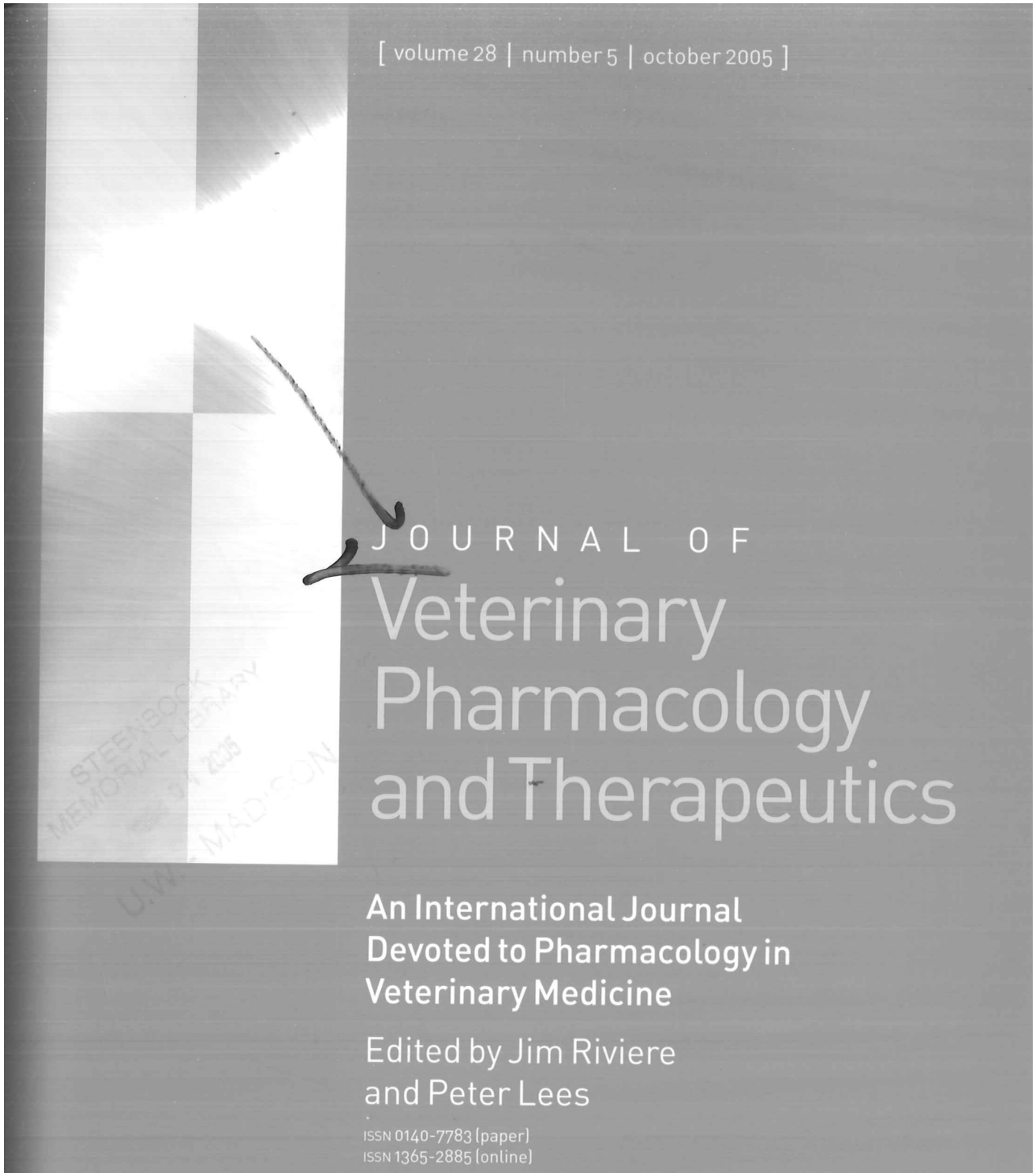
DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.



Veterinary Clinical Pharmacology and Therapeutics, and Chapter of Veterinary Pharmacology of the Australian College of Veterinary Scientists.

