michael F. Roizen, MD*	**25**
	Bioavailability of Sublingual Buprenorphine *John Mendelson, MD* *Peyton Jacob III, PhD* *Robert A. Upton, PhD* *Reese T. Jones, MD* *E. Thomas Everhart, PhD*	**31**
	A Dose-Ranging Study of Azathioprine Pharmacokinetics After Single-Dose Administration of a Delayed-Release Oral Formulation *Bradley J. Zins, MD* *William J. Tremaine, MD* *William J. Sandborn, MD* *Douglas W. Mahoney, MS* *Jeffrey A. McKinney, BS* *Alan R. Zinsmeister, PhD* *Dennis C. Mays, PhD* *James J. Lipsky, MD* *Erik C. Van Os, MD*	**38**
Cardiovascular Pharmacology	**Perindopril/Hydrochlorothiazide Dose Combinations for the Treatment of Hypertension: A Multicenter Study** *Steven G. Chrysant, MD, PhD*	**47**

CONTENTS
(continued)

Safety and Efficacy of Monotherapy with Fantofarone, a Novel Calcium Channel Antagonist, in Patients with Chronic Stable Angina Pectoris **53**

Stephen P. Glasser, MD
Steven N. Singh, MD
Dennis P. Humen, MD
(for the Fantofarone Study Group)

Temporal Variation in the Effects of Ophthalmic Timolol on Cardiovascular and Respiratory Functions in Healthy Men **58**

Megumi Hara Umetsuki, MD
Tsutomu Kotegawa, MD, PhD
Koichi Nakamura, MD, PhD
Shigeyuki Nakano, MD, PhD
Kazuo Nakatsuka, MD, PhD

Psychopharmacology

Alterations in Pharmacodynamics of Anxiolytics in Abstinent Alcoholic Men: Subjective Responses, Abuse Liability, and Electroencephalographic Effects of Alprazolam, Diazepam, and Buspirone **64**

Domenic A. Ciraulo, MD
Jamie G. Barnhill, PhD
Ann Marie Ciraulo, RN
Ofra Sarid-Segal, MD
Clifford Knapp, PhD
David J. Greenblatt, MD
Richard I. Shader, MD

Departments

Erratum **73**

ACCP Announcements **77**

Abstract Submission Form **81**

Bioavailability of Sublingual Buprenorphine

John Mendelson, MD, Robert A. Upton, PhD, E. Thomas Everhart, PhD, Peyton Jacob III, PhD, and Reese T. Jones, MD

Buprenorphine administered sublingually is a promising treatment for opiate dependence. Utilizing a new, sensitive, and specific gas chromatographic electron-capture detector assay, the absolute bioavailability of sublingual buprenorphine was determined in six healthy volunteers by comparing plasma concentrations after 3- and 5-minute exposures to 2 mg sublingual and 1 mg intravenous buprenorphine. The amount of unabsorbed buprenorphine in saliva was measured after 2-, 4-, and 10-minute exposures to 2 mg sublingual buprenorphine in 12 participants. Pharmacokinetic parameters were analyzed by analysis of variance; bioequivalence was evaluated by the Schuirmann two-sided test. The 3- and 5- minute sublingual exposures each allowed 29 ± 10% bioavailability (area under the plasma concentration–time curve unextrapolated) and were bioequivalent. Buprenorphine recovered from saliva after 2-, 4-, and 10-minute exposures was, on average, 52% to 55% of dose. Increased saliva pH was correlated with decreased recovery from saliva. Study results indicate that bioavailability of sublingual buprenorphine is approximately 30%. Sublingual exposure times between 3 and 5 minutes produce equivalent results. Buprenorphine remaining in saliva causes an almost twofold overestimation of bioavailability.

Buprenorphine is a synthetic, lipophilic, potent (20–40 times greater analgesic potency than morphine) oripavine opiate analgesic effective in the treatment of opiate dependence.[1–3] Low oral bioavailability (approximately 14%),[4] caused largely by hepatic first-pass metabolism, makes sublingual administration an attractive alternative for treatment. In clinical trials, buprenorphine was administered as a 30% ethanol solution with participants retaining the dose sublingually for up to 10 minutes. Assessment of the pharmacokinetics of buprenorphine has been hampered by the difficulty in quantifying low plasma levels.[5] By measuring the amount of buprenorphine remaining in saliva after 2.5 or 10 minutes of sublingual exposure, a prior study inferred a sublingual bioavailability of 25% to 50%.[6] Differences in the amount of buprenorphine recovered from saliva with increased exposure were not evident.

Using a recently developed, sensitive, and specific gas chromatographic electron-capture detector (GC-ECD) assay for buprenorphine in plasma, absolute bioavailability of sublingual buprenorphine was estimated by comparing the plasma concentrations achieved with those from an intravenous dose. Sublingual exposure times of 3 and 5 minutes for bioavailability of buprenorphine were compared using the plasma-based method. In a separate study, those bioavailabilities were compared with estimates from a less direct method based upon the amount of buprenorphine recovered in saliva after exposures of 2, 4, and 10 minutes.

MATERIALS AND METHODS

Subjects

Six healthy volunteers (five men, one woman), 21 to 38 years of age (mean ± SD = 29 ± 6 years), partici-

From the Drug Dependence Research Center, Langley Porter Psychiatric Institute (Drs. Mendelson, Upton, Everhart, Jacobs, and Jones), the Department of Biopharmaceutical Sciences (Dr. Upton), and the Division of Clinical Pharmacology and Experimental Therapeutics (Dr. Jacob), University of California, San Francisco, San Francisco, California. Supported in part by United States Public Health Service grants DA01696 and DA00053 and contract No. 271-90-7307 from the National Institute on Drug Abuse, National Institutes of Health. Submitted for publication July 20, 1996; accepted in revised form October 16, 1996. Address for reprints: John Mendelson, MD, Drug Dependence Research Center, Langley Porter Psychiatric Institute, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA 94143-0984.

DOCKET ALARM

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.