

Assistant Professor
Department of Cardiology
Ege University School of Medicine
Bornova
35100 Izmir, Turkey
fax 0090-232-343-53-92
canrfca@yahoo.com

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REFERENCES

- Hunt D, Kertes P, Venables S, Callaghan J, Harrison LC. Exacerbation of bronchial asthma following treatment with amiodarone. Demonstration of an antiadrenergic effect in vitro. *Chest* 1984;86:492-4.
- Drvota V, Haggblad J, Blange I, Magnusson Y, Sylven S. The effect of amiodarone on the β -adrenergic receptor is due to a downregulation of receptor protein and not to a receptor-ligand interaction. *Biochem Biophys Res Commun* 1999;255:515-20.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
- Package insert. Cordarone (amiodarone HCL). Philadelphia: Wyeth Pharmaceuticals, April 2004.
- Imamura H, Kinoshita O, Maruyama K, Izawa A, Uchikawa S, Kumazaki S, et al. Two cases of bronchial asthma after treatment with amiodarone. *Pacing Clin Electrophysiol* 2001;24:1563-5.

Influence of gender on the titration of medications for chronic heart failure

TO THE EDITOR: Studies suggest women with systolic heart failure (HF) experience a poorer prognosis than men,¹ and the apparent excess morbidity and mortality cannot be explained solely by differences in pathology or physiologic response to treatment.² Differences in disease management may contribute to this discrepancy. For example, life-prolonging angiotensin-converting enzyme (ACE) inhibitors are prescribed less often to women despite a lack of contraindications.³ The purpose of our study was to determine whether gender was independently associated with the aggressiveness of dosing established in HF therapies.

Methods. In a retrospective, cohort design, consecutive charts of patients with HF at the university were screened for prescribing data. Inclusion criteria were HF diagnosis after January 1, 1996, left-ventricular ejection fraction (LVEF) $\leq 40\%$, and age ≥ 40 years. Male ($n = 38$) and female ($n = 21$) cohorts were of similar age (mean $\pm$ SD, 64 ± 12 y), race (85% white), HF etiology (76% ischemic), New York Heart Association (NYHA) functional classification (78% II or III), and LVEF ($21\% \pm 7\%$). Doses of angiotensin (AT) antagonists (ACE inhibitors and AT receptor blockers) and β -blockers were standardized to enalapril and metoprolol equivalents, respectively.

Univariate comparisons included the Wilcoxon rank-sum test (age, weight, height, years since HF diagnosis, LVEF) and Fisher's exact test (race, HF etiology, NYHA functional class, comorbid illnesses, concomitant medications, primary care service subspecialty). Multivariate comparisons were based on linear (a natural log transformed response used, where appropriate, to account for skewed distributions) and logistic regression. The multivariate regressions utilized a model that included gender and all other covariates significantly ($\alpha < 0.1$) associated with the response upon univariate analyses.

Discussion. Based on the multivariate analysis, a history of cerebrovascular event, height, female gender, and final diastolic blood pressure were significantly associated with an increased median number of days for an upward titration of AT antagonists. After adjustment for these confounding factors, gender was independently associated with the number of days between dosage titrations ($p = 0.004$). The median number of days between uptitrations was 2.5 times (95% CI 1.4 to 4.7) longer in female than in male patients. Gender was also significantly associated with the odds of requiring more than one visit to uptitrate the dose ($p = 0.01$). The odds of requiring more than one visit on average to uptitrate for women were 34.0 times the odds for men (95% CI 2.0 to 565.2). There were no differences in final mean systolic blood pressure and mean heart rate between genders. There was no significant difference in the final mean maintenance dose of AT antagonists. No differences in uptitration or maintenance doses achieved with β -blockers were observed based on gender.

The results suggest that female gender was associated with less aggressive uptitration of AT antagonists as reflected in a longer median time interval before dosage uptitration and higher odds of requiring more than one clinic visit before dose uptitration when compared with male patients. Despite less aggressive uptitration, maintenance doses achieved were not significantly different for men and women. The reason for slower upward titration of dosage does not appear to be related to hemodynamic tolerability. To our knowledge, as of December 2, 2004, this is the first attempt to characterize the influence of gender on the aggressiveness of dose titration in chronic HF. Although the study results do not provide reasons why women's doses were increased more slowly, the importance of this study lies in the potential to increase awareness over issues related to the management of female cardiovascular patients.

