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ANTICHOLINERGIC MEDICATIONS IN THE OLDER ADULT: A HIDDEN BURDEN

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Abstract

Medications with anticholinergic properties are very common and, as the number of these medications increases, the overall burden on the user increases. Common side effects, such as dry mouth and constipation, are well recognized. However there is increasing evidence that older adults experience cognitive impairment, functional decline, physical impairment and increased mortality with high anticholinergic burden. This high anticholinergic burden can often present acutely as delirium. However, a contribution to long-term cognitive deficits has also been demonstrated. To further complicate the matter, the relationship between the number of medications and adverse effect is not linear. The anticholinergic burden of individual drugs is dependent on many different factors. As a clinician, is it important to conduct regular medication reviews for older adults, paying close attention to medications with anticholinergic properties. The Anticholinergic Cognitive Burden Scale (ACB Scale - http://www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf), the Anticholinergic Drug Scale (ADS), and the Anticholinergic Risk Scale (http://www.kfmc.org/qio/images/docs/Providers/ADE/Anticholinergic%20Risk%20Scale%20Table.pdf AND http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/86F27E6A-B4AE-C03B-7BC1839EF84D70A1/showMeta/0/) are all readily available tools that can assist clinicians in evaluating anticholinergic burden. Discontinuation of these medications can lead to improved cognitive scores, reduction of more common adverse effects such as dry mouth, and an overall improvement in quality of life.

Résumé

Les médicaments avec propriétés anticholinergiques sont très fréquents et leurs effets secondaires augmentent avec leur nombre. Les effets secondaires les plus fréquents tels que la xérostomie et la constipation sont bien connus. Cependant, des données cumulatives suggèrent que la charge anticholinergique chez les personnes âgées entraîne un déclin cognitif, de la perte d'autonomie et augmente les risques de mortalité. Une charge anticholinergique élevée peut se manifester de manière aiguë sous forme de delirium. D'autre part, elle peut aussi contribuer à l'accentuation de déficits cognitifs chroniques. Néanmoins, la relation entre le nombre de médicaments et les effets secondaires n'est pas linéaire. La charge anticholinergique de médicaments individuels dépend de plusieurs facteurs. Comme clinicien, il est important de réviser périodiquement la pharmacopée des patients âgés, en portant une attention particulière aux médicaments avec des propriétés anticholinergiques. Le Anticholinergic Cognitive Burden (échelle ACB), le Anticholinergic Drug Scale (ADS), et le Anticholinergic Risk Scale représentent des outils disponibles pour aider le clinicien dans l'évaluation de la charge anticholinergique. L'arrêt de ces médicaments peut entraîner une amélioration des scores cognitifs, une diminution des effets secondaires tels que la xérostomie, et une amélioration globale de la qualité de vie.

Case

Ms. Potter, an 87-year-old female, was admitted to the hospital after developing a 3-day history of shortness of breath on exertion, episodic fevers and chills, and a cough productive of yellow-green sputum. On day 2, she started having night sweats, which prompted her to come into the emergency department the next morning. On initial assessment, Ms. Potter was febrile and required 2 litres (L) of oxygen to maintain an oxygen saturation of greater than 92%. Chest radiography revealed a right middle lobe consolidation. Ms. Potter was diagnosed with community-acquired pneumonia, started on oral antibiotic therapy, and admitted to the acute medical care ward.

Her past medical history is significant for dyslipidemia, hypertension, type 2 diabetes, atrial fibrillation, congestive heart failure secondary to coronary artery disease with previous myocardial infarctions and a moderately reduced ejection fraction, chronic pain due to osteoarthritis, and gastroesophageal reflux disease. On admission, her medications included atorvastatin, acetyl salicylic acid (ASA), metoprolol, ramipril, furosemide, warfarin, metformin, acetaminophen, ranitidine, and zopiclone prn (as needed) at bedtime.

Shortly after starting antibiotic therapy, Ms. Potter became nauseated. She was prescribed dimenhydrinate prn, which improved her nausea. On her fourth day in hospital, Ms. Potter developed delirium, manifesting as severe agitation, which prompted a prescription for quetiapine. She then developed fluctuating levels of consciousness. Her family reported that during periods of wakefulness, she was confused and having visual hallucinations such as the presence of a cat in her room. She was also complaining of severe abdominal pain.

