Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects

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Objective: *Cross-sensitivity between aspirin and acetaminophen in aspirin-sensitive asthmatic patients has been reported with frequencies ranging from 0% to 29%. The relationship is dose-dependent for acetaminophen challenges, ranging between 300 and 1000 mg.*
Methods: *To determine the prevalence of cross-sensitivity to high-dose acetaminophen, we performed single-blind acetaminophen oral challenges with 1000 mg and 1500 mg in 50 aspirin-sensitive asthmatic patients and in 20 non-aspirin-sensitive asthmatic control subjects.*
Results: *Overall, 17 of 50 (34%) of aspirin-sensitive asthmatic patients reacted to acetaminophen in doses of 1000 to 1500 mg (95% confidence interval: 20% to 49%). By contrast, none of the 20 non-aspirin-sensitive asthmatic patients reacted to acetaminophen (95% confidence interval: 0% to 14%). This difference was highly significant (p = 0.0013), supporting the hypothesis that cross-sensitivity between aspirin and acetaminophen is unique in aspirin-sensitive asthmatic patients.*
Conclusion: *Although high-dose (>1000 mg) acetaminophen cross-reactions with aspirin were significant with respect to frequency (34%), such reactions included easily reversed bronchospasm in only 22%, and were generally mild. We recommend that high doses of acetaminophen (1000 mg or greater) should be avoided in aspirin-sensitive asthmatic patients.*
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Key words: *Acetaminophen, aspirin, analgesic, asthma, cross-reactivity, sensitivity, challenge, provocation, cyclooxygenase*

Cross-sensitivity between aspirin and acetaminophen is known to occur in a dose-dependent relationship in aspirin-sensitive asthmatic subjects.[1] The frequency of cross-sensitivity, however, has not been fully established. A low frequency, or even absence of cross-sensitivity (0% to 6%) has been consistently reported when acetaminophen challenge doses of 650 mg or less were administered (Table I) (Mathison DA, Stevenson DD. Personal communication).[2, 3] Determination of the prevalence of acetaminophen cross-sensitivity in aspirin-sensitive patients, challenged with 1000 mg of acetaminophen, is confined to two conflicting studies by Delaney[4] and Falliers,[5] who found cross-sensitivity rates of 29% and 0%, respectively.

Abbreviations used
FEV_1: Forced expiratory volume in 1 second
NSAID: Nonsteroidal antiinflammatory drug

Among reports in which acetaminophen challenges were used to study the prevalence of cross-sensitivity between aspirin and acetaminophen in asthmatic patients, a tendency toward overestimation of reactions would be expected in those studies in which bronchodilator drugs were withdrawn,[2, 3, 5] resulting in unstable airways. Airway stability was not objectively documented in three

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TABLE I. Review of reported acetaminophen cross-sensitivity in aspirin-sensitive patients with asthma

Year	Author	Acetaminophen challenge dose (mg)	Challenges No. reacted/ No. tested (%)	Aspirin sensitivity proved by challenge
1972	Mathison and Stevenson*	650	0/32 (0)	Yes
1975	Szczeklik et al.[2]	300	0/10 (0)	No
1977	Szczeklik et al.[3]	150-600	3/49 (6)	Yes
1976	Delaney[4]	1000	12/42 (29)	No
1983	Falliers[5]	1000	0/15 (0)	Yes

* Personal communication.

studies.[2, 3, 5] In addition, one study used unusual criteria to determine whether spirometric values revealed significant obstructive changes.[4] Underestimation of cross-sensitivity would be expected in those studies in which acetaminophen challenges were performed with low doses (<1000 mg) (Mathison DA, Stevenson DD. Personal communication)[2, 3] and in older studies in which challenges may have been performed in the refractory period after a respiratory reaction to aspirin.[2, 3, 5]

To clarify the prevalence of acetaminophen cross-sensitivity, we performed a prospective study in 50 known aspirin-sensitive asthmatic subjects and 20 non-aspirin-sensitive asthmatic control subjects by administering sequential challenge doses of 1000 and 1500 mg of pure acetaminophen. As a secondary goal, we examined the risk factors for acetaminophen cross-sensitivity. Additionally, we compared the severity of acetaminophen-induced bronchospastic reactions to corresponding aspirin-induced bronchospastic reactions in the same patients.

