

ADR Focus by Elizabeth Rudy, DVM, RPh

RARE ADVERSE DRUG REACTIONS: DRUG-INDUCED HICCUPS

Reprinted from *Drug Therapy Topics* 2004; 33(2):12-13.

Hiccups (or singultus) are defined as involuntary, spasmodic contractions of the inspiratory muscles followed by the abrupt and delayed closure of the glottis, producing the characteristic “hiccup” sound.¹ They are a universal phenomenon and are generally considered benign and of short duration. However, on rare occasions, hiccups can become “persistent” (lasting for more than 48 hours) or “intractable” (lasting for longer than 1 month).² Reports in the literature link persistent or intractable hiccups to serious patient distress, insomnia, dehydration, malnourishment, and death.³

The most common causes of hiccups include swallowed air, extreme temperatures of ingested food, diet, alcohol, and stress.³ Males and females experience transient hiccups at an equal rate, but persistent or intractable hiccups occur more frequently in males.⁴ Additionally, men experience hiccups more frequently from organic rather than psychogenic causes.⁵ Organic causes for hiccups have been categorized as postoperative (following central nervous system, intra-abdominal, intrathoracic, and urinary tract surgeries) or medical (including thoracic, abdominal, vascular, thyroid, and urinary tract diseases).⁵⁻⁷

Although the pathophysiology of hiccups hasn't been clearly defined, the reflex arc for the phenomenon appears to consist of an afferent limb (composed of the sensory component of the phrenic nerve, vagus nerve, and the sympathetic chain from T-6 to T-12); a central connection (a nondescript anatomical location between C-3 and C-5); and an efferent limb (primarily the phrenic nerve).^{1,3,8} Stimulation of any of the reflex arc limbs may result in hiccups.⁸

Treatment approaches for hiccups include both nonpharmacologic and pharmacologic interventions. Nonpharmacologic treatment attempts to disrupt the hiccup reflex arc by either stimulation or interruption of the vagal afferent limb or by interruption of the phrenic nerve.³ The pharmacologic approach to the treatment of hiccups involves the use of various drugs including anticonvulsants, chlorpromazine, lidocaine, nifedipine, quinidine, haloperidol, amitriptyline, baclofen, and metoclopramide.^{3,9}

Although drugs play a prominent role in the *treatment* of persistent or intractable hiccups, *drug-induced* hiccups are a rarely reported phenomenon. Thompson and Landry performed a comprehensive review of the literature and identified 25 cases of hiccups in which drugs were implicated as the primary cause.⁶ In this study, the most frequently reported causative

(continued next page)

FROM THE EDITOR

Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy & Therapeutics Committee. Following the Committee's review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, “No drug has only one action.” By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you believe is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

Reports in the literature link persistent or intractable hiccups with serious patient distress, insomnia, dehydration, malnourishment, and death.³

Intractable hiccups occur more frequently in men.⁴

The pathophysiology of hiccups has never been clearly defined.

The pharmacologic approach to the treatment of hiccups involves the use of various drugs including anticonvulsants, chlorpromazine, lidocaine, nifedipine, quinidine, haloperidol, amitriptyline, baclofen, and metoclopramide.

Drug-induced hiccups are a rarely reported phenomenon.

Drug-induced hiccups most frequently involve

- corticosteroids
- non-imipramine antidepressants
- dopaminergic agents
- antibiotics, especially β -lactams, macrolides, and fluoroquinolones.

RARE ADVERSE DRUG REACTIONS: DRUG-INDUCED HICCUPS continued

agents were corticosteroids (dexamethasone and methylprednisolone) and benzodiazepines (midazolam and chlordiazepoxide). However, after applying the strict criterion of the Naranjo algorithm to the data, these researchers concluded that there was currently insufficient evidence for any drug to be considered causative in the etiology of hiccups. Thompson and Landry also examined various studies that implicated specific drugs (methohexital, methsuximide, etomidate, ketamine) as the cause of hiccups. However, the researchers noted that assessing causality from this data was difficult for several reasons: the Naranjo algorithm could not be applied due to insufficient study details; and medical conditions, surgical procedures, and pre-existing complications may have been associated with the development of the hiccups.

Bagheri et al. used the French Pharmacovigilance Database to investigate the frequency of reports of drug-induced hiccups.¹⁰ Between 1985 and 1997, 53 cases of drug-induced hiccups were reported to this network. Of the total number of cases, 25% were attributed to corticosteroids, 15% to psychiatric medications (primarily non-imipraminic antidepressants), 13% to neurologic drugs (mostly dopaminergic antiparkinsonians), and 12% to anti-infectious drugs (β -lactams, macrolides, fluoroquinolones). The researchers noted that a diagnosis of drug-induced hiccups is difficult to make and often achieved only through the process of elimination.

