

# Infant Acetaminophen Use Tied to Asthma Later

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Exposure to acetaminophen may be an important risk factor for the development of asthma later in childhood, according to new data from an international asthma study.

In a sample of more than 200,000 children from 31 countries, those children given acetaminophen—known outside the United States as paracetamol—for fever

during their first year of life were approximately 50% more likely to have experienced asthma symptoms at age 6-7 years than were unexposed children. Dr. Richard Beasley of the Medical Research Institute of New Zealand, Wellington, and his colleagues reported that in phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), exposure to acetaminophen in the first year of life was associated with significantly increased risk of severe asthma symptoms,

as well as rhinoconjunctivitis and eczema at 6-7 years (Lancet 2008;372:1039-48).

The prevalence of asthma has increased substantially over the past 50 years, as has the use of acetaminophen in children, the authors wrote. Previous studies have reported associations between asthma risk and exposure to acetaminophen in utero, during infancy, and in late childhood and adulthood in populations from developed and developing countries. Additionally, phase I of ISAAC identified positive asso-

ciations between per-person acetaminophen consumption and asthma prevalence in children, they stated.

The current analysis was designed to evaluate the consistency of the association between acetaminophen and asthma and to investigate one of the proposed biological mechanisms for the link—specifically, that acetaminophen exposure contributes to the development of oxidant-induced airway inflammation caused by reduced concentrations of the antioxidant glutathione in the lung and stimulation of the T helper cell 2 response.

Toward this end, parents and guardians of 205,487 children aged 6-7 years from 73 centers were asked to complete two standardized questionnaires, including a prevalence questionnaire about symptoms of asthma, rhinoconjunctivitis, and eczema, and an environmental questionnaire about possible protective and risk factors for asthma and allergic disorders including the use of acetaminophen in the first year of life and now.

The primary outcome measure for the analysis was the association between acetaminophen use for fever in the first year of life and asthma symptoms at 6-7 years as measured by multivariate analysis.

A total of 194,555 children were included in the analysis of acetaminophen use for fever during the first year of life. Of these, 105,041 had complete covariate data and were included in the multivariate analysis. In this group, the association between asthma symptoms and acetaminophen use in the first year of life was significant (odds ratio 1.46). Similarly, the association between first year acetaminophen use and rhinoconjunctivitis and eczema were significant (OR 1.48 and 1.35, respectively).

Despite the study's power, size, and multinational nature, the findings do not establish causality because of its design, the authors stressed. In the absence of an adequately powered, population-based randomized control trial, "evidence is insufficient to advise parents and health care workers of the risk benefit of taking [acetaminophen] in childhood, or its comparative efficacy and safety with other approaches," they wrote.

In an accompanying editorial, Dr. R. Graham Barr of Columbia University Medical Center, New York, agreed. "The studies to date are suggestive but not definitive enough to recommend a wholesale change in antipyretic use in children. Acetaminophen has known benefits for pediatric febrile illness as well as known toxicities," he wrote. "The drug might contribute to asthma incidence and it might be prudent to minimize casual use of this—and all—drugs in otherwise healthy children. However, we need to take the guesswork out of recommending and prescribing antipyretic drugs for children." What is needed, he wrote, are randomized trials that examine the incidence of childhood asthma, comparing acetaminophen use with an active control such as ibuprofen or placebo (Lancet 2008;372:1011-2). Dr. Beasley reported having received grant support and honoraria for lectures from GlaxoSmithKline Inc., the maker of acetaminophen. ■



**Brief Summary of Prescribing Information** (for complete prescribing information please see package insert)

**INDICATIONS AND USAGE:** SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults. SOMA should only be used for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use has not been established and because acute, painful musculoskeletal conditions are generally of short duration. [see *Dosage and Administration* (2)].

**DOSAGE AND ADMINISTRATION:** The recommended dose of SOMA is 250 mg to 350 mg three times a day and at bedtime. The recommended maximum duration of SOMA use is up to two or three weeks.

#### WARNINGS AND PRECAUTIONS

**Sedation:** SOMA may have sedative properties (in the low back pain trials, 13% to 17% of patients who received SOMA experienced sedation compared to 6% of patients who received placebo) [see *ADVERSE REACTIONS*] and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery. Since the sedative effects of SOMA and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive, appropriate caution should be exercised with patients who take more than one of these CNS depressants simultaneously.

**Drug Dependence, Withdrawal, and Abuse:** In the postmarketing experience with SOMA, cases of dependence, withdrawal, and abuse have been reported with prolonged use. Most cases of dependence, withdrawal, and abuse occurred in patients who have had a history of addiction or who used SOMA in combination with other drugs with abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. To reduce the chance of SOMA dependence, withdrawal, or abuse, SOMA should be used with caution in addiction-prone patients and in patients taking other CNS depressants including alcohol, and SOMA should not be used more than two to three weeks for the relief of acute musculoskeletal discomfort. One of the metabolites of SOMA, meprobamate (a controlled substance), may cause dependence.

