Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period

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Thirty aspirin-sensitive asthmatic patients underwent incremental, oral aspirin challenge until a "positive reaction" ($\Delta FEV_1 \geq 25\%$) occurred. After this reaction, aspirin was readministered in an attempt to achieve "desensitization." This was defined as the ability of the patient to ingest 650 mg of aspirin without experiencing upper or lower respiratory-tract symptoms or a decrease in lung function. To determine the "refractory period" following aspirin desensitization, patients were rechallenged after various intervals (days) without aspirin until a positive reaction recurred. All 30 aspirin-sensitive asthmatic patients were successfully desensitized to aspirin. Individual patient refractory periods ranged from less than 2 days to greater than 5 days, with most patients gradually returning to sensitivity between 2 to 4 days. Cross-desensitization with indomethacin and other nonsteroidal anti-inflammatory drugs was also demonstrated. These studies show that aspirin desensitization can be safely achieved in aspirin-sensitive asthmatic patients; however, this desensitization will gradually disappear over several days when additional aspirin is withheld. (J ALLERGY CLIN IMMUNOL 69:11, 1982.)

In 1919, Ott[1] first reported an asthmatic reaction attributed to aspirin ingestion. Later, Lamson and Thomas[2] and Dysart[3] reported deaths from asthmatic attacks that followed the ingestion of ordinary dosages of aspirin. Since then, several additional descriptions of aspirin-induced respiratory reactions have been reported.[4–9] In 1969, Samter and Beers[7, 8] popularized the aspirin "triad" concept of asthma, nasal polyps, and aspirin sensitivity. Associated cross-reactivity between aspirin and several other chemicals, particularly NSAI drugs, is now widely recognized.[7–16]

The apparent existence of a refractory period after an aspirin hypersensitivity reaction was first recognized by Widal et al.[10] in one patient in 1922. Zeiss and Lockey[17] later reported a 72-hr refractory period after an aspirin reaction in a patient in 1976, and Bianco et al.[18] found refractoriness to inhaled aspirin conjugates after aspirin-provoked bronchoconstriction. At our institution, Stevenson et al.[19] confirmed these findings in two aspirin-sensitive asthmatic patients who became unresponsive to aspirin after positive oral aspirin challenges. These two patients continued to ingest aspirin on a daily basis for over 18 mo without exhibiting any adverse effects. In fact, their clinical courses improved.

This study was designed to further investigate aspirin desensitization after positive oral aspirin challenges. We have determined the dosages of aspirin necessary to produce reactions during aspirin challenges while also demonstrating that all aspirin-sensitive patients can be safely desensitized. In addition, we have identified the length of time after aspirin desensitization when such patients remain resistent or refractory to further adverse effects from this drug.

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Supported by NIAID grants AI-10386-09 and RR 0083.
Received for publication April 6, 1981.
Accepted for publication Sept. 10, 1981.

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0091-6749/82/010011+09$00.90/0

Abbreviations used
NSAI: Nonsteroidal anti-inflammatory
FEV_1: Forced expiratory volume in one second

MATERIALS AND METHODS

Patient population

Asthmatic patients, ages 16 to 65 yr, were selected from the Divisions of Allergy and Clinical Immunology of Scripps Clinic and Research Foundation and Kaiser Permanente Medical Center–San Diego; each patient had a history suggestive of aspirin sensitivity or had aspirin sensitivity that had been previously documented during oral aspirin challenge.

Materials

Capsules containing aspirin (3, 30, 60, 100, 150, and 300 mg) combined with lactose and lactose placebo tablets were prepared by the Scripps Clinic pharmacy. Tablets combining aspirin (325 mg) with magnesium aluminum hydroxide (150 mg) (Ascriptin) were provided by William H. Rorer, Inc. Indomethacin (25 mg) (Indocin), ibuprofen (400 mg) (Motrin), and naproxen (250 mg) (Naprosyn) were purchased commercially.

