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An Unusual Case of Etoricoxib-Induced Hypertension - A Case Report

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Abstract

Background: Drug-induced hypertension is a form of secondary hypertension caused by a response to a drug or medication. Its severity may range from asymptomatic mild to severe elevations in blood pressure levels leading to renal damage as end-organ damage and death in some. Etoricoxib is a selective cyclo-oxygenase enzyme-2 (COX-2) inhibitor that is majorly indicated in the treatment of inflammatory disorders such as rheumatoid arthritis, osteoarthritis, and gout. Etoricoxib selectively inhibits COX-2 thereby inhibiting the conversion of arachidonic acid to prostaglandins (PGs).

Case Presentation: A 48-year-old male patient presented with early morning headaches, nosebleeds, vision changes, and buzzing in the ears. His clinical examination revealed elevated blood pressure (170/100mmHg). A medication history interview was done to collect information regarding his past as well as current medications, which revealed that he had taken 2 tablets of 90 mg etoricoxib for his neck and lower back ache which was prescribed by an orthopedician during his earlier visit. Later he was advised to stop etoricoxib and serial monitoring of blood pressure had fallen to 140/90mmHg and 130/80mmHg respectively not requiring any other antihypertensive therapy.

Conclusion: Regular monitoring of blood pressure is essential in patients who have been prescribed etoricoxib. Other appropriate NSAIDs should be considered for patients who have poor hypertensive control. These elevations in blood pressure levels are usually short-lived and rare hypertensive emergencies are associated with concurrent use of these drugs and are reversed once the suspected drug is de-challenged and thus achieves adequate blood pressure control.

Keywords: ***Cyclo-oxygenase enzyme-2 (COX-2); Prostaglandins (PGs); Hypersensitivity; Necrosis; Non-steroidal anti-inflammatory drugs (NSAIDs); Etoricoxib***

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1. Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) being the standard of care for decades in treating fever, pain and a wide range of other inflammatory diseases are never free of their side effect profile which includes gastrointestinal toxicity, aspirin-induced asthma, tinnitus, hepatotoxicity, and nephrotoxicity. NSAIDs usually act by inhibiting the prostaglandins synthesized by dual isoform enzymes cyclo-oxygenase- 1(COX 1) and cyclo-oxygenase -2 (COX-2). Etoricoxib is one of the latest COX-2 inhibitors developed and is best used in chronic pain and rheumatic conditions having restricted quality of life, including elderly patients with fewer gastrointestinal side effects compared to nonselective NSAIDs. Data was collected from 45,451 patients through 19 clinical trials. Interestingly, to a certain extent, there appeared greater blood pressure elevation with COX-2 inhibitors compared with placebo and nonselective NSAIDs (e.g., ibuprofen and diclofenac). Etoricoxib when used in known hypertensive patients was associated with greater discontinuations due to elevated blood pressure levels when compared to other NSAIDs. The incidence of elevated blood pressure levels has been challenging to quantify due to its relatively uncommon clinical entity, and also due to under-recognition of the occurrence. So, the use of etoricoxib among hypertensive will remain a clinically important etiology of elevated blood pressure levels, making timely and accurate reporting of this incident important for the early detection and awareness of drug-induced hypertension [1,2].

We present a case of hypertension associated with etoricoxib use. Etoricoxib is a selective COX-2 agonist and is supplied as an orally administered tablet. It may be used alone or in combination with other GABA-A agonists such as thiocolchicoside as first-line therapy for muscle spasms and pain. Commonly reported side effects of etoricoxib include nausea, vomiting, dizziness, headache, and sleep disturbances. To date, there has been only one published case report of etoricoxib-associated hypertension [3,4].

2. Case Report

- A 48-year-old male who is a pre-hypertensive who is not on any medication and has a controlled blood pressure of 130/90 mmHg with a DASH diet and appropriate lifestyle modifications, had come for a routine check-up and had a blood pressure of 136/80 mmHg.
- Repeat blood pressure levels were measured on the next visit and were elevated to 166/90 mmHg.
- On taking the patient's history he did not give any change in lifestyle or work atmosphere and also denied the use of any other chronic concomitant medication.
- Since his blood pressure was persistently elevated at 170/100 mmHg on repeated monitoring plan was to start him on medications subsequently.
- When the patient was repeatedly questioned about the use of other medications for any other co-morbid conditions, he confirmed the use of etoricoxib, which was prescribed to him by an orthopedician on a visit for his neck, and lower back ache.
- The patient had admitted that he had taken 2 tablets of 90 mg etoricoxib for his pain which he had denied accepting in his first visit. Later he was advised to stop etoricoxib and serial monitoring of blood pressure had fallen to 140/90 mmHg and 130/80 mmHg respectively not requiring any other antihypertensive therapy.
- Thus, meticulous history taking about the use of chronic concurrent medications emphasizes the importance to know about any changes in the underlying pathology of the patient.

- Salt intake has a greater impact on adequate control of blood pressure in patients especially in an Indian setting the "salt sensitive hypertensive's" restriction in salt intake has a greater influence on lowering the blood pressure levels.