EDITORS

Jim Riviere
Burroughs Wellcome Fund Distinguished Professor, Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606, USA

Peter Lees
Department of Veterinary Basic Sciences, The Royal Veterinary College, Hawkshead Campus, North Mymms, Hatfield, Herts AL9 7TA, UK

REVIEW EDITOR

Mark Papich
Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, USA

BOOK REVIEW EDITOR

Cyril Clarke
264c McElroy Hall, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK 74078, USA

PRODUCTION EDITOR

Rona Gloag *email*: jvp@oxon.blackwellpublishing.com

EDITORIAL BOARD

A. Anadón *Spain*
M. Apley *USA*
D. Baggot *Grenada*
S.A. Brown *USA*
J.F. Burka *Canada*
C.R. Clarke *USA*
A. Craigmill *USA*
P. Delatour *France*
J. Elliott *UK*
J. Fink-Gremmels *The Netherlands*
D. Hennessy *Australia*
L. Horspool *The Netherlands*
C. Lanusse *Argentina*
M.F. Landoni *Argentina*
Q. McKellar *UK*
M. Martinez *USA*
C.S. Nebbia *Italy*
A. Nolan *UK*
M.G. Papich *USA*
E. Petzinger *Germany*
P. Reeves *Australia*
R.A. Sams *USA*
P. Sarasola *Spain*
S. Soback *Israel*
P. Taylor *UK*
P.L. Toutain *France*
L. Trepanier *USA*
R. Vulliet *USA*
Alistair Webb *USA*
T. Whittem *Australia*
R.F. Witkamp *The Netherlands*
Z. Yuan *China*

AIMS AND EDITORIAL POLICY

Information on the actions and interactions of medicinal products in domestic animals is dispersed across a wide variety of sources and much of the available material is difficult to find. However, the increasing interest to which is now being shown in the field is reflected in the emerging discipline of veterinary clinical pharmacology and therapeutics and the creation of organizations in the UK, USA and the continent of Europe concerned specifically with providing improved coordination and communication among pharmacologists and veterinary clinicians. This journal is designed for the publication of topics relating both to the clinical aspects of veterinary pharmacology, and to fundamental pharmacological topics of veterinary relevance. The highest scientific standards will be required of work submitted for publication, and these are matched by the speed and quality of production which the journal provides. Although the *Journal of Veterinary Pharmacology and Therapeutics* has been adopted by four national associations, it is completely international in character and publishes suitable material from all over the world.

VAT at 5%; customers in the EU should also add VAT at 5%, or provide a VAT registration number or evidence of entitlement to exemption. Customers in Canada should add 7% GST or provide evidence of entitlement to exception. The Premium institutional price includes online access to the current and all available previous year electronic issues. For other pricing options or more information about online access to Blackwell Publishing journals, including access information and terms and conditions, please visit http://www.blackwellpublishing.com/jvp

This journal is available online at *Blackwell Synergy*. Visit www.blackwell-synergy.com to search the articles and register for table of contents e-mail alerts.

PUBLISHER

The *Journal of Veterinary Pharmacology and Therapeutics* is published by Blackwell Publishing Ltd, 9600 Garsington Road, Oxford, OX4 2DQ, UK. Tel: +44 (0) 1865 776868, Fax: +44 (0) 1865 714591

Journal Customer Services: For ordering information, claims and any enquiry concerning your journal subscription please contact your nearest office:

UK: Email: customerservices@oxon.blackwellpublishing.com; Tel: +44 (0) 1865 778315; Fax: +44 (0) 1865 471775
USA: Email: subscrip@bos.blackwellpublishing.com; Tel: +1 781 388 8206 or 1 800 835 6770 (Toll free in the USA); **Fax:** +1 781 388 8232
Asia: Email: subs@blackwellpublishingasia.com; Tel: +61 3 8359 1011; Fax: +61 3 8359 1120

BACK ISSUES

Single issues from current and recent volumes are available at the current single issue price from Blackwell Publishing Journals. Earlier issues may be obtained from Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA. Tel: +1 518 537 4700, Fax: +1 518 537 5899, Email: psc@backsets.com

COPYRIGHT AND PHOTOCOPYING

© 2005 Blackwell Publishing Ltd. All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without the prior permission in writing from the Society for the Study of Addiction. Authorization to photocopy items for internal and personal use is granted by the copyright holder for libraries and other users registered with their local Reproduction Rights Organisation (RRO), e.g. Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA (www.copyright.com), provided the appropriate fee is paid directly to the RRO. This consent does not extend to other kinds of copying, such as copying for general distribution for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to Blackwell Publishing Ltd at: journalrights@oxon.blackwellpublishing.com

DISCLAIMER

The Publisher and the Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher or the Editors, neither does the publication of advertisements constitute any endorsement by the Publisher or the Editors, of the products advertised.