METHODS

Subjects

Seventy aspirin-sensitive adult asthmatic patients comprised the study population. Patients selected for acetaminophen challenge were those who came to Scripps Clinic and Research Foundation for evaluation and treatment of possible aspirin-sensitive respiratory disease. All 70 patients had a history compatible with aspirin-induced bronchospasm. In 50 patients (group 1), aspirin sensitivity was documented by means of oral aspirin challenges.[6] Group 2 consisted of 20 asthmatic patients who, despite a history suggesting aspirin sensitivity, underwent oral aspirin challenges without any respiratory reactions.

All patients in group 1 gave histories of mild to severe bronchospasm after ingesting 325 or 650 mg aspirin or one or more nonsteroidal antiinflammatory drug (NSAID) tablets. Group 1 had a mean age of 42 years (range, 20 to 75 years) and consisted of 45 white, one black, two Asian, and two Hispanic subjects. Twenty subjects were male, and 30 were female. Only one patient had a previous adverse reaction to acetaminophen, that being a bronchospastic reaction.

Patients with asthma in group 2 gave less definitive histories of asthma after aspirin or NSAID ingestion. All 20 patients were avoiding aspirin and NSAIDs; but 10 had recurrent nasal polyps, sinusitis, and refractory asthma. Patients in group 2 had a mean age of 49 years (range, 31 to 62 years) and included 11 women and nine men, and all were white. None of these patients had a history of adverse reactions to acetaminophen.

Challenge procedures

All acetaminophen challenges were performed in subjects who were inpatients in the General Clinical Research Center at Scripps Clinic and Research Foundation. Informed consent for procedures, approved by the Human Subjects Committee, was obtained from each patient before challenges began.

Single-blind acetaminophen challenge procedures were performed as follows. (1) Usual medications, such as theophylline and inhaled and systemic corticosteroids, were administered before and during challenges; β-agonists were withheld for at least 14 hours before challenges, antihistamines for 18 hours, and cromolyn for 24 hours. (2) With a wedge spirometer, flow-volume curves and forced expiratory volumes were recorded every hour or sooner and for at least 5 hours after each challenge dose. Asthma was considered to be in remission if forced expiratory volume in 1 second (FEV_1) values recorded over the previous 1 to 2 weeks were at least 70% of the predicted or the best previously recorded value, with an absolute value greater than 1.5 L. (3) Pure acetaminophen powder, 500 mg (provided by McNeil Consumer Products Company, Fort Washington, Pa.), and sucrose were placed in identical opaque capsules by the Scripps Clinic and Research Foundation pharmacy. (4) On the first day of the challenge, two identical placebo capsules were administered at 3-hour intervals during a 9-hour test period. (5) If, during placebo challenges, FEV_1 declined by 15% or more from morning baseline, the challenge process was discontinued, because baseline stability could not be documented. After treatment with systemic corticosteroids, placebo challenges were re-

TABLE II. Results of oral acetaminophen challenges in Groups 1 and 2 asthmatic patients

		ACTM-induced reactions			
		Naso-ocular		Bronchospastic	
	ASA-induced reactions	1000 mg	1500 mg	1000 mg	1500 mg
Group 1	Naso-ocular, 16 patients	1/16 (6%)	4/16 (25%)	0/16 (0%)	0/16 (0%)
Group 1	Bronchospastic, 34 patients	1/34 (3%)	2/34 (6%)	8/34 (24%)	11/34 (32%)
Group 2	Negative ASA challenge, 20 patients	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)

ASA, Aspirin; *ACTM,* acetaminophen.

