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325 mg better than 650
? 81 or other doses?

Effect of Two Aspirin Pretreatment Regimens on Niacin-Induced Cutaneous Reactions

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OBJECTIVE: **To compare the effects of pretreatment with two aspirin regimens and placebo on niacin-induced cutaneous reactions.**

DESIGN: **Randomized, double-blind, placebo-controlled, crossover study.**

SETTING: **Internal medicine clinic in an academic health center.**

PARTICIPANTS: **Forty-two healthy subjects (22 males and 20 females) between the ages of 35 and 65 (mean age 44.2 years) were recruited and completed the study. Subjects received aspirin 325 mg, aspirin 650 mg, and placebo for 4 consecutive days, and on the fourth day also ingested 500 mg of immediate-release niacin 30 minutes after taking aspirin or placebo. They reported the intensity of flushing, headache, pruritus, tingling, and warmth on a 10-cm visual analogue scale. Reactions were evaluated at time 0 (before the niacin dose), and at 15, 30, 60, and 120 minutes following the niacin dose. Cutaneous reactions were compared at each evaluation time and scored by two other methods. The peak intensity was the highest score recorded at any of the four evaluation times after niacin administration. An intensity-time factor was calculated by totaling the scores of each of the four evaluation times.**

MEASUREMENT AND MAIN RESULTS: **The symptom scores for flushing, itching, tingling, and warmth were all significantly reduced by both aspirin regimens ($p < .05$ in all cases), although there were no significant differences between the 325-mg and 650-mg doses. The results were similar for each scoring method.**

CONCLUSIONS: **An aspirin regimen of 325 mg is effective in suppressing niacin-induced cutaneous reactions. Increasing the dose to 650 mg does not provide additional benefit.**

KEY WORDS: **niacin; aspirin; cutaneous reactions; cholesterol; lipids.**
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In patients with established coronary heart disease, beneficial effects of lipid modification with niacin have been demonstrated in various clinical studies. After 15 years of follow-up, patients in the Coronary Drug Project had an 11% reduction in total mortality compared with patients who received placebo.[1] More recent studies have found that treatment with intensive lipid-modifying combinations of niacin plus bile acid sequestrants resulted in increased rates of plaque regression and stabilization compared with less-intensive regimens consisting primarily of dietary modification.[2,3]

Niacin is an effective and inexpensive lipid-modifying agent that produces favorable alterations in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. However, bothersome cutaneous reactions, particularly flushing and pruritus, occur with reported incidences ranging from 82% to 100% and often result in niacin discontinuation by patients.[4,5] Clinicians are reluctant to prescribe niacin because of the high rate of noncompliance, despite the favorable effects on lipid profiles. Although the mechanisms producing niacin-induced cutaneous reactions are not completely understood, there is evidence that such reactions are mediated by a transient prostaglandin release. Aspirin and other prostaglandin inhibitors are effective in suppressing these reactions in the majority of patients.[6–14]

The dosage of aspirin that most effectively reduces cutaneous reactions to niacin has not been determined precisely. Whelan et al. investigated the effectiveness of placebo and aspirin in doses of 80 mg and 325 mg administered 30 minutes prior to a 500-mg dose of niacin.[6] The 325-mg dose of aspirin was more effective in preventing cutaneous reactions than either 80 mg or placebo, which were not significantly different from each other. Flushing and warmth were reduced by the 325-mg dose, but not itching or tingling. It is possible that higher doses of aspirin and pretreatment for several days before niacin administration could further reduce cutaneous reactions to niacin.[15] This study evaluated the effects of placebo and

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aspirin in doses of 325 and 650 mg administered daily for 4 days prior to a 500-mg dose of niacin.