PAPER

Blackwell Publishing's policy is to use permanent paper from mills that operate a sustainable forestry policy, and which has been manufactured from pulp that is processed using acid-free and elementary chlorine-free practices. Furthermore, Blackwell Publishing ensures that the text paper and cover board used in all our journals has met acceptable environmental accreditation standards.

Printed in Singapore

Dr. Reddy's Labs. v. Indivior UK Ltd, IPR2016-01113
INDIVIOR EX. 2014 - 2/11

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Find authenticated court documents without watermarks at docketalarm.com.

NUMBER 5

SCIENTIFIC PAPERS

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration[1]

S. A. ROBERTSON*
B. D. X. LASCELLES*
P. M. TAYLOR† &
J. W. SEAR‡

*Department of Large Animal Clinical Sciences, University of Florida, FL, USA; †Taylor Monroe, Little Downham, Ely, UK; ‡Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK

Present address: Dr B. D. X. Lascelles, Comparative Pain Research Laboratory, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA

Robertson, S. A., Lascelles, B. D. X., Taylor, P. M., Sear, J. W. PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration. *J. vet. Pharmacol. Therap.* **28**, 453–460.

The pharmacokinetics and thermal antinociceptive effects of buprenorphine after intravenous (i.v.) or oral transmucosal (OTM) administration were studied in six adult cats. Plasma buprenorphine concentrations were measured using radioimmunoassay in a crossover study after a dose of 20 μg/kg given by the i.v. or OTM route. Oral pH was measured. Blood for drug analyses was collected before, and at 1, 2, 4, 6, 10, 15, 30, and 60 min and at 2, 4, 6, 8, 12, and 24 h after treatment. Thermal thresholds were measured before treatment, then following treatment every 30 min to 6 h, every 1 hour to 12 h and at 24 hours postadministration. Plasma buprenorphine concentration effect relationships were analyzed using a log-linear effect model. Oral pH was 9 in each cat. Peak plasma buprenorphine concentration was lower and occurred later in the OTM group but median bioavailability was 116.3%. Thermal thresholds increased significantly between 30 and 360 min in both groups. Peak effect was at 90 min and there was no difference at any time between the two groups. There was distinct hysteresis between plasma drug concentration and effect in both groups. Overall, OTM administration of buprenorphine is as effective as i.v. treatment and offers a simple, noninvasive method of administration which produces thermal antinociception for up to 6 h in cats.

(Paper received 21 December 2004; accepted for publication 14 June 2005)

S.A. Robertson, Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, P.O. Box 100136, Gainesville, FL 32610-0136, USA. E-mail: robertsons@mail.vetmed.ufl.edu

INTRODUCTION

The number of pet owning households has increased by over 10% in the past 15 years (Wise *et al.* 2002) and cats are now the most popular pet with current numbers estimated at between 70 and 77.7 million in the US alone. Concurrent with this has been a long awaited increase in the publication of studies relevant to the treatment of pain in this species, which has previously lagged behind the information available for dogs. The misconception that opioids cause excitement or 'morphine mania' in cats has been difficult to dispel. Such reports were based on early literature when large doses were

Robertson *et al.*, 2005). However, a recent European survey of opioid use in veterinary practice reveals that few practitioners (8.1%) used opioids in cats because of lack of knowledge of their pharmacology, fear of side-effects and controlled drug legislation despite the fact that almost 60% of respondents considered their control of pain in this species inadequate (Hugonnard *et al.*, 2004). In these authors opinion, opioids should comprise the backbone of acute pain management and butorphanol, buprenorphine, fentanyl, meperidine (pethidine), morphine, hydromorphone, and oxymorphone have all been used clinically in cats (Lascelles & Waterman, 1997; Lamont, 2002).

