An Observation of the Correlation Between ACEI and ARB Medications and Chronic Pain Medication Utilization in a Community Pharmacy

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Abstract

Background. Bradykinin has shown to affect pain hypersensitivity via reducing the pain threshold when it binds to bradykinin B1 receptors. Bradykinin B1 receptors are upregulated following tissue injury. Thus, any mechanism causing an increase in bradykinin could escalate pain perception. Angiotensin-converting enzyme inhibitors (ACEIs) increase bradykinin by blocking the ACE enzyme from inactivating bradykinin. Angiotensin receptor blockers (ARBs) do not increase bradykinin as much and may not make patients as susceptible to chronic pain by the described expected mechanism. **Objective.** This analysis observed retrospective data from a single community pharmacy to determine if there was a difference between patient groups who chronically used ACEIs and ARBs regarding their use of chronic pain medications. **Methods.** Reports were generated containing all prescription fills of ACEIs and ARBs during the 18-month period and length of therapy was determined from that report per patient. The patients meeting the length of therapy requirements were assessed for pain medication usage to determine presence and length of pain medication therapy. **Results.** The percentage of patients filling chronic pain medications among chronic ACEI patients was 3.99% higher than chronic ARB patients. This was not statistically different. Other evaluated group differences were not statistically significant.

Keywords

ACE inhibitors, angiotensin II receptor antagonists, pain management, diabetes, drug utilization

Background

In the United States, 80 million adults have hypertension,¹ and approximately 7 out of 10 of those adults take medications to treat their hypertension.² Based on the 2014 recommendations from the Eighth Joint National Committee (JNC 8), initial antihypertensive treatment in non-black patients should begin with an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), a thiazide-type diuretic, or a calcium channel blocker. ACEIs or ARBs are also recommended as initial antihypertensive therapy or add-on therapy for any adult with chronic kidney disease regardless of race or diabetes status.³

ACEIs and ARBs both target the renin–angiotensin–aldosterone system to exert their blood pressure lowering effect. ACEIs prevent the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor that acts on the pituitary to increase the secretion of antidiuretic hormone (vasopressin). ACEIs also inhibit aldosterone secretion. Through this inhibition, ACEIs cause vasodilation and diuresis, leading to decreased blood pressure. ARBs block angiotensin II from binding to AT1 receptors directly; AT1

antagonism causes vasodilation, decreased secretion of vasopressin, and decreased secretion of aldosterone.

Thus, both ACEIs and ARBs work on the same physiologic pathways to alter blood pressure, but there are distinct differences in adverse event profiles for these agents. ACEIs increase circulating substance P and bradykinin levels due to the role of ACE in their metabolisms. Both substance P and bradykinin are thought to be involved in the pathogenesis of angioedema.⁴ Substance P is known to be a pro-inflammatory peptide that is secreted by nerves and inflammatory cells, contributing to musculoskeletal inflammatory disease.⁵ Excess bradykinin is believed to cause the chronic dry cough associated with ACEIs in many patients. Bradykinin is a peptide that serves as a vasodilator, contributing to the blood pressure lowering effect of ACEIs. This is thought to be mediated through an interaction between

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ACEIs and bradykinin receptor B2. Bradykinin receptor B1 is synthesized only in response to inflammation, trauma, shock, burn, or allergy. This receptor is thought to be upregulated after injury and thus plays a role in chronic pain and inflammation, leading to hyperalgesia in the presence of supraphysiologic levels of bradykinin.⁶ Based on their mechanisms of action, ARB therapy should not cause the changes in bradykinin and substance P levels that are observed with ACEI therapy.

