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Acetaminophen (2 g and More) May Cause Upper Gastrointestinal Complications

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Abstract

A narrative review was conducted to examine whether acetaminophen caused upper gastrointestinal complications (UGIC). A small case control study reported that odds ratio (OR) for the risk of upper gastrointestinal (GI) bleeding with was 1.2 (<2,000 mg/day: 1.0-1.4), 1.2 (2,000–3,999 mg/day: 0.8-1.7) and 1.0 (≥ 4,000 mg/day: 0.5-1.9). A small case control study reported that acetaminophen was not associated with the risk of upper GI bleeding (multivariate OR 0.8: 0.3-1.9). A systematic review showed that a summary estimate of RR of UGIC was 1.3 (1.2-1.5). A nested case-control study showed that the relative risk (RR) was 3.6 (2.6-5.1) among paracetamol users of more than 2 g daily. A nested case–control study showed an increased risk of UGIC among current users of acetaminophen at doses greater than 2 g (RR 3.7: 2.6–5.1) and 2 g (RR 1.9: 1.4–2.6). A retrospective cohort study showed that patients who took higher-dose acetaminophen (2,601–3,250 or>3,250 mg/day) were more likely to experience GI event compared with those who took low-dose acetaminophen (≦ 2,600 mg/day) (RR 1.27: 1.13–1.43 and RR 1.34: 1.15–1.54, respectively). A population-based retrospective cohort study showed that the risk of GI hospitalization was 1.20 (1.03-1.40) during exposure to acetaminophen (>3g/day) compared with the reference category (acetaminophen ≤3 g/day). It is reasonable to judge that acetaminophen>2,000 mg/day causes UGIC. If acetaminophen>2,000 mg/day is administered, gastroprotective agent is probably necessary. We don't know which gastroprotective agent is optimal. Proton pump inhibitors (PPIs) cause many serious adverse effects. PPIs prevent UGIC due to acetaminophen; however, PPIs exacerbate lower GI complications. If gastroprotective agent is necessary, rebamipide is recommended as a first-line therapy. It is hoped that evidence about these issues will be reported and guidelines will be published.

Keywords: Acetaminophen; Paracetamol; Gastrointestinal complications; Non-steroidal anti-inflammatory drugs; Proton pump inhibitors; Rebamipide; Misoprostol; Histamine-2 receptor antagonists

Introduction

A narrative review was conducted to examine whether acetaminophen caused upper gastrointestinal complications (UGIC).

Acetaminophen does not cause upper gastrointestinal complications

A small case control study (478 cases and 1,263 controls) reported that odds ratio (OR) for the risk of upper gastrointestinal (GI) bleeding was 1.2 (<2,000 mg/day: 95% confidence interval (CI) 1.0-1.4), 1.2 (2,000–3,999 mg/day: 95% CI 0.8-1.7), and 1.0 (≥ 4,000 mg/day: 95% CI 0.5-1.9) [1].

A small case control study (11 cases (acetaminophen 75-800 mg/day) and 25 controls (acetaminophen 150-1,350 mg/day)) reported that acetaminophen was not associated with the risk of upper GI bleeding (multivariate OR 0.8: 95% CI 0.3-1.9) [2].

Acetaminophen causes upper gastrointestinal complications

In the nested case control study (2,105 cases and 11,500 controls), use of paracetamol was associated with a small elevated risk of UGIC (relative risk (RR) 1.3: 95% CI 1.1-1.5) [3]. The RR was 3.6 (95% CI 2.6-5.1) among paracetamol users of more than 2 g daily, whereas smaller doses did not increase the risk [3]. In the nested case control study, compared with nonusers of either any of these drugs, the RR of UGIC for concurrent users of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (2 g and more) was 13.2 (95% CI 9.2–18.9) [3]. Among the twelve studies identified in the systematic review (7,894 cases), estimates of RR of UGIC ranged from 0.2 through 2.0 with a summary estimate of 1.3 (95% CI 1.2-1.5). The estimate did not show the dose of acetaminophen [3].

A nested case–control study was carried out in the UK General Practice Research Database (GPRD) for the period 1993–1994. The study population consisted of 958,397 persons aged 40–79 years who had been enrolled for at least 2 years, and who were free of cancer, esophageal varices, Mallory–Weiss disease, liver disease, coagulopathies and alcohol-related disorders at the start date. The analysis included 2,105 patients and 11,500 control subjects [4]. Overall, use of acetaminophen was associated with a negligible elevated risk of UGIC (RR 1.3: 95% CI 1.1–1.5) [4]. Garcia Rodríguez et al. found an increased risk of UGIC among current users of acetaminophen at doses greater than 2 g (RR 3.7: 95% CI 2.6–5.1) and 2 g (RR 1.9: 95% CI 1.4–2.6), whereas doses below 2 g did not carry an increased risk (RR 0.9: 95% CI 0.8–1.1) [4]. Garcia Rodríguez et al. found a substantial interaction between no aspirin (NA)-NSAIDs and high dose acetaminophen; compared with non-users of either drugs, the RR for concurrent users of NA-NSAIDs and acetaminophen (≥ 2 g) was 16.6 (95% CI 11.0–24.9) and the RR for concurrent users of NA-NSAIDs and acetaminophen (<2 g) was 4.1 (95% CI 3.0–5.7). Garcia

Rodríguez et al. reported that epidemiological data on the association between acetaminophen use and UGIC were limited and inconsistent (pooled RR 1.4: 95% CI 1.0–2.0).