TABLE III. Frequency of bronchospastic reactions to acetaminophen in 34 patients with aspirin sensitivity (bronchospastic type)

	Acetaminophen challenge doses	
Bronchospasm type	1000 mg	1500 mg
Partial bronchospasm	0/34 (0%)	1/34 (3%)
Bronchospasm	6/34 (18%)	8/34 (24%)
Bronchospasm + NOR	2/34 (6%)	2/34 (6%)
Total bronchospasm*	8/34 (26%)	11/34 (32%)

NOR, Naso-ocular reaction.
* Total bronchospasm = partial bronchospasm + bronchospasm + bronchospasm linked to naso-ocular reaction.

peated until airways were stable. (6) If FEV_1 was stable during placebo challenges, single-blind acetaminophen challenges were conducted the next day. An "unblinded" nurse administered three placebo capsules; if no reaction occurred in 3 hours, 1000 mg of acetaminophen (two opaque acetaminophen capsules, 500 mg, and one identical sucrose capsule) was administered. If no reaction occurred after 3 hours, 1500 mg of acetaminophen (three opaque acetaminophen capsules, 500 mg) was administered. (7) Criteria for a positive challenge result were: (a) "bronchospasm," a decline in FEV_1 of 20% or greater relative to the FEV_1 decline of the preceding placebo challenge day; (b) "partial bronchospasm," a decline in FEV_1 of 15% to 19% relative to placebo; (c) "Naso-ocular reaction," nasal congestion or rhinorrhea, paranasal headache together with conjunctival erythema or tearing with or without periorbital edema. For "partial bronchospasm" to be significant, a decline in FEV_1 between 15% and 19% had to be linked to simultaneous naso-ocular reaction. (8) Inhaled β-agonists were administered after a bronchospastic reaction and topical decongestant spray was used intranasally to relieve nasal obstruction.

Statistical analysis

Fischer's exact test was used to calculate probabilities for differences between groups of patients or treatments. Ninety-five percent confidence intervals for binomial probabilities were calculated with the exact method in order to bound the expected proportion of total positive challenges induced by 1000 mg and 1500 mg provoking doses of acetaminophen.

RESULTS

Challenge results for both group 1 and group 2 patients are shown in Table II. Group 1 asthmatic patients, when challenged with aspirin in doses of 30, 60, and 100 mg, experienced the usual spectrum of responses, with 16 patients experiencing naso-ocular reactions without bronchospasm and 34 experiencing bronchospastic reactions. Group 2 patients did not react to aspirin. Within the subcategories of positive reactions to aspirin, acetaminophen cross-reactions are noted, with a clustering of naso-ocular or bronchospastic reactions for both analgesics. Non-aspirin-sensitive asthmatic patients did not react to acetaminophen.

Among the 34 group 1 asthmatic patients who reacted after aspirin challenge with bronchospasm with or without associated naso-ocular reaction, the predominant form of adverse reaction to acetaminophen was also bronchospasm, occurring at a frequency of 24% (8 of 34) at 1000 mg and a cumulative frequency of 32% (11 of 34) when challenged with 1500 mg of acetaminophen. Further description of the subtypes of bronchospastic reactions to acetaminophen is presented in Table III. Naso-ocular reactions alone occurred at a frequency of 3% (1 of 34) at the 1000 mg acetaminophen challenge dose and 6% (2 of 34) at challenge doses up to 1500 mg.

Among the 11 patients who reacted to acetaminophen with bronchospasm, baseline FEV_1 values on the reaction day were normal (>80% predicted) in 10 patients and 73% of predicted value in the remaining patients.

