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Cross sensitivity with acetaminophen in aspirin-sensitive subjects with asthma

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Drugs inhibiting cyclooxygenase regularly cross-react with aspirin (ASA). Although some experiments suggest that acetaminophen (ACETM) is a weak inhibitor of cyclooxygenase in certain tissues, it has not been studied in human lung tissue, and controversy exists whether or not true cross-reactivity occurs between ASA and ACETM. Three ASA-sensitive subjects with asthma, who gave a history of reactions to ACETM, underwent double-blind, placebo-controlled challenges and reacted to 1000 mg of ACETM with a >20% fall in FEV₁. Two patients were desensitized to ASA and then were rechallenged with 1000 mg of ACETM without reaction. Two patients were desensitized to increasing doses of ACETM, achieving refractoriness to 1500 mg, but not 2000 mg. Thus, cross sensitivity between ASA and ACETM was documented when large challenge doses (1000 mg) of ACETM were used. Furthermore, cross desensitization suggests that in ASA-sensitive subjects with asthma, similar mechanisms are likely to be responsible for reactions to ASA, nonsteroidal anti-inflammatory drugs, and ACETM. (J ALLERGY CLIN IMMUNOL 1989;84:26-33.)

ACETM is a commonly used analgesic and antipyretic drug that is often used in place of ASA. Numerous publications have suggested that a small percentage of ASA-sensitive patients with asthma also react to ACETM.¹⁻¹⁴ However, whether or not reported reactions are real and true cross-reactivity occurs continues to be controversial.¹⁵

Drugs, such as NSAIDs, which inhibit cyclooxygenase, are known to regularly cross-react with ASA.^{4,9,15} However, animal experiments have demonstrated that ACETM, depending on the type of tissue studied, variably inhibits,¹⁶⁻³⁵ stimulates,^{18, 29, 35-40} or has no effect^{2, 28, 26, 41-43} on cyclooxygenase. In tis-

Abbreviations used

ACETM: Acetaminophen
ASA: Aspirin
NSAID: Nonsteroidal anti-inflammatory drug
GCR: General Clinical Research Center

sues in which ACETM functions as an inhibitor of cyclooxygenase, its effects are weak, except in brain tissue, in which its pharmacologic effects are similar to other NSAIDs.^{16, 19} This fact has been used to explain its antipyretic-analgesic effects. Studies of the effect of ACETM on cyclooxygenase in human lung tissue have not been reported.

In 1967, Chaffee and Settipane⁴⁴ reported that a patient with ASA-induced angioedema developed severe asthma on ingestion of one 325 mg tablet of ACETM. Confirmatory oral challenges with ASA or ACETM were not performed. Subsequent publications of ACETM challenges in suspected or known ASA-sensitive patients with asthma, in which objective spirometric measurements were used as evidence for

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TABLE I. Review of reported ACETM cross sensitivity in ASA-sensitivity patients with asthma

Year	Author	Acetaminophen challenges		ASA sensitivity proved by challenge
		Challenge dosage (mg)	No. reacted/No. tested (%)	
1971 (single-blind)	Smith ¹	500	3/5 (60)	No
1972* (single-blind)		650	0/32 (0)	Yes
1975 (single-blind)	Szczeklik et al. ²	300	0/10 (0)	No
1976 (single-blind)	Delaney ³	1000	12/42 (28.6)	No
1977 (single-blind)	Szczeklik et al. ⁴	150-600	3/49 (6.1)	Yes
1979 (single-blind)	Spector et al. ⁵	650	2/2 + †(unknown)	Yes
1983 (single-blind)	Falliers ⁶	1000	0/15 (0)	Yes
1983 (double-blind)	Fischer et al. ⁷	600	1/3 (33.3)	Yes
1986 (single-blind)	Henochowicz ⁸	1000	1/1 (100)	No

* Mathison DA, Stevenson DS. Personal communication.

