

The Medical Letter publications are protected by US and international copyright laws.
Forwarding, copying or any other distribution of this material is strictly prohibited.

For further information call: 800-211-2769

The Medical Letter®

On Drugs and Therapeutics

Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 48 (Issue 1237)
June 19, 2006

www.medicalletter.org

IN BRIEF

One Drop or Two?

Many prescriptions for eye drops call for instillation of 1-2 drops. But Medical Letter consultants in ophthalmology seem to agree that all eye drops should generally be given in doses of only one drop.

The volume of a single drop can vary with the viscosity of the solution, the design of the dropper, and patient technique. The average volume of a drop is 35-50 microliters, but can be as high as 75 microliters. An eye brimming with fluid holds 30 microliters at best, so even one drop is often an overdose. A second either washes out the first or increases the possibility of systemic toxicity, and doubles the cost.

When two different drops are being used, they should be instilled at least 5 minutes apart.

Full-Text Search – The Medical Letter web site now has a full-text search available for articles from 2000 to the present. A link to the new search can be found at www.medicalletter.org/html/search.htm.

The Medical Letter®

On Drugs and Therapeutics

EDITOR: Mark Abramowicz, M.D.
DEPUTY EDITOR: Gianna Zuccotti, M.D., M.P.H., Weill Medical College of Cornell University
EDITOR, DRUG INFORMATION: Jean-Marie Pflomm, Pharm.D.
ADVISORY BOARD:
Jules Hirsch, M.D., Rockefeller University
James D. Kenney, M.D., Yale University School of Medicine
Richard B. Kim, M.D., Vanderbilt School of Medicine
Gerald L. Mandell, M.D., University of Virginia School of Medicine
Hans Meinertz, M.D., University Hospital, Copenhagen
Dan M. Roden, M.D., Vanderbilt School of Medicine
F. Estelle R. Simons, M.D., University of Manitoba
Neal H. Steigbigel, M.D., New York University School of Medicine
EDITORIAL FELLOWS:
Jane Gagliardi, M.D., Duke University Medical Center
Monika K. Shah, M.D., Columbia University College of Physicians and Surgeons
SENIOR ASSOCIATE EDITORS: Donna Goodstein, Amy Faucard
ASSISTANT EDITORS: Cynthia Macapagal Covey, Tracy Shields
MANAGING EDITOR: Susie Wong
PRODUCTION COORDINATOR: Cheryl Brown
DIRECTOR OF CME & EDUCATIONAL PROGRAMS: Catherine H. Bingham
VP FINANCE & OPERATIONS: Yosef Wissner-Levy

Founded in 1959 by
Arthur Kallet and Harold Aaron, M.D.

Copyright and Disclaimer: The Medical Letter is an independent nonprofit organization that provides health care professionals with unbiased drug prescribing recommendations. The editorial process used for its publications relies on a review of published and unpublished literature, with an emphasis on controlled clinical trials, and on the opinions of its consultants. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants or donations. The content of The Medical Letter is controlled by the Editor, who declares no conflict. The members of the Advisory Board are required to disclose any potential conflict of interest.

No part of the material may be reproduced or transmitted by any process in whole or in part without prior permission in writing. The editors do not warrant that all the material in this publication is accurate and complete in every respect. The editors shall not be held responsible for any damage resulting from any error, inaccuracy or omission.

Subscription Services

Mailing Address:
The Medical Letter, Inc.
1000 Main Street
New Rochelle, NY 10801-7537

Customer Service:
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
Web Site: www.medicalletter.org
E-mail: custserv@medicalletter.org

Permissions:
To reproduce any portion of this issue, please e-mail your request to: permissions@medicalletter.org

Subscriptions (US):
1 year - \$89; 2 years - \$151;
3 years - \$214. \$44.50 per year for students, interns, residents and fellows in the US and Canada.
CME: \$44 for 26 credits.

E-mail site license inquiries to:
info@medicalletter.org or call 800-211-2769 x315.
Special fees for bulk subscriptions. Special classroom rates are available. Back issues are \$12 each. Major credit cards accepted.

