New warning about the risks of combining ibuprofen and codeine

October 27 2022, by Francisco López-Muñoz and Jose Antonio Guerra Guirao

The European Medicines Agencies (EMA) recommended European countries include new warnings on labels and in package inserts of analgesics, or pain killers, that combine codeine and ibuprofen. This recommendation was agreed at the last meeting of the Pharmacovigilance Risk Assessment Committee (PRAC), held at the end of September 2022.
The aim is to warn consumers of the potential effects these medicines may cause when they are administered at higher doses than recommended or for a very long period of time. These include kidney or gastrointestinal damage and metabolic disturbances, as well as codeine abuse and dependence. The EMA's warning is based on numerous cases reported to health authorities in different European countries, including some with fatal outcomes.

The announcement came as a surprise since these are commonly used analgesic drugs. Ibuprofen is an anti–inflammatory drug, while codeine is a low–potency opioid agent. They are most commonly used alone, but are also combined on occasion—for example, as part of post–surgery analgesia protocols or by chronic pain specialists.

**Safety profile of ibuprofen**

The analgesic and anti–inflammatory effect of ibuprofen is due to its ability to block the synthesis of molecules (prostaglandins) that are released during inflammation. By preventing the synthesis of these molecules, it eliminates pain.

But it turns out that this same mechanism is responsible for the safety problems of this type of drug, such as gastrointestinal damage (by decreasing gastric mucosal protection), renal damage (by decreasing renal blood flow) and, to a lesser extent, cardiovascular damage (by favoring platelet aggregation and thrombus formation).

This may increase the risk of secondary causes of death, including gastrointestinal bleeding or bowel perforation, coronary or renal failure, and stroke. The toxic dose of ibuprofen is 100 mg/kg, and above 400 mg/kg there is already a risk to life.

**Safety profile of codeine**
Codeine is an opioid drug which, among other indications, is authorized as an analgesic, either alone or in combination with other active ingredients. It stimulates a receptor in cells common to all opioids, the µ-type receptor. This is the source of both its therapeutic and toxic effects.

However, because it "binds" less tightly to this receptor than other opioids, its effects are milder than those of morphine. Therefore, it has a moderate-to-weak analgesic action. It is also indicated in the treatment of cough (antitussive) or as an antidiarrheal agent, as it reduces intestinal motility.

**Variability in response**

The pharmacological effect of codeine is due to its conversion to morphine by liver enzymes. This means that depending on the genetic expression of the enzymes in each person, there is great variability in the therapeutic or toxic response to this drug.

Thus, people who express a large amount of these enzymes (called "ultra-rapid metabolizers") can generate very high levels of morphine and present more intense toxic symptoms.

In fact, in 2015, the PRAC conducted a [review of codeine safety, especially in children](#), and concluded that children under 12 years of age are at increased risk of adverse reactions following codeine administration, especially ultra-rapid metabolizers, which is estimated to include 10 % of the Caucasian population.

**The dangers of codeine**

The toxic effects of opioids can be very serious, even fatal. These include respiratory depression (bradypnea/apnea) and central nervous
system depression (sedation or coma). In addition, prolonged use of these drugs, including codeine, although considered a weak opioid, can lead to tolerance and dependence.

Deaths related to codeine use have increased in recent decades. A significant proportion of this increase stems from accidental overdoses, particularly in patients with a history of substance abuse problems, injecting drug use and those diagnosed with chronic pain. The maximum tolerated doses of codeine are 360 mg/day (in immediate-release preparations) and 600 mg/day (in controlled-release formulations).

**Is it safe to combine them?**

When these two drugs are taken together, especially at high doses or for a prolonged period of time, the risk of kidney damage increases. This results in reduced kidney function (kidney failure), which makes it more difficult for acidic substances in the bloodstream to be eliminated into the urine. This kidney failure also results in very low levels of potassium in the blood (hypokalemia), which in turn can cause symptoms such as muscle weakness and dizziness.

In addition, by making renal elimination of both drugs more difficult, their concentrations in blood plasma increase, thereby increasing the already-established risk of toxicity that they had separately. This problem is more pronounced in older patients.

**Overuse of analgesic agents**

For all these reasons, the measure taken by the EMA seems quite appropriate and pertinent. It's important especially because analgesic agents are often overused and some of them, such as codeine and ibuprofen, are considered by many consumers to be harmless drugs that do not cause any safety problems.
This is particularly true in countries where these drugs are dispensed without a prescription, which is where most cases of toxicity from this combination have been reported.

In any case, these types of pharmacovigilance measures, without generating excessive alarm in the population, should always be welcomed, in the interests of greater safety in the consumption of medicines.

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