† At least two of the 69 patients challenged with ACETM were ASA sensitive.

asthmatic reactions to ACETM and/or ASA, are summarized in Table I. A tendency toward overestimating the presence of cross sensitivity would be expected in those studies in which patients with histories that were suspicious for ACETM sensitivity were selected,^{1, 8} bronchodilator drugs were withdrawn,^{1, 2, 4-7} patients with unstable airways participated^{3, 5, 7, 8} or airway stability was unknown,^{1, 2, 4, 6} and in those studies in which unusual criteria were used to determine whether the spirometric values revealed significant obstructive changes.^{3, 6} Underestimation of the presence of cross sensitivity between ASA and ACETM would be expected in those studies in which ACETM challenges were performed with smaller dosages of the drug (<1000 mg)^{1, 2, 4, 5, 7} and in those studies in which ACETM challenge may have been performed in the refractory period after a respiratory reaction to ASA.^{1, 2, 4-7}

The present study was designed to confirm the history of bronchospastic reactions to ingested ACETM in three ASA-sensitive patients with asthma, all of whom stated that ACETM caused asthma attacks. Additionally, we attempted to desensitize patients with reactions to dosages of ACETM greater than their provoking dosage in a manner similar to that used for ASA and NSAIDs in ASA-sensitive subjects with asthma.¹⁵ We also determined if ACETM, in large

dosage, truly behaves like ASA and NSAIDs by participating in cross desensitization after ASA desensitization.⁴⁵

METHOD

Patients

All patients were adults with known reversible obstructive airway disease. Patients were selected because, by history, they observed wheezing after ingesting ACETM. Sensitivity to ASA was proved with oral ASA challenges in all patients.⁴⁶ After admission to the GCRC at Scripps Clinic and Research Foundation, informed consent for procedures approved by the Human Research Committee were obtained for each patient.

Challenge procedure

The double-blind challenge procedure was performed as previously described.⁴⁶ (1) Usual medications, such as theophylline and inhaled and systemic corticosteroids, were administered before and during challenges; β -agonists were withheld 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. Asthma was considered in remission if FEV₁ values were at least 70% of predicted or of the best previously recorded, with an absolute value >1.5 L. (3) Pure ACETM, 500 mg (provided by McNeil Laboratories, Spring House, Pa.), and sucrose were placed in

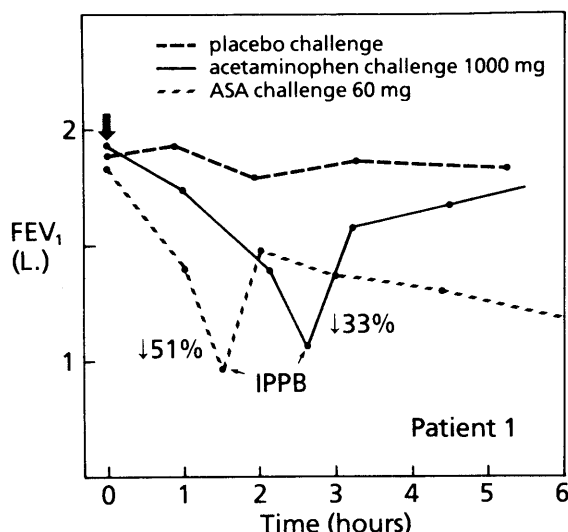


FIG. 1. Negative placebo challenge (2/10/87), positive ACETM challenge (2/11/87), and positive ASA challenge (1/24/84) in patient 1; administration of placebo, ACETM, 1000 mg, and ASA, 60 mg (↓); decline in FEV₁ from morning baseline (%).

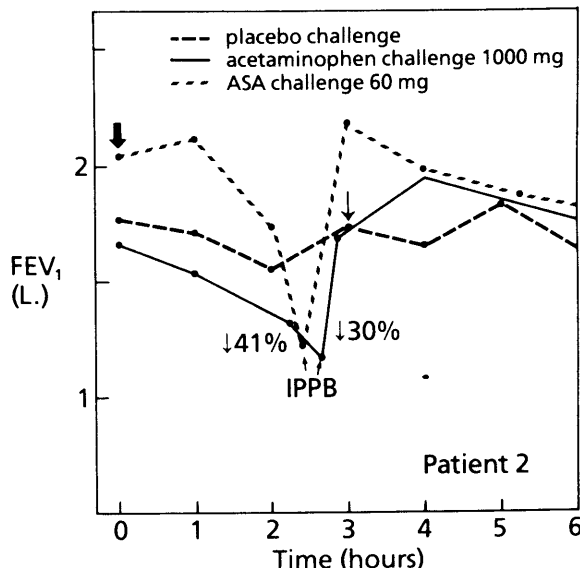


FIG. 2. Positive ASA challenge (6/29/87), negative placebo challenge (6/25/87), and positive ACETM challenge (6/26/87) in patient 2; administration of ASA, 60 mg, placebo, and ACETM, 1000 mg (↓); administration of placebo only (↓); decline of FEV₁ from morning baseline (%).