Copyright 2006. ISSN 1523-2859

METHYLPHENIDATE PRODUCTS FOR ADHD

DRUG	FORMULATIONS	DURATION OF ACTION	TYPICAL PEDIATRIC DOSAGE	COST ¹
Dexmethylphenidate				
<i>Focalin</i> (Novartis)	2.5, 5 or 10 mg tabs	5-6 h	10 mg PO bid, 4 hours apart	\$ 72.00
<i>Focalin XR</i>	5, 10 or 20 mg caps	8-12 h	20 mg PO in AM	96.60
Methylphenidate				
short-acting (immediate release)				
generic	5, 10 or 20 mg tabs	3-5 h	20 mg PO bid (or 10 mg tid)	32.40
<i>Ritalin</i> (Novartis)	5, 10 or 20 mg tabs			75.60
<i>Methylin</i> (Mallinckrodt)	5, 10 or 20 mg tabs; 2.5, 5 or 10 mg chewable tabs; 5 or 10 mg/5 mL PO solution			28.20
intermediate-acting				
generic	20 mg tabs	3-8 h	40 mg PO in AM	52.80
<i>Metadate ER</i> (Celltech)	10 or 20 mg tabs			51.60
<i>Methylin ER</i> (Mallinckrodt)	10 or 20 mg tabs			54.60
<i>Ritalin SR</i> (Novartis)	20 mg tabs			113.40
long-acting				
<i>Metadate CD</i> (Celltech)	10, 20, 30, 40, 50 or 60 mg caps	8-12 h	40 mg PO in AM	105.30
<i>Ritalin LA</i> (Novartis)	10, 20, 30 or 40 mg caps			91.50
<i>Concerta</i> (Alza)	18, 27, 36 or 54 mg tabs	10-12 h	36 mg PO in AM	104.10
<i>Daytrana</i> (Noven/Shire)	Transdermal patch ² ; see table below	10-12 h	15- or 20-mg patch in AM	149.10

1. Cost for 30 days' treatment, based on most recent data (April 30, 2006) from retail pharmacies nationwide available from Wolters Kluwer Health. *Daytrana* price based on AWP provided by manufacturer.

2. *Daytrana* is supplied in sealed trays containing 10 or 30 patches in individual pouches.

A transdermal patch formulation of methylphenidate (*Daytrana* – Noven/Shire) has been approved by the FDA for treatment of attention-deficit/hyperactivity disorder (ADHD) in patients ≥ 6 years old. Like other methylphenidate products, the patch is a schedule II controlled substance. According to the manufacturer, it will be available in pharmacies by the end of June.

PHARMACOKINETICS — After application of the patch, methylphenidate is not detected in plasma for about 3 hours (range 1-6 hours). Plasma concentrations of the more pharmacologically active *d*-enantiomer (*d*-MPH) peak after about 7-9 hours. In children, following a single transdermal methylphenidate application of about 9 hours, plasma concentrations were similar to those found with equivalent doses of long-acting oral methylphenidate (*Concerta*), but after repeat daily dosing, concentrations were almost double those of the oral drug, suggesting increased absorption with chronic dosing. The mean elimination half-life of *d*-MPH after removal of the patch (8-10 hours of wear time) is about 3-4 hours.¹

CLINICAL STUDIES — In a 2-week, double-blind, randomized crossover trial, 79 children 6-12 years old with

ADHD wore a methylphenidate or placebo patch 9 hours a day for 1 week and then crossed over to the other treatment.² The primary endpoint was the mean score on the Department subscale of the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Teacher Rating Scale measured at postdose hours 2 through 9 in a laboratory classroom setting. SKAMP-D scores were significantly better with the methylphenidate patch at all time points compared to placebo. Patients treated with the methylphenidate patch also attempted and answered correctly more math problems on the Permanent Product Measure of Performance (PERMP) scale.