In summarizing the results of the challenges in the Group 1 (aspirin-sensitive) asthmatic patients, it is important to understand that all 50 patients gave a history of significant bronchospastic reactions after ingesting either 325 or 650 mg of aspirin

TABLE IV. Acetaminophen challenge results in 50 patients with aspirin-sensitive asthma

Reactions	ACTM 1000 mg 2/50 (4%)	ACTM 1500 mg 6/50 (12%)
Bronchospastic reactions		
Pure bronchospasm	6/50 (12%)	8/50 (16%)
Bronchospasm and NOR	2/50 (4%)	2/50 (4%)
Partial bronchospasm and NOR	0/50 (0%)	1/50 (2%)
Total bronchospasm	8/50 (16%)	11/50 (22%)
Total positive challenges	10/50 (20%)	17/50 (34%)
95% CI*	10-34	20-49

ACTM, Acetaminophen; *NOR,* naso-ocular reaction; *CI,* confidence interval.
* For proportion of total positive challenges.

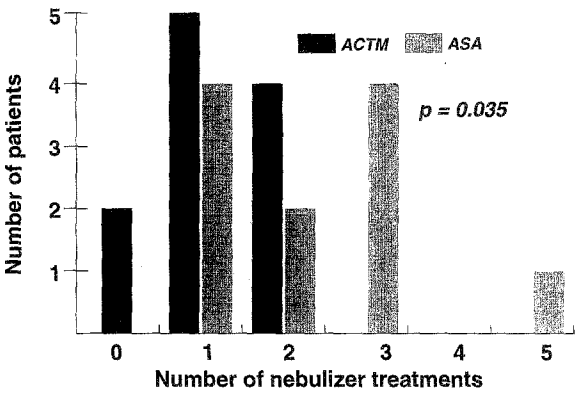

FIG. 1. Number of nebulizer treatments per patient required to reverse induced bronchospastic reactions; comparison of acetaminophen challenges with aspirin challenges. *ACTM,* Acetaminophen; *ASA,* aspirin.

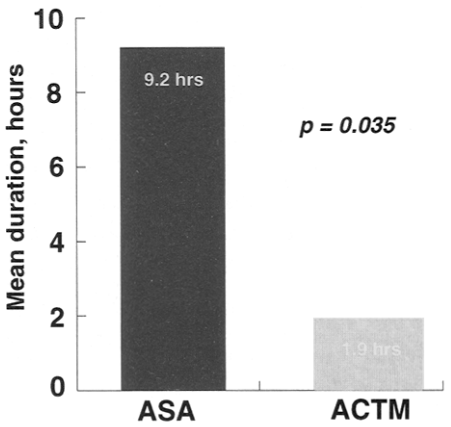

FIG. 2. Duration, in hours, of acetaminophen-induced bronchospastic reactions compared with corresponding aspirin-induced bronchospasm. *ACTM,* Acetaminophen; *ASA,* aspirin.

(or equivalent NSAIDs). Despite the fact that some of these patients reacted with only naso-ocular responses on aspirin challenges when exposed to small doses of aspirin (60 or 100 mg), all 50 were considered to be true aspirin-sensitive asthmatic patients. The occurrence of only naso-ocular symptoms in some aspirin-sensitive asthmatic patients resulted from conservative aspirin challenge methods. Oral aspirin challenges are designed to minimize respiratory reactions by starting with one twentieth of the highest challenge dose of aspirin and slowly advancing to the first "threshold dose," which produces a spectrum of respiratory reactions. Therefore even though 16 of 50 patients reacted to 30 or 60 mg of aspirin with naso-ocular symptoms alone, this should not be interpreted to mean that 650 mg of aspirin would induce the same minimal reactions in these same patients. In fact, the opposite is true. In essence, all 50 patients were aspirin-sensitive asthmatic patients and therefore are presented as such for purposes of understanding cross-sensitivity in Table IV. Therefore the total number of positive acetaminophen challenge results in these group 1 (aspirin-sensitive) asthmatic patients is 17 of 50 (34%), for a 95% confidence interval of 20% to 49%.

Among the 20 asthmatic patients in group 2 (negative aspirin challenge result up to doses of 650 mg of aspirin), there were no positive acetaminophen challenge results (0 of 20), for a 95% confidence interval of 0% to 14%. The difference between the frequencies of positive acetaminophen challenges for Groups 1 and 2 asthmatics was highly significant, (Fisher's exact test, $p = 0.0013$). Because there is no overlap of the 95% confidence interval for proportion of total positive acetaminophen challenge results between group 1 and group 2 asthmatic patients, the two populations are statistically different.