identical opaque capsules by the Scripps Clinic and Research Foundation pharmacy. (4) On the first day of the challenge, two placebos were administered every 3 hours during a 9-hour test period in a single-blind manner. (5) If, during placebo challenges, the FEV₁ values declined by 16% or more from the morning baseline, the study was stopped, since baseline stability could not be demonstrated, and placebo challenges were repeated the next day. (6) If the placebo challenges were stable, double-blind ACETM challenges were conducted on the following day. (7) An "unblinded" nurse selected two opaque placebo capsules, two identical opaque ACETM capsules, 500 mg, and one capsule of each, and randomly placed each pair into envelopes labeled No. 1, No. 2, and No. 3, to be administered by the "blinded nurse" in that order at 3-hour intervals. (8) If the FEV₁ declined by 20% or more, the study was stopped, and the data were interpreted. If the FEV₁ values declined by ≤16% during the 3 hours after placebo challenge and a 20% or more decline had occurred after the dose of ACETM, the challenge was considered to be positive. (9) Nebulized isoetharine (0.25 ml), diluted in normal saline, was inhaled via intermittent positive-pressure breathing after a positive challenge.

ACETM desensitization procedure

After a respiratory reaction to ACETM had been induced and subsided, the same dosage of ACETM, which provoked the original reaction, was reintroduced. The minimum time interval between dosages was 3 hours. If the reaction occurred a second time, the dosage was repeated again. When reactions ceased after that dosage of ACETM, the dosage was increased by 500 mg, and the process was repeated.

Cross desensitization procedure

After ACETM desensitization procedures, ASA desensitization was performed, as described in previous publications.^{47, 48} When patients could ingest a least 325 mg of ASA without adverse effect, they were then rechallenged with their original provoking dose of ACETM, and serial flow-volume curves and forced expiratory volumes were recorded. The time interval between completion of ASA desensitization and ACETM rechallenge was 3 hours.

RESULTS

Patient 1

A 70-year-old white woman with a history of perennial allergic rhinitis, sinusitis, and asthma, requiring chronic oral corticosteroids for control, experienced a severe asthma attack, requiring emergency treatment, after the ingestion of two ASA tablets in 1975. This was confirmed by oral ASA challenges for research purposes (in 1977, 1979, 1983, 1984, and 1986), all of which produced typical asthmatic and rhinitic respiratory reactions (Fig. 1).

By history, she reported that in 1986 she experienced wheezing after the ingestion of two Extra-Strength Tylenol (McNeil Laboratories) (ACETM, 1000 mg); however, it was noted that she tolerated one Extra-Strength Tylenol without adverse effects. She underwent a preliminary double-blind, placebo-controlled challenge with Tylenol, and 1000 mg of Tylenol was associated with a 32% decline in FEV₁.

TABLE II. ACETM challenges

Patient No.	No. of challenges	Provoking dose (mg)	% Decrease FEV ₁
1	2	1000	32-33
2	1	1000	30
3	1	1000	25

with concomitant nasal reaction in 1986. She was desensitized to 1000 mg, and then 1500 mg of Tylenol, but three consecutive attempts to achieve desensitization with 2000 mg of Tylenol were not successful. Further attempts to challenge with large-dose acetaminophen were suspended to avoid possible liver toxicity.

To rule out the possibility that the results of the initial Tylenol challenge may have been due to "inactive ingredients" in the Tylenol, in February 1987, she underwent double-blind, placebo-controlled challenge with pure ACETM. No adverse symptoms nor fall in FEV₁ could be demonstrated during the preceding baseline day of placebo challenges. However, the next day, although she did not react to 500 mg of ACETM or placebos, 1000 mg of ACETM was followed by a 33% decline in FEV₁ (Fig. 1).

Gastric intolerance to ASA precluded institution of ASA challenge or desensitization.