The link between bradykinin and nociception has been investigated previously. In 1995, a rodent study by Irvine et al tested rats with hypertension for their response to painful heat stimuli.⁷ In hypertensive rats, there is usually a delayed response or increased latency. When these rodents were treated with an ACEI, the latency of response decreased. However, when rodents were treated with an alternative antihypertensive class, the latency did not differ significantly from untreated values. This decrease in latency may indicate increased sensitivity to painful stimuli while being treated with an ACEI. In a 1998 trial by Guasti et al, patients with hypertension being treated with an ACEI were evaluated for changes from baseline without treatment.⁸ A significant decrease of both pain threshold and tolerance was found after approximately 6 months of ACEI therapy, but this decrease did not lead to hypersensitivity. A population-based case-control study by de Mos et al reported current use of ACEIs to be associated with an increased risk of complex regional pain syndrome (odds ratio, adjusted: 2.7).⁹ The authors believed this increased risk to be associated with the increased circulating levels of bradykinin and substance P. Bellucci et al evaluated synovial fluid samples from participants with osteoarthritis of the knee and found that increased levels of bradykinin was correlated with increased inflammation markers (eg, interleukin-6) and cartilage degradation.¹⁰

While ACEIs and ARBs exert their antihypertensive effects through altering the effect of angiotensin II in the body, ARBs do not affect the metabolism of bradykinin as ACEIs do through their effect on ACE. If ACEIs truly play a significant role in increasing pain duration and decreasing pain tolerability, there should be a statistical difference in the rate of utilization of common pain medications chronically, such as nonsteroidal anti-inflammatory drugs, opioids, gabapentin, and pregabalin in patients using ACEIs compared to the rate of utilization of the same medications in patients using ARBs. For this study, a 5% difference was hypothesized to provide statistical significance based on anticipated sample size. The theory of ACEI potentiating chronic pain has been demonstrated in several animal studies and laboratories but has little documentation in humans. The goal of this study is to fill a gap in knowledge and to determine if this facet of antihypertensive therapy is worth considering in patients who may be more prone to experience chronic pain.

This study will review patient pharmacy records from a single Fruth Pharmacy to evaluate if there is a potential correlation between the utilization of chronic ACEIs and chronic pain medications. Since ACEIs and ARBs are used interchangeably in common disease states, this study will also assess if ARBs are as highly associated as ACEIs with concurrent pain medication use. A difference in usage could mean that a patient's pain, while possibly derived from their disease state, is potentiated by increased bradykinin. A difference in the rate of pain medication use between patients taking ACEIs and ARBs could implicate ACEI as a potential causative agent of hyperalgesia.

Methods

The study setting was a single community pharmacy (Fruth Pharmacy) located in Charleston, West Virginia. Any patient 18 years of age or older who received medications at this pharmacy was eligible in the population sample. No exclusion criteria other than age were applied. Prescriptions were evaluated for any patient in the sample who used an ACEI or an ARB chronically during an 18-month period at the single community pharmacy. Chronic use of blood pressure medication was defined as at least 12 months of the 18-month period. This length of therapy was chosen as this shows a patient averaged taking the medication 2 out of every 3 days (for 66.67% adherence, which is above average for chronic diseases in community dwelling patients).¹¹ This study was approved by and conducted in compliance with the requirements of the Institutional Review Board of Charleston Area Medical Center Health Education and Research Institute located in Charleston, West Virginia.

This was an observational retrospective review of patient charts to identify concomitant use of specific drug classes. Blinding was not necessary as no group received active treatment. No follow-up was conducted. No placebo or sham procedures were employed. Patient charts were reviewed based on either ACEI or ARB use. Patients who received chronic ACEI therapy were considered the treatment group. Patients who received chronic ARB therapy were considered the control group. Patients in either group who received chronic pain medication were considered to display the observed effect. For this study, chronic pain medication use was considered to be 9 months of the 18-month period. As pain medication may be used on an as needed basis, this length of time shows that patients used a medication at least every other day on average. Other studies have used various methods to determine use of chronic pain medications and to describe different types of chronic pain.^{12,13} However, to keep the data and discussion simple, there was no attempt to differentiate type of pain. In order to simplify the data processing, 9 months of pain medication use during the observed 18-month timeframe was considered chronic pain medication usage.¹¹