Flow-volume spirometry values were obtained on a Model 570 Wedge spirometer, with results displayed on a Model 585 pulmodigitizer and recorded on a Model 562 X-Y-T recorder (Med Science Co., St. Louis, Mo.)

Aspirin challenge procedure

Patients were admitted to the General Clinical Research Center at Scripps Clinic and Research Foundation, where they underwent aspirin challenges. Informed consent for procedures approved by the Human Research Committee was obtained.

Patients were selected only if their asthma was in relative remission. Each patient was required to produce the following minimum spirometric values prior to aspirin challenge: FEV_1 $\geq$1.50 L and $\geq$70% of prior recorded best value. Patients continued their usual corticosteroid and methylxanthine medications; antihistamines, cromolyn, and inhaled sympathomimetics were discontinued 24 hr prior to the procedure. All challenges were started in the morning. As a precaution, an antecubital vein was canulated with a 20-gauge catheter and a normal saline solution was infused. Emergency resuscitative equipment was present.

Placebo challenges were conducted to obtain baseline spirometric values. Aspirin challenges were then performed by progressive, incremental oral administration of aspirin at 1 to 3-hr intervals. As the study progressed, 3-hr intervals between aspirin dosages were used exclusively. Sequential dosages of aspirin were individualized for each patient. Baseline flow-volume spirometry was performed prior to the challenge and every 30 min thereafter until completion of the study. Spirometry was performed more frequently and dosages of aspirin were *suspended* or *modified* when

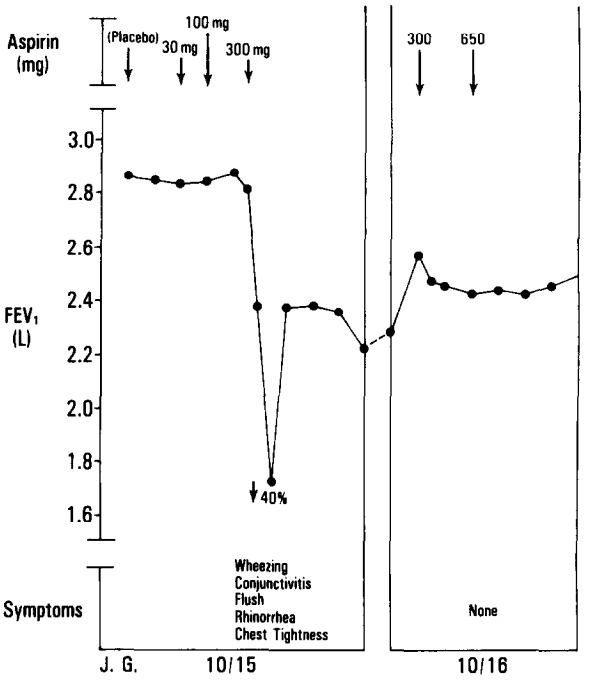

FIG. 1. Positive aspirin challenge after ingestion of 430 mg of aspirin. Desensitization was achieved on the following day when this patient ingested 650 mg of aspirin and did not experience any symptoms or change in FEV_1.

symptoms or signs of aspirin reaction reappeared. A "positive reaction" was defined as a fall in FEV_1 of $\geq$25% below baseline. Nebulized isoetharine (0.25 ml) diluted in normal saline was inhaled by each patient who experienced a positive reaction. Further challenges were not restarted until the patient's spirometric value had returned to near baseline levels, usually 2 to 24 hr. Aspirin was then readministered at the dosage that produced the earlier response and increased sequentially until 650 mg as a single dose was tolerated or a second reaction occurred. This procedure was repeated until each patient became unresponsive to 650 mg of oral aspirin. This was considered to be the desensitized state.

Indomethacin and other NSAI drug challenge procedures

Oral indomethacin, ibuprofen, and naproxen challenge procedures were similar to that described for the aspirin challenge except for the doses administered. Indomethacin (25 mg) was taken orally, followed in 2 to 3 hr by 50 mg if no reaction occurred. Ibuprofen (400 mg) and naproxen (250 mg) were administered as a single dose.