Following reports of a high incidence of hiccups (>30%) in patients undergoing chemotherapy, Takiguchi et al. reviewed database information from Japanese pharmaceutical companies in an attempt to determine the frequency of hiccups associated with the use of specific chemotherapeutic agents.¹¹ Results from their review showed that hiccups occurred in 0.39% of chemotherapy patients on average (range = 0.08–6.03%). The authors point out that the high incidence of hiccups reported previously could be accounted for by the fact that most cancer chemotherapy regimens consist of multiple drugs including not only cytotoxic agents, but also corticosteroids and 5-HT₃ receptor antagonists. Combination drug therapy would make it difficult or impossible to identify the specific causative agent of hiccups.

There are multiple case reports in the recent literature that propose a cause and effect relationship between therapy with specific medications and the development of hiccups. These reports include the development of hiccups following treatment with oral perphenazine, thoracic epidural betamethasone/lidocaine injection, oral dexamethasone, imipenem/cilastatin injection, and oral oxandrolone.^{1,3,8,12,13}

Based on the limited information available, establishing a solid causal relationship for drug-induced hiccups is a difficult task. However, noting the ongoing reports in the literature that propose a link between specific medications and the induction of hiccups, the collection and analysis of more data to further elucidate the true frequency and nature of this elusive adverse drug reaction is recommended.

(see next pages for references)

RARE ADVERSE DRUG REACTIONS: DRUG-INDUCED HICCUPS continued**REFERENCES**

1. Miyaoka H, et al. Perphenazine-induced hiccups [letter]. *Pharmacopsychiat* 1999;32:81.
2. Cymot TC. Retrospective analysis of hiccups in patients at a community hospital from 1995-2000. *J Natl Med Assoc* 2002;94:480-83.
3. Slipman CW, et al. Persistent hiccup associated with thoracic epidural injection. *Am J Phys Med Rehabil* 2001;80(8):618-21.
4. Fischer CM. Protracted hiccup—a male malady. *Trans Am Neurol Assoc* 1967;1:128-29.
5. Souadjian JV, et al. Intractable hiccup: etiologic factors in 220 cases. *Postgrad Med* 1968;43:72-77.
6. Thompson DF, et al. Drug Induced hiccups. *Ann Pharmacother* 1997;31:367-9.
7. Launois S, et al. Hiccup in adults: an overview. *Eur Respir J* 1993;6:563-75.
8. Lossos IS. Comment: drug-induced hiccups [letter]. *Ann Pharmacother* 1997;31:1264.
9. Calvo E, et al. Cervical phrenic nerve block for intractable hiccups in cancer patients [letter]. *J Natl Cancer Inst* 2002;94(15):1175-76.
10. Bagheri H, et al. [Drug-induced hiccup: a review of the France pharmacologic vigilance database]. *Therapie* 1999;54(1):35-39.
11. Takiguchi Y, et al. Hiccups as an adverse reaction to cancer chemotherapy [letter]. *J Natl Cancer Inst* 2002;94(10):772.
12. Lucina M, et al. Imipenem/cilastatin-associated hiccups [letter]. *Ann Pharmacother* 1992;26:1459.
13. Dickerman RD, et al. The steroid-responsive hiccup reflex arc: competitive binding to the corticosteroid receptor? *Neuroendocrinol Lett* 2003;24(3-4):167-169.

New Warnings for MRI Contrast Agents Containing Gadolinium

The labeling for five gadolinium-containing contrast agents (Magnevist[®], MultiHance[®], Omniscan[®], OptiMARK[®], and ProHance[®]) now carry strong new warnings. These contrast agents are often used to improve the visibility of internal structures when patients undergo MRI procedures.

The new black-box warning describes risk factors and screening procedures for a serious condition related to gadolinium exposure called nephrogenic systemic fibrosis (NSF). NSF is characterized by fibrosis of the skin, muscle, and internal organs. It is debilitating and potentially fatal.

The warning states that patients with renal failure, hepato-renal syndrome, or liver transplants have a higher risk of developing NSF following the administration of gadolinium-based agents. Clinicians should avoid using gadolinium-based contrast agents for high-risk patients unless the diagnostic information is essential and cannot be obtained in any other way.