A 2-week unpublished trial in 270 children 6-12 years old, summarized in the package insert, also compared the methylphenidate patch with placebo, but used a long-acting oral methylphenidate (*Concerta*) as an active control. ADHD symptoms measured by the Attention Deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS-IV) improved significantly more with transdermal and oral methylphenidate than with placebo. The study was not designed (not adequately powered) to detect differences in efficacy between the two methylphenidate formulations.

ADVERSE EFFECTS — Systemic effects with the patch have been dose-related and similar to those with oral forms of methylphenidate. In the trial that used long-acting oral methylphenidate as an active control, nausea, vomiting, decreased appetite, anorexia, weight loss, emotional lability and insomnia occurred more frequently with the patch than with oral

TRANSDERMAL METHYLPHENIDATE

PATCH SIZE	DELIVERY RATE*	DOSE/ 9 HOURS*
12.5 cm ²	1.1 mg/hr	10 mg
18.75 cm ²	1.6 mg/hr	15 mg
25 cm ²	2.2 mg/hr	20 mg
37.5 cm ²	3.3 mg/hr	30 mg

*According to the manufacturer.

methylphenidate. Tics were reported in 7% of patients using the patch compared to only 1% of those taking oral methylphenidate. In a long-term, open-label study that included 191 children wearing the patch for 12 hours a day for up to 40 months, the incidence of anorexia was 46% and that of insomnia was 30%.

Erythema and pruritus at the application site were common in short-term clinical studies. Contact sensitization to the patch, which has occurred, might lead to development of systemic sensitization to other forms of methylphenidate, precluding further use of the drug.

Due to reports of sudden death in patients with structural cardiac abnormalities taking methylphenidate, an FDA committee has recommended adding a black box warning to the labeling of all ADHD drugs against use in such patients.³ Mild growth suppression has been reported with long-term use of ADHD drugs and may be dose-related; adult height generally appears to be normal in patients who took these drugs during childhood.⁴⁻⁶

DRUG INTERACTIONS — The methylphenidate patch should not be used with a monoamine oxidase inhibitor (MAOI) or within 14 days of stopping one. Methylphenidate may inhibit the metabolism and might increase the toxicity of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors

Conivaptan (*Vaprisol*) for Hyponatremia

Conivaptan hydrochloride (*Vaprisol* – Astellas), a vasopressin antagonist, has been approved by the FDA for short-term intravenous (IV) treatment of euvolemic hyponatremia in hospitalized patients. Euvolemic hyponatremia is most often caused by the syndrome of inappropriate ADH secretion (SIADH), or by hypothyroidism or adrenal insufficiency. The drug has not been approved for treatment of hypervolemic hyponatremia, which is associated with congestive heart failure (CHF), cirrhosis and renal disease. It should not be used in hypovolemic hyponatremia, such as occurs when fluid losses are replaced by excessive amounts of hypotonic solutions.

MECHANISM OF ACTION — Arginine vasopressin (AVP), also called anti-diuretic hormone, binds to V_2 receptors in the renal collecting duct and, through insertion of aquaporins, increases the permeability of the collecting duct to water. Conivaptan is a V_2 -receptor antagonist; it decreases the permeability of the

PHARMACOLOGY

Drug Class	Arginine vasopressin (AVP) receptor antagonist
Mechanism of action	Antagonizes V_2 receptors in the renal collecting duct, resulting in excretion of free water (aquaresis)
Formulation	20 mg in 4-mL sterile glass ampules
Distribution	99% protein bound
Metabolism	Hepatic by CYP3A4
Excretion	Feces (83%); urine (12%, 1% unchanged)
Elimination half-life	5 hrs

renal collecting duct to water, resulting in excretion of free water.