Determination of refractory period

After achieving the desensitized state, most patients underwent sequential aspirin challenges at intervals of 2, 3, 4, and 5 days. During these intervals aspirin was withheld. The refractory period was defined as the interval in days between the last ingestion of aspirin and the recurrence of a positive oral aspirin challenge.

TABLE I. Aspirin desensitization in 30 aspirin-sensitive asthmatics

Patient	First positive aspirin challenge			Total No. of aspirin reactions prior to desensitization
	Cumulative dose (mg)	ΔFEV_1 (%)	Nasal symptoms*	
I. P.	33	25	0	3
A. P.	33	55	4+	5
C. S.	60	32	4+	2
P. S.	60	27	4+	2
R. S.	100	67	4+	2
A. G.	120	50	4+	1
M. N.	133	46	4+	6
F. Va.	133	31	4+	2
G. J.	133	28	4+	1
M. R.	133	27	3+	2
S. W.	150	60	4+	3
E. A.	280	25	4+	1
F. Vo.	280	25	1+	1
N. F.	300	58	3+	1
G. W.	325	44	1+	2
K. B.	325	65	4+	1
B. P.	325	34	4+	1
T. J.	383	35	4+	2
A. O.	400	26	1+	1
N. H.	430	34	3+	1
J. G.	430	40	3+	1
S. Sh.	450	50	4+	2
R. B.	450	47	3+	1
P. E.	508	37	4+	1
C. H.	550	30	4+	1
M. S.	605	51	4+	1
C. M.	650	31	4+	1
V. G.	725	25	3+	1
S. Sk.	785	25	4+	1
M. C.	1083	26	0	1

*Nasal symptoms: 0 = none, 1+ = mild rhinorrhea/congestion, 2+ = moderate rhinorrhea/congestion, 3+ = severe rhinorrhea/congestion, 4+ = total nasal obstruction.

RESULTS

Aspirin challenges and desensitization

All 30 aspirin-sensitive asthmatic patients were desensitized to the adverse effects of aspirin by oral aspirin challenges. Details of these challenges are presented in Table I. Cumulative provoking dosages of aspirin ranged from 33 to 1083 mg. Declines in FEV_1 values ranged from 25% to 65%. Nasal congestion and/or rhinorrhea was provoked in all but two patients. Eleven patients initially reacted to cumulative dosages of 150 mg of aspirin or less. Twelve patients reacted to dosages of aspirin between 280 mg and 450 mg, and seven patients reacted to dosages of aspirin equal to or greater than 508 mg (Table II). In no patient was placebo challenge followed by symptoms or changes greater than 10% in FEV_1 values. Neither urticaria nor angioedema occurred as a consequence of aspirin challenge in any patient.

A representative aspirin desensitization is illustrated in Fig. 1. This patient underwent graded oral aspirin challenge, receiving a total of 430 mg of aspirin. This was followed by a 40% decline in FEV_1 values associated with symptoms of wheezing, chest tightness, rhinorrhea, and nasal congestion. Chest symptoms were partially reversed after inhaled isoetharine. The following day she tolerated 325 and then 650 mg of aspirin without adverse response, illustrating desensitization. Eighteen of the 30 patients became desensitized after their initial aspirin reaction, as did the patient illustrated in Fig. 1. However, 12 patients experienced more than one aspirin-induced reaction prior to achieving desensitization. Nine of

