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Hypertensive Encephalopathy Triggered by Indomethacin Use

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ABSTRACT

We present the case of a man in his 70s who developed acute confusion from hypertensive encephalopathy triggered by indomethacin. He was recently prescribed indomethacin, a non-steroidal anti-inflammatory drug (NSAID) for headaches. However, his headaches were in the context of worsening hypertension that was treated with trandolapril. The use of indomethacin consequently worsened his underlying condition. On presentation to the emergency department, his blood pressure was 190/110 mmHg. Bloodwork including electrolytes, glucose, metabolic studies, renal and liver function were within normal limits; infectious workup including blood and urine cultures subsequently returned negative; and brain computed tomography and magnetic resonance imaging revealed no acute process to explain his presentation. Indomethacin was discontinued and the patient's hypertension was treated with amlodipine. Both his confusion and underlying headaches resolved as his blood pressure normalized. The patient was diagnosed with hypertensive encephalopathy triggered by indomethacin. NSAID use can trigger blood pressure decompensation, especially in patients with underlying hypertension; this effect is particularly pronounced in patients treated with anti-hypertensive medications that inhibit the renin-angiotensin-aldosterone (RAS) system. Symptomatic treatment with NSAIDs is not without potential harm; it is important to carefully consider a patient's underlying diagnosis, indication for therapy and risk for adverse effects.

JEL Classification: General Medicine, Pharmacology and Pharmacy, Toxicology

1 | Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a commonly used class of medication for a broad variety of indications. However, they are known to have a number of side effects that need to be taken into consideration and monitored for, if they are prescribed [1]. Common side effects include, but are not limited to, acute kidney injury, peptic ulcer disease and upper gastrointestinal bleeding, exacerbation of congestive heart failure, as well as hypertension. Blood pressure elevation secondary to NSAIDs is particularly pronounced in patients with pre-existing hypertension [1], and especially in patients treated with agents that inhibit the renin-angiotensin-aldosterone (RAS) system [2].

In this case report, we describe a patient on trandolapril who developed hypertensive encephalopathy after being started on indomethacin to treat headaches that were actually a symptom of his underlying uncontrolled hypertension. This case highlights both a severe presentation of a NSAID side effect, and also the importance of establishing a diagnosis before instituting empiric symptomatic therapy that may potentially worsen the underlying condition.

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Summary

- NSAIDs can trigger blood pressure decompensation, particularly in patients with underlying hypertension treated with RAS blocking agents.
- This case exemplifies the risk of treating symptoms without first understanding the diagnosis. Our patient's headaches were secondary to elevated blood pressure, and using NSAIDs exacerbated the underlying problem leading to hypertensive encephalopathy.

2 | Case History/Examination

A man in his 70s with a history of hypertension, gastroesophageal reflux disease and gout presented to the emergency department (ED) with an episode of confusion lasting several hours. His home medications were trandolapril 4 mg orally once a day and pantoprazole 40 mg orally once a day. Ten days before this ED presentation he reported a headache at a walk-in clinic, for which he was prescribed indomethacin 25 mg orally three times a day as needed. The headache occurred daily in the context of poorly controlled blood pressure and was not associated with any other focal neurologic symptoms, infectious symptoms, or recent trauma. On the day of presentation, the patient was noted to be confused, disoriented, and unable to recall events of the prior week. At the time of arrival to the ED, he was hypertensive with a blood pressure of 190/110 mmHg. He was disoriented to place, person, and time and the remainder of his neurological examination was normal with no focal neurologic deficits.

3 | Methods (Differential Diagnosis, Investigations, and Treatment)

Bloodwork including complete blood count, electrolytes and extended electrolytes, creatinine, liver enzymes, serum glucose, international normalized ratio (INR), prothrombin, cardiac markers and thyroid stimulating hormone (TSH) were all within normal limits (Table 1). Infectious workup including blood and urine cultures eventually returned negative. Computed tomography and magnetic resonance imaging of the brain, which were completed after the blood pressure was controlled, showed no acute process with no evidence of a stroke, bleed, or structural abnormality to explain his presentation. This workup effectively ruled out the alternative differential diagnoses that included metabolic, infectious or structural causes for his acute confusion.

TABLE 1 | Laboratory investigations.

Hemoglobin (140–180 g/L)	151
Leukocytes (4.0–11.0 × 10^9/L)	5.7
Platelets (150–400 × 10^9/L)	182
Sodium (135–145 mmol/L)	138
Potassium (3.2–5.0 mmol/L)	5.0
Chloride (100–110 mmol/L)	102
Bicarbonate (23–29 mmol/L)	28
Anion Gap (5–11 mmol/L)	8
Calcium (2.20–2.62 mmol/L)	2.25
Magnesium (0.70–1.10 mmol/L)	0.84
Phosphate (0.80–1.40 mmol/L)	1.18
Creatinine (64–110 μmol/L)	114 μmol/L (to 95 μmol/L after isotonic intravenous fluids and discontinuation of NSAID and ACE inhibitor)
AST (7–40 U/L)	19
ALT (7–40 U/L)	16
ALP (40–150 U/L)	72
Glucose (3.8–7.7 mmol/L)	5.2
INR (0.9–1.2)	1.1
Prothrombin (9.9–14.1 s)	12.3
Troponin I. High Sensitivity (< 27 ng/L)	6
CK (< 241 U/L)	133
TSH (0.350–4.940 mIU/L)	1.617