3. Discussion

Drug-induced elevated blood pressure levels are caused due to wide range of drugs, both prescription and non-prescription, and are termed drug-induced drug-induced hypertension. Drug-induced hypertension may range in severity from asymptomatic mild to severe elevations in blood pressure levels leading to renal damage as end-organ damage and death in some. Currently, many drugs are suspected to cause drug-induced hypertension, NSAIDS cause elevated blood pressure by influencing prostaglandin production causing adverse renal effects. The current case report etoricoxib may increase the blood pressure levels in a dose-dependent way and represents an interaction between the drug and the prostaglandin synthesis leading to elevated blood pressure levels. The majority of drugs that are involved in elevating blood pressure levels are not associated with any hypertensive risks in preclinical and clinical stage testing of the drug. Several factors contribute to the underreporting of incidence as occurrence may be noted in fewest of the patients exposed to the drug, relatively small population of clinical drug trials concerning detecting such an uncommon adverse effect, etc. This can be, best explained with a similar COX- 2 inhibitor rofecoxib (Vioxx) which was, best used in juvenile arthritis, migraine, and acute pain had a greater risk of elevating the systolic and diastolic blood pressures when compared to other traditional NSAIDs. This drug was voluntarily withdrawn from the market in 2004 concerning the increased risk of elevated blood pressure levels, and greater risk of heart attack and stroke. Therefore, it may not be of greater importance until the drug comes into the market and thousands of patients are exposed to the drug and its adverse effect gets to be recognized. This is a major limitation for clinicians in reporting the adverse effects suspected by Food and Drug Administration [5,6].

Elevated blood pressure levels after the administration of a drug might be challenging as there are no specific diagnostic tests related to elevations in blood pressure levels that exist only serial monitoring could predict elevations in blood pressure. The diagnosis of this drug-induced hypertension may be even more challenging in case the patient has any other underlying co-morbid conditions and concurrent use of any other drugs which may elevate the blood pressure.

In the present case hypertension due to etoricoxib was the most likely etiology of the patient's elevated blood pressure. Extensive monitoring to rule out other causes for hypertension showed the elevation in his blood pressure levels was only associated with the drug as the patient neither had any other conditions nor used any other drugs which contribute to the elevations in the blood pressure.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have potential impacts on blood pressure. NSAIDs inhibit both cyclooxygenase (COX-1) and COX-2 isoforms, which prompts a decrease in prostaglandin synthesis. The advantages and the awful effects of this class of drugs are widespread. Drug-induced hypertension related to NSAIDs is because of the renal impact of these medications. In particular, NSAIDs cause enzyme-related increments in sodium and water retention. Dose-related administration of these drugs leads to sodium water retention, this effect is more pronounced with COX-2 inhibitors when compared to other NSAIDs.

The COX-1 and COX-2 enzymes both originated in the kidney in the glomerulus and the macula densa respectively. The specific location of these isoforms in the kidney has an impact on renal function. The prostaglandins produced by COX-1 maintain renal homeostasis by promoting vasodilation in the renal vascular bed, decreasing renal vascular resistance and thereby, increasing renal perfusion. Prostaglandins created by the COX-2 isoenzyme have diuretic and natriuretic effects. In patients who are hemodynamically compromised, the impacts of the two isoenzymes are fundamental for the upkeep of renal perfusion, as a result of their vasodilatory impacts. Since NSAIDs inhibit the synthesis of COX-1 and COX-2 prostaglandins, renal effects are more pronounced in 1% to 5% of NSAID users. COX -2 plays an important role in maintaining the natriuresis when inhibited leads to sodium water retention and further activates vasoconstrictive substances such as endothelin 1 and hence thereby induction of hypertension in normotensive or controlled hypertensive patients.

Assessment of causality in the suspected adverse drug reaction remains a challenge however two scales were used to assess the severity of ADR. Naranjo causality assessment scale was used which gave a score of 7(5-8 probable). Another standardized measure or the causality used is the WHO-UMC scale which is the gold standard for the assessment of the severity of the events for individual case reports and also established a probable/likely relationship between the drug and the adverse event. Hence, the assessment of severity on both scales indicated a probable relationship between the drug and the occurrence of ADR. The drug was however de-challenged after elevation in blood pressure levels and Re-challenge with etoricoxib was not attempted in our patient due to concerns for his safety.

Pharmacoepidemiological Data also suggest that the existing co-morbid conditions and physiochemical properties of the classes of drugs also play an important role in elevating blood pressure. Pharmacokinetics suggest that etoricoxib is extensively metabolized by the liver and excreted by urine and henceforth is not recommended in patients with End Stage Renal Disease (ESRD) which in turn imposes the risk of hypertension.

Two meta-analyses also showed evidence of elevated blood pressure with selective NSAIDS in comparison to other traditional NSAIDs. Among these selective COX-2 inhibitors such as rofecoxib and etoricoxib have the highest evidence of elevating the blood pressure in comparison to other drugs such as celecoxib. In an RCT conducted there were 397 incidences of hypertension-related ADR and 81 discontinuations of a drug due to any hypertension-related ADR which was relatively high in comparison to celecoxib and diclofenac. Therefore, there exists greater evidence of safety profile for celecoxib and other NSAIDs in comparison to etoricoxib. Hence, future cases associated with such an elevation in blood pressure with concurrent use of etoricoxib should be, reported and efforts should be made to depict the underlying mechanism for the occurrence of the incident [7,8].

4. Conclusion

Etoricoxib being an effective analgesic drug has the advantage over other traditional NSAIDS and is used for osteoarthritis, gouty arthritis, etc. There is very less evidence about etoricoxib elevating the blood pressure levels in controlled hypertensive or normotensive patients. Acute elevations in blood pressure should be suspected in patients with the use of etoricoxib, which is a primary cause of secondary hypertension (drug-induced). These elevations in blood pressure levels are usually short-lived and rare hypertensive emergencies are associated with concurrent use of these drugs and are reversed once the suspected drug is de-challenged, thus achieving adequate blood pressure control. Hence, the use of etoricoxib should be contraindicated in

patients who have poor hypertensive control. And in the 'patients who have BP >140/90 mmHg. In cases where the use of etoricoxib is mandatory' patients should be added with antihypertensive therapy and monitored for two weeks after the start of the treatment and regularly thereafter.

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