The drug also antagonizes V_{1A} receptors in blood vessels and the heart. Stimulation of V_{1A} receptors leads to vasoconstriction and increases intracellular calcium levels in cardiac myocytes. It also increases protein synthesis in the myocardium, leading to cardiac hypertrophy.¹

STANDARD TREATMENT — Standard treatments for **acute** symptomatic euvolemic and hypervolemic hyponatremia include hypertonic saline infusion, fluid restriction and diuresis. For **chronic** asymptomatic (duration >48 hours) euvolemic and hypervolemic hyponatremia, treatments can include management of the underlying illness, fluid restriction, diuresis and provision of dietary solutes. The antibiotic demeclocycline (*Declomycin*, and others), which also inhibits the action of AVP, is sometimes used in euvolemic patients, but it can be nephrotoxic. Overly rapid correction of serum sodium with these treatments, particularly in patients with chronic hyponatremia, can cause neurologic complications due to osmotic demyelination.

CLINICAL STUDIES — Clinical trials were conducted using both oral and IV formulations of conivaptan. Oral conivaptan has about one-third the potency of the same amount of drug given IV. In an unpublished randomized trial, summarized in the package insert, 56 **euvolemic** patients with a mean initial serum sodium of 124 mEq/L received 40 or 80 mg of IV conivaptan per day, or placebo, in addition to standard care, primarily fluid restriction (≤ 2 L/day). The drug was given as a continuous infusion for 4 days following an IV loading dose of 20 mg over 30 minutes on day 1. In the 40-mg group, 67% of patients achieved an increase in serum sodium ≥ 6 mEq/L or a normal serum sodium concentration (≥ 135 mEq/L) after 4 days' treatment, compared to 29% with placebo. The cumulative effective water clearance by day 4 was 2.9 L with conivaptan, compared to 1.8 L in the placebo group.

In a 5-day study using oral conivaptan in 74 patients with **euvolemic or hypervolemic hyponatremia**, significantly more conivaptan-treated patients achieved a normal serum sodium or an increase of ≥ 6 mEq/L (48% with placebo, 71% with 40 mg, 82% with 80 mg).²

In a randomized, placebo-controlled double-blind trial in 142 patients with **heart failure** (New York Heart Association class III or IV), none of them hyponatremic, those receiving a single IV dose of conivaptan 10, 20 or 40 mg had a significant increase in urine output and decrease in urine osmolality. Those receiving 20 or 40 mg also had a significant decrease in pulmonary capillary wedge and right atrial pressures.¹

ADVERSE EFFECTS — Infusion site reactions, mostly mild, have occurred in about 50% of patients treated with conivaptan. Headache, thirst, hypokalemia, hypertension, vomiting, diarrhea and orthostatic hypotension have occurred in more than 5%. Overly rapid correction of serum sodium (defined as >12 mEq/L/24hr) occurred in 9% of patients in clinical trials, but none had permanent sequelae.

PREGNANCY — Conivaptan in less-than-therapeutic doses has caused adverse effects in animal fetuses. It is classified as category C for use in pregnancy (risk cannot be ruled out).

DRUG INTERACTIONS — Conivaptan is a substrate and inhibitor of CYP3A4. It is contraindicated for use with strong 3A4 inhibitors, such as itraconazole (*Sporanox*, and others), clarithromycin (*Biaxin*, and others) or ritonavir (*Norvir*), and should be given cautiously with other drugs metabolized by 3A4.³ Two cases of rhabdomyolysis have been reported in patients on statins who were treated with conivaptan.

DOSAGE AND COST — The initial dose of conivaptan is 20 mg IV over 30 minutes once, followed by a continuous infusion of 20 mg over 24 hours. If the response is insufficient, subsequent doses can be increased to 40 mg/24 hours. The total duration of treatment should not exceed 4 days. The cost of a 20-mg vial of conivaptan is \$315, according to the manufacturer.

CONCLUSION — Conivaptan hydrochloride (*Vaprisol*) is an arginine vasopressin (AVP) receptor antagonist now approved only for short-term IV treatment of euvolemic hyponatremia. Data supporting its use are limited, and overly rapid correction of serum sodium is a

concern. Its safety and efficacy for the treatment of heart failure remain to be established. □

1. J Udelson et al. Acute hemodynamic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001; 104:2417.
2. JK Ghali et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin-receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab* 2006; 91:2145.
3. CYP3A and drug interactions. *Med Lett Drugs Ther* 2005; 47:54.