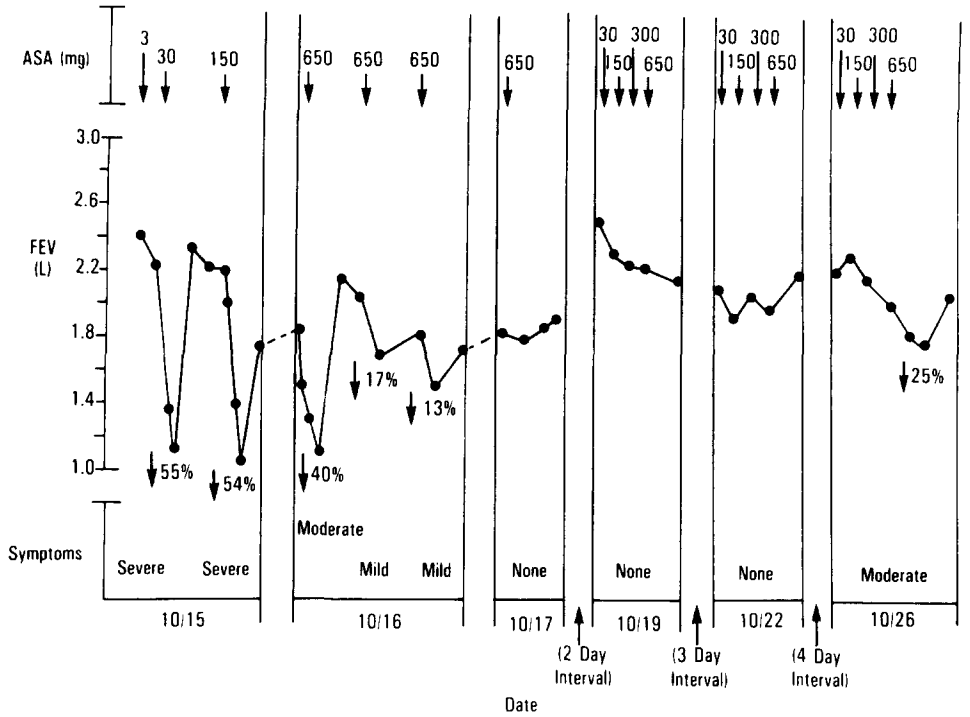

FIG. 2. Multiple aspirin reactions (10/15, 10/16) prior to aspirin desensitization on 10/17. Continued refractoriness to aspirin demonstrated at 2- and 3-day interval challenges (10/19, 10/22). Subsequent return to aspirin sensitivity shown by challenge after a 4-day interval without aspirin (10/26).

TABLE II. Provoking dosages of aspirin in 30 aspirin-sensitive patients

Cumulative dose of aspirin producing positive challenge	No. of patients	No. of patients experiencing more than one aspirin reaction during desensitization
≤150 mg	11	9 (82%)
280-450 mg	12	3 (25%)
≥508 mg	7	0 (0%)
Total	30	12 (40%)

these 12 patients had initial aspirin reactions at dosages less than 150 mg, and no patient initially reacting to a dosage greater than 508 mg of aspirin experienced an additional reaction prior to becoming desensitized (Table II). As shown in Fig. 2, patient A. P. experienced multiple aspirin reactions prior to desensitization. Initially, 33 mg of aspirin elicited a severe naso-ocular and asthmatic response on October 15. Additional challenges on the same day and on October 16 elicited similar results. Only after the sixth aspirin challenge, on the third day of hospitalization, was desensitization finally achieved. On October 19 and 22 she was able to tolerate 1130 mg of aspirin (approximately 34 times her initial provoking dose) without adverse response.

Refractory periods

In 16 patients we were able to establish the length of the refractory period after desensitization by means of repeated aspirin challenges (Table III). Again, a challenge was considered positive only after a fall in FEV_1 values of ≥25%; however, seven patients did develop some mild symptoms during "negative" challenges carried out at shorter intervals. In general, the return to aspirin sensitivity appeared in a gradual manner. Typically, during repeat challenges, larger dosages of aspirin were needed to produce proportionately the same or milder symptoms when compared with the initial challenge. The distribution of refractory periods is shown in Fig. 3. Three patients had refractory periods of less than 2 days, four had refractory periods between 2 and 3 days, six had refractory periods between 3 and 4 days, two had refractory periods between 4 and 5 days, and one patient was found to be refractory 5 days after aspirin desensitization.