The magnitude of the decline in FEV_1 resulting from acetaminophen-induced bronchospastic reactions was not significantly different from corresponding aspirin-induced bronchospasm. However, the mean provoking dose of aspirin that induced bronchospastic reactions was 47 mg, as compared with a mean dose of 1227 mg for acetaminophen.

Fig. 1 shows the mean number of nebulizer treatments per patient required to reverse analgesic-induced bronchospastic reactions: acetaminophen, 1.2 (range, 0 to 2) compared with aspirin-induced bronchospasm, 2.6 treatments (range, 1 to 5) ($p = 0.035$).

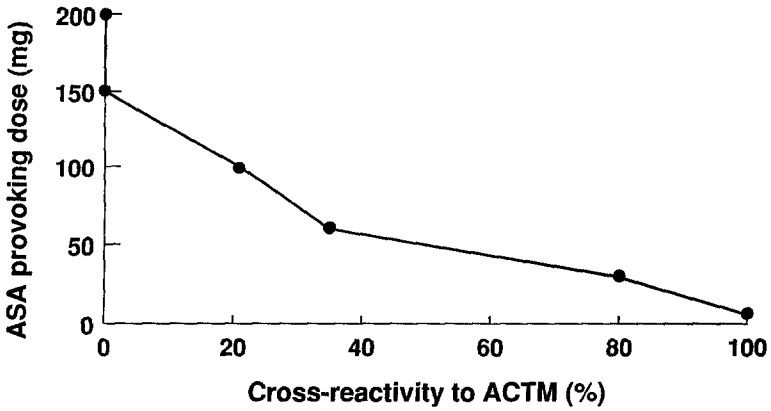

FIG. 3. Aspirin provoking dose and frequency of cross-reactivity to acetaminophen. *ACTM,* Acetaminophen; *ASA,* aspirin.

Fig. 2 shows the duration, in hours, of acetaminophen-induced bronchospastic reactions (mean, 1.9 hours). This was significantly shorter than the corresponding duration of aspirin bronchospastic reactions (9.2 hours, $p = 0.008$).

In Fig. 3, the aspirin provoking dose and corresponding frequency of cross-reactivity to acetaminophen are shown for the 50 aspirin-sensitive asthmatic patients. When 30 mg of aspirin or less provoked bronchospasm, five of six (83%) patients experienced cross-reactivity to acetaminophen. In contrast, none of the four patients in whom the aspirin provoking dose was 150 mg or greater experienced cross-reactivity ($p = 0.08$).

DISCUSSION

Delaney[4] and Falliers[5] reported conflicting data regarding the prevalence of acetaminophen cross-sensitivity in the aspirin-sensitive asthmatic subjects who were challenged with acetaminophen. In both studies patients were challenged with 1000 mg of acetaminophen. Delaney[4] reported a cross-sensitivity of 29% (12 of 42), as opposed to the 0% (0 of 15) prevalence reported by Falliers.[5]

Overestimation bias in the study by Delaney[4] might have resulted from several aspects of the design. The criteria for establishing the presence of a bronchospastic reaction were not clearly stated; specifically, a reaction was defined qualitatively only as "a rapid decline in FEV_1 compared with placebo." Given these imprecise criteria, the single-blind nature of this study may have additionally contributed to false-positive interpretations of the challenge data. Finally, some of the bronchospastic responses in Delaney's study[4] may have actually been recordings of unstable asthma, because patients with unstable airways (FEV_1 values <1.5 L) participated in challenges. A full day of placebo challenges, before acetaminophen challenges, was not included in his study.