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Tien MH Ng PharmD BCPS

Assistant Professor
Department of Pharmacy Practice
University of Nebraska Medical Center
Omaha, Nebraska
Assistant Professor
Department of Pharmacy
University of Southern California School of Pharmacy
1985 Zonal Avenue
Los Angeles, California 90089-9121
fax 323/442-1681
tienng@usc.edu

Julie A Stoner PhD

Assistant Professor
Department of Preventative and Societal Medicine
University of Nebraska Medical Center

Tom D Sears MD

Associate Professor
Department of Internal Medicine
University of Nebraska Medical Center

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REFERENCES

- Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, et al. Natural history and current practices in heart failure. *J Am Coll Cardiol* 1993;22(suppl):14A-19A.
- Philbin EF, DiSalvo TG. Influence of race and gender on care process, resource use and outcomes in congestive heart failure. *Am J Cardiol* 1998;82:76-81.
- Chin MH, Goldman L. Factors contributing to the hospitalization of patients with congestive heart failure. *Am J Public Health* 1997;87:643-8.

Medication labeling errors in non-English-speaking patients

TO THE EDITOR: Medication errors can occur at any stage from physician prescription, through pharmacy transcription and dispensing, to administration to the patient.¹ End-user education, which requires effective patient communication, is a mandatory step in the process of safe medication use and serves as a final check on errors that have persisted through the system.²

A national adult literacy survey reported that 40 million Americans are considered illiterate,³ and the 2000 census reported that 45 million Americans speak a language other than English at home.⁴ Some pharmacies have attempted to overcome the latter concern by providing education on prescribed medications and medication labeling in the patient's native language. Although seemingly useful, this is not a requirement by any state board of pharmacy.

We describe 2 pharmacy dispensing labeling errors, in which adverse events may have been prevented by removing the language barrier from the medication error equation.

Case 1. A 30-day-old Hispanic girl with non-English-speaking parents and a history of anoxic brain injury and seizures presented with lethargy and decreased appetite. She had been discharged from the neonatal intensive care unit 5 days pri-

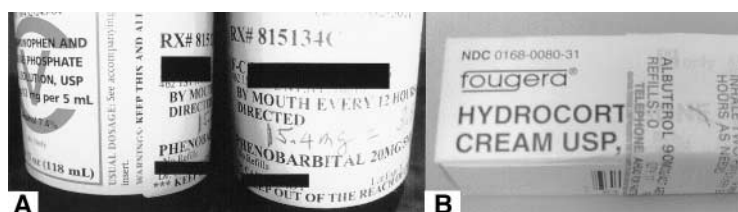


Figure 1. A bottle of Tylenol #2 was relabeled as phenobarbital by the pharmacy (A); hydrocortisone 1% cream was mislabeled "albuterol" (B).

or with a prescription for phenobarbital elixir 20 mg/5 mL twice daily that was filled by the outpatient hospital pharmacy. In the emergency department (ED), it was discovered that a bottle of Tylenol #2 (acetaminophen 120 mg plus codeine 12 mg/5 mL) had been relabeled by the pharmacy as phenobarbital 20 mg/5 mL (Figure 1A). The infant's serum acetaminophen concentration was 2.7 µg/mL (therapeutic range 10–30), urine tested positive for opiates, and serum phenobarbital concentration was negative. She recovered with conservative therapy.

Case 2. A 37-year-old non-English-speaking South Asian man with a history of asthma treated with albuterol presented to the ED with a severe exacerbation. Following several nebulized albuterol treatments and oral prednisone, his symptoms resolved completely. Concerns for the recurrence of such a severe attack while on appropriate outpatient therapy prompted the physician to ask the patient to demonstrate the method by which he used his albuterol inhaler. The patient removed from his pocket a box containing a tube of hydrocortisone 1% cream and applied it to the inside of his nostrils. Further inspection of the box revealed that it had a label affixed to it by the outpatient hospital pharmacy that read "albuterol" with directions to use "two puffs every 6 hours as needed" (Figure 1B).

Discussion. Recognition of errors provides an opportunity for health-care professionals to improve our systems of delivering care. In both cases, errors were made in 2 of the steps identified by the Institute for Safe Medication Practices: medication labeling and patient education.⁵ Had the involved parties been able to read the medication labels and thereby note that the pharmacy-affixed label and the manufacturer label described 2 different medications, the outcome of these errors may have been prevented by the end users—the patients. The addition of computerized translation programs in all pharmacies to provide multilingual prescription labeling and drug information may allow patients to become more effective participants in the prevention of medication errors.