Data concerning the refractory periods of seven additional patients were incomplete. However, patients C. S., E. A., and A. O. (Table I) were refractory at 2 days, N. F. at 3 days, and K. B. at 4 days, but these patients were not available for additional challenges. Patient S. Sh. had a 20% decline in FEV_1 value at the 2-day interval. B. P. developed mild nasal symptoms without a decrease in FEV_1 values

when challenged at a 3-day interval and severe nasal symptoms without decrease in FEV_1 values when challenged after a 4-day interval. In one patient (P. S.), indomethacin was substituted for aspirin in the repeat challenges. She was completely refractory to a cumulative dose of 75 mg of indomethacin when challenged after 3 days, and exhibited a 12% decrease in FEV_1 values after a challenge with a 4-day interval and a 15% decrease in FEV_1 values at a challenge carried out after 5 days to the same cumulative dose. She experienced a typical positive reaction to 50 mg of indomethacin when challenged 6 days later. Thus 20/23 patients tested had refractory periods longer than 2 days. The remaining seven patients were not available for any repeat challenges.

Aspirin/indomethacin cross desensitization

Cross-desensitization with aspirin and indomethacin was carried out in three patients. Results from one of these patients (G. J.) are shown in Figs. 4A and 4B. After ingestion of a total of 133 mg of aspirin given in increasing dosages, this patient's FEV_1 value decreased by 28%, accompanied by flushing, rhinorrhea, and wheezing (Fig. 4A). After resolution of these symptoms, desensitization was documented by her ability to tolerate 325 followed by 650 mg of ingested aspirin without symptoms or spirometric changes. After a 2-day interval without aspirin, refractoriness to aspirin persisted. After a 3-day interval, again without ingesting aspirin, she developed mild nasal symptoms and an 8% decline in FEV_1 value during aspirin challenge. These mild symptoms heralded her subsequent aspirin reaction at the 4-day interval, at which time her FEV_1 value declined by 32% but was accompanied by only moderate symptoms when compared with those of her initial reaction. Further ingestion of aspirin that afternoon showed that the desensitized state had again returned.

Over the next 2 days, the patient took 325 mg of aspirin daily at home. Cross-tolerance to other NSAI agents was then documented by her ability to ingest ibuprofen, then indomethacin, and then naproxen on consecutive days without reaction (Fig. 4B). After a 6-day interval without ingesting aspirin or other NSAI drugs, she was rechallenged to determine sensitivity to indomethacin. As shown, she exhibited a positive response to this challenge, which demonstrated sensitivity to this cross-reactive drug. The following day she received 650 mg of aspirin without any symptoms, showing refractoriness to aspirin after indomethacin desensitization.

Two other aspirin-sensitive patients underwent identical challenges with aspirin and indomethacin and cross-desensitization was again established. In addition, six other patients were able to tolerate indomethacin while refractory to aspirin, although prior or subsequent indomethacin sensitivity was not established by oral challenges.

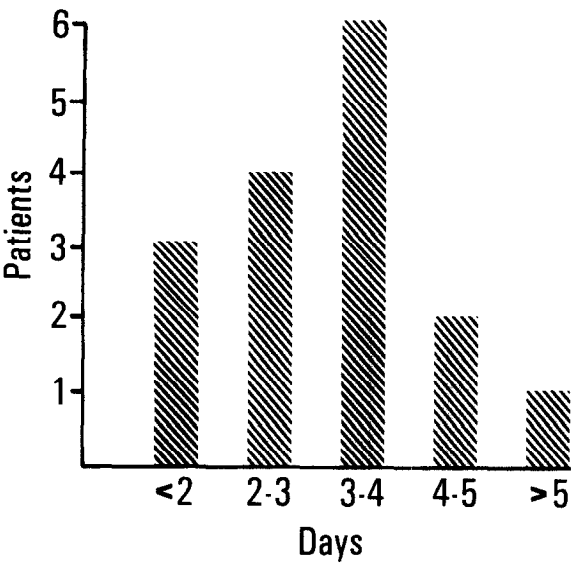

FIG. 3. Distribution of refractory periods after aspirin desensitization in 16 aspirin-sensitive asthmatics.

