Weill Cornell Medical College

2013 AUG 16 A 11:55

Marcus M. Reidenberg, M.D., F.A.C.P.
Professor of Pharmacology,
Medicine and Public Health
Head, Division of Clinical Pharmacology

Weill Cornell Medical College
1300 York Avenue, Box 70
New York, NY 10065

Telephone: 212-746-6227
Fax: 212-746-8835
E-mail: mmreid@med.cornell.edu

Aug. 12, 2013

Division of Dockets Management, FDA
Dep't HHS
5630 Fishers Lane, room 1061
Rockville, MD 20852

Citizen Petition

The undersigned submits this petition to request the Commissioner of Food and Drugs to add a warning to the labeling of all nonprescription drugs products containing an ingredient with anticholinergic or histamine H1 inverse agonist effects.

Action Requested

The Commissioner of Food and Drugs should add a warning to the labeling of all nonprescription drug products containing an ingredient with anticholinergic or histamine H1 inverse agonist effects that this product can cause a confusional state including impaired attention, disorientation, and decreased power of concentration. Furthermore, this impairment of thinking, added to the similar effect of other prescription and nonprescription drug products containing drugs with the same effects can increase the degree of impaired cognition leading to an acute confusional state or delirium, especially in older people who are more at risk for this effect than younger people.

Statement of Grounds

As early as 1971, case reports were published suggesting that the confusional state following certain medications was due to the anticholinergic effect of the medicines. In 1972, Janowsky, et al, published a placebo-controlled study showing that the confusional state caused by some drugs with anticholinergic effects was not affected by

2013-6839

FDA-2013-P-1001

CP

placebo but was improved by physostigmine confirming the anticholinergic mechanism for the confusion.

Tune, et al, (1992) assessed the 25 drugs most commonly prescribed for the elderly for anticholinergic activity and found 10 had levels associated with impairment in normal elderly subjects. The American Geriatrics Society 2012 Beers criteria for potentially inappropriate medications for older adults include 12 first generation antihistamine H1 receptor antagonists/reverse agonists, many of which are nonprescription drugs. All have central nervous system activity (Brunton LL, et al., 2011).
Recently, the concept of anticholinergic risk or burden has been developed to help understand the hazard of cognitive impairment from multiple medications, each having anticholinergic activity. Duran, et al, reviewed multiple published risk scales and identified 100 drugs as having this activity and a way to sum the anticholinergic activity of each to determine the anticholinergic burden for a medication regimen of multiple drugs. Many of the high potency anticholinergic drugs on the list are nonprescription antihistamines including chlorphenamine, cyproheptadine, diphenhydramine, and hydroxyzine.

Many population-based observational studies have been published showing worse performance in elderly taking drugs with anticholinergic activity than controls who don't take these drugs. Two examples are Ancelin, et al (2006) and Landi, et al (2007). The idea that anticholinergic drugs and especially first generation antihistamines cause cognitive impairment has been so well documented that it is now standard textbook content in geriatrics (Halter JB, et al, 2009), neurology (Roper and Samuels, 2009), and internal medicine (Goldman and Schafer, 2012).

There are two prospective controlled trials showing the same thing. The first trial by Sunderland, et al (1987) showed that patients with dementia of the Alzheimer type had marked impairment to 0.25 mg doses of scopolamine compared to matched elderly control subjects. The other study by Pomara, et al (2008) showed normal healthy elderly with the APOE E4 gene (carriers) had impaired recall and mental slowness compared to non-carriers when given 2 mg trihexyphenidyl orally in a randomized double-blind placebo controlled study. These studies show that some subjects are at more risk than others for the confusion-causing effects of anticholinergic drugs.

Additional risk of prolonged anticholinergic drug therapy is an increase in the severity of amyloid plaque and neurofibrillary tangles seen in autopsied Parkinson's disease patients who were receiving anticholinergic drugs compared to those who had not received these drugs (Perry, et al, 2003). Another study found that subjects receiving 3 or more months of anticholinergic medications had an increased chance of becoming mildly cognitively impaired than those not receiving anticholinergic medications (Cai, et al, 2012).

