An observational study on the proves of the risk in the combination of Diclofenac and Ibuprofen

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Introduction
Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature. They’re often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain [1].

Work of NSAID’s
Prostaglandins are produced within the body’s cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding [2].

Specific uses
- headaches,
- arthritis,
- ankylosing spondylitis,
- sports injuries, and
- menstrual cramps.

Ketorolac (Toradol) is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with narcotics. Aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heart attacks in
individuals at high risk for strokes and heart attacks. NSAIDs also are included in many cold and allergy preparations.

**Celecoxib** (Celebrex) is used for treating familial adenomatous polyposis (FAP) to prevent the formation and growth of colon polyps [3].

**Safety combinations**

Short-term studies of paracetamol/ibuprofen combinations in acute pain have not identified specific safety concerns other than those already known to be associated with the individual active ingredients. However, one study of 13 weeks found the use of combined paracetamol/ibuprofen may increase the risk of bleeding over and above that associated with the individual drugs, suggesting caution should apply to long-term use. A retrospective cohort study that analyzed the health insurance records of more than 640,000 patients aged 65 years and older found the combination of an NSAID and paracetamol to be associated with increased risk of hospitalization for gastrointestinal events, compared with either drug alone. While co-administration with a proton pump inhibitor appeared to mitigate this risk, the combination was still associated with double the risk of hospitalizations compared with paracetamol alone. Hazard ratio for combination: 2.55 (95% confidence interval [CI] 1.98 to 3.28) compared with paracetamol alone ≤ 3 g/day, and 1.63 (95% CI: 1.44 to 1.85) compared with NSAID alone [1-3].

**Diclofenac and Ibuprofen**

Having studied data from nearly 30,000 patients with a history of cardiac arrest, researchers conclude that over-the-counter NSAIDs should only be available in pharmacies and at low doses and quantities. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with increased cardiovascular risk for the past ten years, but the link between NSAIDs and cardiac arrest specifically has not been examined. To investigate, researchers used the Danish Cardiac Arrest Registry to identify 28,947 patients who had had an out-of-hospital cardiac arrest between 2001 and 2010. The data showed that 3,376 were treated with an NSAID up to 30 days before their cardiac arrest [3].

**Results**

The results, published in the *European Heart Journal: Cardiovascular Pharmacotherapy* [1] (2017;356:100-107), also showed that the NSAID diclofenac was linked to a 50% increased risk of cardiac arrest (odds ratio [OR] 1.50, 95% confidence interval [CI] 1.23–1.82) while ibuprofen was linked to a 31% increase in risk (OR 1.31, 95% CI 1.14–1.51). The researchers say that any conclusions on causality should be made with caution but recommend that over-the-counter NSAIDs should only be available at pharmacies, in limited quantities, and at low doses.

**Author Contribution**

All authors Contributed equally

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