Rahme et al. conducted that a retrospective cohort study of subjects ages>or=65 years who received a prescription for acetaminophen or NSAIDs between 1994 and 1996 [5]. The study included 26,978 patients in the NSAIDs cohort and 21,207 in the acetaminophen cohort. After adjustment for propensity scores, patients who took higher-dose acetaminophen (2,601–3,250 or>3,250 mg/day) were more likely to experience GI event (hospitalizations, ulcers, dyspepsia, GI prophylaxis) compared with those who took low-dose acetaminophen (≦ 2,600 mg/day) (RR 1.27: 95% CI 1.13–1.43 and RR 1.34: 95% CI 1.15–1.54, respectively) [5]. These higher-dose acetaminophen users experienced similar rates of GI events as patients who took high-dose NSAIDs (RR 0.98: 95% CI 0.85–1.13). Compared with patients who took high-dose NSAIDs, the RR for acetaminophen users was 0.59 (≦ 650 mg/day: 95% CI 0.51–0.69), 0.73 (651–1,300 mg/day: 95% CI 0.66–0.81), 0.78 (1,301–1,950 mg/day: 95% 0.71–0.86), 0.73 (1,951–2,600 mg/day: 95% CI 0.67–0.80), 0.93 (2,601–3,250 mg/day: 95% CI 0.82–1.05), and 0.98 (>3,250 mg/day: 95% CI 0.85–1.13) [5]. Patients taking both NSAIDs and acetaminophen were more likely to experience GI events than patients taking only high-dose NSAIDs (RR 1.13: 95% CI 1.01–1.27).

Rahme et al. conducted a population-based retrospective cohort study using data obtained from the government of Quebec health insurance agency databases and the hospital discharge summary database [6]. The cohort included 644,183 elderly (65 year of age or older) patients [6]. Among nonusers of proton pump inhibitors (PPIs), the risk of GI hospitalization was 1.20 (95% CI 1.03-1.40) during exposure to acetaminophen (>3 g/day), 1.63 (95% CI 1.44-1.85) during exposure to traditional NSAIDs (tNSAIDs), and 2.55 (95% CI 1.98-3.28) during exposure to the combination of tNSAIDs and acetaminophen compared with the reference category (acetaminophen ≤3 g/day without PPIs)[6]. Rahme et al. compared lower GI hospitalizations in PPIs users versus nonusers for all study drugs (tNSAIDs and/or acetaminophen) respectively and the risk in PPIs users was higher by 61–71% for all study drugs [6]. Compared with times on lower doses (≤3 g/day) of acetaminophen without PPIs, the adjusted hazard ratio (HR) of upper/lower, upper, and lower GI hospitalization was 0.95 (95% CI 0.81–1.11), 0.73 (95% CI 0.60–0.89), 1.70 (95% CI 1.27–2.26), respectively, during times on lower doses (≤3 g/day) of acetaminophen and PPIs [6]. We should be interpreted with caution because of a possible residual selection bias occurring if, for example, patients with greater pain and a higher risk of GI bleeding were prescribed higher doses of acetaminophen rather than lower doses [6]. We cannot exclude the possibility that PPIs users were at a higher risk of lower GI events because of the reasons for which the PPIs were prescribed [6].

American College of Rheumatology

The American College of Rheumatology (ACR) recommended initiation of acetaminophen in the full dosage up to 4,000 mg/day in patients with knee osteoarthritis and hip osteoarthritis [7]. A letter to the editor named "Is acetaminophen at a daily dose of 2,000 mg and higher safe? Comment on the article by Hochberg et al. [7]"was published for the article. The letter to the editor quoted the aforementioned four articles [3-6]. In the medical community, non-answer to letter to the editor means to acknowledge that the opinion of the letter to the editor is correct. It is an abnormal situation, because the article is a clinical practice guideline published by ACR [8].

Discussion

A case control study published by Lewis et al. showed that OR for the risk of upper GI bleeding with acetaminophen was 1.2 (2,000–3,999 mg/day: 95% CI 0.8-1.7) and 1.0 (≥4,000 mg/day: 95% CI 0.5-1.9), however, it was a small case control study[1]. A case control study published by Sakamoto et al. was a small case control study and the study showed safety of acetaminophen [2]. However, the four studies [3-6] Which showed that acetaminophen caused UGIC were large studies. The systematic review showed that a summary estimate of RR of UGIC was 1.3 (95% CI 1.2-1.5), although the estimate did not show the dose of acetaminophen [3]. In summary, it is reasonable to judge that acetaminophen is likely to cause UGIC. What is the cut-off point of acetaminophen causing UGIC? It is estimated that acetaminophen less than 2,000 mg/day does not cause UGIC. It is possible that acetaminophen 2,000 mg/day or more causes UGIC. Given gray zone, we should recognize that acetaminophen>2,000 mg/day may cause UGIC. If acetaminophen>2,000 mg/day is administered, gastroprotective agent is probably necessary. Acetaminophen 2,000 mg/day is a gray zone. These are based on evidence however, it is my personal surmise. At this time, there are no guidelines about it.