METHODS

A randomized, double-blind, placebo-controlled, crossover study was conducted using healthy subjects between the ages of 35 and 65 years who were recruited via an announcement in the newsletter of an academic health center. None of the subjects had previously taken niacin in doses sufficient to modify plasma lipids. Exclusion criteria included a known hypersensitivity or contraindication to niacin or aspirin; a history of diabetes mellitus, gout, peptic ulcer disease, hepatic dysfunction, renal dysfunction, coagulopathies, or hypotension; and women who were experiencing vasomotor symptoms associated with menopause or who had the potential to become pregnant and were not taking adequate birth control. Subjects were not allowed to receive vasoactive drugs or anticoagulants for 1 week before or during the study. They were instructed to refrain from smoking, eating, alcohol, and caffeine-containing or hot beverages for at least 2 hours before taking the niacin doses.

Subjects received each of the following three regimens in a randomized crossover fashion: 325 mg of aspirin followed by 500 mg of niacin, 650 mg of aspirin followed by 500 mg of niacin, and placebo followed by 500 mg of niacin. They received either aspirin or placebo for 4 consecutive days and on the fourth day ingested 500 mg of immediate-release niacin 30 minutes after taking aspirin or placebo. The randomization procedure was such that subjects had an equal chance of assignment to each of the six possible treatment sequences. There was at least a 7-day washout period between each treatment. Subjects reported the intensity of flushing, pruritus, tingling, warmth, and headache on a 10-cm visual analogue scale. They evaluated these reactions at time 0 (before niacin), and at 15, 30, 60, and 120 minutes following niacin administration.

Comparisons for each reaction were made at each of the four evaluation times (i.e., 15, 30, 60, and 120 minutes). Two other methods were also used to score the extent of the cutaneous reactions. Peak intensity was the highest score recorded at any of the four evaluation times after niacin administration. To quantify a combined measure of the intensity and duration of cutaneous reactions, an intensity-time factor was also calculated by totaling the scores from each of the four evaluation times. Differences in the extent of the various cutaneous reactions were tested for significance using repeated-measures analysis of variance (ANOVA). Post hoc pairwise comparisons with Scheffe's Test were performed in cases in which a significant ANOVA result was obtained. A p value of .05 or less was considered to be statistically significant for all comparisons.

The proportion of subjects experiencing a reaction of moderate or greater intensity for each of the three regimens was determined by counting those individuals with at least one score of 6 or higher for any of the five reactions. The χ^2 test was used to evaluate differences between the three regimens. The StatMost for Windows (DataMost Corporation, Salt Lake City, Utah) software was used for all statistical analysis.

The study was approved by the Institutional Review Board of the University of Nebraska. Written informed consent was obtained from each subject prior to participation.

RESULTS

Forty-two subjects (22 males and 20 females) were recruited and completed the study, with a mean age of 44.2 years (SD 8.4 years). The subjects were generally in good health. Although 15 subjects reported taking prescription drugs, few other medical problems were reported by the study participants. Two subjects were receiving levothyroxine, while two others were receiving postmenopausal hormone replacement therapy. One subject was receiving a triphasic oral contraceptive product. Two other subjects had recently converted to purified protein derivative (PPD) positive status and were completing 6-month courses of isoniazid. Two subjects reported well-controlled seizure disorders (one treated with phenytoin and the other with phenobarbital). Two other subjects had arthritic disorders; one required both ibuprofen and injectable gold, while the other was treated with ketoprofen. Occasional use of terfenadine for allergies was reported by one subject, while two others were taking antidepressants. One subject used a corticosteroid cream for localized psoriasis. Only 4 (9.5%) of the 42 subjects smoked cigarettes.

The symptom scores for the various cutaneous reactions are summarized in Table 1 and graphically displayed in Figures 1–5. The symptom scores for flushing, itching, tingling, and warmth were all significantly reduced by both aspirin regimens ($p < .05$ in all cases), although there were no significant differences between the 325-mg and 650-mg doses. The results were similar using both the peak intensity and the intensity-time factor to measure the extent of the reactions. For each of the four reactions, significant differences in symptom scores were seen between placebo and either of the aspirin regimens at the 30- and 60-minute evaluation times, but not at 15 or 120 minutes. No significant differences were seen at any time between the two aspirin regimens.

