U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen

Safety Announcement

[8-1-2013] The U.S. Food and Drug Administration (FDA) is informing the public that acetaminophen has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. Acetaminophen is a common active ingredient to treat pain and reduce fever; it is included in many prescription and over-the-counter (OTC) products.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain acetaminophen. These reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Other drugs used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDS, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions, which is already described in the warnings section of their drug labels.

Anyone who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever reducer should **stop the drug** and seek medical attention right away. Anyone who has experienced a serious skin reaction with acetaminophen should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Health care professionals should be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions.

This new information resulted from the Agency's review of the FDA Adverse Event Reporting System (FAERS) database and the medical literature[1-20] to evaluate cases of serious skin reactions associated with acetaminophen (see Data Summary). It is difficult to determine how frequently serious skin reactions occur with acetaminophen, due to the widespread use of the drug, differences in usage among individuals (e.g., occasional vs. long-term use), and the long period of time that the drug has been on the market; however it is likely that these events (i.e., SJS, TEN, and AGEP) occur rarely.

FDA will require that a warning be added to the labels of prescription drug products containing acetaminophen to address the risk of serious skin reactions. FDA will also request that manufacturers add a warning about serious skin reactions to the product labels of OTC acetaminophen drug products marketed under a new drug application and will encourage manufacturers of drug products marketed under the OTC monograph do the same.

FDA has prepared a list of questions and answers to provide more information about this safety issue.

Facts about acetaminophen

- It is widely used in both prescription and over-the-counter (OTC) products to reduce pain and fever.
- It is available in single-ingredient drug products and in fixed-dose combination drug products (i.e., a combination of two or more ingredients in a single drug product).

Additional Information for Patients and Consumers

- Acetaminophen is available alone in single-ingredient products and also combined with other medicines in products used to treat colds, coughs, allergies, pain, and sleeplessness.
- Acetaminophen is an ingredient in many over-the-counter (OTC) and prescription medicines. On OTC medicines, the word "acetaminophen" appears on the front of the package and on the Drug Facts label under the Active Ingredient(s) section. On prescription medicines, the label may spell-out acetaminophen or it may have a shortened version of it such as "APAP," "acet," "acetamin," or "acetaminoph." If you aren't sure if your medicine contains acetaminophen, ask a pharmacist or your health care professional for additional information.
- Acetaminophen may rarely cause serious skin reactions. Symptoms may include skin reddening, rash, blisters, and the upper surface of the skin may become separated from the lower layers.
- Serious skin reactions can occur even if you have taken acetaminophen in the past without any problems.
- If you develop any skin rash or reaction while using a medicine containing acetaminophen, stop the medicine and seek medical attention immediately. A health care professional will evaluate you to determine if you are experiencing a serious skin reaction.
- If you have had a serious skin reaction with acetaminophen, do not take it or any products containing acetaminophen again. Doing so could cause you to have another serious skin reaction.
- Talk to your health care professional if you have any questions or concerns about acetaminophen or other pain relievers/fever reducers.
- Other medicines used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions. However, having experienced a serious skin reaction with acetaminophen does not necessarily mean that you will also experience the reaction with other pain reliever/fever reducer medicines.

- Report side effects from acetaminophen to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Additional Information for Health Care Professionals

- Rarely, acetaminophen can cause serious, potentially fatal skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).

- The evidence supporting causality primarily comes from a small number of cases published in medical literature in which patients were rechallenged with acetaminophen and had a recurrence of the serious skin reaction.[1-3] Other supportive data include reports from the FDA Adverse Event Reporting System (FAERS) database and case control studies (see Data Summary).[21-26]

- Inform patients about the signs of serious skin reactions and that use of acetaminophen should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

- Inform patients that acetaminophen may be an ingredient in over-the-counter (OTC) and prescription fixed-dose combination drug products, including those used to treat colds, coughs, allergy, pain, and sleeplessness.

- Other drugs used to treat fever and pain/body aches (e.g., NSAIDs) also carry the risk of causing serious skin reactions. However, there does not appear to be cross-sensitivity between acetaminophen and other pain reliever/fever reducer drugs.

- Report adverse events involving acetaminophen to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of this page.