Patient 2

A 75-year-old white man with a history of sinusitis, nasal polyps, and asthma, requiring chronic oral corticosteroids for control, had experienced severe asthma, requiring emergency treatment after the ingestion of two ASA on two separate occasions and Indocin (Merck Sharp & Dohme, West Point, Pa.) and Nalfon (Dista Products Co., Indianapolis, Ind.) on other occasions. In January 1987, ASA sensitivity was confirmed by oral ASA challenge that was followed by ASA desensitization, as described in previous publications.^{47, 48} Because of noncompliance, the patient became sensitive to ASA again and was admitted to the GCRC for repeat ASA desensitization in June 1987. On the day of admission, through an on-call communication error, he ingested one Extra-Strength Tylenol (ACETM, 500 mg) for relief of musculoskeletal pain, and in 2 hours he experienced wheezing, chest tightness, and nasal congestion with a 22% decline in FEV₁. He had tolerated without adverse effect one Extra-Strength Tylenol on multiple previous occasions.

He then underwent double-blind, placebo-controlled challenge with pure ACETM. During the

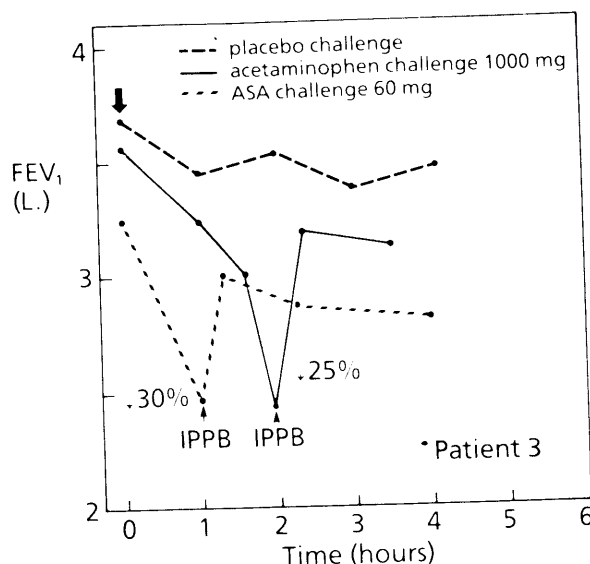


FIG. 3. Negative placebo challenge (8/17/87), positive ACETM challenge (8/18/87), and positive ASA challenge (8/19/87) in patient 3; administration of placebo, ACETM, 1000 mg, and ASA, 60 mg (↓); decline in FEV₁ from morning baseline (%).

preceding baseline day, he responded to single-blind placebo challenges with a maximal decline in FEV₁ of 16%. However, the next day, 1000 mg of ACETM was followed by a 30% decline in FEV₁ (Fig. 2). Because the patient was administered the reacting dose of ACETM before placebo challenge that day, the test was considered only conditionally positive and was repeated the following day. No adverse symptoms nor fall in FEV₁ was demonstrated with placebos, but once again 1000 mg of ACETM elicited a positive reaction with a 25% decline in FEV₁. He was then successfully desensitized to 1000 mg and 1500 mg of ACETM (Table III); however, further desensitization to larger doses was not attempted to avoid potential hepatic toxicity.

ASA challenge, followed by desensitization, as described in previous publications,^{47, 48} was then performed; after desensitization with ASA was established, the patient was rechallenged with 1000 mg of ACETM without any subsequent decline in FEV₁ values.

Patient 3

A 44-year-old white woman with a history of perennial rhinitis, sinusitis, and asthma required frequent courses of antibiotics and bursts of oral corticosteroids for control of sinusitis and associated asthma. After the ingestion of two ASA, on two separate occasions, she experienced chest tightness,

wheeze, and nasal congestion requiring emergency treatment. An oral ASA challenge in 1982 documented ASA-sensitive asthma.

In April 1987, while she was hospitalized for asthma and headache, she ingested two Tylenol (ACETM, 650 mg) for pain relief, and within 30 minutes experienced an asthma attack requiring treatment with metaproterenol by inhalation.

In August 1987, she received a burst of prednisone to stabilize asthma in preparation for admission to the GCRC, where she underwent double-blind, placebo-controlled challenge with pure ACETM. During the preceding baseline day, her FEV₁ values declined by <16% after all-day placebo challenges. The next day, although no adverse symptoms nor fall in FEV₁ could be demonstrated after 500 mg of ACETM or placebo, 1000 mg of ACETM was followed by a 25% decline in FEV₁ (Fig. 3).