With regard to headache, the repeated measures ANOVA procedure produced some significant results ($p = .050$ for peak intensity, $p = .039$ for intensity-time factor, and $p = .035$ at the 30-minute evaluation time). However, pairwise testing with Scheffe's Test did not produce significant differences between the three regimens. Headache occurred infrequently and was generally of mild intensity. Only 14 (33%) of the 42 subjects reported headache occurring with any of the three regimens, and only 6 (14%) of the subjects reported any headache intensity of 3 or greater.

Table 1. Scores for Cutaneous Reactions After Placebo and Aspirin Regimens

Symptom	Mean (SD)					
	15 Minutes	30 Minutes	60 Minutes	120 Minutes	Peak Intensity*	Intensity-Time Factor†
Flushing						
Placebo (P)	3.00 (3.30)	4.18 (2.92)	3.88 (2.72)	1.77 (2.24)	5.69 (2.87)	12.83 (7.75)
Aspirin 325 mg	2.88 (3.01)	2.36 (2.37)	1.81 (1.61)	1.21 (1.80)	3.88 (2.86)	8.26 (6.97)
Aspirin 650 mg	2.24 (2.39)	2.27 (2.47)	1.83 (2.30)	1.10 (1.88)	3.55 (2.74)	7.75 (6.97)
p Value‡	.314	<.001	<.001	.142	<.001	<.001
Pairwise comparisons§		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg
Itching						
Placebo (P)	1.17 (1.87)	2.20 (2.17)	2.85 (2.47)	1.29 (1.64)	3.59 (3.55)	7.45 (5.85)
Aspirin 325 mg	1.07 (1.81)	1.04 (1.47)	0.88 (1.06)	0.74 (1.67)	2.00 (2.37)	3.99 (4.94)
Aspirin 650 mg	0.94 (1.54)	1.14 (1.67)	1.08 (1.86)	0.88 (1.93)	2.05 (2.30)	3.69 (5.08)
p Value‡	.798	<.001	<.001	.248	<.001	<.001
Pairwise comparisons§		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg
Tingling						
Placebo (P)	2.37 (2.43)	3.18 (2.47)	2.36 (2.23)	1.24 (2.05)	4.18 (2.35)	9.14 (6.27)
Aspirin 325 mg	2.05 (2.46)	1.18 (1.45)	1.07 (1.40)	0.71 (1.29)	2.69 (2.50)	5.07 (4.88)
Aspirin 650 mg	1.81 (2.23)	1.48 (2.25)	0.99 (1.82)	0.62 (1.32)	2.52 (2.49)	4.70 (6.25)
p Value‡	.418	<.001	<.001	.108	<.001	<.001
Pairwise comparisons§		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg
Warmth						
Placebo (P)	3.36 (3.21)	4.21 (2.89)	3.37 (2.53)	1.43 (2.28)	5.73 (2.71)	12.03 (7.13)
Aspirin 325 mg	2.95 (3.04)	2.38 (2.49)	1.62 (1.48)	0.79 (1.41)	3.95 (2.87)	7.52 (5.74)
Aspirin 650 mg	2.35 (2.68)	2.57 (2.67)	1.87 (2.37)	0.86 (1.60)	3.63 (2.86)	7.42 (7.21)
p Value‡	.159	.001	<.001	.108	<.001	<.001
Pairwise comparisons§		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg		P > 325 mg P > 650 mg	P > 325 mg P > 650 mg
Headache						
Placebo (P)	0.45 (1.31)	0.60 (1.52)	0.43 (1.38)	0.19 (1.09)	0.79 (1.82)	1.65 (4.47)
Aspirin 325 mg	0.31 (0.87)	0.57 (1.50)	0.38 (1.34)	0.24 (1.25)	0.71 (1.57)	1.50 (4.46)
Aspirin 650 mg	0.12 (0.40)	0.12 (0.50)	0.17 (0.70)	0.12 (0.40)	0.33 (0.87)	0.52 (1.53)
p Value‡	.073	.035	.186	.595	.050	.039

**Highest symptom score at any of the four evaluation times (i.e., 15, 30, 60, or 120 minutes) after niacin administration.*
†Total of symptom scores at all four evaluation times.
‡Repeated measures ANOVA.
§p < .05 via Scheffe's Test.