Introduction

When starting any new medications, especially in a hospital, it is crucial to consider the risks along with the potential benefits of that medication. Many medications have anticholinergic properties, which are often not appreciated as having such an effect (greater than 600 different drugs).[1] Anticholinergic adverse effects, including the impact on cognition, can be profound. In older adults, especially those with pre-existing cognitive impairment, there is increasing evidence that further cognitive decline, functional decline, physical impairment, and increased mortality are associated with high anticholinergic burden from medications.[2] This is in addition to the decreased quality of life associated with other anticholinergic adverse effects that include sedation, dry mouth, constipation, and blurred vision.

Acetylcholine receptors are widely distributed throughout the body, and their stimulation plays a role in the parasympathetic or the "rest and digest" system. Anticholinergic medications block acetylcholine receptor binding and lead to inhibition of the parasympathetic drive.[3] Adverse effects commonly seen with anticholinergic medications are those physiological responses associated with the "flight or fight" response, or sympathetic stimulation.

Montastruc et al. explored the misnomer "anticholinergic" and suggested that the class be renamed "antimuscarinic" to better identify the receptors involved and ultimately better describe the clinical profile of these medications.[2] Two different cholinergic receptors are known—muscarinic and nicotinic receptors (Figure 1). Nicotinic receptors are ligand-gated ion channels, mainly located on autonomic ganglia and skeletal muscles. Nicotinic activation causes a rapid increase in cellular permeability to sodium and calcium, which leads to depolarization and excitation. Muscarinic receptors, intracellularly coupled to a G-protein, are mainly located in the central nervous system (hippocampus, cortex, thalamus) but are also in the peripheral nervous system on autonomic effector cells innervated by postganglionic parasympathetic nerves (i.e., smooth and cardiac muscles)." [3,4] Montastruc et al. pointed out that anticholinergic medications predominantly affect the muscarinic receptors and hence manifest symptoms of activating both the central and peripheral nervous systems.[5]

It is important to note that although anticholinergic medications predominantly affect the muscarinic receptors, not all medications display the same degree of anticholinergic effect. Within every drug class, there are differing degrees of muscarinic receptor potency, pharmacokinetic variability, and the possibility of endogenous substances contributing to the overall clinical picture.[4] And to complicate matters, their negative effects are not linearly related to dosage such that higher doses do not always correlate with a greater adverse effect.[6] This makes the clinical use of these drugs challenging when trying to balance the therapeutic and adverse effects.

Search Strategy

PubMed and Cochrane Library databases were searched using the terms "anticholinergics" combined with "Elderly" or "Geriatric." The search was limited to English language articles. No date limit was set. Pertinent studies were identified on the basis of titles and abstracts, relevant information, and study population. Additional resources were identified through reference lists from identified articles. Case studies, case series, and editorials were excluded. Our search revealed 92 articles in both PubMed and the Cochrane Library. Twenty articles were selected for inclusion. The authors can be contacted for further search details.

Adverse Effect Profile

As mentioned, anticholinergic medications predominantly act on muscarinic receptors. These receptors are located centrally in the brain and peripherally in the eyes, secretory glands, heart, lungs, gastrointestinal tract, genitourinary tract, and skin.[7] The wide distribution of muscarinic receptors throughout the body results in numerous clinical presentations of varying severity.

Often the anticholinergic properties of a medication are used in a therapeutic role. An example of this would be the use of oxybutynin in the treatment of stress incontinence. However, anticholinergic properties are prevalent in almost every drug category, including antidepressants (e.g., paroxetine), antipsychotics (e.g., quetiapine, haloperidol), muscle relaxants (e.g., cyclobenzaprine), cardiovascular agents (e.g., furosemide, metoprolol), gastrointestinal agents (e.g., loperamide, ranitidine), and opioids. Thus, anticholinergic properties are present in a wide range of drugs, and the adverse drug events caused by drugs with anticholinergic properties is likely higher than suspected.