4 | Conclusion and Results (Outcome and Follow-Up)

The patient was admitted, the indomethacin was discontinued, and his hypertension was managed with amlodipine only, replacing the trandolapril. He was treated with amlodipine orally starting at 5 mg then titrated to effect to a total dose of 5 mg orally twice a day and then consolidated to amlodipine 10 mg orally once a day. Specifically, management was per clinical practice guidelines, reducing mean arterial pressure (MAP) by no more than 25% within the first hour, and then targeting near 160/110 mmHg over the first 48 h, followed by titration to normal blood pressure targets thereafter [3, 4]. Once the blood pressure was controlled, our patient's confusion resolved. Throughout hospitalization his headaches also began to improve as he remained normotensive. In follow-up several months later, his headaches resolved completely with continued blood pressure control. In light of his negative infectious, metabolic, and structural workup and with his improvement after drug discontinuation and blood pressure control, he was diagnosed with hypertensive encephalopathy triggered by indomethacin use. This diagnosis is further substantiated by the application of the Naranjo Adverse Drug Reaction Probability Scale where our patient's case scores a 6, indicating a probable adverse drug reaction [5]. The patient was counseled to avoid NSAIDs in the future, including indomethacin, in particular because of his risk for blood pressure dysregulation.

5 | Discussion

The adverse effects of NSAIDs on blood pressure remains an important consideration, particularly in patients with pre-existing hypertension [1]. A meta-analysis reported an

average increase in mean arterial pressure of 5 mmHg in patients treated with NSAIDs, including patients with treated or untreated hypertension, as well as healthy volunteers [6]. The pathophysiologic effect of NSAIDs on hypertension is mediated by the inhibition of prostaglandin synthesis, which is associated with decreased natriuresis and enhanced vasoconstriction [7]. This also leads to impaired renal blood flow and glomerular filtration rate, further exacerbating blood pressure control [7, 8].

Patients treated with antihypertensive medications that reduce blood pressure through inhibition of the RAS system appear to be at higher risk for destabilization of blood pressure control with NSAIDs compared to other antihypertensive agents, such as calcium channel blockers (CCB) [7]. Morgan et al. conducted a cross-over trial that randomized patients to antihypertensive therapy with the angiotensin-converting enzyme (ACE) inhibitor enalapril or the dihydropyridine CCB amlodipine, and then treated patients with indomethacin or placebo separated by a one-week washout period [2]. Blood pressure was measured using 24-h ambulatory blood pressure monitoring [2]. Indomethacin caused a rise in blood pressure by an average of 10/5 mmHg in patients taking enalapril, while blood pressure did not change significantly in patients taking amlodipine [2]. It was hypothesized that patients treated with an ACE inhibitor experience an unchecked rise in blood pressure in the setting of NSAID use because ACE inhibitors interfere with the compensatory negative feedback of NSAID-related sodium retention and volume expansion on plasma renin activity and angiotensin II levels [2]. This results not only in blood pressure rise but also in combined detrimental effects on renal function. This pronounced rise in blood pressure in patients controlled with RAS blocking agents has consistently been shown [9–11]. Moreover, given the risk for concomitant acute kidney injury, dose escalation of RAS blocking agents would not be appropriate, and treatment guidelines recommend changing to an alternative agent such as a calcium channel blocking agent [8].

Our patient's transient episode of confusion was a manifestation of hypertensive encephalopathy triggered by indomethacin use. Hypertensive encephalopathy is a hypertensive emergency, and its pathophysiology is characterized by cerebral edema resulting from a sudden and severe increase in arterial pressure exceeding the capacity of neurovascular autoregulation [12]. Patients typically present with gradual onset of headaches, and may progress to confusion, visual deficits, seizures, and coma [12]. In very severe cases, neuroimaging may demonstrate associated findings of white matter edema within the parieto-occipital regions or pontine abnormalities; when these radiologic findings are identified, the clinical syndrome is referred to as reversible posterior leukoencephalopathy syndrome or hypertensive brainstem encephalopathy, respectively [12]. Patients with hypertensive encephalopathy should be treated urgently by lowering the blood pressure into the autoregulatory range, at which point the neurologic symptoms typically resolve [3, 4, 12].

This case highlights both the risk of hypertension secondary to NSAIDs as well as the danger of treating a symptom without identifying the root cause. Using NSAIDs to treat hypertension-induced headaches only exacerbated the underlying problem and resulted in hypertensive encephalopathy. Once the etiology of our patient's headache was determined to be hypertension, lowering the blood pressure and discontinuing offending medications led to a resolution of symptoms.

Author Contributions

Jane Plitman: conceptualization, formal analysis, writing – original draft, writing – review and editing. **Vanessa Raco:** conceptualization, formal analysis, writing – original draft, writing – review and editing. **Peter E. Wu:** conceptualization, formal analysis, supervision, writing – original draft, writing – review and editing.

Ethics Statement

This report did not necessitate formal review and approval from an institutional review board or ethics committee.

Consent

The authors have obtained written informed consent from the patient for publication. Information has been de-identified to the best extent possible.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request.

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