The new labeling contains other recommendations, including:

- Before using these agents, all patients should be evaluated for renal failure.
- The dose recommended in the product labeling should not be exceeded and gadolinium-containing agents should not be re-administered until sufficient time has elapsed to ensure elimination of the prior dose.
- Consider prompt dialysis for hemodialysis patients that require gadolinium-enhanced contrast procedures.

Additional information about this new gadolinium warning is available at <http://www.fda.gov/medwatch/safety/2007/safety07.htm#Gadolinium>.

UPDATE “DRUGS THAT INDUCE HEART FAILURE”

The July and August (2007) issues of *Drug Therapy Topics* (V36N7 and V36N8) contained a two-part article reviewing the drugs known to be associated with the development of heart failure. Since the publication of the article, FDA has issued separate communications regarding two drug classes newly linked to heart-related concerns.

PROTON PUMP INHIBITORS:

Two separate long-term clinical studies in patients with severe gastroesophageal reflux disease (GERD) associated the use of omeprazole (Prilosec[®]) and esomeprazole (Nexium[®]) with an increased risk of heart attacks, heart failure, and heart-related sudden death. After reviewing these and other data submitted by the company, FDA concluded that collectively, the data fail to suggest an increased risk of heart problems for patients treated with a proton pump inhibitor. Healthcare providers were urged not to change their prescribing practices and patients were urged not to change their use of proton pump inhibitors at this time.

Read the complete MedWatch Safety Alert and FDA communication about the ongoing safety review at: <http://www.fda.gov/medwatch/safety/2007/safety07.htm#Omeprazole>

THIAZOLIDINEDIONE DRUGS:

After reviewing postmarketing adverse event reports, FDA determined that an updated label with a boxed warning on the risks of heart failure is needed for the entire thiazolidinedione class of antidiabetic drugs. Currently two thiazolidinedione drugs are FDA approved: rosiglitazone (Avandia[®]) and pioglitazone (Actos[®]). The strengthened warning advises healthcare professionals to observe patients for the signs and symptoms of heart failure (e.g., excessive, rapid weight gain, shortness of breath, edema) after starting drug therapy. Patients who develop heart failure should receive appropriate management for the heart failure and use of the thiazolidinedione drug should be reconsidered.

Read the complete MedWatch Safety Alert and FDA Press Release at: http://www.fda.gov/medwatch/safety/2007/safety07.htm#rosi_pio

DRUG THERAPY TOPICS • VOL. 36, NO. 9

- ADR FOCUS—Rare Adverse Drug Reactions: Drug-Induced Hiccups; p39-42
- New Warnings for MRI Contrast Agents Containing Gadolinium; p41
- Update on “Drugs That Induce Heart Failure”; p41
- August P & T Committee Actions; p42

- Download the UW Medicine e-Drug Formulary to your PDA; p42

THE D-ZONE • VOL. 36, SUPP. 4

- Antibiotic Cross-Reactivity: A Quartet of Scenarios; S13-S16

UNIVERSITY OF
WASHINGTON

DRUG INFORMATION CENTER

BOX 354735 SEATTLE, WA 98195-4735

PHARMACY AND THERAPEUTICS COMMITTEE ACTIONS

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S), & COST [‡]	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE*
Aripiprazole (Abilify [®])	IV: 9.75 mg/mL (1.3mL)	Antipsychotic	Agitation associated with schizophrenia or bipolar mania	9.75mg IV
Continuous Renal Replacement Therapy Solutions	All commercially available formulations of two bicarbonate-based dialysis solutions, PrismaSate [®] (6 formulations) and PrismaSol [®] (7 formulations), were added to the UW Medicine formulary for use as continuous renal replacement therapy (CRRT). Use of the CRRT order form is required for the prescribing of these solutions by UW Medicine practitioners.			
OTHER ACTIONS				
Radiopharmaceuticals	The P&T Committee approved the 2007 Standard Dose List for Radiopharmaceuticals.			

[‡] Contact pharmacy for information on drug costs.

* Refer to product labeling for full prescribing information.

DOWNLOAD THE UW MEDICINE e-DRUG FORMULARY TO YOUR PDA

The UW Medicine Drug Formulary lists the drug products available for prescribing to UW patients and contains full-text clinical information from *A-to-Z Drug Facts*. The Formulary is updated during the third week of every month following UW Medicine Pharmacy and Therapeutics Committee meetings. The Formulary can be accessed electronically from HealthLinks by entering the word “formulary” in the search box. Choose the “UW Medicine Drug Formulary for Palm” or “UW Medicine Drug Formulary for PocketPC” hyperlink. The drug list requires 2MB of free space while the drug list with the *A-to-Z Drug Facts* requires 6MB of free space. Downloading is simple.