Acetaminophen has been believed not to cause UGIC. It was one of the advantages of acetaminophen. However, acetaminophen>2,000 mg/day may cause UGIC, indicating that acetaminophen>2,000 mg/day has lost one of the advantages. We have two options. One is the administration of acetaminophen less than 2,000 mg/day, and the other is the concurrent administration of acetaminophen>2,000 mg/day and gastroprotective agent.

If a combination with gastroprotective agent is necessary, acetaminophen is equivalent to NSAIDs on that point. In case that acetaminophen is administered with gastroprotective agent, what is the best gastroprotective agent? We do not know which gastroprotective agent is optimal. It is similar to the situation of NSAIDs.

PPIs are promising candidate. However, PPIs cause many serious adverse effects such as Clostridium difficile infection, fracture, fall, pneumonia (either community or hospital acquired), cardiovascular events and deaths, chronic kidney disease, acute kidney injury [9]. PPIs were independent risk factor for small intestinal injury or exacerbated NSAIDs-induced small intestinal injury [9]. If PPIs are administered in combination with acetaminophen, advantage of acetaminophen that there are few and/or mild adverse effects, disappears.

Strictly speaking, the analgesic effect of acetaminophen is unknown. The mechanism that acetaminophen causes GI complications is further unknown. Many studies reported the efficacy of gastroprotective agent on NSAIDs. However, few studies reported the efficacy of gastroprotective agent on acetaminophen. As mentioned previously, PPIs prevented UGIC due to acetaminophen however, PPIs exacerbated lower GI complications [6], like NSAIDs. It is unknown whether other gastroprotective agent shows the same effect as in NSAIDs. PubMed does not show whether misoprostol, histamine-2 receptor antagonists (H2RAs), and rebamipide are effective to reduce UGIC due to acetaminophen.

A systematic review and meta-analysis showed that rebamipide acted better than placebo against short-term NSAIDs-induced gastroduodenal injury [9]. Moreover, rebamipide prevented NSAIDs-induced small bowel damage [9]. Rebamipide was equal to or not superior to traditional strategies (including PPIs, H2RAs and misoprostol treatment) against short-term NSAIDs-induced gastroduodenal injury [9]. To my knowledge, at this time the adverse effects such as dementia, fracture, renal dysfunction, cardiovascular events, infection, low total motile sperm count, and deaths have not reported, however, these adverse effects will be reported in the future[9]. It is unknown whether rebamipide shows the same effect as in NSAIDs. From here on out, it is my personal opinion, not based on evidence. In the countries where rebamipide is available, rebamipide is recommended as a first-line therapy to prevent GI complications due to acetaminophen. The biggest disadvantage of rebamipide is that it is available only in some Asian countries (Philippines, Thailand, Vietnam, the Republic of Korea, China, Cambodia, Indonesia, and Japan) and Egypt. In the countries where rebamipide is not available, misoprostol is recommended as a first-line therapy.

The combination of acetaminophen and NSAIDs is more likely to cause GI events than NSAIDs alone [5]. Especially, the combination of acetaminophen (≥ 2 g) and NSAIDs is further more likely to cause GI events [3-4]. Acetaminophen and NSAIDs are effective for nociceptive pain. Strictly speaking, the analgesic mechanism of acetaminophen is unknown. It is unknown whether the combination of acetaminophen and NSAIDs is an excellent treatment to enhance the analgesic effect or a dangerous treatment to increase GI event. In case of the combination of acetaminophen and NSAIDs, we do not know which gastroprotective agent is optimal.

We do not know about the risk of concomitant use of acetaminophen and drugs that are likely to cause GI complications such as steroid and antiplatelet agent. In such a case, we do not know whether gastroprotective agent is necessary, and which gastroprotective agent is optimal. The problems raised in this article are almost neglected. It is hoped that evidence about these issues will be reported and guidelines will be published.

Conclusion

The problems of GI complications due to acetaminophen are almost neglected. We should recognize that acetaminophen>2,000 mg/day may cause UGIC. If acetaminophen>2,000 mg/day is administered, gastroprotective agent is probably necessary. We do not know which gastroprotective agent is optimal.

We do not know about the risk of concomitant use of acetaminophen and drugs that are likely to cause GI complications such as steroid and antiplatelet agent. It is unknown whether the combination of acetaminophen and NSAIDs is an excellent treatment to enhance the analgesic effect or a dangerous treatment to increase GI event. In case of the combination of acetaminophen and NSAIDs, we do not know which gastroprotective agent is optimal. It is hoped that evidence about these issues will be reported and guidelines will be published.

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Conflict of Interest

None.

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