Patients were identified who filled their ACEI or ARB for at least 12 months out of an 18-month period ranging from May 1, 2013, to November 1, 2014. The identified patients were considered chronic users of ACEI or ARB therapy. The patients who used ACEIs or ARBs chronically had their profile reviewed to determine whether they filled pain medications. Pain medications that were evaluated for use included opioids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants other than trazodone, lidocaine patches, gabapentin, or pregabalin. Tricyclic antidepressants, gabapentin, and pregabalin were included because these medications are commonly used to treat neuropathic pain. Prescription reviews were conducted by the authors and those recognized for data evaluation contribution. The abstraction process required the reviewer to evaluate prescription records for quantity of ACEI or ARB medication prescription fills in the given time period. All 3 reviewers were trained and discussed data evaluation throughout the extraction process. No reliability test for multiple reviewers was conducted.

The number of patients chronically using ACEI or ARB therapy was evaluated to see if there was a difference in the amount of patients treated for diabetes. This was evaluated in an effort to ensure equal rates of disease in each group as diabetes status could contribute to increased pain medication utilization secondary to peripheral neuropathy. Diabetes status was determined by chart review. Patients who were identified for inclusion from the ACEI and ARB usage had their prescription profile assessed for any presence of diabetes therapy within the study period. Any patient with medications used therapeutically for blood glucose management or blood glucose testing supplies within the study period was considered to have diabetes. Other disease states could have affected the need for pain management and were considered. However, pharmacy records would not have clearly indicated the presence of these disease states due to a multitude of indications for common therapies for pain-inducing disease states (eg, rheumatoid arthritis or chronic migraines).

Patients using chronic ACEI or ARB therapy were evaluated for prescription pain medication usage and their length of treatment with pain medications was determined. The number of patients with each duration of pain therapy (no usage, more than 6 months, more than 9 months, and more than 12 months) in the same 18-month period with chronic ACEI or ARB therapy was determined.

Endpoints

This study aimed to evaluate if 20% or more of chronic ACEI patients require chronic pain medication, as any less than 20% would be unlikely to have any correlation other than chance. The percentage of chronic ARB patients that require chronic pain medication as previously described

Table 1. Baseline Demographics of Patients in ACEI and ARB Groups.

	Total Patients	Average Age	Number of Patients With Diabetes	Percentage of Patients With Diabetes
ACEI	636	60.8 years	168	26.42%
ARB	326	63.7 years	83	25.46%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Baseline Demographics of Patients in Chronic ACEI and ARB Groups^a.

	Total Patients	Average Age	Number of Patients With Diabetes	Percentage of Patients With Diabetes
Chronic ACEI	302	63.4 years	83	27.48%
Chronic ARB	156	65.5 years	44	28.21%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^aChronic ACEI and ARB groups met or exceeded 12 months of ACEI or ARB therapy during the study period.

was evaluated to see if there was at least a 5% difference between ACEI and ARB therapy. Additionally, the percentage of chronic ACEI or ARB patients who were being treated for diabetes was determined.

Statistical Analysis

Percentages of patients in each group were calculated. Differences between group percentages were noted. A χ^2 calculation was used to determine if there was a statistical difference between the categorical data of the ACEI and ARB groups in patients who had used pain medications chronically.

Results

Baseline characteristics from the population of patients filling any ACEI or ARB prescription within the study period are available in Table 1. The ACEI group had a total of 636 patients, and the ARB group had 327 patients. The ACEI group averaged 60.8 years of age, and the ARB group averaged 63.7 years. There was not a statistical difference in ages between the groups. Of the total population of ACEI patients, 168 (26.42%) had treatment for diabetes. Of the total population of ARB patients, 83 (25.46%) had treatment for diabetes. This is a between-group difference of less than 1% and was not statistically significant.

Baseline characteristics from the population of chronic ACEI or ARB usage (12 months or more) within the study period are available in Table 2. The chronic ACEI group

Table 3. Utilization of Chronic Pain Medication Based on Minimum Length of ACEI or ARB Therapy.

