Brief Report

Potentially Procholinergic Effects of Medications Commonly Used in Older Adults

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ABSTRACT

Background: Older adults are susceptible to a variety of illnesses, many of which can be treated with medications that may need to be used for the long term. Considerable attention has been paid to drugs that, in addition to their intended function, may have an anticholinergic effect that results in undesirable side effects, including impairment in cognition. Cholinesterase inhibitors are used as procholinergic drugs to improve cognitive dysfunction in Alzheimer's disease. We hypothesized that some of the drugs commonly used by older adults might, in addition to their intended function, also have procholinergic effects by virtue of inhibiting cholinesterases.

Objective: To determine the potential procholinergic nature of some of the commonly used drugs by examining their cholinesterase inhibiting properties.

Methods: The Ellman spectrophotometric method was used with human acetylcholinesterase and butyrylcholinesterase, in the absence and presence of increasing concentrations of each test drug. To compare inhibition potencies, from enzyme kinetic data, we determined half maximal inhibitory concentration (IC_{50} values) for each cholinesterase by each drug.

Results: Of the 28 drugs examined, over half (17/28) inhibited one or both of the human cholinesterases. The inhibition potencies were often within 1 to 2 orders of magnitude of reversible cholinesterase inhibitors currently used to treat Alzheimer's disease. These included trazodone, quetiapine, risperidone, indapamide, and perindopril.

Conclusions: Many drugs used by older adults for other reasons have potentially clinically relevant procholinergic effects. The effect of cumulative cholinesterase inhibition merits clinical evaluation. (*Am J Geriatr Pharmacother.* 2011;9:80–87)

Key words: acetylcholinesterase, aged, butyrylcholinesterase, citalopram, donepezil, Ellman method, galantamine, indapamide, perindopril, procholinergic, quetiapine, ranitidine, risperidone, trazodone.

Accepted for publication February 2, 2011.
doi:10.1016/j.amjopharm.2011.02.003
1543-5946/$ - see front matter

INTRODUCTION

As people age, they are more susceptible to a wide variety of illnesses. Many of these illnesses can be treated to some extent with medications, which often need to be used long term. This can be problematic, because as individuals take more medications, they are at a greater risk of an adverse medication reaction.[1] The basis of adverse medication reactions varies, but importantly include drug–drug interactions. Adverse effects from drug–drug interactions can result from single chemical events that alter each other's activity. Adverse effects of drugs used in combination can also arise from their cumulative small effects, especially in people who, through age-related illnesses and frailty, are more susceptible to such harm.[2,3]

The cholinergic system offers an important illustration of combined drug effects, as many medications have substantial anticholinergic activity. Even drugs that individually are only weakly anticholinergic can cumulatively have clinically important consequences. For example, the risk of delirium is related to the total anticholinergic drug load, which can arise from either the use of a small number of well-known anticholinergic medications (such as amitriptyline or oxybutynin) or from the summative burden of drugs with weak anticholinergic effects.[4] Similarly, total anticholinergic burden has been related to impaired physical and cognitive function[5] and to the attenuation of the efficacy of treatment with donepezil in people with Alzheimer's disease (AD).[6]

The cholinergic system also offers possibilities for how some drugs can have unintended side effects that might enhance cholinergic function, potentially contributing either to procholinergic adverse events (eg, diarrhea, syncope) or even enhancing desirable effects. These considerations are of special interest where any of the 3 mainstay drugs (donepezil, galantamine, and rivastigmine) used to treat AD[7] are employed. Each of these drugs inhibits both acetylcholinesterase (AChE) and butrylcholinesterase (BuChE), albeit to varying extents.[8] Other drugs also have cholinesterase-inhibiting activity as an unintended effect. For example, we have shown that several commonly used 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins"), including lovastatin and simvastatin, inhibit BuChE,[9] in addition to their primary intended role of inhibiting cholesterol production. In consequence, the objective of this study was to investigate whether other medications, commonly used in older adults, might also exhibit procholinergic properties arising from the inhibition of cholinesterases.

MATERIALS AND METHODS

Materials

We selected drugs from several classes that we have observed as being commonly prescribed for patients in our memory clinic, which generally sees older adults with multiple medical problems. Human recombinant AChE (EC 3.1.1.7), acetaminophen, amitriptyline, atenolol, carbamazepine, citalopram, digoxin, dimenhydrinate, enalapril, fenoprofen, fluoxetine, flurbiprofen, furosemide, hydrochlorothiazide, ibuprofen, indapamide, indomethacin, metoprolol, omeprazole, oxybutynin, paroxetine, perindopril, prednisone, ranitidine, risperidone, tolmetin, and trazodone were purchased from Sigma-Aldrich (Oakville, Ontario, Canada). Acetylsalicylic acid was purchased from Caledon Laboratories (Georgetown, Ontario, Canada) and quetiapine from Ontario Chemicals (Guelph, Ontario, Canada). BuChE (EC 3.1.1.8), purified from human plasma (10 U = 0.16 nmol) was a gift from Dr. Oksana Lockridge (University of Nebraska Medical Center, Omaha, Nebraska).

Methods

Cholinesterase Activity

The activity of AChE and BuChE was determined by a modification[8] of the Ellman method,[10] using acetylthiocholine or butyrylthiocholine as substrates, respectively. Briefly, a working 5,5'-dithio-bis (2-nitrobenzoic acid) (DTNB) solution was prepared by mixing 3.6 mL of a stock solution, containing 10 mM DTNB and 20 mM sodium bicarbonate in 0.1 M phosphate buffer at pH 7.0, with 96.4 mL of 0.1 M phosphate buffer at pH 8.0. The assays were carried out by mixing 1.35 mL of buffered DTNB working solution (pH 8.0), 0.05 mL (0.05 U) of either AChE or BuChE solution in 0.1% aqueous gelatin, and 0.05 mL of 50% aqueous acetonitrile or 0.05 mL of a solution of the drug to be tested (usually starting with at least 5 mM and diluted serially) in a cuvette of 1 cm path-length. Absorbance of this solution was calibrated to zero and the reaction was commenced by adding 0.05 mL of 4.8×10^{-3} M stock solution of aqueous acetylthiocholine or butyrylthiocholine to produce reaction mixtures with a substrate concentration of 1.6×10^{-4} M. The final reaction volume was 1.5 mL, and reactions were performed at 23°C. The rate of change of absorbance (ΔA/min), reflecting the rate of hydrolysis of substrate, was recorded every 5 seconds for 1 minute, using a Milton-Roy ultraviolet/