With placebo, 25 (60%) of the 42 subjects experienced a reaction of moderate or greater intensity (i.e., a symptom score of 6 or more for at least one of the reactions). The occurrence of such reactions was lower with both aspirin regimens, occurring in 17 (41%) of the subjects with the 325-mg regimen and 12 (29%) of the subjects with the 650-mg regimen ($\chi^2 = 14.1$, $df = 2$, $p < .001$). However, a comparison of the two aspirin regimens revealed no significant differences ($\chi^2 = 0.84$, $df = 1$, $p = .36$).

DISCUSSION

Bothersome cutaneous reactions significantly limit the utility of niacin as a lipid-modifying agent. Cutaneous reactions appear to accompany rising concentrations of nicotinic acid in the blood and subside once a constant level is reached.[14] Niacin-induced cutaneous reactions have been attributed to prostaglandin-mediated mechanisms,[8] and Morrow et al. have identified the skin as a major site of prostaglandin release following niacin administration.[16] With continued administration, some patients develop tolerance to these reactions accompanied by decreased amounts of prostaglandin production.[12,17] However, for niacin to be used successfully in the management of dyslipidemias, strategies to minimize bothersome cutaneous reactions are necessary. Several inhibitors of prostaglandin synthesis have been used for prevention of niacin-induced cutaneous reactions, but aspirin is the

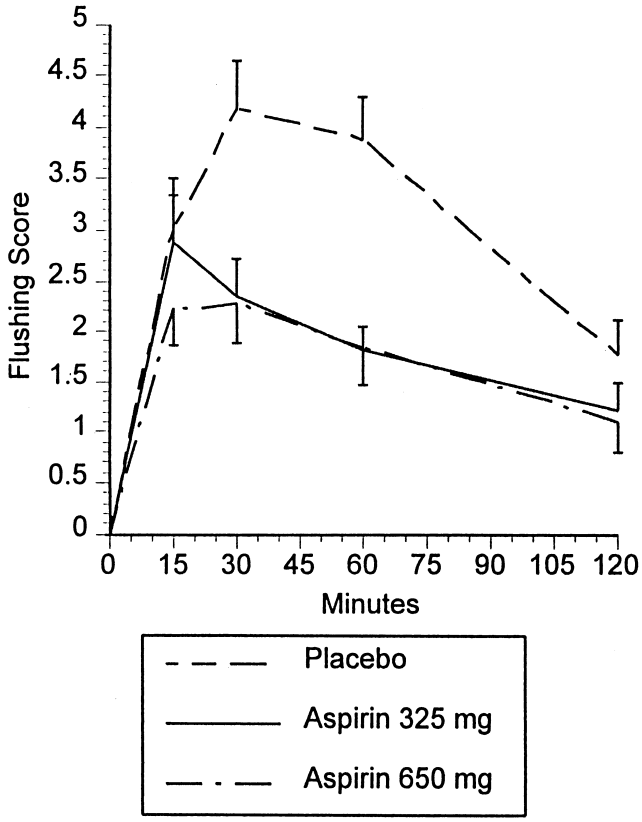

FIGURE 1. Plot of flushing intensity (mean ± SEM) versus time in patients receiving immediate-release niacin 500 mg following pretreatment with placebo, aspirin 325 mg, and aspirin 650 mg.

