Central Nervous System Safety of Anticholinergic Drugs for the Treatment of Overactive Bladder in the Elderly

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ABSTRACT

Background: Overactive bladder (OAB) is characterized by urgency and increased frequency of micturition, with or without urinary urge incontinence. Anticholinergic agents are important in the treatment of OAB. However, concerns have emerged about their central nervous system (CNS) safety and the associated risk of cognitive impairment.

Objective: This article describes the CNS adverse effects of anticholinergic drugs used for the treatment of OAB, with particular emphasis on their use in the elderly. Its objective is to help physicians make optimal choices when selecting anticholinergic treatment for OAB.

Methods: Relevant data from the literature were identified primarily through a MEDLINE search of articles published through December 2003. The search terms included *overactive bladder, central nervous system, anticholinergic,* and *antimuscarinic.* This was not intended to be a systematic review, and articles were chosen for inclusion based on their pertinence to the focus on treatment of OAB in the elderly.

Results: Several anticholinergic drugs are available for the treatment of OAB, including oxybutynin, tolterodine, trospium chloride, and propiverine (not available in the United States). Among the agents reviewed, penetration of the blood–brain barrier (as predicted by lipophilicity, polarity, and molecular size and structure) is highest for oxybutynin, lower for tolterodine, and lowest for trospium chloride; limited data are available for propiverine. The total anticholinergic drug burden may also be important in determining the potential for CNS adverse effects. The spectrum of anticholinergic CNS adverse effects ranges from drowsiness to hallucinations, severe cognitive impairment, and even coma. The immediate-release (IR) and extended-release (ER) formulations of oxybutynin have been associated with cognitive impairment. In the only published clinical trial that was identified, no significant differences in CNS adverse effects were observed between the IR and ER formulations of tolterodine. There were few clinical data on the use of propiverine in patients with OAB. Trospium chloride has shown favorable CNS tolerability in postmarketing surveillance studies.

Conclusion: When considering treatment choices for patients with OAB, particularly the elderly, the potential CNS adverse effects of each anticholinergic agent must be weighed against the severity of OAB symptoms. (*Clin Ther.* 2005;27:144–153) Copyright © 2005 Excerpta Medica, Inc.

Key words: overactive bladder, anticholinergic drugs, central nervous system, drug safety.

INTRODUCTION

Overactive bladder (OAB) is associated with symptoms of urinary urgency with or without urge incontinence, increased urinary frequency, and nocturia.[1] The incidence of OAB increases with age, with approximately 1 in 4 individuals aged >65 years experiencing symptoms of this condition.[2]

Anticholinergic agents are widely used worldwide as the principal therapeutic agents for OAB,[3] although in some countries, the concept of OAB is not yet extensively recognized and therapeutic agents are approved based on conventional disease categories, such as neurogenic bladder or unstable bladder.[4] Anticholinergic agents such as oxybutynin, tolterodine, propiverine (not available in the United States), and trospium chloride are used in the treatment of the foregoing conditions[3] and also play a role in the treatment of OAB.

Although anticholinergic agents are clinically effective for the relief of OAB symptoms, treatment has

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been associated with a high frequency of adverse effects (AEs), such as dry mouth, constipation, and blurred vision. In some cases, these AEs may be troublesome enough to necessitate discontinuation of therapy.[5] AEs associated with anticholinergic drugs may occur because muscarinic cholinergic receptors are present in a number of organs in addition to the bladder.[6] Cholinergic neurons are prominent in the central nervous system (CNS) and play an important role in cognition and memory.[7] CNS AEs manifesting as cognitive impairment can have important consequences, particularly in the elderly, who may have limited cognitive reserve and be unable to recognize cognitive impairment in themselves.[8] Thus, elderly patients have a high risk both for OAB and for CNS AEs potentially associated with pharmacotherapy for this disorder.

This article describes the CNS AEs of anticholinergic drugs currently used for the treatment of OAB, with particular focus on their use in the elderly. Its objective is to help physicians make optimal choices when considering treatment options for OAB.

METHODS

Relevant data from the literature were identified primarily through a MEDLINE search of articles published through December 2003. The search terms included *overactive bladder, central nervous system, anticholinergic*, and *antimuscarinic*. The reference lists of identified articles were searched for additional pertinent publications. This was not intended to be a systematic review, and articles were chosen for inclusion based on their pertinence to the focus on treatment of OAB in the elderly.

COGNITIVE IMPAIRMENT IN ELDERLY PATIENTS—THE ROLE OF ANTICHOLINERGIC DRUGS

The symptoms of OAB may exacerbate the CNS effects of medications. For example, nocturia, a primary symptom of OAB, may result in sleep deprivation, which can have detrimental effects on psychological performance (eg, cognitive slowing, memory impairment).[9] Older people with cognitive impairment are at increased risk of falls,[10] and urinary urge incontinence is also associated with an increased risk of falls and fractures in elderly patients.[11] Although medications that increase cognitive impairment may exacerbate the risk of falls associated with OAB symptoms, this risk must be balanced against the possibility that an anticholinergic agent may eliminate the risk of falls and fractures associated with rushing to the bathroom to avoid incontinence.

Drug-induced cognitive impairment is a common problem in the elderly.[12] Many drugs can produce this effect in susceptible patients, but psychoactive drugs are the most common causes of drug-induced cognitive impairment.[12] Commonly implicated drug classes include the benzodiazepines, opioids, tricyclic antidepressants, and anticholinergics.[13–15] Anticholinergic effects have been identified in many drugs other than those classically considered to have major anticholinergic effects.[12] Indeed, many drugs with anticholinergic properties (Table I), including those with a poorly recognized secondary anticholinergic effect,[14] are frequently prescribed for the elderly without considering the potential for CNS and peripheral nervous system AEs.

More than any single agent, it is the total burden of anticholinergic agents that may determine the development of CNS AEs.[12] Many patients are receiving >1 drug with anticholinergic effects.[15] For example, in a claims database analysis involving 5902 representative elderly nursing home residents, Blazer et al[15] reported that over 1 year, 59% (3482) of the sample received ≥1 drug with anticholinergic properties, and 0.7% (41) received ≥5 anticholinergic medications concomitantly. It appeared that the physicians managing patients receiving concomitant neuroleptics and tricyclic antidepressants did not attempt to minimize the potential for anticholinergic effects when making their drug choices.

In some instances, physicians may dismiss as an effect of aging what is actually drug-induced cognitive impairment in an elderly patient. The need for proper diagnostic evaluation to distinguish drug-induced cognitive impairment from age-related dementia was underscored by the findings of Larson et al,[16] who reported that drug-induced cognitive impairment accounted for ~10% of elderly patients evaluated for dementia in their clinic. Patients, too, may fail to recognize their reduced level of cognitive functioning. In a study by Kay et al,[17] healthy volunteers received the antihistamine diphenhydramine, a potent, centrally acting anticholinergic agent. Even those subjects who reported no sedation after treatment displayed impaired performance on measures of divided attention (paying simultaneous attention to multiple matters or stimuli), working memory, and vigilance.