

Hypertensive Crisis: The Causative Effects of Nonsteroidal Anti-Inflammatory Drugs

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Abstract

62 year-old female presents with hypertensive urgency while taking daily NSAIDs. This case demonstrates the effect of NSAIDs on BP, an often over-looked etiology of secondary hypertension. The detrimental effects of NSAIDs upon blood pressure have been well documented. The report reiterates and reviews the severity of the problem. We will review the existing literature and discuss the importance of small increases in blood pressure.

Keywords: Hypertension; NSAID-induced hypertension; Chronic pain

Case Report

A High Pressure Situation

A 62 year-old white female with no documented past medical history of hypertension or any other chronic disease state presented to the Emergency Department with severe occipital headache and was found to have hypertensive urgency, with initial blood pressure (BP) of 225/110 mmHg. She had started taking OTC ibuprofen 3200-4000 mg daily for three weeks due to cervical-spine radicular pain. Her clinical course is outlined in detail in Table 1. Physical exam revealed flushing and mild non-pitting edema of the digits. Ophthalmologic and cardiac exams were normal as was the electrocardiogram (ECG). Initial work-up revealed a normal renal function with 2+ proteinuria on urinalysis, mild hypokalemia that resolved spontaneously, and a CT head that was negative for hemorrhage. She initially received 0.2 mg of clonidine and the ibuprofen was discontinued. When she saw her primary care physician the following day, BP was 170/100 mmHg; she was started on 100/25 mg of losartan/HCT, an angiotensin-receptor blocker/thiazide combination and 5 mg of amlodipine, a calcium channel blocker, for Stage II hypertension. The patient was then seen by a hypertension specialist; 5 mg nebivolol, a β_1 cardioselective vasodilating β -blocker, was added and home BP measurements were initiated. Home BP documented that BPs soon decreased to <120/80 mmHg, after which amlodipine and losartan/HCT were tapered off and nebivolol alone continued. The patient was noted to have a white-coat hypertension pattern, but on continued follow up has done very well as again indicated in Table 1. It does appear that she had pre-existing hypertension prior to her acute episode.

Discussion

NSAID-induced hypertension

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications in the USA; more than 29 million adults are reported to be regular users of NSAIDs [1]. Often thought of as benign medications, NSAIDs have been shown to have a number of serious side effects including hypertension, renal failure, gastrointestinal bleeding, bronchospasm, and severe cardiovascular complications such as myocardial infarction, stroke, and congestive heart failure. This case demonstrates the effect of NSAIDs on BP, an often over-looked etiology of secondary hypertension. We will review the existing literature and discuss the importance of small increases in blood pressure. The mechanism of action of NSAIDs involves blocking the conversion of arachidonic acid to the inflammatory prostaglandins (PG) and thromboxane A [2]. Found in the renal cortex, PGI_2 functions as a vasodilator and promotes sodium excretion. PGE₂, excreted in the

renal medulla, also promotes vasodilation, inhibits sodium resorption, as well as inhibits free water resorption by blunting the effect of antidiuretic hormone (ADH) (Figure 1). Therefore, the net effect of these inflammatory agents is vasodilation and excretion of sodium and water. When these prostaglandins are inhibited, the opposite effect occurs-retention of sodium and water and relative vasoconstriction. Additionally, PG may have direct effects on the vasculature. PG may inhibit endothelin-1, a known vasoconstrictor. This is the postulated mechanism for NSAID-induced hypertension [2,3]. Patients who are particularly vulnerable to these effects include elderly, those with chronic kidney disease (CKD), and diabetes. Further, it has been established that NSAIDs may blunt the effects of other anti-hypertensive drugs such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, ARBs, and beta blockers, leading to resistant hypertension [3,4-6]. Many studies throughout the years have attempted to characterize the exact effect of NSAIDs on hypertension. In a large meta-analysis published in 1994 including 38 randomized, placebo-controlled trials (as well as 12 randomized non-placebo controlled trials), supine mean BP was increased by 5 mmHg with NSAID use (95% CI 1.2-8.7 mmHg) [7]. Another meta-analysis from 2005 showed an increase in systolic/diastolic BP of 2.83/1.34 mmHg in patients using nonselective NSAIDs when compared to cyclooxygenase-2 inhibitors [8]. Also in 2005, the APPROVE trial investigators reported that 19% of patients on naproxen developed hypertension, although this result did not reach statistical significance [9]. In fact, numerous trials have demonstrated a non-statistically significant, modest increase in BP related to NSAID use. Much of the existing research on this topic is limited by data that was underpowered to assess for changes in BP, did not use standardized BP data acquisition protocols, were not placebo-controlled, or involved various NSAIDs at various dosages. Additionally, these studies utilized retrospective survey analysis, allowing for considerable recall bias. Significant increases in BP have also been reported in trials that analyze NSAID use in hypertensive patients. Hypertensive adults in the TARGET trial showed an increase in systolic/diastolic BP of 2.1/0.5 mmHg in patients using naproxen and ibuprofen when compared to lumiracoxib, however, no placebo was used [2,10]. A meta-analysis in

