Implications and future direction of the effect of reducing acetaminophen dosage in prescription combination drugs on mitigating hepatotoxicity

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Dear editor, Acetaminophen is the most widely used pain relief medication around the globe. It is used as an antipyretic and treat various medical ailments, including mild to moderate pain[1]. However, studies have shown that acetaminophen is associated with several adverse consequences, among which hepatotoxicity is the most pronounced[2]. However, despite its well know side-effects and risk of hepatotoxicity, acetaminophen is widely prescribed and its overdosing is a serious issue. Moreover, many combination of medications prescribed for pain relief do contain acetaminophen as its component. Often a single dose of such combinations contains two or more drugs of which many recipient remain ignorant that they are ingesting acetaminophen in the prescribed combination of drugs. This ignorance can lead to overdosing of acetaminophen and subsequent risk of hepatotoxicity[3].

On January 13, 2011, the U.S FDA addressed this issue by asking manufacturers to limit acetaminophen dosage from 750 mg/tablet to 325 mg/tablet in combination acetaminophen and opioid medications. The U.S FDA also asked all its manufacturers to place a box warning on all the combination medications that contain acetaminophen as its component, stating its association with liver injury[4].

A recent study published in JAMA, March 2023, further authenticated this ruling[5]. The study assessed the impact of U.S FDA's decision to limit the amount of acetaminophen dose to 325 mg/tablet in prescription combination opioid drugs on the incidence of subsequent hospitalization and acute liver failure. It was found that predicted incidence of hospitalization, a day prior to FDA announcement was 12.2 cases/ 100000 hospitalizations whereas in 2019 it was reduced to 4.4 cases/ 100000 hospitalizations. Prior to the announcement the percentage of acute liver failure caused by acetaminophen and opioid toxicity rose by 07% per year and it fell by 16% annually after the announcement. Hence, it was concluded that U.S FDA's decision of limiting acetaminophen dosage to 325 mg/tablet in combination drugs helped in reducing the incidents of acetaminophen related hepatotoxicity[5].

The above stated study showed satisfying statistics regarding the decline hepatotoxicity with lower doses of acetaminophen in prescription combination drugs. However, the matter is still not totally resolved because the U.S FDA's decision of reducing acetaminophen dosage was limited to the prescription combination medications and excluded the acetaminophen drugs available over-the-counter. These over-the-counter medicines are still widely used worldwide. The biggest issue with these over-the-counter medications is their availability without prescription and hence are widely self-medicated leading towards the risk of acetaminophen associated hepatotoxicity[6]. Therefore, in view of the aforementioned study, we require a call for action to thoroughly investigate this issue and lower the amount of acetaminophen in over-the-counter medications too to avoid further risk associated with acetaminophen toxicity.

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