Conclusion:

The above data show that cognitive impairment can occur in patients receiving drugs with anticholinergic activity. The degree of impairment relates to the sensitivity of the person, often the age, and the total amount of anticholinergic activity received by the person. Most of the drugs with this activity are prescribed by physicians who can control the total amount of prescribed anticholinergic medication received by the patient. But potent first generation antihistamines are nonprescription and can be added to the regimen by anybody, usually without knowing that they may lead to a confusional state. When this occurs in an elderly person, the cause may be attributed to something else and not to the added "safe" over-the-counter drug product. For this reason, we think that all nonprescription drug products with anticholinergic activity or inverse agonist histamine H1 activity should have an appropriately worded warning that they can cause confusion, impaired attention, disorientation, and decreased power of concentration.

Environmental Impact.
A warning in the labeling has no effect on the environment.

References

American Geriatrics Society 2012 Beers Criteria update Expert Panel. American Geriatrics Society Updated Beers criteria for potentially inappropriate medication use in older adults. JAGS, 2012; DOI: 10.1111/j.1532-5425.2012.03923.x

Ancelin ML, Artero S, Portet F, Dupuy A-M, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 2006. DOI: 10:1136/bmj.38740.439664.DE

Brunton LL, Chabner BA, Knollmann BC., eds, Goodman and Gilman's The Pharmacologic Basis of Therapeutics. New York, Mc Graw Hill, 2011, pp. 918-919.

Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. Alzheimer's and Dementia 2012; DOI: 10.1016/j.jalz.2012.02.005

Duran CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur j Clin Pharmacol 2013 DOI: 10.1007/s00228-013-1499-3.

Goldman L, Schafer AI, eds. Goldman's Cecil Medicine, 24th ed, New York, Elsevier, 2012, p.670.

Halter JB, et al., eds. Hazzard's Geriatric Medicine and Gerontology. 6th edition. New York, McGraw Hill, 2009, p.765.

Janowski DS, David JM, El-Yousef MK, Serkerke HJ. Amer J Psychiat 1972;129:136-7Perry EK, Kilford L, Lees AJ, Burn DJ,Perry RH. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. Ann Neurol 2003; 54: 235-8

Landi F, Russo A, Liperoti R, Cesari M, Barillaro C, Pahor M, Bernabei R, Onder G. Anticholinergic drugs and poopuoation function among frail elderly population Clin Pharmacol Ther 2007; 81:235-41

Pomara N, Belzer K, Hernando R, Pena CDL,Sidtis JJ. Increased mental slowing associated wtih the APOE e4 allele after trihexyphenidyl oral anticholinergic challenge in healthy elderly. Am J Geriatr Psychiatry. 2008; 16: 116-24.

Roper AH, Samuels MA, eds. Adams and Victors Principles of Neurology, New York, Mc Graw Hill, 2009, p. 404, 406

Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller EA III, Murphy DL. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls. Arch Gen Psychiatry 1987; 44:418-26.

Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delerium. Am J Psychiatry 1992; 149: 1393-4.

Certification

The undersigned certifies, that, to the best of knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petitioner.

Marcus M. Reidenberg, MD
1300 York Ave., Box 70
New York, NY 10065

Brittany Carson

212 746-6227

PRIORITY MAIL

D STATES POSTAL SERVICE

UNITED STATES POSTAL SERVICE

1004

20852

U.S. POSTAGE PAID NEW YORK,NY 10021 AUG 12, 13 AMOUNT

$14.55

00095010-13

RETURN RECEIPT REQUESTED

NAL RESTRICTIONS APPLY:

forms are required. Consult the nal Mail Manual (IMM) at pe.usps.gov etail associate for details.

RETURN RECEIPT REQUESTED

PLACE STICKER AT TOP OF ENVELOPE TO THE RIGHT OF THE RETURN ADDRESS. FOLD AT DOTTED LINE.

CERTIFIED MAIL™

7012 1640 0000 [illegible] 5461

AUG 15 2013

From:/Expéditeur:

M. Reidenberg
1300 York Ave
NY, NY 10065

To:/Destinataire:

Dkt DOCKETS MGMT
FDA
5630 Fishers Lane, Room 1061
Rockville, MD 20852