Title
Tizanidine: An overlooked alternative muscle relaxant for older patients.

Author
Knight, Emmanuel M

Publication Date
2022-10-31

Peer reviewed

Tizanidine: An Overlooked Alternative Muscle Relaxant for Older Patients

Emmanuel M Knight, Pharm.D.[1]

[1] Department of Pharmaceutical Services, University of California Los Angeles – Santa Monica Medical Center, Santa Monica, CA

Corresponding Author:

Emmanuel Knight, Pharm.D., UCLA Santa Monica Medical Center, Department of Pharmaceutical Services, 1250 16th Street, Santa Monica, CA 90404; phone: (424) 259-8500; email: eknight@mednet.ucla.edu

Abstract word count: N/A

Main text word count: 1059

Tables: 2

Funding sources: The author did not receive any external funding for this work.

Running head: Tizanidine in Geriatrics

INTRODUCTION

Muscle relaxants have been a mainstay treatment option for disease states and musculoskeletal conditions characterized by painful spasms for decades. In more recent years, muscle relaxants are also often prescribed as a postsurgical multimodal approach to reduce the need for opioid medications.[1] While the majority of muscle relaxants have been utilized for many years and may be an appropriate choice in younger adult patients, literature has shown that most have been found to increase the risk of potentially dangerous adverse effects in older adults. Particularly, in adults 65 years of age or older, the concern is pertaining to anticholinergic adverse effects, sedation, and weakness, which can be detrimental in older patients.[2,3] Given these concerns and the questionable efficacy of these medications at doses tolerated in geriatric patients, most of the available muscle relaxants are included on The American Geriatrics Society (AGS) Beers Criteria of potentially inappropriate medications for older adults.[4,5]

Although these medications should be avoided if clinically feasible, recent literature suggests utilizing adjunctive options in order to avoid other analgesics that impose their own inherent risks in older adults (e.g., opioids, benzodiazepines).[6-13] Questions often arise whether the choice of muscle

relaxant matters in older patients; or if there are potentially safer options available that do not contain strong recommendations to avoid use from the AGS Beers Criteria, available literature, or drug references. These questions are best answered by examining the pharmacology of muscle relaxants, evaluating their clinical utility, and reviewing the recommendations of the currently published guidelines.

Generally, muscle relaxants are classified into two categories: antispasmodics and antispastics. Although these classes are often incorrectly prescribed interchangeably, these medication categories have different therapeutic indications that must be taken into account based on their mechanisms of action.

Antispasmodics

Antispasmodics are typically centrally-acting skeletal muscle relaxants (SMR) that have varying mechanisms of action, however are believed to work primarily by causing sedation or by preventing pain signals from the nerves to the brain (Table 1).[3,14,15] This class of medications are usually prescribed as short-term adjunctive treatment for skeletal muscle spasms and/or concomitant pain (e.g., low back pain, neck pain). Antispasmodics are not typically indicated for spasticity conditions. Commonly used centrally-acting SMR include cyclobenzaprine, methocarbamol, carisoprodol, metaxalone,

chlorzoxazone, and orphenadrine, all of which appear on the AGS Beers Criteria with strong recommendations to avoid use.[5] Most of these medications are highly anticholinergic and have many possible adverse effects including sedation, dry mouth (increases risk of aspiration), falls (increases risk of fractures), and constipation (increases risk of constipation-induced delirium).[16-18] These adverse effects and subsequent complications can reduce the quality of life and ability to perform activities of daily living (ADLs) in older adults.

Antispastics

Antispastics is another category of muscle relaxants and this class of medications work on the spinal cord or muscle cells (Table 2).[3,19,20] The term spasticity refers to a symptom and characteristic of certain neurological injuries or disease (e.g., cerebral palsy, stroke, multiple sclerosis, spinal cord injury, traumatic brain injury) which may cause certain muscles to involuntarily contract simultaneously. As opposed to antispasmodics, patients on antispastics often need to be on these types muscle relaxants for longer periods given the chronic nature of conditions they are indicated to treat. Antispastic muscle relaxants include baclofen, dantrolene, tizanidine, and diazepam. These muscle relaxants appear to have more targeted and clearly defined mechanisms of action compared to antispasmodics.

