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Significant Dose Differences in Donepezil Purchased From the United States and Canada

Chong-Zhi Wang, PhD, Guang-Jian Du, PhD, Zhong Zhen, MD, PhD, Tyler Calway, BS, and Chun-Su Yuan, MD, PhD

Department of Anesthesia & Critical Care, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637.

Background

Donepezil is a cholinesterase inhibitor that is commonly used to ameliorate the symptoms of Alzheimer disease (1). Because the high cost of this drug can be a burden to patients, consumers often purchase a generic form online from pharmacies based in Canada.

Objective

To measure the content of donepezil in tablets purchased from the United States and Canada and to compare the measured dose with the labeled dose.

Methods

We purchased brand-name donepezil tablets (Aricept, Eisai, Woodcliff Lake, New Jersey). We also purchased brand-name donepezil tablets from a hospital pharmacy in China in a package labeled “Eisai, China.” Using an Internet search engine, we selected 3 drugstores in Canada on the basis of high frequency of their appearance in our search. These Web sites listed donepezil as “generic.” We placed 5 prescription orders at these stores between March 2010 and September 2010 and received packages from India that contained tablets manufactured by Cipla, an Indian pharmaceutical company. We could not determine whether the tablets were packaged by Cipla or another company, a practice that is not unusual in some Asian countries.

We measured the dose of donepezil in tablets using high-performance liquid chromatography following the procedures of the U.S. Pharmacopeia (2) with a donepezil standard that we obtained from AstaTech (Bristol, Pennsylvania).

Findings

The ultraviolet spectra on high-performance liquid chromatography of all tablets from the United States, China, and Canada were similar to the donepezil standard, which indicated that the tested samples had the same chemical structure. Donepezil tablets purchased from the United States and China contained the dose that was on the label (99.6% and 101.0%, respectively). In contrast, the 5 orders of generic donepezil tablets from Canada contained only 58.4% to 67.1% of the dose on the label ($P < 0.01$, paired t test) (Table).

Discussion

Dose differences of the size that we found might have clinical consequences. For example, a dose of 5 to 10 mg of donepezil per day is used to treat mild to moderate Alzheimer disease. In 2010, the U.S. Food and Drug Administration (FDA) approved a donepezil dose of 23 mg per day for treatment of moderate to severe Alzheimer disease, but only after patients had been taking 10 mg daily for at least 3 months (3). A patient who received a labeled dose of 10 mg of donepezil per day for 3 months that was purchased from Canada could have been receiving only 6.3 mg per day. It is unknown whether a transition from 6.3 mg to 23 mg daily induces more adverse drug effects than a transition from 10 mg to 23 mg daily.

Generic drugs approved by the FDA are essentially identical to the brand-name drug in dose, strength, route of administration, safety, efficacy, and intended use (4). They must be bioequivalent, meaning that the ratios of generic to brand-name drug that compare the medications must be within the CI of 0.80 to 1.25 for the maximum plasma concentration of the drug and the area under the plot of drug plasma concentration against time after drug administration. The ratio is typically very close to 1.00; however, these assurances are not provided unless the FDA approves the drug. The donepezil we analyzed that was manufactured by Cipla was not FDA-approved.

In the past 10 years, medications have become more accessible for purchase from foreign countries via the Internet. Many consumers in the United States cross the border to purchase medications from Canada and other countries for economic reasons (5). We found remarkable dose differences between donepezil tablets from the United States compared with those from Canada, which increases the possibility that similar dose differences also exist in other drugs. As a result, we believe that drug quality deserves more attention from patients and their families, healthcare professionals, and regulatory authorities.

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References

1. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev.* 2006 CD001190. [PMID: 16437430].
2. U.S. Pharmacopeia. Authorized USP Pending Standards, Donepezil Hydrochloride Tablets. Rockville, MD: The United States Pharmacopeial Convention; 2008. Accessed at www.usp.org/pdf/EN/pendingStandards/donepezilHydrochlorideTablets_v1.pdf on 1 February 2011
3. Katz, R. U. S. Food and Drug Administration. Letter to Martina Struck, Ph.D, regarding NDA 022568, NDA Approval. Accessed at www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022568s000ltr.pdf on 1 February 2011
4. U. S. Food and Drug Administration. Generic Drugs: Questions and Answers. Silver Spring, MD: U.S. Food and Drug Administration; 2010. Accessed at www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm on 1 February 2011
5. Quon BS, Firszt R, Eisenberg MJ. A comparison of brand-name drug prices between Canadian-based Internet pharmacies and major U.S. drug chain pharmacies. *Ann Intern Med.* 2005; 143:397–403. [PMID: 16172438]. [PubMed: 16172438]

Table

Donepezil Samples and the Variation Between Labeled and Measured Doses.

Product Name	Manufacturer	Lot Number	Cost per Tablet, \$	Where Purchased	Labeled Dose, mg	Measured Dose, mg	Percentage of Labeled Dose (SD)
Donepezil (Aricept)	Eisai, Woodcliff Lake, New Jersey	004407	7.96	University of Chicago Hospital Pharmacy; Chicago, Illinois	10	9.96	99.6 (0.7)
Donecept-10 (generic) *	Cipla, Mumbai, India	DJ9788	0.65	Canada Drugs Online; Vancouver, British Columbia, Canada (www.canadadrugsonline.com)	10	5.84	58.4 (0.2)
Donecept-10 (generic) *	Cipla, Mumbai, India	DJ0558	0.79	Medstore International; Winnipeg, Manitoba, Canada (www.medstoreinternational.com)	10	6.48	64.8(1.8)
Donecept-10 (generic) *	Cipla, Mumbai, India	DJ0026	0.68	NorthWestPharmacy.com; Langley, British Columbia, Canada (www.northwestpharmacy.com)	10	6.71	67.1 (0.7)
Donecept-5 (generic) *	Cipla, Mumbai, India	DJ9787	0.63	Canada Drugs Online; Vancouver, British Columbia, Canada (www.canadadrugsonline.com)	5	3.15	62.9 (0.7)
Donecept-5 (generic) *	Cipla, Mumbai, India	DJ0408	0.70	Medstore International; Winnipeg, Manitoba, Canada (www.medstoreinternational.com)	5	3.08	61.6(0.5)

* These product names did not appear on the store Web site but appeared on the drug packages.