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Advantages, disadvantages, and specific administration method of acetaminophen

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Abstract

Acetaminophen is not necessarily safe in childhood and pregnancy. However, acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy. Fever and pain during pregnancy and in childhood themselves are probably associated with adverse gestational and childhood outcomes. Acetaminophen should be used at the lowest effective dosage and for the shortest time. It is reasonable to judge that acetaminophen>2,000 mg/day causes upper gastrointestinal complications. If acetaminophen>2,000 mg/day is administered, gastroprotective agent is probably necessary. Acetaminophen 2,000 mg/day is a gray zone. Proton pump inhibitors cause many serious adverse effects. If proton pump inhibitors are administered with acetaminophen, the advantages of acetaminophen that acetaminophen provides slight and mild adverse effects disappear. Nobody knows which gastroprotective agent is optimal in combination with acetaminophen (>2,000 mg/day). It is reasonable to judge that acetaminophen is ineffective for low back pain and pain due to osteoarthritis. It is true that acetaminophen causes various adverse effects including serious adverse effects. However, it is also true that acetaminophen (<2,000 mg/day) is safer than non-steroidal anti-inflammatory drugs (NSAIDs). If analgesic effects of acetaminophen (<2,000 mg/day) and NSAIDs are the same, NSAID should not be administered. Conversely, when analgesic effects of NSAIDs are stronger than those of acetaminophen, administration of NSAIDs for more than 2 weeks is acceptable.

Introduction

Acetaminophen had been believed to be a safe analgesic and antipyretic medication, especially in childhood and pregnancy. According to recent articles, it is not necessarily safe. In this article, advantages, disadvantages, and specific administration method of acetaminophen are shown.

Safety in childhood and in pregnancy

Prenatal exposure to acetaminophen is associated with cerebral palsy, autism spectrum disorder, communication problems, hyperactivity/impulsivity symptoms, attention-deficit/hyperactivity disorder, attention and executive function problems, language delay, lower intelligence quotient, behavioral problems, shorter anogenital distance in male infants, decreased relative numbers of hematopoietic stem cells in cord blood, wheeze, and asthma [1,2]. Acetaminophen use in childhood is associated with autism spectrum disorder [3,4], asthma [5-14], wheezing [15,16], rhinitis [17,18], community acquired pneumonia [19], obesity [20,21], atopic eczema [22,23], allergic diseases [24,25], hypersensitivity reactions [26] and acute kidney injury [27]. We should recognize that acetaminophen is danger in childhood and pregnancy [2]. However, acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy [1,2]. Fever and pain during pregnancy and in childhood themselves are probably associated with adverse gestational [1,2] and childhood outcomes. Acetaminophen should be used at the lowest effective dosage and for the shortest time [1,2]. We should use acetaminophen in childhood and pregnancy only when needed and no safer option for pain or fever relief is available [1,2].

Safety of 2 g and more acetaminophen

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: 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) [28]. A small case control study reported that acetaminophen was not associated with the risk of upper GI bleeding (multivariate OR 0.8: 95% CI 0.3-1.9) [29]. A systematic review showed that a summary estimate of RR of upper gastrointestinal complications (UGIC) was 1.3 (95% CI 1.2-1.5) [30]. A nested case-control study showed that the relative risk (RR) was 3.6 (95% CI 2.6-5.1) among paracetamol users of more than 2 g daily [30]. 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: 95% CI 2.6–5.1) and 2 g (RR 1.9: 95% CI 1.4–2.6) [31]. 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: 95% CI 1.13–1.43 and RR 1.34: 95% CI 1.15–1.54, respectively) [32]. A population-based retrospective cohort study showed that the risk of GI hospitalization was 1.20 (95% CI 1.03-1.40) during exposure to acetaminophen (>3g/day) compared with the reference category (acetaminophen ≤3 g/day) [33]. It is reasonable to judge that acetaminophen>2,000 mg/day causes UGIC [34]. If acetaminophen>2,000 mg/day is administered, gastroprotective agent is probably necessary [34]. Acetaminophen 2,000 mg/day is a gray zone [34]. We don't know which gastroprotective