Length of ACEI or ARB Therapy	Chronic Pain Medication Use in ACEI Group	Chronic Pain Medication Use in ARB Group	Percent Difference Between ACEI and ARB Groups
≥6 months	25.62%	22.12%	3.49%
≥9 months	24.33%	21.39%	2.94%
≥12 months	24.50%	20.51%	3.99%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

had a total of 302 patients, and the chronic ARB group had 156 patients. The chronic ACEI group averaged 63.4 years of age, and the chronic ARB group averaged 65.5 years. There was no statistical difference in ages between the groups. Of the population of chronic ACEI patients, 83 of the 302 patients (27.48%) had treatment for diabetes. Of the population of chronic ARB patients, 44 of the 156 patients (28.21%) had treatment for diabetes. This is a between-group difference of less than 1% and was not statistically significant.

There were 302 ACEI patients that had at least 12 months of ACEI therapy. Of the chronic ACEI patients, 74 (24.5%) had received at least 9 months of pain therapy (Table 2). This exceeded the 20% target expected. There were 156 patients who received at least 12 months of ARB therapy. Of those patients, 32 (20.51%) received at least 9 months of pain therapy. This is a between-group difference of 3.99%. This did not meet the targeted 5% difference that was determined prior to conducting the study to be the goal difference.

The percentage of patients receiving chronic pain medication in the ACEI and ARB groups based on length of therapy with an ACEI or ARB can be seen in Table 3 along with the percent difference in utilization of chronic pain medications between ACEI and ARB groups. The data showed a consistent usage of more chronic pain usage in patients receiving ACEI therapy versus ARB therapy for greater than 6 months. These data hint that there could be a difference between the groups, which may continue and expand as treatment duration elongates. However, the between-group differences were not statistically significant.

The number of chronic pain patients in chronic ACEI and chronic ARB groups was determined and analyzed (Table 4). Of the 302 chronic ACEI patients, 24.50% of those patients utilized chronic pain medications. Of the chronic ARB patients, 20.51% of those patients utilized chronic pain medications. There was a 3.99% difference in number of chronic pain patients between groups with more chronic pain patients in the chronic ACEI group. This difference was not statistically significant according to the χ^2

Table 4. Comparison of Patients in Chronic ACEI and ARB Groups Taking Chronic Pain Medications.

	Total Patients	Chronic Pain Patients	Percentage of Chronic Pain Patients ^a
Chronic ACEI therapy	302	74	24.50%
Chronic ARB therapy	156	32	20.51%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^a($\chi^2 = 0.9209$; $P = .337$).

test ($\chi^2 = 0.9209$; $P = .337$). No trends between the groups were noted for any specific pain medication class.

Discussion

In this retrospective observational evaluation of patients chronically (more than 12 months in an 18-month period) using ACEI or ARB therapy at a single community pharmacy, there was no statistical difference in chronic (at least 9 months of therapy) pain medication usage between the 2 groups. Patients in both chronic ACEI and ARB groups exceeded the minimum of 20% expected amount of chronic pain medication usage. However, there was a trend showing that after 6 months or more of ACEI therapy a higher percentage of patients required chronic pain therapy (Table 3). In fact, in patients with 3 months or less of ACEI or ARB therapy, ARB patients were treated 9.19% more for chronic pain compared to the ACEI group. In every comparison of patients treated for longer than 6 months with ACEI or ARB therapy, the higher percentage of chronic pain patients was observed in the ACEI group. Due to the small sample size, a much larger difference would need to have been observed in order for the data to be statistically significant.

Other studies have shown that there could be a link between ACEI therapy and pain threshold.^{8,9} Some of the current data regarding increased bradykinin leading to increased pain experience was documented in rats.⁷ However, Bellucci et al observed an increase in knee inflammation and cartilage damage in humans.¹⁰ Based on statistical power and significance, this retrospective evaluation does not support these previous findings. Yet there are several contributing reasons that this may have occurred. This was a retrospective observational study without ability to control multiple influencing factors. Patients were evaluated by pharmacy prescription data exclusively. Patient diagnoses or physician chart data to rule out unrelated likely pain causes (eg, cancer or neuropathy) were not accessible. With the data source assessed, patients could not be excluded based on any other pain-associated condition. Efficacy of hypertension management and clinical outcomes, including cardiovascular, could not be determined

from our data. These factors could clinically affect therapy choice.