She was then challenged, reacted to, and was desensitized to ASA,^{47, 48} and rechallenged with 1000 mg of ACETM without significant decrease in FEV₁ values.

DISCUSSION

In this study, we performed double-blind, placebo-controlled ACETM-ingestion challenges with doses of pure ACETM up to 1000 mg in three known ASA-sensitive patients with asthma, selected because their histories suggested ACETM-associated asthma. Serial pulmonary function tests in all three subjects were stable during the preceding day of placebo challenges, but all three subjects experienced bronchospastic reactions to 1000 mg of ACETM with a decline in FEV₁ of >20% (Table II).

Beginning in 1975, Szczeklik et al.² published a series of important observations noting an inverse relationship between the potency of analgesics as inhibitors of prostaglandin synthesis *in vitro* and the doses of these drugs required to induce an asthma attack in ASA-sensitive patients with asthma. It follows that ACETM, functioning as a weak inhibitor of cyclooxygenase, might occasionally cross-react with ASA when it is administered in large doses (≥ 1000 mg), as in the present study. Delaney³ found no cross-reactivity when challenges were performed with 500 mg of paracetamol (ACETM in the United States), but by increasing the provoking dosages of paracetamol to 1000 mg, cross-reactive asthma was induced in 12/42 (28%) of ASA-sensitive patients with asthma. A dose-related decline in FEV₁ values after ACETM challenge was also demonstrated by Henochowicz⁸ in a case report of a probable ASA-sensitive patient with asthma in whom placebo provoked a 2% decline, 325 mg of ACETM provoked an

11% decline, 650 mg provoked a 26% decline, and 1000 mg provoked a 56% decline.

Such a dose-dependent response might explain why previous ACETM challenges performed at Scripps Clinic and Research Foundation (Mathison DA, Stevenson DS. Personal communication.) in 32 ASA-sensitive subjects with asthma, with 650 mg of ACETM as the maximal provoking dose, did not produce any cross-reactivity, and perhaps why Szczeklik et al.⁴ found only 3/49 (6%) of ASA-sensitive patients with asthma reacting when they were challenged with a provoking dose of paracetamol in the range of 150 to 600 mg.

It is noteworthy that Falliers⁶ challenged 15 ASA-sensitive patients with 1000 mg of ACETM and found no cross sensitivity. However, it is unclear if Falliers performed ACETM challenges in the refractory period after a respiratory reaction to ASA.

In the present article, all three subjects reacted to only 1000 mg provoking dosages of ACETM on challenge. Two patients had undergone challenges with 500 mg dosages without adverse effect, strongly suggesting a dose-dependent response. The remaining patient was not challenged with the 500 mg dose but had, by history, tolerated 500 mg of Extra-Strength Tylenol (ACETM) on all but one previous occasion.

The weak inhibition of cyclooxygenase by ACETM compared to ASA also appears to correlate with the severity of the provoked bronchospastic reactions. In general, the decline in FEV₁ values after ACETM challenge was of lesser magnitude and more gradual than after ASA challenge with low dose (60 mg) for each patient (Figs. 1 to 3); the ACETM-induced bronchial reaction responded promptly to a few inhalations of isoetharine. Such bronchodilator responses are in contrast to most ASA-induced asthmatic reactions, typified in patients 1 and 3 in whom initial bronchodilator response to a β -agonist was soon followed by a second decline in FEV₁ values and return of asthma symptoms. Indeed, the usual course of ASA-induced asthma occurs during a number of hours and requires multiple inhalation treatments with β -agonist.⁴⁶

A major purpose of this article was to report cross desensitization between ASA and ACETM, a phenomenon not previously reported and essential if true cross-reactivity is occurring between these drugs. Indeed, cross desensitization occurs routinely between ASA and all NSAIDs that inhibit cyclooxygenase.⁴⁵ In our current study, two patients were challenged with ASA after ACETM-induced asthmatic reactions. They reacted to ASA, were repeatedly challenged with ASA until they were desensitized to this drug,⁴⁸ and then were rechallenged with ACETM, 1000 mg. Since no asthmatic reactions occurred on rechallenge to this

original provoking dose of ACETM, we conclude that cross desensitization had occurred and that ACETM in large doses (≥ 1000 mg) behaves like other NSAIDs and ASA.