DISCUSSION

The primary finding in this study was that all 30 aspirin-sensitive asthmatic patients could be rendered unresponsive to the adverse effects of aspirin after positive oral aspirin challenge. Refractory periods were studied in 23 patients and ranged from less than 2 days for the shortest refractory period to greater than 5 days for the longest, with the greatest number of patients returning to sensitivity between 2 to 4 days. Cross-desensitization between aspirin and indomethacin, as well as with other NSAI drugs, was accomplished, demonstrating the nonspecificity of this phenomenon.

Although desensitization is commonly associated with immunologically mediated reactions, neither the sensitivity in this syndrome to aspirin nor the subsequent loss of this sensitivity ("desensitization") implies such a mechanism. Several studies have failed to demonstrate skin-sensitizing antibodies to aspirin in aspirin-sensitive asthmatics by either direct or passive cutaneous testing.[20, 21] Furthermore, the sera of aspirin-sensitive patients, when passively transferred to monkeys, does not confer sensitivity to these animals.[21, 22] Moreover, cross-sensitivity between aspirin and many other structurally distinct compounds, such as the NSAI drugs, is widely recognized in this syndrome.[13–16] Often reactions to these anti-inflammatory drugs occur upon the first exposure, sug-

TABLE III. Refractory period in 16 aspirin-sensitive asthmatics

	Initial challenge			Refractory challenges (interval days between ASA ingestion)											
				2 days			3 days			4 days			5 days		
Patient	ASA (mg)	FEV_1 (%)	NS*	ASA (mg)	FEV_1 (%)	NS	ASA (mg)	FEV_1 (%)	NS	ASA (mg)	FEV_1 (%)	NS	ASA (mg)	FEV_1 (%)	NS
F. Va.	133	31	4+	260	28	3+									
M. N.	133	46	4	650	25	0									
G. W.	325	44	1+	325	30	0									
T. J.	383	35	4+	650	0	0	775	35	2+						
N. H.	430	34	3+	650	14	0	300	30	3+						
J. G.	430	40	3+	650	0	0	650	27	1+						
M. S.	605	51	4+	975	0	0	325	43	3+						
A. P.	33	55	4+	480	11	0	1130	3	0	1130	25	2+			
G. J.	133	28	4+	975	3	0	975	8	1+	325	25	2+			
M. R.	133	27	3+	975	14	0	650	17	0	325	31	1+			
C. H.	550	30	4+				875	3	0	550	33	2+			
C. M.	650	31	4+	650	8	0	650	19	0	650	31	2+			
S. Sk.	785	25	4+				650	4.7	2+	650	35	3+			
P. E.	508	37	4+				650	0	0	650	2	1+	650	25	2+
V. G.	725	25	3+							650	6	1+	1300	25	1+
I. P.	33	25	0	755	31	0				625	0	0	1185	0	0

ASA = aspirin; NS = nasal symptoms.
*For description of nasal symptom grades see Table I.

gesting a mechanism other than immune recognition.

Recently, interest has centered on the role of prostaglandins in producing the aspirin reaction. All known NSAI drugs, including aspirin, possess the common property of prostaglandin synthetase (cyclo-oxygenase) inhibition.[23] The exact mechanism whereby this action of prostaglandin inhibition might promote the hypersensitivity response, however, is speculative. It has been proposed that prostaglandins might act directly on bronchial smooth muscles, with the administration of NSAI drugs selectively altering the ratio of "dilating" (PGE_2) vs "constricting" ($PGF_{2\alpha}$) prostaglandins presented to the airways.[24] More recently, it has been suggested that blockade of the cyclo-oxygenase pathway for arachidonic acid metabolism might increase the production of products of the lipoxygenase pathway, most notably leukotrienes C and D (slow-reacting substance of anaphylaxis), which are capable of stimulating bronchospasm.[25–27]