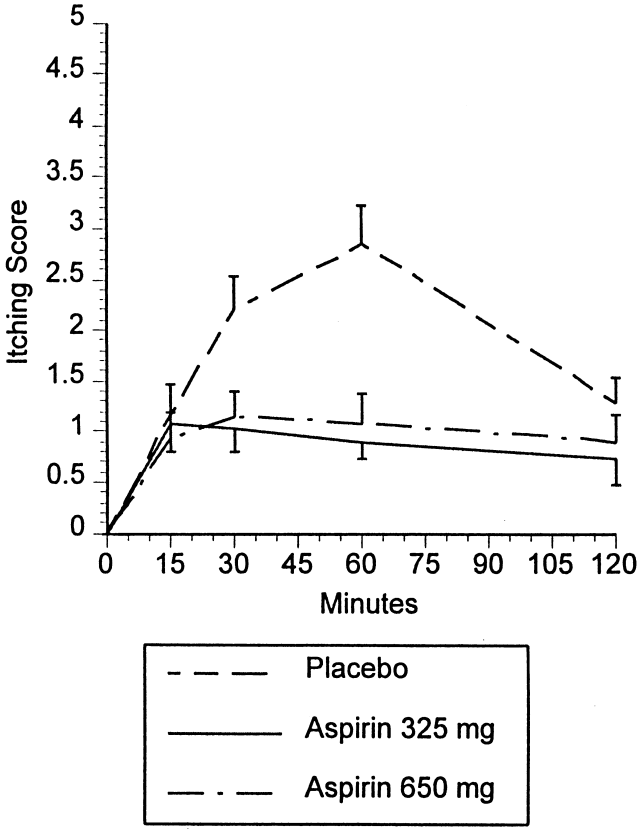

FIGURE 2. Plot of itching intensity (mean ± SEM) versus time in patients receiving immediate-release niacin 500 mg following pretreatment with placebo, aspirin 325 mg, and aspirin 650 mg.

most commonly used drug and has been most extensively studied.

We compared placebo with aspirin administered in daily doses of 325 mg and 650 mg. In an attempt to achieve maximum prostaglandin inhibition, we administered each of the regimens daily for four doses prior to challenge with a 500-mg dose of immediate-release niacin. We found both aspirin regimens to be significantly better than placebo in reducing symptom scores for flushing, itching, tingling, and warmth. However, we did not find the 650-mg dose of aspirin to be any better than 325 mg. This finding was consistent regardless of the method used to compare symptom scores and also when the two regimens were compared on the proportion of subjects experiencing a reaction of at least moderate severity.

Our findings are similar to those of other investigators and suggest that administering aspirin in doses above 325 mg will provide little additional benefit in reducing cutaneous reactions due to niacin. Wilkin et al. evaluated the effects of pretreatment with 975 mg of aspirin on reducing the intensity of flushing as measured by changes in malar thermal circulation index (MTCI).[11] Niacin was administered over a range of doses: 0.71 mg/kg body weight, 1.49 mg/kg, 2.86 mg/kg, and 5.71 mg/kg. Compared with placebo, pretreatment with aspirin reduced the intensity of flushing significantly for the two highest niacin doses, but even with aspirin pretreatment, the subjects still had substantial changes in MTCI indicating that flushing still occurred. Jay et al. evaluated aspirin pretreatment in subjects receiving 250 mg of niceritrol, a niacin analogue with a lower potential for cutaneous reactions compared to niacin.[18] The 300-mg and 600-mg aspirin doses both reduced the severity of flushing compared with placebo, but there was not a significant difference between the two aspirin regimens.

300 mg

Our study was not designed to evaluate specifically the effect of aspirin pretreatment for 4 days prior to niacin administration versus the effect of pretreatment with single doses of aspirin. However, when our results are compared with those of Whelan et al.,[6] it appears that pretreatment beyond a single aspirin dose adds modest benefit at best. The differing methods used in the two studies make direct comparisons problematic. Although Whelan et al. did not report data on the intensity of cutaneous reactions at the 325-mg dose, 72% of the 25 subjects reported flushing, 72% reported warmth, 60% reported itching, and 68% reported tingling. In our study, 17 (41%) of the 42 subjects reported a reaction of moderate or greater