Data Summary

FDA reviewed the FDA Adverse Event Reporting System (FAERS) database and the medical literature for evidence of an association between acetaminophen and Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). The evidence supporting causality between acetaminophen and serious skin reactions primarily comes from a small number of published cases in which patients were rechallenged with acetaminophen and had a recurrence of a serious skin reaction.[1-3]

- In one case, a 7-year-old girl with fever and sore throat was treated with three doses of acetaminophen (10 mg/kg), and 12 hours later, she developed an erythematous rash over her gluteal region and legs. Her condition worsened, and she was admitted to a hospital. Her skin biopsy was compatible with TEN. Six months later, an allergist questioned the diagnosis of TEN due to acetaminophen and performed an oral rechallenge with acetaminophen 250 mg. No other drugs were used. Thirty minutes later, the patient developed diffuse urticaria and erythema and was readmitted to the hospital.[1]

- In another case, an 11-year-old boy was hospitalized for SJS. He had taken acetaminophen for a cold and presented to medical attention with malaise, fever, and erythematous macules that progressed to erosive, hemorrhagic lesions. Laboratory testing included a biopsy that was compatible with SJS. A later oral test with acetaminophen (clinicians were unaware the original reaction was associated with acetaminophen) resulted in erythema multiforme, diagnosed clinically with a compatible biopsy.[2]

- In a third case, an 83-year-old man took acetaminophen and multiple other drugs for a hip replacement. He was admitted to the hospital with an erythematous rash with hundreds of small, nonfollicular pustules; biopsy showed subcorneal pustules, spongiosis, papillary edema, and a perivascular infiltrate consistent with AGEP. All drugs were stopped with resolution of the eruption and widespread desquamation. Skin patch tests with acetaminophen only resulted in subcorneal pustules. He experienced a recurrence of AGEP with subsequent administration of intravenous propacetamol, a prodrug of acetaminophen.[3]

In addition to the three positive rechallenge cases, the medical literature contained several cases of SJS, TEN, and AGEP (3, 17, and 6 cases, respectively) in which the only drug administered prior to the reaction was acetaminophen, or acetaminophen hypersensitivity was demonstrated by skin testing or other means.[1-20] There were no deaths reported in the literature, but the majority of cases required hospitalization. All cases resolved with discontinuation of the drug.

A search of FAERS from 1969 to 2012 identified 91 cases of SJS/TEN and 16 cases of AGEP, which resulted in 67 hospitalizations and 12 deaths. The majority of the cases involved single-ingredient acetaminophen products. A small number of cases involved injectable acetaminophen products or oral acetaminophen/opioid fixed-dose combination products. Indications for acetaminophen use varied between pyrexia and analgesia, and the majority of the reported doses were consistent with labeled dosing recommendations.

Of the 91 cases of SJS/TEN, 6 were categorized as probable cases associated with acetaminophen, with the rest categorized as possible cases. Of the 16 cases of AGEP, 1 was categorized as a probable case associated with acetaminophen, with the rest categorized as possible cases. These seven probable cases had a confirmed diagnosis of SJS/TEN or AGEP by a dermatologist and/or histological findings temporally associated with acetaminophen; confounding medications were not administered within two weeks preceding the events. The time to event, which was measured from the initiation of acetaminophen to the onset of cutaneous signs and symptoms, ranged from less than 24 hours to 8 days. Among these probable cases, six people were hospitalized and one died.

FDA's review of five SJS/TEN case-control studies and one of AGEP indicated that risks of SJS/TEN may be increased with the use of acetaminophen and were generally independent of the effects of other drugs.[21-26] However, all but two of these case control studies failed to address the possible presence of *protopathic bias*, which in this setting refers to a false increase in the risk of SJS/TEN attributable to acetaminophen, due to its use to treat fever, a prodromal symptom of SJS/TEN. In one of the two studies that controlled for the confounding effect of protopathic bias by limiting the acetaminophen

exposure period to a time preceding the prodromal period, acetaminophen remained significantly associated with SJS/TEN.[26]

References

1. Halevi A, Ben-Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. Ann Pharmacother 2000;34:32-4.

2. Trujillo C, Gago C, Ramos S. Stevens-Johnson syndrome after acetaminophen ingestion, confirmed by challenge test in an eleven-year-old patient. Allergol Immunopathol (Madr) 2010;38:99-100.