The central side-effect profile of anticholinergics includes sleep disturbances, memory deficits, global cognitive deficits, psychotic symptoms, and delirium. Anticholinergics that do not cross the blood–brain barrier have been proven to have less central adverse drug reactions; however, they continue to be active peripherally.[5] Peripheral side effects include decreased sweating leading to hyperthermia and heat stroke, mydriasis and associated blurred vision, decreased lacrimation,

decreased thirst reflex, increased and thickened bronchial secretions, tachyarrhythmia, xerostomia, decreased gastric acidity, decreased peristalsis, constipation, decreased gastric emptying, and increased bladder tone.[5,8]

Anticholinergics and Cognitive Impairment

The subacute and chronic effects of anticholinergic drugs on cognition can resemble deficits that occur with dementia syndromes. This can lead to overdiagnosis of dementia and unrecognized adverse drug effects in the older adult population.[9]

Studies have shown that anticholinergic medications impair various cognitive functions, including working memory, episodic memory, processing speed and praxis, and can result in global cognitive impairment.[6] This predisposition is related to age-related deficits in central cholinergic transmission, deficient drug metabolism caused by age-related changes in hepatic blood flow and decreased activity of cytochromes, decreased renal excretion caused by age-related decline in estimated glomerular filtration rate (eGFR), and increased permeability of the blood–brain barrier.[1] In addition to the normal age-related physiological changes, Rudolph et al. having shown that patients with underlying dementias are more susceptible to the cognitive effects of anticholinergics.[10]

In the community-dwelling adult, high serum anticholinergic activity has been associated with decreased MMSE (Mini-Mental State Examination) scores.[11] Cancelli et al. demonstrated that community-dwelling older adults taking anticholinergic medications and having anticholinergic scores of 2 or 3 on a scale ranging from 0 to 3 (0 = no effect; 3 = severe) scored at or below the 10th percentile on the MMSE compared with adults not taking such medications. It was also noted that the participants in the moderate-to-severe anticholinergic group had scores in or greater than the 90th percentile on the Geriatric Depression Scale.[1] Their study found a linear trend between the number of anticholinergic medications and low cognitive performance, suggesting dose-dependent effect on performance.[1]

Fox et al. revealed an association between a score of 5 or more on Boustani's Anticholinergic Cognitive Burden (ACB) Scale with an MMSE score of 0.70 points lower than those without anticholinergic drug use (p <0.001). In the long-term, an ACB score of 4 or more has been shown to be related to a greater decline (0.34 points) in the MMSE compared with those not on anticholinergic medications. After adjusting for age, gender, baseline MMSE, education, social class, number of anticholinergic medications, and number of health conditions, Fox et al. also revealed an increase in mortality at 2 years. Twenty percent of study participants with an ACB score of 4 or higher died at the end of the 2 year follow-up period compared with 7% of the group without anticholinergic drugs. For every additional ACB point, the risk of dying increased by 26%.[12]

Key Points

- *Many commonly used medications have varying degrees of anticholinergic effects.*
- *In addition to their acute and subacute central effects, commonly presenting as delirium, anticholinergics can contribute to long-term deficits in cognition.*
- *Their peripheral side effects contribute to decreased mobility, function, and quality of life in the setting of acute, subacute, and long-term use.*
- *As the number of medications with anticholinergic properties increases, the overall anticholinergic burden increases, leading to increased risk of adverse drug effects.*
- *Medication review is essential when treating older adults, with special attention paid to anticholinergic burden.*

Anticholinergics, Mobility, and Function

Mobility is an essential component of the overall health and function of the older adult. Mobile community-dwelling older adults have been shown to have lower incidences of morbidity and mortality.[13] The central and peripheral adverse drug effects of anticholinergics can greatly affect mobility in the older adult. Specifically, dizziness, sedation, and mydriasis (leading to blurred vision) can lead to an acute and chronic decline in mobility and function. Cao et al. demonstrated increased balance difficulty in anticholinergic medication users (odds ratio [OR] = 4.9; 95% confidence interval [CI], 2.0–12.0), in addition greater difficulty with activities of daily living (ADLs) (OR = 3.4; 95% CI, 1.7–6.9).[14] Landi et al. also assessed the effect of anticholinergic medications on patients' mobility. Their study revealed that anticholinergic medication users were less physically active and, after adjusting for age and comorbidities, displayed poor physical performance, decreased muscle strength, and a decline in functional status. Declines in these domains became more pronounced with an increase in the number of anticholinergic medications used.[15]

Although older adults may be on numerous medications that can contribute to frailty, the effect of certain medications can be more significant than others. Hilmer et al. demonstrated that when anticholinergics and sedative medications were excluded, an increasing number of medications were no longer associated with a trend in poor physical performance status.[11]

Role for Medication Review

In the older patient, anticholinergic medications can cause harmful effects that may go undiagnosed. These effects can be acute, subacute, or chronic and can significantly affect cognition, function, and quality of life. Thus, it is important to review the adverse drug effects of all the medications on an individual patient's medication list.

