A look at the possible causal relationship between anticholinergic medication load and dementia and Alzheimer’s Disease pathology

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Introduction

Anticholinergic drugs are a very common class of drugs prescribed for a wide variety of conditions including overactive bladder, incontinence, allergies, depression, and more. Furthermore, medications targeted at other mechanisms of action have anticholinergic activity as a secondary mechanism often due to the promiscuous nature of nicotinic and especially muscarinic receptors. Their mechanism of action is typically to block acetylcholine, rarely to act as agonists. Acetylcholine is among the most ubiquitous of neurotransmitters, responsible for many actions of the brain and human body. It has come to the attention of medical professionals that anticholinergics are being prescribed too heavily in the elderly population (65 years of age and older). This is becoming an issue because there is increasing evidence and findings that display cases concluding that anticholinergics can exacerbate and possibly even cause dementia in patients. This information is important for prescribers who must make decisions that best benefit their patient, with special consideration to cognitive effects when prescribing medications to the elderly.

Materials and methods

The method for obtaining information for this research was to use an internet database called SciFinder provided by LECOM. Research topics were entered for a search, and the database retrieved the abstracts pertaining to the desired subjects. Overall, approximately 200 relevant to marginally relevant abstracts were analyzed to determine which would be most beneficial for further study. Ten full papers were requested from the LECOM library for deeper analysis, and eight of those papers were used to cite information for this research paper. A comprehensive list of medications believed and proved to have anticholinergic effects was found, and three medications were selected for further investigation. Their structures were studied for characteristics similar to other anticholinergic medications.

Results

Alzheimer’s Disease (AD) is characterized by pathological damage in the CNS. An interesting idea behind the inner workings of this disease is called tau pathology. Tau pathology is essential for neuron activity. Toxic tau results from neurodegeneration which is characteristic of Alzheimer’s Disease. One of the most established causes of dysfunctional tau in AD is the hyper phosphorylation of tau. This dysfunction leads to both loss of tau function and gain of toxic tau that causes inhibition and disruption of microtubules. The cause of AD has proven elusive to researchers with causal theories coming and going over the past few decades, despite much tantalizing evidence. Spinning that evidence into a story that would withstand the test of time and further inquiry has not yet taken place.

In order to get closer to this answer, a very large and lengthy prospective study that included non-demented patients and close monitoring of duration and dosage information on anticholinergic drugs would need to be done. To date, such a study has not been recorded.

Neurological studies are currently underway by various research groups to assess the effects of anticholinergics on neuropathology. These studies commonly use a murine model, affording the capability to analyze changes on a histological level. One such study recently showed a tau pathology may spread along neuronal networks which correspond to AD pathology. This study included testing PS19 mice with two anticholinergic drugs, tetrabenazine (Aranee, TP) and propiverine (BUP-4, PP), and one cholinergic agent, donepezil (Aricept, DZ). The results showed a strong tau pathology in the TP-treated mice, an intermediate tau pathology in PP treated mice, and a decreased tau pathology in DZ treated mice compared to non-treated mice. Another study in a murine model examined the microglial activation that precedes the tau pathology. Activated microglia in the CNS is an inflammatory response to damage in the neurons that can lead to the release of cytokines and other inflammatory factors.

Depressed microglial activation was seen in the DZ treated mice, moderate activation was seen in the PP treated mice, and diminished microglial activation was seen in the TP treated mice. Lastly, JNK was evaluated in these mice. JNK is involved in tau phosphorylation and the regulation of stress responses and normal biological processes. Suppression of JNK could be related to neuronal survival, and it was observed that DZ strongly suppressed JNK activity in the neurons that can lead to the release of cytokines and other inflammatory factors.

A study conducted by Shelly Gray, et al. revealed that 797 participants, 23.3% of the total participants, developed dementia after 7.3 years of anticholinergic use. The most common anticholinergic medications used were tricyclic antidepressants, first-generation antihistamines, and blinder antimuscarinics. 637 of the 797 participants (79.9%) were considered to have possible or probable AD development. The chemical make-up of the various drugs used commonly in the elderly and also considered to have anticholinergic effects is a feature that warrants further investigation.

Conclusions

Studies such as those cited in this research that have been carried out to observe the effects of anticholinergics on cognition and related endpoints have promising results but have quite a few limitations that make the results difficult to apply due to the many unanswered questions. It is important to note that none of the studies mentioned here were able to decipher the exact mechanism that anticholinergics may play a role in the development or risk of dementia and AD.

It is hard to assess this mechanism, however, because it is not a simple proposition to study of an AD or demented patient concurrent with the drugs they use. Researchers also would be reasonably expected to have a difficult task in trying to form a study group large enough to have positive, viable results. Current findings in research and their limitations need to be considered when assessing whether or not anticholinergic medications should be used for the treatment of various conditions in geriatric populations, especially those already diagnosed with dementia or Alzheimer’s Disease.

Literature


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For further information

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