Falliers's failure to identify acetaminophen cross-sensitivity may have been due to the performance of acetaminophen challenges during the refractory period after positive aspirin challenges.[5] Cross-desensitization between aspirin and acetaminophen has been documented.[1] According to Falliers's protocol, challenges with aspirin, acetaminophen, and placebo were performed in random order, at intervals as short as 3 days, which is well within the refractory period that occurs after a positive aspirin challenge.[7, 8]

We performed single-blind acetaminophen challenges in 50 aspirin-sensitive and 20 non-aspirin-sensitive asthmatic patients and interpreted the pulmonary function data with strict criteria for bronchospasm. A full day of placebo challenges preceded any challenges with either acetaminophen or aspirin. Our acetaminophen challenges were performed before any aspirin challenges and could not have been within the refractory period after an aspirin reaction.

Among naso-ocular reactors to aspirin, induced naso-ocular reactions to acetaminophen were dose-dependent, occurring for 1000 mg of acetaminophen in 6% and for 1500 mg of acetaminophen in 25%. Among bronchospastic reactors to aspirin, acetaminophen-induced reactions were predominantly bronchospastic and were also dose-dependent, occurring for 1000 mg in 24% and for 1500 mg in 32%. Less common were acetaminophen-induced naso-ocular reactions occurring for 1000 mg in 3% and for 1500 mg in 6%. In all 50

aspirin-sensitive asthmatic patients, acetaminophen cross-reactivity was 34% (17 of 50).

This prevalence contrasts strikingly with the prevalence of 0% cross-reactivity found in asthmatic control subjects who were not aspirin-sensitive, strongly implying that acetaminophen-induced respiratory reactions are specifically cross-reactive to aspirin in aspirin-sensitive asthmatic patients. Furthermore, the fact that cross-desensitization occurs between aspirin and acetaminophen in aspirin-sensitive asthmatic patients[1] is further evidence that cross-sensitivity, rather than random reactions, occurred.

We found that the acetaminophen-induced bronchospastic reactions were milder than those induced by aspirin in two ways. First, the duration of bronchospasm was significantly shorter for acetaminophen ($p = 0.008$); and second, significantly fewer bronchodilator treatments were required to reverse bronchospasm ($p = 0.035$). The acetaminophen-induced bronchospasm was similar in magnitude (Δ FEV_1) to that induced by aspirin in the same patients; but a mean of only 47 mg of aspirin provoked bronchospasm, as compared with 1,227 mg of acetaminophen.

Although the purpose of this study was not to explore the possible mechanisms of cross-sensitivity, we did note a relationship between low aspirin provoking dose and increased likelihood of acetaminophen cross-sensitivity. The shared property of cyclooxygenase inhibition may explain this relationship.[2, 3] Aspirin-sensitive patients who are exquisitely sensitive to low provoking doses of aspirin might have been more sensitive to the weak inhibition of cyclooxygenase associated with acetaminophen.

On the basis of the data presented here and in previous reports,[1] we have the following recommendations regarding the use of acetaminophen in aspirin-sensitive asthmatic patients and asthmatic patients in general: (1) In patients known to be aspirin-sensitive, high doses of acetaminophen (1000 mg or greater) should be avoided, particularly if it is known that the threshold of aspirin sensitivity is to doses of 100 mg or less of aspirin. (2) Most asthmatic patients, whether or not they are aspirin-sensitive, should be able to ingest acetaminophen at doses 650 mg or less with a small risk of bronchospasm.[3] (3) The currently recommended maximum dose of acetaminophen (1000 mg) falls into a gray area. Extrapolating from our present data, and because at least 10% of all asthmatic patients are aspirin-sensitive,[8, 9] our results suggest that only 2.4% of all asthmatic patients are at risk of experiencing brief, easily reversible bronchospasm on ingestion of 1000 mg of acetaminophen. However, it must be stressed that the patients in our study had stable asthma with normal or near normal baseline lung function. We do not have any data regarding the severity of reactions that might occur in acetaminophen-sensitive patients if 1000 mg of acetaminophen were to be ingested during a state of uncontrolled asthma.

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