**Seizures:** There have been postmarketing reports of seizures in patients who received SOMA. Most of these cases have occurred in the setting of multiple drug overdoses (including drugs of abuse, illegal drugs, and alcohol) [see *Overdosage*].

#### ADVERSE REACTIONS

**Clinical Studies Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice.

The data described below are based on 1387 patients pooled from two double blind, randomized, multicenter, placebo controlled, one-week trials in adult patients with acute, mechanical, lower back pain [see *Clinical Studies*]. In these studies, patients were treated with 250 mg of SOMA, 350 mg of SOMA, or placebo three times a day and at bedtime for seven days. The mean age was about 41 years old with 54% females and 46% males and 74% Caucasian, 16% Black, 9% Asian, and 2% other. There were no deaths and there were no serious adverse reactions in these two trials. In these two studies, 2.7%, 2%, and 5.4%, of patients treated with placebo, 250 mg of SOMA, and 350 mg of SOMA, respectively, discontinued due to adverse events; and 0.5%, 0.5%, and 1.8% of patients treated with placebo, 250 mg of SOMA, and 350 mg of SOMA, respectively, discontinued due to central nervous system adverse reactions. Table 1 displays adverse reactions reported with frequencies greater than 2% and more frequently than placebo in patients treated with SOMA in the two trials described above.

Table 1. Patients with Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (n=560) n (%)	SOMA 250 mg (n=548) n (%)	SOMA 350 mg (n=279) n (%)
Drowsiness	31 (6)	73 (13)	47 (17)
Dizziness	11 (2)	43 (8)	19 (7)
Headache	11 (2)	26 (5)	9 (3)

**Postmarketing Experience:** The following events have been reported during postapproval use of SOMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Cardiovascular:** Tachycardia, postural hypotension, and facial flushing [see *Overdosage*]. **Central Nervous System:** Drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, and seizures [see *Overdosage*]. **Gastrointestinal:** Nausea, vomiting, and epigastric discomfort. **Hematologic:** Leukopenia, pancytopenia.

#### DRUG INTERACTIONS

**CNS Depressants:** The sedative effects of SOMA and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. Therefore, caution should be exercised with patients who take more than one of these CNS depressants simultaneously. Concomitant use of SOMA and meprobamate, a metabolite of SOMA, is not recommended [see *Warnings and Precautions*].

**CYP2C19 Inhibitors and Inducers:** Carisoprodol is metabolized in the liver by CYP2C19 to form meprobamate [see *Clinical Pharmacology*]. Co-administration of CYP2C19 inhibitors, such as omeprazole or fluvoxamine, with SOMA could result in increased exposure of carisoprodol and decreased exposure of meprobamate. Co-administration of CYP2C19 inducers, such as rifampin or St. John's Wort, with SOMA could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed an induction effect on CYP2C19. The full pharmacological impact of these potential alterations of exposures in terms of either efficacy or safety of SOMA is unknown.

#### USE IN SPECIFIC POPULATION

**Pregnancy:** Pregnancy Category C. There are no data on the use of SOMA during human pregnancy. Animal studies indicate that carisoprodol crosses the placenta and results in adverse effects on fetal growth and postnatal survival. The primary metabolite of carisoprodol, meprobamate, is an approved anxiolytic. Retrospective, post-marketing studies do not show a consistent association between maternal use of meprobamate and an increased risk for particular congenital malformations. **Teratogenic effects:** Animal studies have not adequately evaluated the teratogenic effects of carisoprodol. There was no increase in the incidence of congenital malformations noted in reproductive studies in rats, rabbits, and mice treated with meprobamate. Retrospective, post-marketing studies of meprobamate during human pregnancy were equivocal for demonstrating an increased risk of congenital malformations following first trimester exposure. Across studies that indicated an increased risk, the types of malformations were

inconsistent. **Nonteratogenic effects:** In animal studies, carisoprodol reduced fetal weights, postnatal weight gain, and postnatal survival at maternal doses equivalent to 1-1.5 times the human dose (based on a body surface area comparison). Rats exposed to meprobamate in-utero showed behavioral alterations that persisted into adulthood. For children exposed to meprobamate in-utero, one study found no adverse effects on mental or motor development or IQ scores. SOMA should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

**Labor and Delivery:** There is no information about the effects of SOMA on the mother and the fetus during labor and delivery.

**Nursing Mothers:** Very limited data in humans show that SOMA is present in breast milk and may reach concentrations two to four times the maternal plasma concentrations. In one case report, a breast-fed infant received about 4-6% of the maternal daily dose through breast milk and experienced no adverse effects. However, milk production was inadequate and the baby was supplemented with formula. In lactation studies in mice, female pup survival and pup weight at weaning were decreased. This information suggests that maternal use of SOMA may lead to reduced or less effective infant feeding (due to sedation) and/or decreased milk production. Caution should be exercised when SOMA is administered to a nursing woman.