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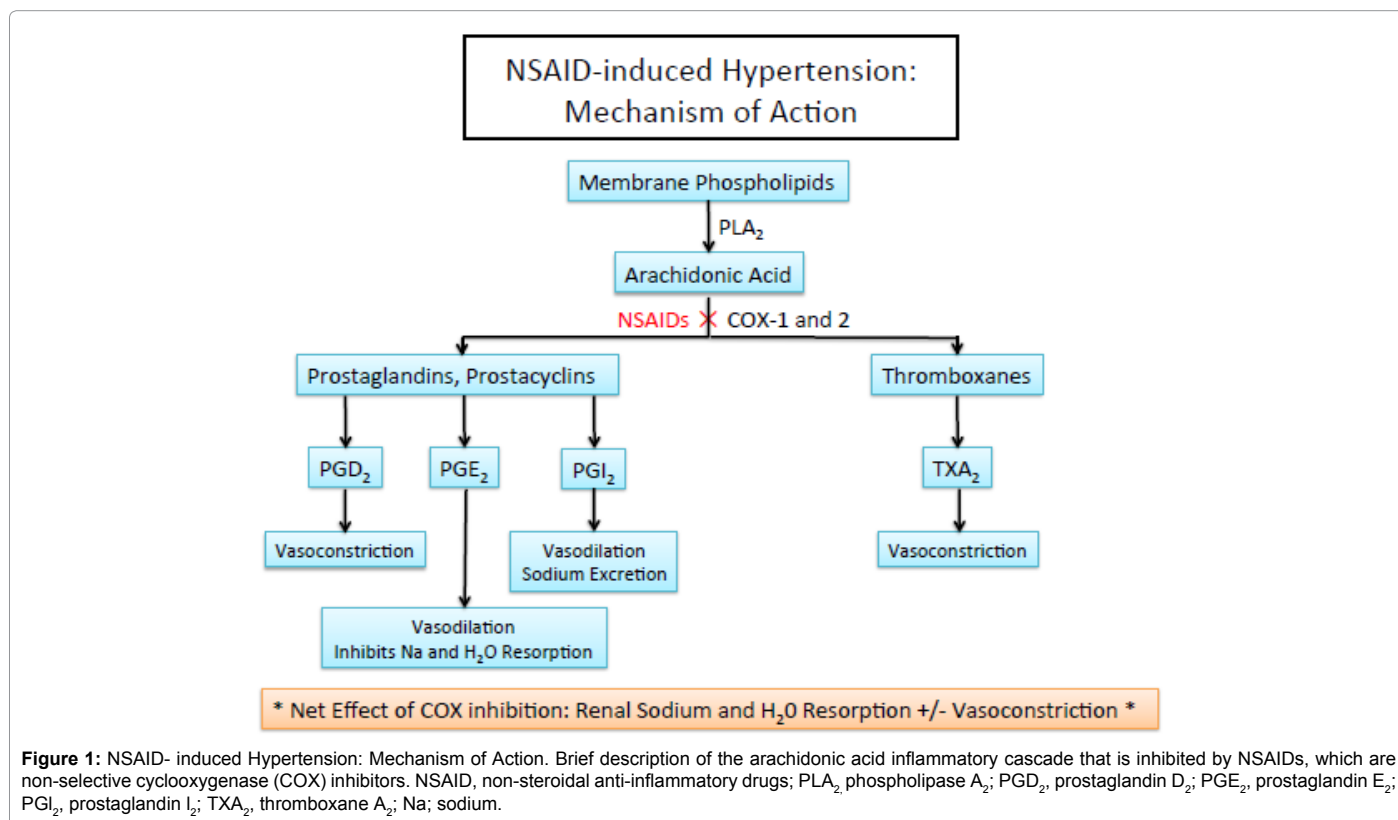
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Date	BP (mmHg)	Medications	Comments
11/13/2013		Ibuprofen 800 mg	Left cervical spine radiculopathy; pain management specialist prescribes ibuprofen 800 mg daily; she takes 4-5 tablets daily
11/17/2013	225/110	Stop Ibuprofen 800 mg Clonidine 0.2 mg	Patient goes to ER for severe occipital headache; given clonidine 0.2 mg with reduction in BP to 139/89' Workup includes BUN/Cr 19/0.5, GFR 125, K 3.3, 2+ protein on urinalysis, brain CT periventricular white matter disease most likely representing small vessel ischemic change and chronic left caudate nuclear lacunar infarction
11/18/2013	172/100	Stop clonidine Start losartan/HCT 100/25 mg daily Start amlodipine 5 mg daily	Seen by PCP; complaints include flushing, mild cough, dry cough, mild dyspnea, questionable hand edema medications changed
11/25/2013	176/86	Losartan 100/25 mg daily Amlodipine 5 mg daily Add nebivolol 5 mg	Seen by hypertension specialist; fundoscopic and cardiac exams are normal as is ECG. No further complaints of headache; instructed to begin home BP monitoring
12/04/13	150/79	Stop amlodipine Continue losartan 100/25 mg Continue nebivolol 5 mg	Home AM BP now 120/80 PM 115/75 white coat hypertension identified
02/05/2014		Stop losartan 100/25 Continue nebivolol 5 mg	Urine now negative for protein; microalbumin/creatinine ratio 23
04/30/2014	167/88	Start/Stop metoprolol Resume nebivolol 5 mg	PCP changed nebivolol to metoprolol; nebivolol resumed per patient request; no further flushing or conjunctival injection
7/20/2014	153/91	Nebivolol 5 mg	Home systolic BP now 125-135; urine microalbumin 23
11/09/2014	147/92	Nebivolol 5 mg	Home BP remains well controlled
02/16/2016	159/80	Nebivolol 5 mg	Home BP <120/80; home BP 160/110 after brief attempt to stop nebivolol