The adverse effects of anticholinergics do not always directly correlate with the use of a single strong anticholinergic agent but, rather, can reflect the accumulation of multiple medications with varying degrees of anticholinergic effects (e.g., oxybutynin versus combination of warfarin, cyclobenzaprine, and loperamide). Thus, the relationship is noted to be nonlinear. This nonlinear relationship also holds true for the dosage of individual anticholinergics such that the risk of side effects does not increase proportionally to an increase in dose (–e.g., low- versus high-dose hydroxyzine).[16] This makes it challenging when trying to determine what medications need to be discontinued when adverse anticholinergic effects are encountered.

To assist with this difficult task, clinically validated scales are available, including the Anticholinergic Cognitive Burden Scale (ACB Scale), the Anticholinergic Drug Scale (ADS), and the Anticholinergic Risk Scale. The ACB Scale takes into account the severe effects of medications on

cognition and contains commonly prescribed and over-the-counter medications.[17] It provides a cumulative score accounting for the combined anticholinergic burden of multiple medications. The ADS[18] and the Anticholinergic Risk Scale (ARS), although similar, do not take into consideration the cognitive effects of the medications but, rather, the serum anticholinergic activity associated with a given anticholinergic and the central (excluding cognitive impairment) and peripheral effects, respectively.[17] Each scale has been validated, but the ADS is limited by the availability of serum anticholinergic activity level assays, making the ARS and ACB scales more clinically applicable.

Discontinuation of anticholinergic medications can not only decrease the incidence of acute side effects such as delirium and urinary retention but is also associated with long-term positive effects. Kersten et al. in a randomized controlled trial, showed a significant improvement (p <0.01) in immediate and delayed recall from baseline to 8 weeks after a multidisciplinary drug review, where anticholinergic drugs were discontinued or replaced with drugs of lesser or no anticholinergic activity. This was completed in long-term nursing home residents with a total ADS score of 3 or greater.

Summary

Medications with anticholinergic properties that are commonly prescribed include over-the-counter medications. The adverse effect profile may include acute, subacute, or long-term effects on cognition, function, mobility, and overall quality of life. The benefits of discontinuing those drugs on both short- and long-term outcomes are profound, so a medication review that considers anticholinergic burden is strongly recommended in every older adult. It can be challenging to balance the therapeutic benefits and the adverse drug effects of anticholinergic medications. However, the available validated tools can assist in these decisions and provide guidance for selecting alternative medicines with the same therapeutic potential but without the adverse effects. If a medication with anticholinergic properties is crucial for therapy (e.g., dimenhydrinate in severe vertigo), then a trial should be initiated, with careful attention paid to the adverse effects (especially the cognitive effects) and with the intent of reviewing regularly the need and the presence of adverse effects.

Conclusion of Case

A medication review revealed that Ms. Potter was on numerous medications with anticholinergic properties. The addition of dimenhydrinate and quetiapine to her pre-existing medications of warfarin, furosemide, ranitidine, and metoprolol increased her anticholinergic burden and contributed to her acute cognitive decline. In addition to the delirium, her physical examination revealed a nontympanic abdomen, which suggested constipation, and a tender, palpable, enlarged bladder, which suggested urinary retention, requiring the insertion of an indwelling catheter.

The dimenhydrinate and quetiapine were discontinued, the dosage of metoprolol was adjusted, and a proton pump inhibitor was substituted for ranitidine. Ms. Potter's cognition gradually improved, and she returned to baseline cognitive function. Her bowel and bladder functions improved, and with ambulation, both returned to normal. She was discharged home after a short period of rehabilitation.

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Conflict of Interest

None to declare.