**Pediatric Use:** The efficacy, safety, and pharmacokinetics of SOMA in pediatric patients less than 16 years of age have not been established.

**Geriatric Use:** The efficacy, safety, and pharmacokinetics of SOMA in patients over 65 years old have not been established.

**Renal Impairment:** The safety and pharmacokinetics of SOMA in patients with renal impairment have not been evaluated. Since SOMA is excreted by the kidney, caution should be exercised if SOMA is administered to patients with impaired renal function. Carisoprodol is dialyzable by hemodialysis and peritoneal dialysis.

**Hepatic Impairment:** The safety and pharmacokinetics of SOMA in patients with hepatic impairment have not been evaluated. Since SOMA is metabolized in the liver, caution should be exercised if SOMA is administered to patients with impaired hepatic function.

**Patients with Reduced CYP2C19 Activity** have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients [see *Clinical Pharmacology*].

#### DRUG ABUSE AND DEPENDENCE: [see *Warnings and Precautions*]

**OVERDOSAGE:** Overdosage of SOMA commonly produces CNS depression. Death, coma, respiratory depression, hypotension, seizures, delirium, hallucinations, dystonic reactions, nystagmus, blurred vision, mydriasis, euphoria, muscular incoordination, rigidity, and/or headache have been reported with SOMA overdoses. Many of the SOMA overdoses have occurred in the setting of multiple drug overdoses (including drugs of abuse, illegal drugs, and alcohol). The effects of an overdose of SOMA and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) can be additive even when one of the drugs has been taken in the recommended dosage. Fatal accidental and non-accidental overdoses of SOMA have been reported alone or in combination with CNS depressants.

**Treatment of Overdosage:** Basic life support measures should be instituted as dictated by the clinical presentation of the SOMA overdose. Induced emesis is not recommended due to the risk of CNS and respiratory depression, which may increase the risk of aspiration pneumonia. Gastric lavage should be considered soon after ingestion (within one hour). Circulatory support should be administered with volume infusion and vasopressor agents if needed. Seizures should be treated with intravenous benzodiazepines and the recurrence of seizures may be treated with phenobarbital. In cases of severe CNS depression, airway protective reflexes may be compromised and tracheal intubation should be considered for airway protection and respiratory support.

The following types of treatment have been used successfully with an overdose of meprobamate, a metabolite of SOMA: activated charcoal (oral or via nasogastric tube), forced diuresis, peritoneal dialysis, and hemodialysis (carisoprodol is also dialyzable). Careful monitoring of urinary output is necessary and overhydration should be avoided. Observe for possible relapse due to incomplete gastric emptying and delayed absorption. For more information on the management of an overdose of SOMA, contact a Poison Control Center.

#### NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long term studies in animals have not been performed to evaluate the carcinogenic potential of carisoprodol. SOMA was not formally evaluated for genotoxicity. In published studies, carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay in the absence of metabolizing enzymes, but was not mutagenic in the presence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells with or without the presence of metabolizing enzymes. Other types of genotoxic tests resulted in negative findings. Carisoprodol was not mutagenic in the Ames reverse mutation assay using *S. typhimurium* strains with or without metabolizing enzymes, and was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells.

SOMA was not formally evaluated for effects on fertility. Published reproductive studies of carisoprodol in mice found no alteration in fertility although an alteration in reproductive cycles characterized by a greater time spent in estrus was observed at a carisoprodol dose of 1200 mg/kg/day. In a 13-week toxicology study that did not determine fertility, mouse testes weight and sperm motility were reduced at a dose of 1200 mg/kg/day. In both studies, the no effect level was 750 mg/kg/day, corresponding to approximately 2.6 times the human equivalent dosage of 350 mg four times a day, based on a body surface area comparison. The significance of these findings for human fertility is not known.

**PATIENT COUNSELING INFORMATION:** Patients should be advised to contact their physician if they experience any adverse reactions to SOMA.

**Sedation:** Since SOMA may cause drowsiness and/or dizziness, patients should be advised to assess their individual response to SOMA before engaging in potentially hazardous activities such as driving a motor vehicle or operating machinery [see *Warnings and Precautions*].

**Avoidance of Alcohol and Other CNS Depressants:** Patients should be advised to avoid alcoholic beverages while taking SOMA and to check with their doctor before taking other CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or other sedatives [see *Warnings and Precautions*].

**SOMA Should Only Be Used for Short-Term Treatment:** Patients should be advised that treatment with SOMA should be limited to acute use (up to two or three weeks) for the relief of acute, musculoskeletal discomfort. If symptoms still persist, patients should contact their healthcare provider for further evaluation.

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