Table 1: Clinical course.



1993 with 1324 patients, 92% of which were hypertensive, demonstrated statistically significant changes in blood pressure observed only in the hypertensive patient group [11]. Though various NSAIDs were analyzed, indomethacin and naproxen had the largest mean arterial pressure increases of 3.59 mmHg and 3.74 mmHg, respectively. In these and other studies, hypertensive patients on ACE-inhibitors and beta-blockers specifically had more severe elevations in BP while taking NSAIDs. The significance of these modest increases in BP due to

NSAID use is related to the severe cardiovascular sequelae of elevated BPs. There is a known linear correlation between increasing BP and ischemic heart disease and stroke mortality even in patients with no history of vascular disease. Further, a decrease in systolic BPs by only 2 mmHg can decrease the risk of ischemic heart disease mortality by 7% and decrease stroke mortality by 10% [12]. While physicians are trained to maintain BPs of less than 140/90 mmHg for a most patients as a result of the Joint National Committee (JNC) 7 guidelines, this

blanket approach does not allow for recognition and treatment of increases of BP from a patients' baseline that falls below this cutoff. The development of individual increases in BP that fall below threshold of 140/90 definition is called the iceberg effect, and implies that the problem of elevated BPs from baseline is often unrecognized. In fact, even when below the JNC 7 cutoff for hypertension, a prospective metaanalysis of one million patients showed that increases of systolic/diastolic BPs of 20/10 mmHg led to a two-fold increase in cardiovascular event rates. In summary, lower BPs (at least down to 115/75 mmHg) are associated with fewer cardiovascular events [12].

Conclusion

As this case demonstrates, NSAIDs have associated cardiovascular risks with their use even though the public often consider them benign. Widely prescribed and taken over-the-counter especially in the elderly, NSAIDs have the ability to cause resistant hypertension by causing sodium and water retention as well as limiting the vasodilatory effects of the systemic vasculature. While often only modest increases in BP have been observed, continuing evidence demonstrate this may increase patients' cardiovascular risk and mortality. These BP increases may be more pronounced in the elderly, diabetics, CKD patients, and in previously hypertensive patients on anti-hypertensive regimens. Further randomized controlled trials powered for BP changes are necessary to further assess specific BP effects from NSAIDs and their clinical outcomes. When patients are taking NSAIDs, it is important to monitor home BPs and inform patients of the cardiovascular risks of elevated BPs in an effort to promote informed decision-making. If elevated BPs occur, discontinuation of NSAIDs is a necessary first-line approach.

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