We attempted to desensitize two patients with increasing doses of ACETM (Table III). It is intriguing that in one of the two patients in whom ACETM desensitization was attempted, desensitization with >1500 mg could not be achieved, despite three challenges with 2000 mg of ACETM. Because of our concern about larger doses inducing hepatic toxicity, it is unknown whether further attempts at desensitization with larger doses of ACETM would have been successful. It may not be possible to settle this issue because the doses suspected to achieve this result may be too large for human safety.

Since ACETM inhibits cyclooxygenase in a weak and reversible manner,²⁴ unlike the potent and permanent inhibition of cyclooxygenase caused by covalent binding to cyclooxygenase demonstrated to occur with ASA/NSAIDs,^{49, 50} desensitization to ACETM may not be possible. Indeed, there appeared to be little evidence of a refractory period after a positive ACETM challenge, as demonstrated by patients 2 and 3, who had positive ASA challenges on the day after positive ACETM challenges, suggesting a rapidly reversible refractoriness after positive ACETM challenge.

In human lung tissue, effect of ACETM on cyclooxygenase has not been reported. In animal experiments, ACETM has been demonstrated not to have an effect on lung tissue cyclooxygenase,^{18, 26} unlike the inhibitory effects on lung tissue reported for ASA and other NSAIDs.^{18, 26, 51, 52} Cross sensitivity and cross desensitization between ASA and ACETM implies, on the basis of the behavior of ASA/NSAIDs, that ACETM will be demonstrated to be an inhibitor of cyclooxygenase in human lung tissue if large enough concentrations of the drug are used during *in vitro* assays.

Our study was not designed to establish the prevalence of ASA and ACETM cross sensitivity, since our three patients were specifically selected for this study because of their strong histories suggesting such cross-reaction. In point of fact, data concerning the prevalence of ACETM cross sensitivity in ASA-sensitive patients challenged with 1000 mg of ACETM are confined to the conflicting studies by Daleny³ and Falliers.⁶ To clarify this issue, a prospective study of known ASA-sensitive subjects with asthma, administered challenges of 1000 and 1500 mg of ACETM, is necessary. Only then will a percentage risk of cross sensitivity be available.

Given the fact that cross sensitivity between ASA

TABLE III. ACETM: Attempted desensitization

Date	Dosage (mg)	% Decrease FEV ₁
Patient 1		
9/29/86	1000	32
9/30/86	1000	0
	1500	25
10/1/86	1500	33
	1500	43
10/2/86	1500	5
	2000	32
10/3/86	2000	39
	2000	24
Patient 2		
6/27/87	1000	25
6/28/87	1000	6
	1500	19
	1500	7

and ACETM exists, what is the risk of severe reactions to ACETM, and are lower doses safe? Answers to these questions are not readily apparent. Patient 1 takes ACETM, 1000 mg, for severe headache while she is at home. Since she receives relief of headaches from this treatment dosage, she willingly and successfully treats the mild ACETM-induced asthma with two inhalations of a β -agonist nebulizer. Her ACETM-induced asthma is well controlled, and she is at little risk for a severe reaction.

Patient 3, in contrast, took only 650 mg of ACETM as an inpatient, when her asthma was active, and experienced a severe asthma attack. This same patient, while she was taking prednisone and with excellent control of asthma in our GCRC, tolerated ACETM, 500 mg, without adverse effect and experienced only a mild asthma episode after taking 1000 mg of ACETM.

Therefore, recommendations are difficult to outline, and more information is needed. In the meantime, patients with stable asthma appear to be at little risk, even if they are ingesting two Extra-Strength Tylenol caplets (500 mg per caplet). By contrast, more severe reactions could occur in subjects with poorly controlled asthma, even at dosages of ACETM in the order of 500 mg or less.

In conclusion, true cross-reactivity with ACETM has been demonstrated to occur in ASA-sensitive patients with asthma. Large challenge doses (1000 mg) of ACETM were required to induce asthmatic reactions to ACETM, suggesting a weak inhibitory effect on cyclooxygenase, as has been demonstrated by *in vitro* studies. Cross sensitivity and cross desensi-

tization between ASA and ACETM suggest that in ASA-sensitive subjects with asthma, similar mechanisms are likely to be responsible for reactions to ASA/NSAIDs and ACETM.

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