uncommon after buprenorphine, meperidine or butorphanol (Taylor *et al.*, 2001; Dixon *et al.*, 2002; Robertson *et al.*, 2003a). In contrast to hydromorphone, buprenorphine has not been associated with hyperthermia (Wegner *et al.* 2004; Niedfeldt & Robertson, In press). The disposition of buprenorphine (10 μg/kg) after intravenous (i.v.) and intramuscular (i.m.) administration in cats has been reported (Taylor *et al.* 2001). Buprenorphine (10 μg/kg) has been administered to cats by the oral mucosal route and was well accepted (Robertson *et al.*, 2003b). In that study uptake was verified by plasma drug analysis but no efficacy data were reported. Based on changes in thermal thresholds i.m. doses of 10 μg/kg resulted in a slow onset (2 h) of analgesia but once established this lasted at least 6 h (Robertson *et al.*, 2003a). The slow onset but long duration of this opioid is thought to be related to slow receptor binding and disassociation (Nolan *et al.*, 1987). Based on the positive attributes of buprenorphine the purpose of this study was to compare the pharmacokinetic and analgesic effects of a higher dose than previously reported in cats given by the i.v. and oral transmucosal (OTM) route and to model the kinetic data with drug effect.

METHODS

All procedures were approved by, the Institutional Animal Care and Use committee at the University of Florida. Six cats (five spayed females, one castrated male), aged 1–3 years with a weight range 4.1–6.6 kg were used in this study. All cats were considered healthy based on clinical examination and hematological and biochemical analyses.

On the day before each study, cats were anesthetized with isoflurane vaporized in oxygen. A 20 g 12 cm polyurethane catheter (Arrow International, Reading, PA, USA) was inserted in the jugular vein and secured with suture material and a light bandage (Vetrap™ bandaging tape, 3M™, St Paul, MN, USA). A cephalic catheter was placed in the contralateral vein in those cats scheduled to receive i.v. buprenorphine. In both the i.v. and OTM administration groups the forelimb was bandaged so that the researcher performing thermal threshold testing was unaware whether or not a catheter was in place. The left or right lateral thorax was shaved according to a predetermined randomized schedule and cats were weighed before recovering from anesthesia.

Food but not water was withheld for 6 h before each study, and both food and water were offered 1 h after drug administration. All cats received 20 μg/kg of buprenorphine hydrochloride (Buprenex®, Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA, USA) administered from a 1 mL syringe with the standard pH chart and recorded. After treatment, cats were observed for vomiting, salivation and behavioral changes. Pharmacokinetic and thermal threshold studies were conducted concurrently.

Pharmacokinetic study

Blood samples were withdrawn from the jugular catheter before and at 1, 2, 4, 6, 10, 15, 30, 45, and 60 min, and at 2, 4, 6, 12, and 24 h after drug dosing. The volume of blood collected was adjusted for each individual so that less than 10% of the cat's total blood volume was removed over the 24-hour study period (1.5–2.0 mL per sample). An equal volume of 0.9% saline was injected after each sample was withdrawn. Blood was transferred to lithium heparin tubes and centrifuged (2000 *g*) for 10 min. Plasma was separated and stored at −20 °C for a maximum of 3 months before buprenorphine assays were performed.

Drug analysis

Plasma buprenorphine concentrations were measured using an Iodine^{125}-labeled radio-immunoassay (Buprenorphine double antibody RIA kit, EuroDPC Ltd, Glyn Rhonwy, Gwynnedd, UK). The limit of detection of the assay was 0.1 ng/mL. In the concentration range of 0.1–6.0 ng/mL the inter- and intra-assay coefficient of variation (CV) was 5.9–7.4%; at higher concentrations the inter-assay CV was 7.7–18% (Taylor *et al.*, 2001). Plasma concentrations were linear over one and twofold dilutions and recovery was greater than 95%. The radioimmunoassay shows some cross-reactivity with buprenorphine-3-glucuronide (B-3-G) (DPC Product Characteristics). The metabolites of buprenorphine in cats have not been identified.

Thermal threshold testing

The thermal threshold testing system used was that described by Dixon *et al.* (2002). Briefly, a heater element and temperature sensor housed in a small probe was held against the cats' thorax with an elasticized band and pressure bladder to ensure consistent contact. The skin temperature was recorded before each test, then the heater activated. When the cat responded by flinching, turning or jumping the stimulus was terminated and the threshold temperature recorded. The testing system was designed to terminate heating when a temperature of 55 °C was reached. Three baseline temperatures were recorded at 15-minute intervals before treatment. A single person (BDXL) performed the thermal threshold tests and was blinded to the treatment. Thermal thresholds were measured every 30 min to 6 h, every 1 hour to 12 h and at 24 h postadministration. The

Dr. Reddy's Labs. v. Indivior UK Ltd, IPR2016-01113
INDIVIOR EX. 2014 - 5/11

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.