Although antispastics have activity in upper motor neuron syndromes and antispasmodics are used for peripheral muscle pain and spasms, an important consideration is that tizanidine and diazepam have both antispastic and antispasmodic activity.[3,19-23] Moreover, given the dual properties of tizanidine and diazepam, some literature supports these medications to be of benefit therapeutically for antispasmodic indications as well.[3]

Of the antispastic agents, only diazepam, a long-acting benzodiazepine, appears on the AGS Beers Criteria with a strong recommendation to avoid use. Diazepam is recommended to be avoided due to increased sensitivity and decreased metabolism in older adults and subsequent increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents.

DISCUSSION

Given the association of SMR on mortality, hospitalizations, and emergency department visits in older patients, determining a preferred option may be beneficial to help guide prescribing in this patient population.[24] The most common indications for SMR include spasticity disorders and acute musculoskeletal pain. More interestingly, muscle relaxants are also becoming a common adjunctive analgesic in surgical settings to reduce the reliance on opioids with the goal of avoiding overuse and abuse. There is

recent literature that supports use of tizanidine to reduce opioid consumption and pain scores in both perioperative and postoperative settings.[25]

Although there is a lack of comparative studies between the commonly used antispasmodic muscle relaxants, there is literature that shows tizanidine is effective when used for non-spasticity related acute muscle spasms (e.g., acute low back pain). In a systemic review comparing the efficacy of SMR for spasticity and musculoskeletal conditions, only tizanidine was found effective in a substantial number of trials for both spasticity and musculoskeletal conditions. The systemic review analyzed the results of trials evaluating the efficacy of baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, diazepam, metaxalone, methocarbamol, orphenadrine, and tizanidine. Outcomes assessed in the review included improvement in functional outcomes, muscle tension, stiffness, daily living activity, sleep impairment, and pain severity.[3] In terms of adverse effects between SMR, there is insufficient data to distinguish differences in overall safety between agents.

Using Tizanidine in Geriatrics

If the decision is made to prescribe tizanidine in a geriatric patient, as with any newly prescribed medication it should be initiated at the lowest effective

dose and duration (e.g., 2 mg every 8-12 hours), usually in combination with acetaminophen (preferred) or nonsteroidal anti-inflammatory drugs (NSAIDS).[26,27] Generally, tizanidine should still be used in caution with careful monitoring of renal and hepatic function in light of its reduced clearance in renal impairment and potential to cause reversible elevations of liver enzymes in some patients.[3] Of note, tizanidine is only currently commercially available as tablets and capsules, therefore if a patient is unable to take solid dosage forms, temporary use of a different parenteral SMR may be warranted.

CONCLUSION

Considering the evidence that tizanidine has been shown to be effective in the commonly used indications for all SMR and that there is no evidence to suggest the same degree of severe side effects compared to other agents, it may be the best overall initial option in most older adults.

ACKNOWLEDGEMENTS

Conflicts of Interests: The author has no conflicts of interest to disclose.

Author Contributions: The sole author listed performed all aspects of the review of literature and preparation of this work.

Sponsor's Role: None

REFERENCES

1. Gong L, Dong JY, Li ZR. Effects of combined application of muscle relaxants and celecoxib administration after total knee arthroplasty (TKA) on early recovery: a randomized, double-blind, controlled study. J Arthroplasty. 2013 Sep;28(8):1301-5.
2. Spence MM, Shin PJ, Lee EA, et al. Risk of injury associated with skeletal muscle relaxant use in older adults. Ann Pharmacother. 2013 Jul-Aug;47(7-8):993-8.
3. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004 Aug;28(2):140-75.
4. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015 Nov;63(11):2227-46.
5. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-694.
6. Mattison R, Midkiff S, Reinert JP, et al. Muscle relaxants as adjunctive analgesics in the perioperative setting: A review of the literature. J Perioper Pract. 2021 Aug 5:17504589211015627

7. Maust, Donovan T et al. “Strategies Associated With Reducing Benzodiazepine Prescribing to Older Adults: A Mixed Methods Study.” Annals of family medicine vol. 20,4 (2022): 328-335. doi:10.1370/afm.2825
8. Yorkgitis, Brian K, and Gabriel A Brat. “Postoperative opioid prescribing: Getting it RIGHTT.” American journal of surgery vol. 215,4 (2018): 707-711. doi:10.1016/j.amjsurg.2018.02.001
9. Sullivan, Denise et al. “Exploring Opioid-Sparing Multimodal Analgesia Options in Trauma: A Nursing Perspective.” Journal of trauma nursing : the official journal of the Society of Trauma Nurses vol. 23,6 (2016): 361-375. doi:10.1097/JTN.0000000000000250
10. American Society of Anesthesiologists Task Force on Acute Pain Management. “Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management.” Anesthesiology vol. 116,2 (2012): 248-73. doi:10.1097/ALN.0b013e31823c1030
11. Manchikanti, Laxmaiah et al. “Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines.” Pain physician vol. 20,2S (2017): S3-S92.