Jessica A Fulton DO

Fellow
Medical Toxicology
Bellevue Hospital Center and New York University
Medical Center
New York City Poison Control Center
455 First Avenue, Room 123
New York, New York 10016-9102
fax 212/447-8223
jessicafulton@yahoo.com

Lewis S Nelson MD FACEP FACMT

Director
Medical Toxicology Fellowship Program
Associate Director
New York City Poison Control Center
Attending Physician
Department of Emergency Medicine
Bellevue Hospital Center and New York University Medical Center
Assistant Professor of Clinical Surgery/Emergency Medicine
New York University School of Medicine

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REFERENCES

- Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274:29-34.
- McKay CA, Vena J. The medical toxicologist and medication errors. *Int J Med Toxicol* 2004;7:1.

- Youmans SL, Schillinger D. Functional health literacy and medication use: the pharmacist's role. *Ann Pharmacother* 2003;37:1726-9. DOI 10.1345/aph.1D070
- Flores G, Laws MB, Mayo SJ, Zuckerman B, Abrev M, Medina L, et al. Errors in medical interpretation and their potential clinical consequences in pediatric encounters. *Pediatrics* 2003;111:6-14.
- Institute for Safe Medication Practices Web site. www.ismp.org (accessed 2004 Oct 25).

Minocycline has no effect on the fibrinolytic activity of alteplase

TO THE EDITOR: Alteplase (tissue plasminogen activator) is the only Food and Drug Administration–approved treatment for acute ischemic stroke, but must be administered within 3 hours of symptom onset. Due to this short time window, it is estimated that only 1.6% of patients with ischemic stroke in the US receive alteplase.¹ There is, therefore, a need for new treatments that will benefit more patients.

Evidence suggests that minocycline is protective in rodent models of stroke even when administered 5 hours after the onset of ischemia.²⁻⁴ Minocycline has also been shown to be protective in models of other neurologic diseases.⁵ The neuroprotective effects of minocycline include reduction of inflammation by inhibiting microglial activation and prevention of apoptosis by inhibiting caspases.^{2,5} It is possible that minocycline may benefit patients presenting too late to receive alteplase. It is also possible that coadministration of alteplase and minocycline after ischemic stroke may confer greater benefit than alteplase alone. Before clinical trials to test the benefits of coadministration, it is important to determine whether minocycline has any effects on the activity of alteplase. The purpose of this study was to investigate the effect of minocycline on clot lysis by alteplase.

Methods. Recombinant alteplase was obtained in single-chain form from Cayman Chemical (Ann Arbor, MI). Methods were based upon a published protocol for the spectrophotometric measurement of clot lysis.⁶ Briefly, the dye Coomassie Brilliant Blue R-250 was bound to proteins in diluted plasma from human donors, and clots were formed by adding thrombin. The clots were washed, fresh diluted plasma was added, and the amount of lysis in the presence of various agents was measured by increasing absorbance at 540 nm due to the release of dye-bound proteins from the clot. Measurements were taken every 20 minutes for 3 hours, plus a final measurement after complete lysis occurred. Experiments were performed once in 7 individuals.

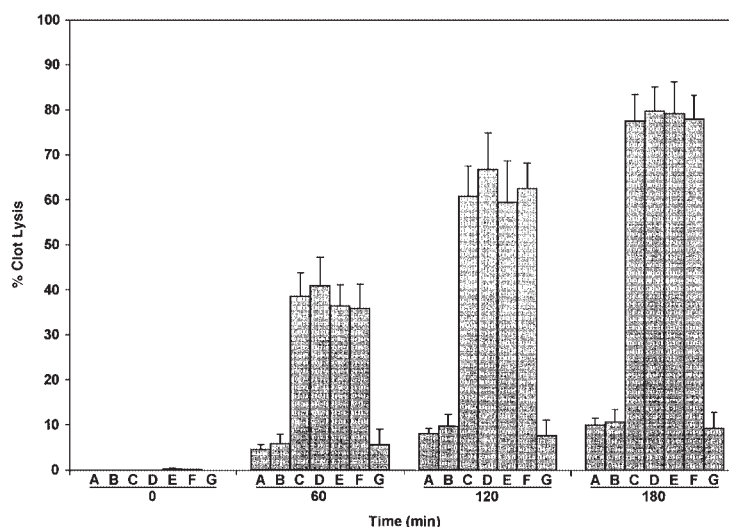


Figure 1. The effect of minocycline on clot lysis by alteplase. The mean amount of clot lysis obtained at 0, 60, 120, and 180 minutes is shown for each treatment. A = control, no drug treatment; B = minocycline 10 µg/mL; C = alteplase 8.3 µg/mL; D = alteplase 8.3 µg/mL + minocycline 2 µg/mL; E = alteplase 8.3 µg/mL + minocycline 5 µg/mL; F = alteplase 8.3 µg/mL + minocycline 10 µg/mL; G = alteplase 8.3 µg/mL + PAI-1 8.3 µg/mL. PAI-1 = plasminogen activator inhibitor.