Alternatively, there is considerable evidence to suggest that the respiratory mast cell may play the central or initiating role in this reaction. Clinically, an aspirin reaction resembles IgE-mediated anaphylaxis, which is the consequence of the effects of mast cell–derived products. Several reports have further shown pretreatment with antihistamines[28] and/or disodium cromoglycate[29–32] to blunt the typical aspirin respiratory response. Integrating these findings, one might suggest that aspirin and related compounds initiate the hypersensitivity response through a nonimmunologic interaction with the mast cell. Possibly the intrinsic defect in this syndrome might occur at the mast cell level. Certainly a slow "leak" of mediators from defective mast cells could explain the chronic respiratory mucosal inflammation and the peripheral eosinophilia typically found in these patients even when avoiding aspirin. One potential mechanism for initiating mast cell discharge might be a sudden fall in available prostaglandin E, which is recognized as a product that stabilizes the mast cell and inhibits mediator release.[15, 33–36] Once this initial interaction and discharge had occurred, release of preformed mediators (e.g., histamine) might be expected to produce the early signs and symptoms of the reaction. Thereafter, the secondary production of leukotrienes C and D and/or the chemotactic substances 5-hydroperoxy-eicosatetraenoic acid and hydroxy-eicosatetraenoic acid might occur, either derived directly from lung mast cells or more likely through secondary activation of macrophages. These lipoxygenase products could further intensify and prolong the severity of the aspirin-provoked attack.

Continued aspirin ingestion might produce desensitization through one of several mechanisms. Aspirin might stimulate a population of lung mast cells to continue to release mediators until the cells are totally

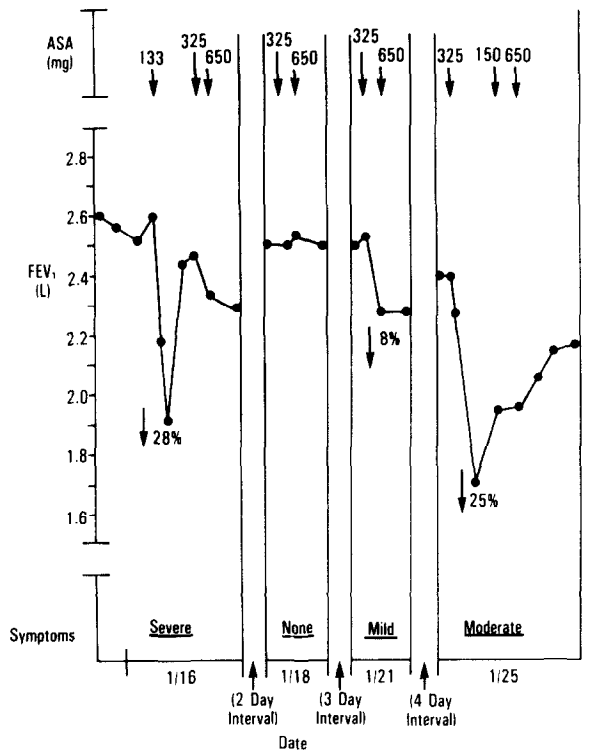

FIG. 4A. Aspirin reaction, desensitization, and determination of the refractory period.