12. Richards BL, Whittle SL, Buchbinder R. Muscle relaxants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008922.
13. Beebe FA, Barkin RL, Barkin S. A clinical and pharmacologic review of skeletal muscle relaxants for musculoskeletal conditions. Am J Ther 2005;12(2):151.
14. Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management. Pract Pain Manag. 2016;16(5).
15. See S, Ginzburg R. Choosing a skeletal muscle relaxant. American family physician. 2008;78(3):365-370.
16. Castejón-Hernández S, Latorre-Vallbona N, Molist-Brunet N, et al. Association between anticholinergic burden and oropharyngeal dysphagia among hospitalized older adults. Aging Clin Exp Res. 2021 Jul;33(7):1981-1985.
17. Stewart C, Taylor-Rowan M, Soiza RL, et al. Anticholinergic burden measures and older people's falls risk: a systematic prognostic review. Ther Adv Drug Saf. 2021 May 31;12:20420986211016645.
18. Linton A. Improving management of constipation in an inpatient setting using a care bundle. BMJ Qual Improv Rep. 2014 Jul 15;3(1):u201903.w1002.
19. Kita M, Goodkin DE. Drugs used to treat spasticity. Drugs 2000;59(3):487–495.

20. Daidoff RA. Pharmacology of spasticity. Neurology 1978;28(9 Pt 2):46–51.
21. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs 1997;53(3):435–452.
22. Nance PW. Tizanidine: An α2-agonist imidazoline with antispasticity effects. Today’s Ther Trends 1997;15(1):11–25.
23. Cook JB, Nathan PW. On the site of action of diazepam in spasticity in man. J Neurol Sci 1967;5(1): 33–37.

24. Alvarez CA, Mortensen EM, Makris UE, et al. Association of skeletal muscle relaxers and antihistamines on mortality, hospitalizations, and emergency department visits in elderly patients: a nationwide retrospective cohort study. BMC Geriatr. 2015 Jan 27;15:2.
25. Mattison R, Midkiff S, Reinert JP, et al. Muscle relaxants as adjunctive analgesics in the perioperative setting: A review of the literature. J Perioper Pract. 2021 Aug 5:17504589211015627.
26. Pareek, Anil et al. “Aceclofenac-tizanidine in the treatment of acute low back pain: a double-blind, double-dummy, randomized, multicentric, comparative study against aceclofenac alone.” European spine journal : official publication of the European Spine Society, the

European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society vol. 18,12 (2009): 1836-42. doi:10.1007/s00586-009-1019-4.

27. Van Tulder, Maurits W et al. “Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the cochrane collaboration.” Spine vol. 28,17 (2003): 1978-92. doi:10.1097/01.BRS.0000090503.38830.AD

LEGENDS

Table 1. Antispasmodic Muscle Relaxants

Antispasmodics	Mechanism of Action
Cyclobenzaprine	Reduces tonic somatic motor activity influencing both alpha and gamma motor neurons.
Methocarbamol	Causes skeletal muscle relaxation by general central nervous system depression.
Carisoprodol	Precise mechanism not established; Clinical effects have been attributed to central nervous system depression.
Metaxalone	Precise mechanism not established; Clinical effects have been attributed to central nervous system depression. No direct effect on contractile mechanism of striated muscle, nerve fibers, or motor end plates.
Chlorzoxazone	Acts on the spinal cord and subcortical areas of the brain to inhibit polysynaptic reflex arcs involved in causing and maintaining skeletal muscle spasms.
Orphenadrine	Precise mechanism not established; May work as an indirect skeletal muscle relaxant by central atropine-like effects.

Table 2. Antispastic Muscle Relaxants

Antispastics	Mechanism of Action
Baclofen	Inhibits transmission of monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals.
Dantrolene	Acts directly on skeletal muscle by interfering with release of calcium ion from the sarcoplasmic reticulum.
Tizanidine	Alpha 2-adrenergic agonist which increases presynaptic inhibition; Greatest effect on polysynaptic pathways; Overall reduces facilitation of spinal motor neurons.
Diazepam	Binds to benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation.