Salsalate cross-sensitivity in aspirin-sensitive patients with asthma

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Ten aspirin (ASA)-sensitive patients with asthma underwent double-blind, placebo-controlled oral challenges with salsalate followed by ASA-sensitive confirmatory challenges. All 10 patients sustained asthmatic reactions to ASA, but only two developed respiratory reactions to 2 gm of salsalate. In these two patients, repeat confirmatory challenges with 2 gm of salsalate reproduced the same asthmatic reactions. Both patients were desensitized to ASA, and cross-desensitization with 2 gm of salsalate was then achieved. We conclude that salsalate, a weak inhibitor of cyclooxygenase in vitro, is less likely than ASA to induce asthma in known ASA-sensitive patients with asthma but may occasionally cross-react in these patients. Such reactions were mild and easily treated with β_2-agonists. (J ALLERGY CLIN IMMUNOL 1990;86:749-58.)

In 1971, Vane,[1] using rat stomach and colon tissues for in vitro studies, reported that ASA and NSAIDs shared a common pharmacologic effect, namely, the inhibition of an enzyme, prostaglandin synthetase (cyclooxygenase). Indomethacin was found to be 20 times more potent than ASA in inhibiting prostaglandin synthetase, whereas sodium salicylate was considerably less potent. Since that time, it has been demonstrated that those NSAIDs that inhibit prostaglandin synthetase in vitro induce asthmatic reactions when they are ingested by known ASA-sensitive subjects with asthma.[2-4]

Salsalate (salicylsalicylic acid) is an effective anti-inflammatory agent that is used in the treatment of arthritis.[5] Salsalate is a dimer of salicylic acid and is depicted in Fig. 1, along with salicylic acid and ASA for comparison. Before absorption, while it is in the

Abbreviations used
ASA:	Aspirin
NSAID:	Nonsteroidal anti-inflammatory drug
GCRC:	General Clinical Research Center at Scripps Clinic and Research Foundation
LTC$_4$:	Leukotriene C$_4$
PGE$_2$, PGE$_4$, and PGF$_2$:	Prostagalandins E$_2$, E$_4$, and F$_2$

small intestine, salsalate is partially hydrolyzed to two molecules of salicylic acid. Metabolic studies demonstrate that the predominant fraction of orally administered salsalate is converted to salicylic acid, whereas a much smaller fraction of salsalate (15%) is absorbed unchanged and converted to a glucuronide conjugate before excretion in the urine.[6, 7] The effects of salsalate and salicylic acid on prostaglandin synthesis in vitro and in vivo are inconsistent.[8-11]

Although salsalate has not been systematically studied in ASA-sensitive subjects with asthma, one study demonstrated changes in lung-function values after ingestion of sodium salicylate (a major metabolite of salsalate) in a few ASA-sensitive patients with asthma.[12] A case report of one patient with nasal polyps, asthma and rheumatoid arthritis, who developed asthmatic attacks after ASA and naproxen, is available.[13] This interesting patient underwent oral challenges with tartrazine (no adverse effect), low-dose
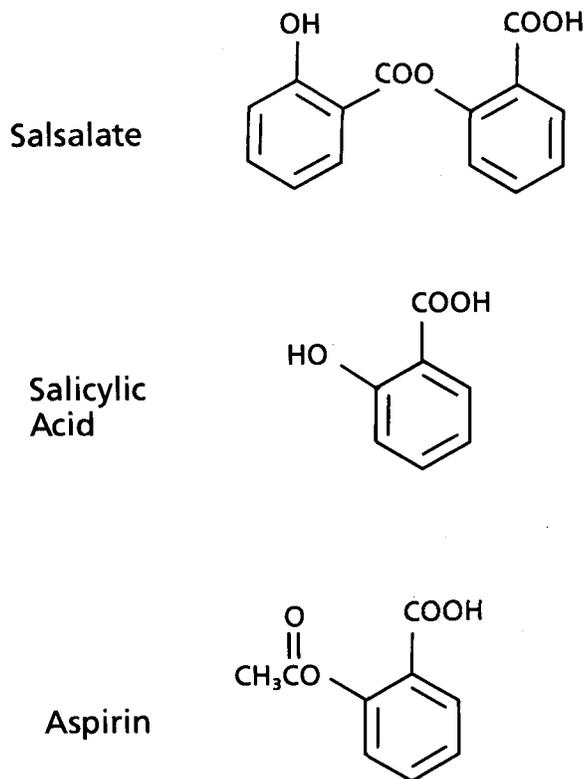
FIG. 1. Molecular structures of salsalate, salicylic acid, and aspirin.

salsalate, 50 mg (60 minutes later she developed urticaria, chest tightness, and a 17% decline in the peak flow rate), and low-dose choline magnesium trisalicylate, 100 mg (30 minutes later she developed angioedema, wheezing, chest tightness, and a 25% decline in peak flow rate).

The present study was designed to evaluate cross-sensitivity of salsalate in known ASA-sensitive patients with asthma and with particular emphasis on increasing the challenge doses of salsalate to therapeutic levels. It appeared logical to assume that if cross-reactivity were to occur, we would need to challenge with full therapeutic doses of salsalate because this drug is presumed to be a weak inhibitor of cyclooxygenase.

MATERIAL AND METHODS

Ten otherwise healthy volunteer ASA-sensitive patients with asthma, whose expiratory flow curves were normal (FEV$_1$, ≥70% of predicted or best previously achieved for that individual), were enrolled in the study. All patients gave a prior history of an asthmatic reaction to ASA/NSAIDs or had undergone asthmatic reactions to ASA in the GCRC. Patients were admitted at a time when their asthma was in relative remission. If medications were

needed, patients continued to take corticosteroids (inhaled, seven patients; and/or systemic, nine patients) and theophylline. During the study, adjustments were made in corticosteroids and theophylline doses for most patients to maintain stability of lung function. Sympathomimetics, antihistamines, and cromolyn were stopped 24 hours before entering the study.

FEV$_1$ was measured every hour during the challenge periods. On day 1, placebo challenges were conducted at 3-hour intervals to establish stability of the asthma. If asthma was not stable, the patient was either discharged and readmitted at a later date or treated in the GCRC until stability was achieved and the baseline placebo-treatment day yielded a variation of <15% change in FEV$_1$ values during the 11-hour study. Starting on day 2 and continuing through day 3, double-blind, oral challenges with salsalate (Disalcid, 0.5 gm; 3M Pharmaceuticals, St. Paul, Minn., and specially made matching 0.125 gm capsules) and nonlactose-containing matching placebos were performed at 3-hour intervals. The smallest dose of salsalate was administered first, followed by larger doses in sequence, including a prerandomized matching placebo dose inserted in the challenge sequence of each day. The salsalate-challenge doses were 0.25, 0.5, 1, and 2 gm. Spirometry measurements were recorded at 1, 2, and 3 hours after the first two doses and up to 5 hours after the third dose on each day. Study design required FEV$_1$ values to decline by ≥20% from baseline to demonstrate significant bronchial obstruction. Patients experiencing a significant decrease in FEV$_1$ did not receive additional salsalate challenges at that time. These patients were asked to return to the GCRC to undergo repeat double-blind challenges with placebo and salsalate.

Nasal reactors

Signs and symptoms of reactions in the upper airway were simultaneously recorded. A positive response consisted of rhinorrhea plus any of the following: ocular chemosis, injection and periorbital swelling, nasal congestion, and paranasal sinus pain.

ASA challenges

All 10 ASA-sensitive patients then underwent single-blind, oral ASA challenges.[14] ASA desensitization was then performed[15] and completed in all 10 patients. Bronchospastic reactions to ASA and salsalate were treated with aerosolized isoetharine HCl (Bronkosol; Winthrop Pharmaceuticals, New York, N.Y.) delivered by intermittent positive-pressure breathing machine or hand-held nebulizer. Nasal and ocular reactors were treated with oxymetazoline HCl (Afrin nasal spray; Schering Pharmaceuticals, Kenilworth, N.J.) and/or naphazoline HCl (Vasocon-A opthalmic drops; Iolab Pharmaceuticals, Willowdale, Ontario, Canada).

RESULTS

Eight of 10 patients completed the placebo challenges, followed by the double-blind, salsalate challenges without any objective adverse respiratory effects. One of eight patients complained of chest
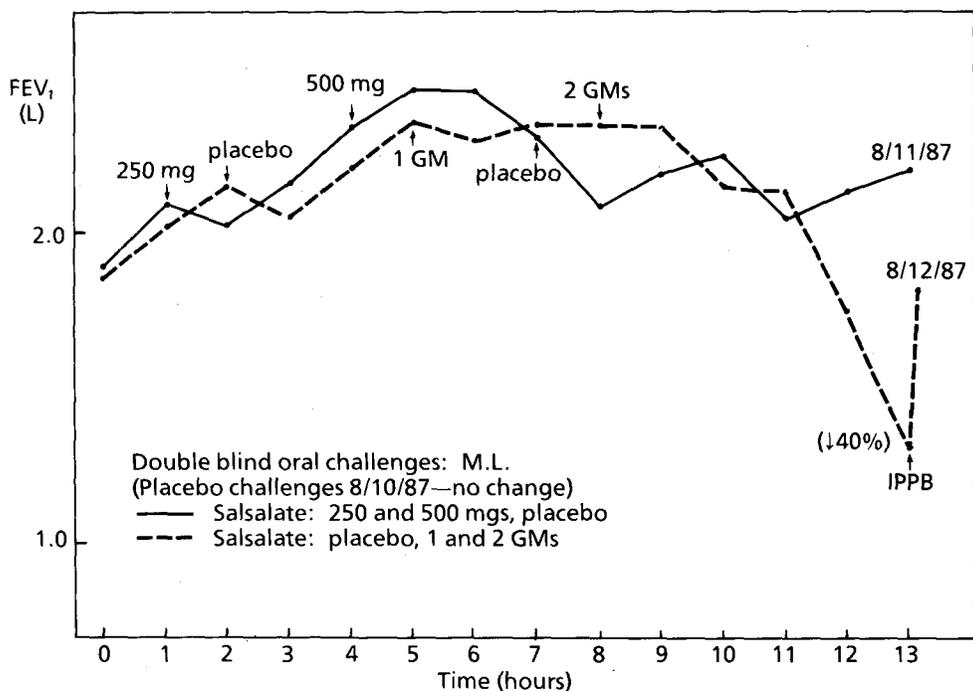
FIG. 2. Double-blind salsalate challenges in patient M. L. on August 11 and 12, 1987, illustrating a 40% decline in FEV_1 values after 2 gm of salsalate.
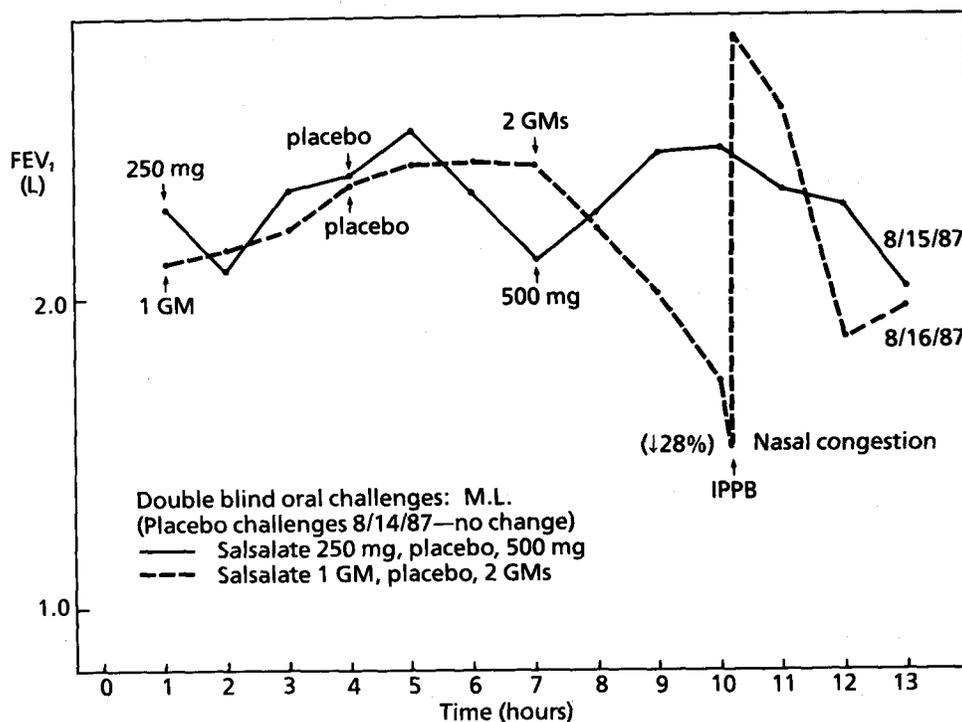

FIG. 3. Confirmatory double-blind, salsalate challenges in patient M. L. on August 15 and 16, 1987, again demonstrating a significant (28%) decline in FEV_1 values after 2 gm of salsalate. Nasal congestion incrased during salsalate challenges.
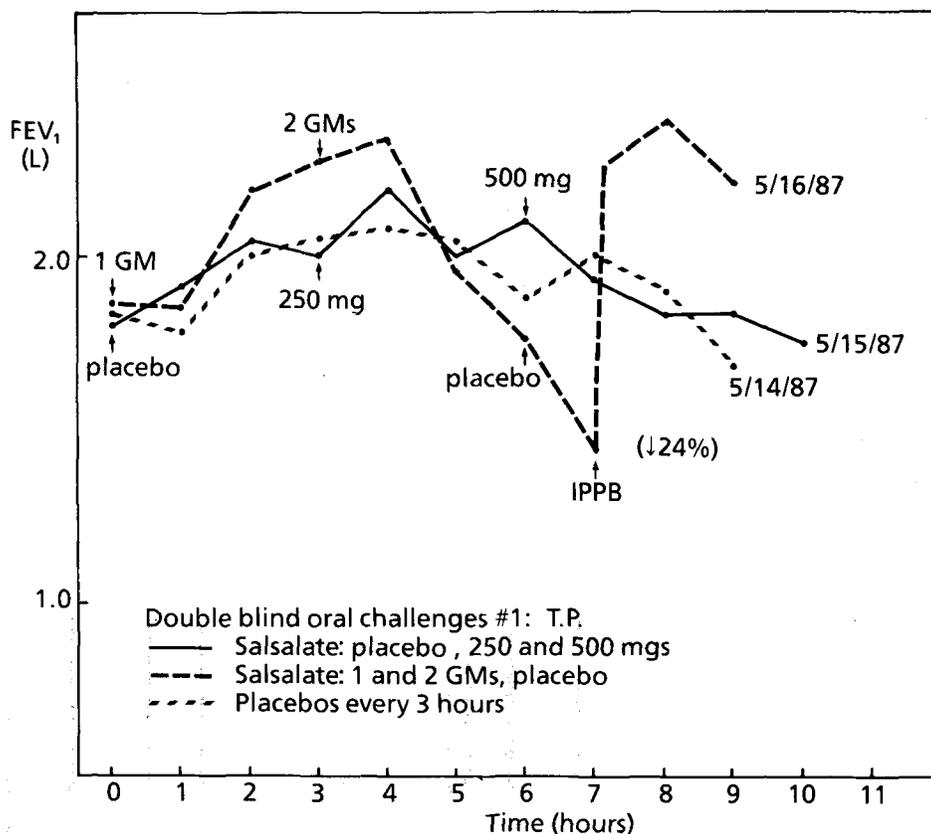
FIG. 4. Double-blind, salsalate challenges in patient T. P. on May 15 and 16, 1987, with a 24% decline in FEV₁ values after 2 gm of salsalate.

tightness on day 2 of the salsalate challenge, but lung-function studies remained normal during that challenge day. All eight patients underwent oral ASA challenges with resulting respiratory reactions, experiencing a >20% decline in FEV₁ values after ASA. Five of the eight patients also developed upper respiratory tract reactions (classic responders).

Two of the 10 patients were found to have stable baseline challenges with placebo and then experienced a ≥20% decline in FEV₁ after ingesting 2 gm of salsalate during both the first and confirmatory double-blind challenges. Upper respiatory tract reactions were also noted but only after the confirmatory challenges. These data are depicted in Figs. 2 to 5. ASA challenges were positive in both patients (Figs. 6 and 7) who also were desensitized to ASA (Figs. 8 and 9). Unfortunately, one patient (M. L.) had unstable airways at the end of ASA desensitization and, after reintroduction of salsalate, 2 gm, experienced a decline of FEV₁ values of 26% (Fig. 8). However, critical review of the challenge procedure that day reveals that the morning baseline FEV₁ value was low, a finding consistent with active asthma in this patient. Therefore, the decline of 26% in FEV₁ values could

not be unequivocally attributed to salsalate and may, in fact, have been spontaneous asthma activity. Unfortunately for logistical reasons, the challenge could not be repeated during that GCRC admission. Two months after discharge, the patient underwent sinus surgery. She returned to the GCRC 8 months later, while she continued treatment with ASA to maintain desensitization, and was challenged with salsalate, 2 gm, without adverse effect (Fig. 10). The second patient was desensitized to ASA and ingested 2 gm salsalate the next day without any change in FEV₁ value (Fig. 9).

Confidence band statistical analysis

Assuming random patient enrollment in the study, the 95% confidence interval is 7% to 56%; (i.e., between 7% to 56% of the ASA-sensitive population with asthma is predicted to cross-react if doses of 2 gm of salsalate are administered).

DISCUSSION

Only 2/10 ASA-sensitive patients with asthma were found to react also to salsalate in this double-blind, placebo-controlled, oral challenge study.
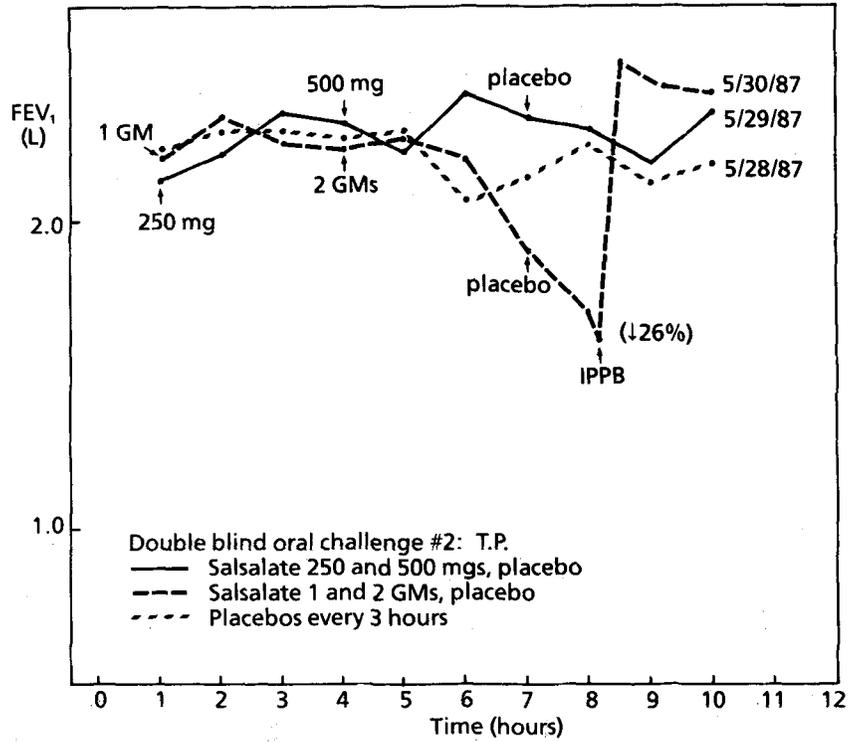
FIG. 5. Confirmatory double-blind, salsalate challenges in patient T. P. on May 29 and 30, 1987, again illustrating a significant (26%) decline in FEV_1 values after 2 gm of salsalate. Nasal congestion increased during salsalate challenges.
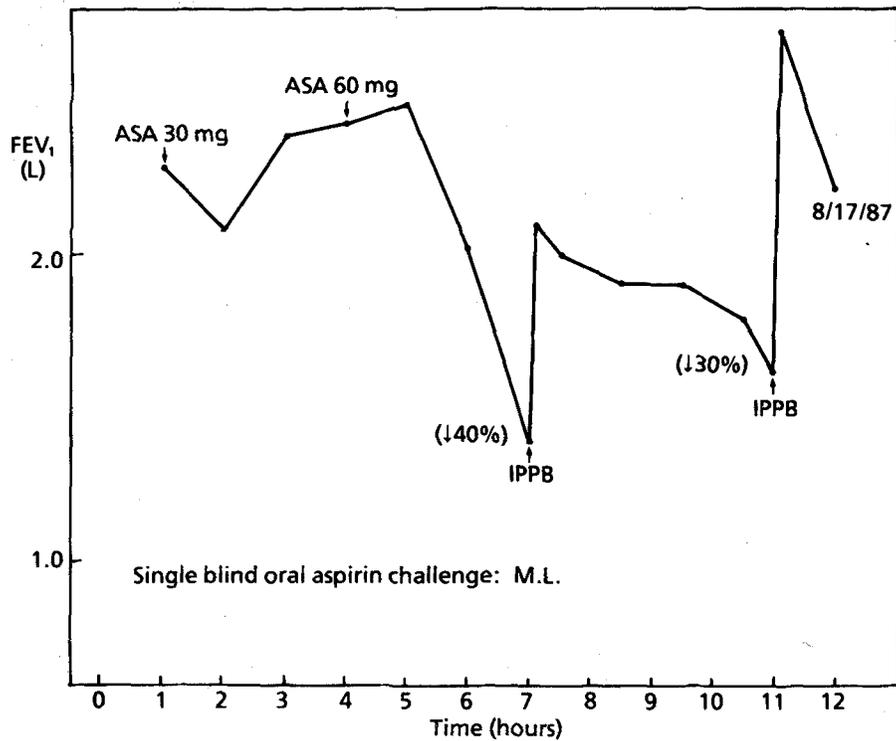

FIG. 6. Single-blind ASA challenge in patient M. L. on August 17, 1987, illustrating a 40% decline in FEV_1 values after 60 mg of ASA.
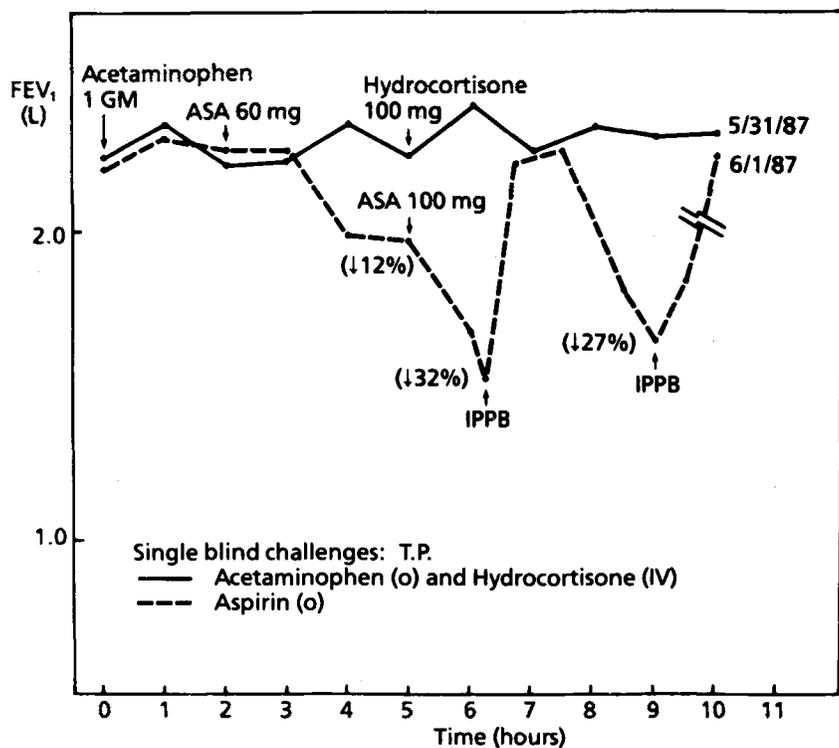
FIG. 7. In patient T. P., challenge with acetaminophen and hydrocortisone on May 31, 1987, were negative. ASA challenge with 100 mg on June 1, 1987, produced a 32% decline in FEV_1 values.
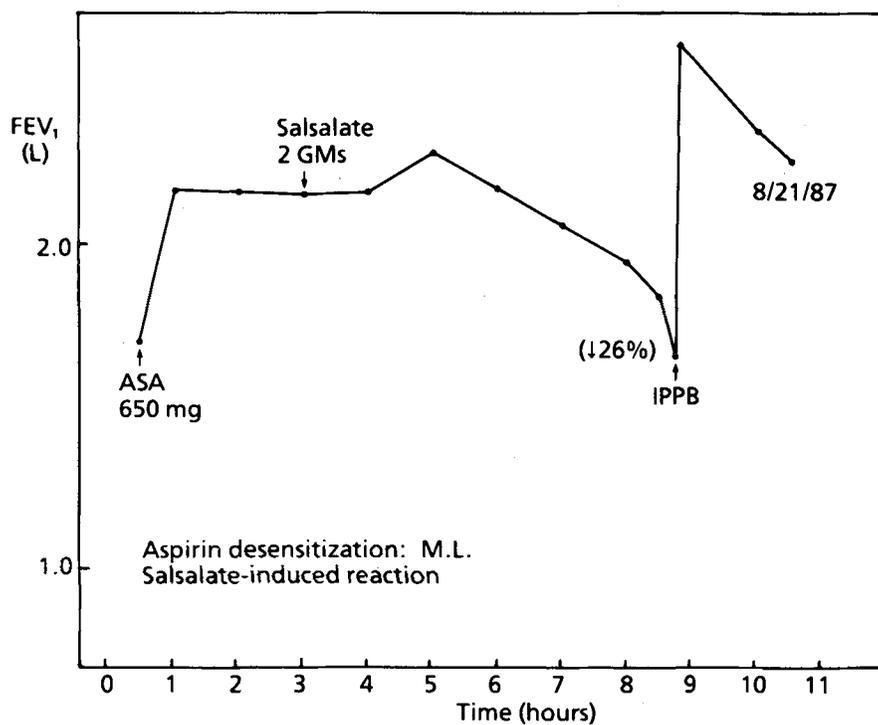

FIG. 8. After ASA desensitization, patient M. L. was rechallenged with salsalate, 2 gm. A 26% decline in FEV_1 value after 2 gm of salsalate occurred, depending on where the baseline FEV_1 value was established.
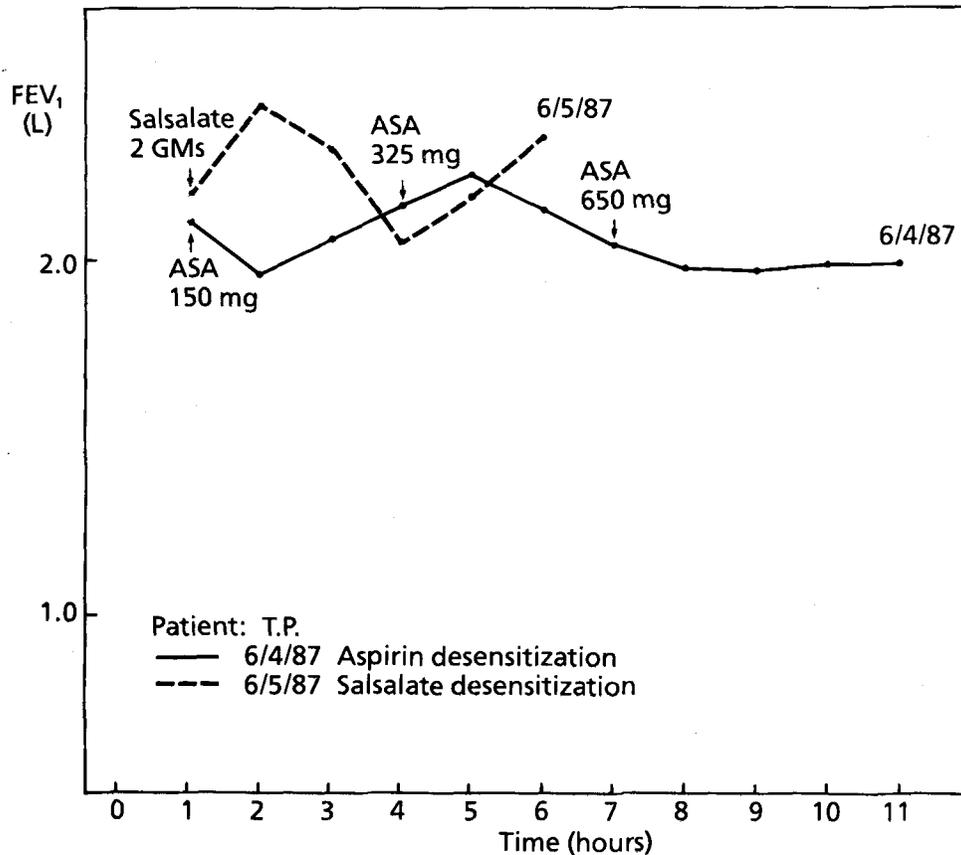
FIG. 9. After ASA desensitization on June 4, 1987, patient T. P. underwent challenge with 2 gm of salsalate without measurable effect on FEV₁ values.

Therefore, between 7% and 56% of the ASA-sensitive population with asthma is predicted to be sensitive to salsalate if dosages of 2 gm are used. By deduction, smaller doses of salsalate (1 gm or less) would be expected to induce asthmatic reactions in a smaller percentage of ASA-sensitive patients; in fact, these doses did not induce asthmatic reactions in any of our 10 ASA-sensitive patients. This study does not address the issue of salsalate sensitivity in the general population.

Currently, the mechanisms by which ASA/NSAIDs induce respiratory reactions are only partially clarified and understood.[4] Since the blockade of cyclooxygenase by ASA/NSAIDs is universal,[1] such inhibition, by itself, cannot account for the specificity of the ASA-induced reactions, which occur in only a minority of patients with asthma.[3] Therefore, it is essential to focus on simultaneous biomolecular events to define, accurately, the mechanisms of these reactions. One interesting possibility is the formation of arachidonic products[16] during ASA-induced respiratory reactions. These lipoxygenase products, acting as powerful vasodilators, bronchoconstrictors, and

chemotactic factors, are excellent candidates to initiate and perpetuate ASA-induced reactions.[16, 17] The work by Ferreri et al.[17] measured LTC_4 in nasal secretions during ASA-induced respiratory reactions and found elevated LTC_4 levels. Nasal secretions of patients with tolerant asthma or normal subjects did not contain LTC_4 either before or during ASA ingestion. LTC_4 was not found in nasal secretions after ASA desensitization in the same patients who had formed LTC_4 during ASA-induced nasal reactions. By contrast, PGE_4 was reduced (inhibited) in the nasal secretions of all patients and control subjects, demonstrating that the universal effect of ASA on cyclooxygenase enzymes was operative and by itself could not account for the reaction. The above findings are interesting because they suggest that ASA stimulates unknown lung cells to form archidonate at the same time that cyclooxygenase is inhibited by ASA. Only the 5-lipoxygenase pathway is then available for metabolism of the formed arachidonate, thus ensuring rapid formation of leukotriene products. Such observations do not prove that LTC_4 causes the nasal reactions and only by implication suggest that similar
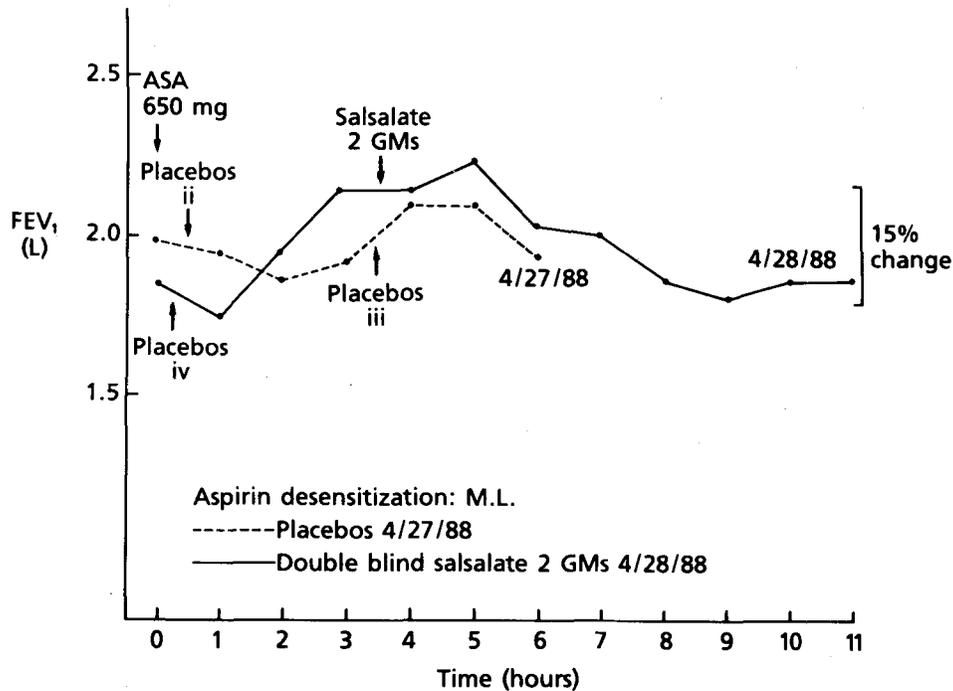
FIG. 10. After 8 months of ASA desensitization and treatment with daily ASA, 650 mg twice a day, patient M. L. underwent placebo challenge (April 27, 1988) and then challenge with 2 gm of salsalate without adverse effect.

mechanisms might occur in the bronchial tree. Furthermore, other mechanisms involving other mast cell products could be coparticipants, either in the initiation or even perpetuation of the reactions.

With respect to our current study of salsalate, the above observations on the potential mechanisms of ASA-induced respiratory reactions do suggest that drugs, which prevent arachidonate from passing through the cyclooxygenase pathway, share a potential to induce a bronchoconstrictor response in the respiratory tract of ASA-sensitive subjects with asthma.[2-4, 17] If salsalate is cross-reacting in some ASA-sensitive patients, we would therefore expect that salsalate, or its major metabolite, salicylic acid, should inhibit cyclooxygenase in vitro and presumably in vivo. With bovine seminal vesicles and a system of conversion of ^{3}H-arachidonic acid into PGE_2 and PGF_2, in vitro effects of salsalate, ASA, and indomethacin were compared. At a concentration of 10^{-4} mol/L, percent inhibition of prostaglandin synthesis was salsalate, 13.6; ASA, 48.6; and indomethacin, 97.1 (3M Pharmaceuticals data on file). These data indicate that salsalate is a weak inhibitor of cyclooxygenase in vitro when it is compared to ASA and indomethacin.

In one study, oral administration of salsalate did not significantly inhibit aggregation of human platelets.[18] In another study, oral administrations of ASA and salsalate were compared with respect to their effects on levels of arachidonate metabolites in the serum and urine in 10 healthy volunteers.[11] The results indicated minimal suppression of serum (platelet-derived) thromboxane B_2 and PGE_2 after 3 days of administration of salsalate (3 gm/day), whereas virtually complete suppression occurred after administration of ASA (3.9 gm/day for up to 3 days). Salsalate was almost as potent as ASA in suppressing urinary excretion of PGE_2 and a metabolite of PGF_2. Unfortunately, studies of the effects of salsalate on human or animal pulmonary cells are not available.

The above discussion is critical to our deductive reasoning regarding potential cross-reactivity in ASA-sensitive patients with asthma because of the following points: First, all NSAIDs that cross-react with ASA inhibit cyclooxygenase in mammalian tissues in vitro.[2] Second, the dosage of NSAIDs that inhibit cyclooxygenase in vitro is roughly equivalent to the dosage of the drug that induces respiratory reactions in ASA-sensitive subjects with asthma.[2] Third, in all instances in which ASA desensitization has been at-

tempted in ASA-sensitive subjects wsith asthma, this procedure has been successful,[19] and furthermore, cross-desensitization between ASA and the NSAIDs routinely occurs.[3, 15, 17]

Salsalate reactions cannot be unequivocally characterized as being identical to reactions induced by ASA and the NSAIDs. However, the preponderance of data are consistent with the notion that salsalate, and its major metabolite, salicylic acid, are weak inhibitors of cyclooxygenase and that large doses of the drug are required to inhibit cyclooxygenase in vitro and induce asthmatic reactions in ASA-sensitive subjects with asthma. Cross-desensitization was clearly demonstrated for patient T. P. (Fig. 9), but the sequence of events in the second patient (Fig. 8) is more convoluted. Unfortunately, after undergoing desensitization with ASA and receiving ASA, 0.65 gm, in the morning, the patient was unable to remain in the GCRC another 24 hours because of personal reasons. Therefore, as a compromise, she was administered salsalate, 2 gm, at that time (Fig. 8) and sustained a mild decline in FEV_1 values, which could have been due to unstable airways. Eight months later, while she was desensitized to ASA, she returned to the GCRC and was challenged with salsalate again. At that time, there were not any adverse effects, and the FEV_1 values remained stable. Our interpretation is that, when the patient initially experienced a decline in FEV_1 value with salsalate after ASA desensitization, she was incompletely desensitized and therefore still had hyperirritable airways after her ASA-induced respiratory reactions, giving the appearance of a lack of cross-desensitization. When her airways became stable, she returned at a later date and was found to be cross-desensitized to salsalate.

From a practical standpoint, as with other NSAIDs, it appears prudent to warn ASA-sensitive patients with asthma about the potential adverse effects of salsalate. Since many subjects with asthma are already avoiding ASA and are in an unknown category with respect to ASA sensitivity, these subjects with asthma should be considered potential reactors to salsalate. Whether or not reactions to salsalate actually occur at dosages <2 gm is not clear, although our data do not support such a hypothesis. In one previous case report,[13] 50 mg of salsalate was associated with urticaria and some wheezing in a patient sensitive to many challenge materials, but FEV_1 values were not obtained, and peak flow measurements were marginally changed. Furthermore, this female patient reacted to a low dose of another nonacetylated salicylate, choline magnesium trisalicylate. It appears unlikely that her

case represents an extension of the shared pharmacologic effects of NSAIDs on cyclooxygenase, particularly because of the low dose of salsalate and the urticarial type of reaction.

Finally, in view of the mildness of the reactions to salsalate in our two patients, it should be safe to challenge patients with salsalate at starting doses of 0.5 to 1 gm of salsalate and increase up to 2 gm. Even in known ASA-sensitive subjects with asthma, 8/10 of our patients could take 2 gm of salsalate without any adverse effect. If additional salsalate reactors were identified by challenges, they could also be managed with ASA desensitization and then cross-desensitization with salsalate.[15] The opposite approach of desensitization to salsalate was not attempted, and it is therefore not known whether or not such an approach would be possible. Another weak cyclooxygenase inhibitor, acetaminophen, was a poor desensitizing analgesic in patients demonstrated to be sensitive to it,[20] although cross-desensitization after ASA desensitization was clearly demonstrated in these patients.

In summary, weak inhibitors of prostaglandin synthesis appear to cross-react in a minority of patients sensitive to ASA/NSAIDs and only when large doses of drug are presented. This supports the concept that those analgesics, such as salsalate and acetaminophen, which are weak inhibitors of cyclooxygenase in vitro, are less likely to induce respiratory reactions in known ASA-sensitive subjects with asthma.[4, 20]

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