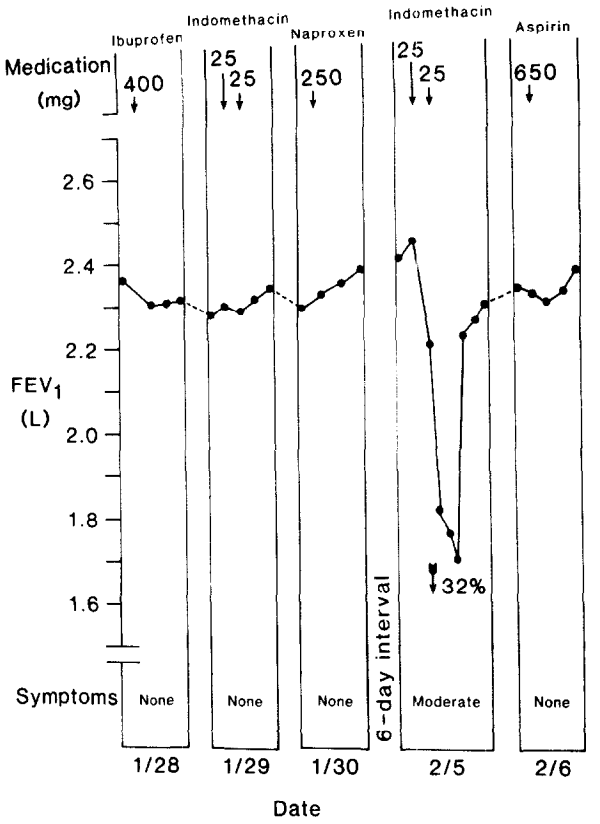

FIG. 4B. Cross-desensitization between aspirin and three NSAI drugs, with subsequent indomethacin sensitivity demonstrated on 2/5.

depleted of their mediators. This hypothesis is consistent with the experimental evidence that regranulation of mast cells after degranulation typically occurs over days,[37] which also would be consistent with our observations regarding the refractory period after aspirin desensitization. Another possibility is that mast cell activity might become suppressed secondary to a direct, drug-related inhibitory action. It is recognized that NSAI drugs can produce a direct dose-related inhibition of rat mast cell mediator release, presumably through depletion of mast cell ATP.[38–40] A further explanation for aspirin desensitization might be the development of tachyphylaxis of the bronchial smooth muscle receptors to participating mediators. Finally, any hypothesis to explain the desensitization phenomenon based on a disorder of leukotriene generation or metabolism must be postponed until more is known about this pathway.

A major concern of this study was the safety of conducting multiple aspirin challenges. Over 100 challenges were completed within this study period, and reactions were generally mild and transient. The potential danger of this procedure, however, should not be minimized. Many reports in the literature describe severe and even fatal reactions after aspirin ingestion in sensitive asthmatic patients.[1–7] To prevent such responses, we advocate pretreating all patients aggressively until their asthma is in remission. We do not begin an aspirin challenge unless the patient's baseline FEV_1 value is equal to or greater than 70% of best predicted FEV_1 value and above an absolute value of 1.5 L. Furthermore, a placebo challenge carried out on the day before must show stable FEV_1 values during this trial challenge. In addition, a slowly progressive challenge schedule is followed, in which small dosages of aspirin are given initially, with 3 hr allowed to pass to fully evaluate a patient's response before giving the next higher dose. Close monitoring of patient's spirometry and symptoms allows challenges to be suspended when early sensitivity symptoms become apparent and allows rapid treatment to be initiated when appropriate. Such procedures are conducted only in a specialized setting by personnel familiar with these techniques. Our results have demonstrated that aspirin challenges and desensitization can be performed safely.

Several practical applications may be extrapolated from this work. Future ingestive challenges with aspirin and related drugs must now allow appropriate refractory intervals after previous challenges to correctly interpret results. Previous studies of such se-

quential challenges might now need reinterpretation in light of these findings. Next, the therapeutic use of aspirin or other NSAI drugs in aspirin-sensitive patients with co-existing chronic rheumatic, cardiovascular or neurologic syndromes may now be possible after aspirin desensitization. And finally, potential therapeutic benefits of producing prolonged aspirin desensitization by daily administration of aspirin to aspirin-sensitive patients are currently under investigation in our institution.

We express our appreciation to Kathleen Lee, R.N., for her help in the performance of these challenges, and to Shari Brewster for her assistance in the preparation of this manuscript.

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