



# The Journal of Clinical Pharmacology

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

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**Toxicology Evaluation and Single Intravenous  
Dose Studies in Human Subjects**

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**$\beta$ -Blocker Use in Systolic Heart Failure and  
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**The Eleventh International Conference on AIDS:  
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---

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Hypertension: A Multicenter Study**

---

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Fantofarone, a Novel Calcium Channel  
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Angina Pectoris**

---

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Timolol on Cardiovascular and Respiratory  
Functions in Healthy Men**

---

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

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COMPLETE CONTENTS INSIDE

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## CONTENTS

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

Psychopharma

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**CONTENTS**  
(continued)

1	<b>Safety and Efficacy of Monotherapy with Fantofarone, a Novel Calcium Channel Antagonist, in Patients with Chronic Stable Angina Pectoris</b>	<b>53</b>
4	<i>Stephen P. Glasser, MD</i> <i>Steven N. Singh, MD</i>	<i>Dennis P. Humen, MD</i> <i>(for the Fantofarone Study Group)</i>
7	<b>Temporal Variation in the Effects of Ophthalmic Timolol on Cardiovascular and Respiratory Functions in Healthy Men</b>	<b>58</b>
	<i>Megumi Hara Umetsuki, MD</i> <i>Tsutomu Kotegawa, MD, PhD</i> <i>Koichi Nakamura, MD, PhD</i>	<i>Shigeyuki Nakano, MD, PhD</i> <i>Kazuo Nakatsuka, MD, PhD</i>
20	<b>Psychopharmacology Alterations in Pharmacodynamics of Anxiolytics in Abstinent Alcoholic Men: Subjective Responses, Abuse Liability, and Electroencephalographic Effects of Alprazolam, Diazepam, and Buspirone</b>	<b>64</b>
25	<i>Domenic A. Ciraulo, MD</i> <i>Jamie G. Barnhill, PhD</i> <i>Ann Marie Ciraulo, RN</i> <i>Ofra Sarid-Segal, MD</i>	<i>Clifford Knapp, PhD</i> <i>David J. Greenblatt, MD</i> <i>Richard I. Shader, MD</i>
	<b>Departments</b>	
	<b>Erratum</b>	<b>73</b>
	<b>ACCP Announcements</b>	<b>77</b>
31	<b>Abstract Submission Form</b>	<b>81</b>
38	<b>Permission to Photocopy Articles.</b> This publication is protected by copyright. Permission to photocopy must be secured in writing from: Permissions Department, Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106-3780, FAX: 215-238-4419; OR Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, FAX: 508-750-4470; OR UMI, Box 49, 300 North Zeeb Road, Ann Arbor, MI 48106-1346, FAX: 313-761-1203.	

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# 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  $29 \pm 10\%$  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.*

**B**uprenorphine is a synthetic, lipophilic, potent (20–40 times greater analgesic potency than morphine) oripavine opiate analgesic effective in the treatment of opiate dependence.<sup>1–3</sup> Low oral bioavailability (approximately 14%),<sup>4</sup> 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.<sup>5</sup> 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%.<sup>6</sup> 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  $\pm$  SD =  $29 \pm 6$  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.

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