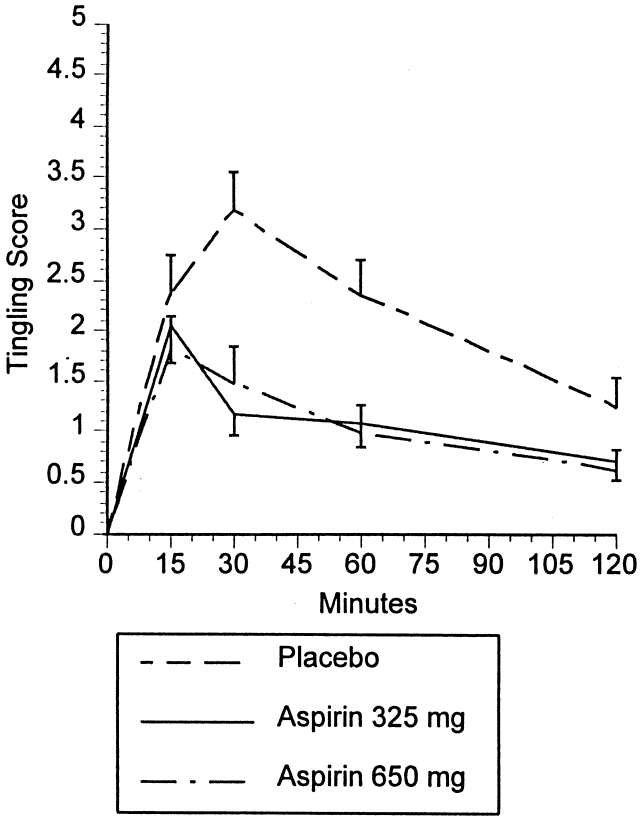

FIGURE 3. Plot of tingling intensity (mean ± SEM) versus time in patients receiving immediate-release niacin 500 mg following pretreatment with placebo, aspirin 325 mg, and aspirin 650 mg.

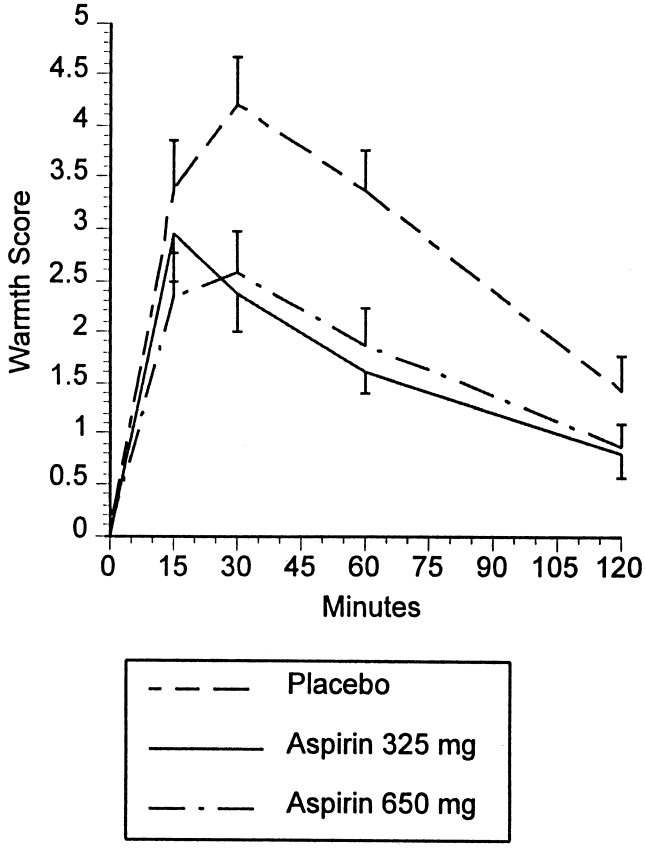

FIGURE 4. Plot of warmth intensity (mean ± SEM) versus time in patients receiving immediate-release niacin 500 mg following pretreatment with placebo, aspirin 325 mg, and aspirin 650 mg.

intensity. Our 325-mg and 650-mg aspirin regimens produced reductions in warmth, flushing, itching, and tingling, whereas the 325-mg single-dose regimen of Whelan et al. reduced only warmth and flushing.