The data source reviewed did allow for attempts to control a few variables. Patient age and likely diabetes status were able to be calculated. There was no drastic difference in age between chronic ACEI and ARB groups as the groups were within 2 years of each other. Presence of diabetes was thought to be a likely confounder due to the disease effect of peripheral neuropathy and recommended use of an ACEI or ARB first-line for blood pressure control in this population. The number of diabetes patients were very similar with 27.48% of patients in the ACEI group having therapy for diabetes compared to 28.21% in the ARB group.

This study was grossly underpowered. Due to the sample size, at least an 8% difference in pain medication usage would be required to observe a statistically significant difference. Clearly, the effect was smaller than 8%, after only a 3.99% difference between the groups was calculated. Due to this difference, this is an area that requires further research. This study could be conducted with several thousand patients in each group to allow the study enough power to calculate a statistical difference between the groups even if the difference observed were less than 5%.

Other limitations of this study include the lack of previous information about patients such as prior use of pain medications or prior use of ACEI or ARB therapy. Patients in this study were using ACEI or ARB therapy with or without pain medication for varying lengths of time. This lack of information is due to conducting a retrospective, observational study of a snapshot time frame. Medication strength was not considered and would have been beneficial to compare high-dose ACEI therapy instead of all ACEI therapy. For purposes of this study, length of therapy was expected to cause bradykinin buildup, but drug strength should certainly be evaluated also. There is currently little knowledge of whether drug strength or duration would be most likely to contribute to bradykinin buildup and cause a potential clinical effect. However, evaluating medication strength would have underpowered the study even further. Regardless, it should be addressed if larger studies on this subject are undertaken. Additionally, controlled, prospective trials would be better able to control for other chronic conditions that include pain in their symptomology whereas this retrospective review could not control for presence of these comorbidities.

The nearly 4% difference in pain medication utilization between ACEI and ARB groups, while not statistically significant, could be clinically significant at the true population level. According to JNC 8, ACEIs and ARBs are first-line treatments for many patients with hypertension. The American Heart Association estimates that there are over 80 million people in the United States with hypertension.¹ Over this 18-month period at a single community pharmacy,

there were 638 adult patients who were prescribed an ACEI. The 3.99% difference would mean that the number needed to harm with chronic pain would be 25 for taking an ACEI, which could be easily attenuated by changing blood pressure medication class. Clearly, this possibility needs to be examined more in depth by a study with enough power to more accurately determine the risk of increased incidence of chronic pain.

The design of the study did not allow for evaluation of over-the-counter (OTC) medication usage or adherence to prescription medications. Only prescription refill data were available for evaluation. As several nonsteroidal anti-inflammatory drugs are available OTC, patients could easily be self-treating chronically without a prescription record. Many of the patients could also be using acetaminophen OTC chronically without a prescription record. Alternatively, some patients may have been treated for several acute problems such as tennis elbow, knee surgery, or kidney stones, which would confound the pharmacy data. The prescription data that were filled and picked up by or on behalf of the patient were the only data available for assessment. However, there is no way to know if patients are taking the medication with any degree of regularity. This study operated on the assumption that if a patient takes the medication home, then the patient uses the medication as intended. There is no mechanism for assessing adherence retrospectively that would be accurate.

Conclusion

This analysis did not have enough patients, and thus power, to confirm a statistical difference even if there had been a 5% difference between chronic ACEI and ARB groups. This study did show a 3.99% difference between the ACEI and ARB groups. Although not statistically significant, this information could be clinically significant to many patients treated for hypertension. Hopefully, this early work will encourage other larger studies to enhance the general understanding and awareness of the possibility that ACEIs may contribute to the incidence of chronic pain.

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Declaration of Conflicting Interests

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