3. Leger F, Machet L, Jan V, Machet C, Lorette G, Vaillant L. Acute generalized exanthematous pustulosis associated with paracetamol. Acta Derm Venereol 1998;78:222-3.

4. Bygum A, Gregersen JW, Buus SK. Acetaminophen-induced toxic epidermal necrolysis in a child. Pediatr Dermatol 2004;21:236-8.

5. Bouziri A, Khaldi A, Hamdi A, Borgi A, Ghorbel S, Kharfi M, et al. Toxic epidermal necrolysis complicated by small bowel intussusception: a case report. J Pediatr Surg 2011;46:e9-11.

6. Reese D, Henning JS, Rockers K, Ladd D, Gilson R. Cyclosporine for SJS/TEN: a case series and review of the literature. Cutis 2011;87:24-9.

7. Dragojevic-Simic V, Vukovic J, Kovacevic A. Paracetamol-induced toxic epidermal necrolysis in adult: clinical pharmacology unit case report. Basic & Clinical Pharmacology & Toxicology. Volume 105(Supplement 1):98.

8. Verneuil L, Ratajczak P, Allabert C, Leboeuf C, Comoz F, Janin A, et al. Endothelial cell apoptosis in severe drug-induced bullous eruptions. Br J Dermatol 2009;161:1371-5.

9. Yamane Y, Aihara M, Tatewaki S, Matsukura S, Kanbara T, Yamakawa Y, et al. Analysis of treatments and deceased cases of severe adverse drug reactions--analysis of 46 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Arerugi 2009;58:537-47.

10. Pyo KS, Heung YD, Jung KS, Hyeong CS, Soo CN. A case of toxic epidermal necrolysis (TEN) induced by nonsteroidal anti-inflammatory drug (NSAID) in Emergency Medical Center. Toxicology Letters 2008;180(Supplement 5):S140.

11. Yun SJ, Choi MS, Piao MS, Lee JB, Kim SJ, Won YH, et al. Serum lactate dehydrogenase is a novel marker for the evaluation of disease severity in the early stage of toxic epidermal necrolysis. Dermatology 2008;217:254-9.

12. Gerdts B, Vloemans AF, Kreis RW. Toxic epidermal necrolysis: 15 years' experience in a Dutch burns centre. J Eur Acad Dermatol Venereol 2007;21:781-8.

13. Prins C, Kerdel FA, Padilla RS, Hunziker T, Chimenti S, Viard I, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol 2003;139:26-32.

14. Takeuchi Y, Katagiri K, Hatano Y, Fujiwara S. A case of toxic epidermal necrolysis due to acetaminophen. Sainichi Hifu 2004;56:1-10.

15. Khare KC, Khare S, Mathew G. Stevens Johnson syndrome with keratitis following paracetamol injection. Indian J Dermatol Venereol Leprol 1997;63:209.

16. Szepietowski J, Wasik F, Szybejko-Machaj G, Maj J. Toxic epidermal necrolysis successfully treated with cyclosporin: report of three cases. J Eur Acad Dermatol Venereol 1997;9:169-72.

17. Sezer E, Sezer T, Koseoglu D, Filiz NO. Acute generalized exanthematous pustulosis in a child. Pediatr Dermatol 2007;24:93-5.

18. Wohl Y, Goldberg I, Sharazi I, Brenner S. A case of paracetamol-induced acute generalized exanthematous pustulosis in a pregnant woman localized in the neck region. Skinmed 2004;3:47-9.

19. Mashiah J, Brenner S. A systemic reaction to patch testing for the evaluation of acute generalized exanthematous pustulosis. Arch Dermatol 2003;139:1181-3.

20. De Coninck AL, Van Strubarq AS, Pipeleers-Marichal MA, Huyghens LP, Suys ET, Roseeuw DI. Acute generalized exanthematous pustulosis induced by paracetamol. A case with severe hemodynamic disturbances. Dermatology 1996;193:338-41.

21. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.

22. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol 2007;157:989-96.

23. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35-44.

24. Gau SS, Chao PF, Lin YJ, Chang CJ, Gau CS. The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: a nested matched case-control study. J Clin Psychopharmacol 2008;28:509-17.

25. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther 2010;88:60-8.

26. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, Flahault A, Kelly JP, et al. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics 2009;123:e297-304.