The beneficial effects of the two aspirin regimens were seen primarily at the 30-minute and 60-minute evaluation times. Examination of Figures 1–4 reveals that with placebo and both aspirin regimens, subjects experienced an initial onset of the various cutaneous reactions at 15 minutes. The reactions continued to increase with placebo, peaking at either 30 or 60 minutes after niacin administration. However, aspirin administration blunted the intensity of the reactions, so that by 30 minutes they were of equal or lesser intensity as compared with 15 minutes. By 120 minutes, the reactions had subsided to the point where there were no significant differences between the placebo and two aspirin regimens.

We also evaluated the effect of the aspirin regimens in preventing headache. Although aspirin administration had no significant effect in preventing headache, the low incidence and intensity of headache indicates that it was not a particularly important reaction in most of the subjects.

A limitation of our study is its lack of power to detect small, but potentially important, differences between the two aspirin regimens. Because we had no prior knowledge of the population standard deviation for the various cutaneous reactions as measured on our visual analogue scale, it was not possible to perform power calculations prior to the study. However, using our data for flushing, with our observed standard deviation being used as an estimate of the population standard deviation, we calculated our study to have a power of approximately 67% for the detection of a 0.33-unit difference in peak intensity. The power for other study variables (with the exception of headache) would most likely be similar given the similar standard deviations that we found.

A second limitation of our study is that it does not utilize the niacin dosing strategy typical in clinical practice. We used a 500-mg niacin dose to elicit niacin reactions that would be readily recognized by our subjects. To help facilitate development of tolerance to niacin reactions, therapy is usually initiated at dosages in the range of 100 mg three times daily and the dosage is increased over several weeks. In spite of this strategy, cutaneous reactions to niacin are often unbearable, and 325 mg of aspirin is often given prior to each niacin dose to improve its tolerability. Patients typically receive final niacin doses ranging from 1 to 6 g daily on a long-term basis. When ni-

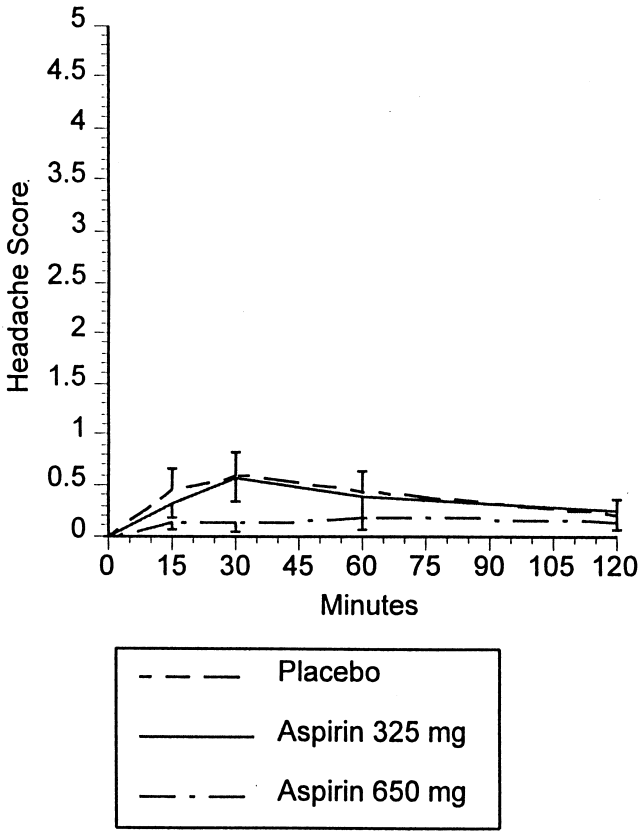

FIGURE 5. Plot of headache intensity (mean ± SEM) versus time in patients receiving immediate-release niacin 500 mg following pretreatment with placebo, aspirin 325 mg, and aspirin 650 mg.

acin is administered over a prolonged period, differential doses of aspirin may have effects different from those found in our study. Also, the typical patient receiving niacin for lipid modification is older than our subjects, whose mean age was 44 years.

In spite of these limitations, our findings are in agreement with previous work that supports pretreatment with a 325-mg dose of aspirin prior to administration of niacin. Doses above 325 mg do not appear to add benefit.

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