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agent is optimal [35] [34]. Proton pump inhibitors (PPIs) cause many serious adverse effects. If PPIs are administered with acetaminophen, the advantages of acetaminophen that acetaminophen provides slight and mild adverse effects disappear. Acetaminophen (<2,000 mg/day) without gastroprotective agent or acetaminophen (>2,000 mg/day) with effective and safe gastroprotective agent is recommended. Nobody knows what is effective and safe gastroprotective agent [34,35]. Rebamipide is one of candidates, and I administer acetaminophen (>2,000 mg/day) in combination with rebamipide. However, there is no evidence of efficacy and rebamipide can be administered in few countries (Philippines, Thailand, Vietnam, the Republic of Korea, China, Cambodia, Indonesia, Japan, and Egypt).

Acetaminophen is not effective in low back pain and pain due to osteoarthritis

Randomized open-label trial showed that acetaminophen 2,400 mg/day has comparable analgesic effects on acute low back pain (LBP), based on at least a noninferiority margin, compared with loxoprofen 180 mg/day at 4 weeks [36]. A multicenter, double-blind, randomized, clinical trial showed that pain treatment with acetaminophen 4,000 mg/day was not inferior to that with diclofenac 150 mg/day or the combination of acetaminophen 4,000 mg/day and diclofenac 150 mg/day in acute minor musculoskeletal extremity trauma, both in rest and with movement [37]. A retrospective study showed that no difference in analgesic effects between non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen at the latest 2 weeks after injury or surgery [38]. A systematic review and meta-analysis (2006-2016) showed that acetaminophen was found to have a relative (%) changes value close to that of oral NSAIDs [39].

However, recent systematic review and/or meta-analysis usually showed that acetaminophen was ineffective for LBP and pain due to osteoarthritis (OA). The American College of Physicians developed a guideline for systemic pharmacologic therapies for LBP using a systematic review and reported as follows: New evidence found that acetaminophen was ineffective for acute LBP [40]. Cochrane Database Systetatic Review showed the efficacy and safety of paracetamol for non-specific LBP [41]. It showed as follows: Paracetamol does not produce better outcomes than placebo for people with acute LBP, and it is uncertain if it has any effect on chronic LBP [41]. A systematic review and meta-analysis showed that paracetamol was ineffective in the treatment of LBP and provided minimal short-term benefit for people with OA [42]. A network meta-analysis showed as follows; On the basis of the available data, we see no role for single-agent paracetamol for the treatment of patients with OA irrespective of dose [43]. A network meta-analysis showed that acetaminophen was likely the least efficacious intervention option on the treatment of knee and/or hip OA [44]. A network meta-analysis showed no role for single-agent paracetamol for the treatment of patients with knee and hip OA irrespective of dose on the basis of the available data [45].

Acetaminophen is safer than NSAIDs

It is true that acetaminophen causes various adverse effects including serious adverse effects. However, it is also true that acetaminophen (<2,000 mg/day) is safer than NSAIDs. If analgesic effects of acetaminophen (<2,000 mg/day) and NSAIDs are the same, NSAID should not be administered. In this case, acetaminophen (<2,000 mg/day) and NSAIDs may be equally effective, or they may be equally ineffective. In a clinical practice, placebo cannot be administered, therefore, it is impossible to distinguish between true analgesic effects and placebo effects in each medicine. In either case, if analgesic effects of acetaminophen (<2,000 mg/day) and NSAIDs are the same, NSAIDs should not be administered. Conversely, when analgesic effects of NSAIDs are stronger than those of acetaminophen, administration of NSAIDs for more than 2 weeks is acceptable. If analgesic effects of acetaminophen (<2,000 mg/day) and NSAIDs are the same in patients with LBP or OA, should acetaminophen (<2,000 mg/day) be administered? Even if analgesic effect of acetaminophen is placebo effect, acetaminophen with mild adverse effects should be administered, if analgesic effects of acetaminophen and NSAIDs are the same.

Conclusion

Acetaminophen is not necessarily safe. However, it is safer than NSAIDs. If analgesic effects of acetaminophen (<2,000 mg/day) and NSAIDs are the same, acetaminophen should be administered.

Disclosure and Conflicts of interest

No conflicts of interest

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