The Effect of Aspirin on Niacin-Induced Cutaneous Reactions

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Background. Niacin (nicotinic acid) is one of the first-line agents recommended for the treatment of hyperlipidemia. Bothersome cutaneous reactions (flushing, feeling of warmth, itching, and tingling), however, often limit patient acceptability and tolerability. The National Cholesterol Education Program recommends giving aspirin or another nonsteroidal anti-inflammatory drug before administering niacin. Lack of scientific data supporting this recommendation, however, led to this randomized, double-blind, placebo-controlled trial to evaluate the efficacy of 80 mg of aspirin and 325 mg of aspirin in reducing these cutaneous reactions.

Methods. Thirty-one healthy subjects were randomized into one of four groups. Each group completed four different treatment regimens (placebo–placebo; 80 mg of aspirin–500 mg of niacin; 325 mg of aspirin–500 mg of niacin; and placebo–500 mg of niacin). Subjects received one of each of the four treatment regimens on separate visits that were at least 24 hours apart. Intensity and tolerability of cutaneous reactions were evaluated by an intensity rating scale and a visual analog scale.

Results. Results indicate that 325 mg of aspirin is significantly better than 80 mg of aspirin in decreasing intolerability to niacin. Aspirin reduced the incidence of warmth and flushing associated with niacin, but not the itching and tingling.

Conclusions. It appears from this pilot study that preceding niacin with 325 mg of aspirin will decrease the warmth and flushing associated with niacin.

Key words. Aspirin; niacin; flushing. *J Fam Pract 1992; 34:165-168.*

Niacin (nicotinic acid) is one of the drugs of choice for the treatment of high blood cholesterol, as it has a desired effect on all the lipid components.[1] It lowers total, low-density, and very low-density lipoproteins as well as triglycerides, and increases high-density lipoprotein levels. Niacin has been shown to reduce long-term mortality and recurrent myocardial infarctions.[2,3] Niacin offers several potential advantages over other available agents: it is effective, safe for long-term use, inexpensive, available in several strengths, and does not require a physician's prescription. The major disadvantage associated with niacin is the adverse effects that frequently occur. These are generally reversible, however, with reduction of the dose or discontinuation of the drug.

Bothersome cutaneous adverse reactions do often limit patient acceptance and tolerability of niacin. Flushing of the face and trunk have been reported in 92% to 100% of patients receiving the drug.[3–5] Feelings of warmth, tingling, and itching also occur, although with less frequency than the flushing.[3,4] Although tolerance will develop to these cutaneous reactions with continued use, patients often discontinue the medication before this occurs. Several studies indicate that some of these cutaneous reactions may be prostaglandin mediated.[6–11] This has led to the recommendation by several authors and the National Cholesterol Education Program (NCEP) that treatment with niacin be preceded by a dose of aspirin, an agent that inhibits prostaglandin synthesis.[1,5,12–17] The NCEP guidelines, however, do not suggest a specific dose of aspirin.[1] One study gave no more information than "one aspirin tablet."[17] Other authors have recommended doses ranging from 120 mg to 650 mg of aspirin administered 30 to 60 minutes before niacin.[5,12–16] Only one study[18] to date has evaluated the influence of aspirin (975 mg) on the flushing reaction induced by niacin. Two other studies[19,20] have been conducted that used niceritrol, an agent not available in the United States, which, when ingested, is hydrolyzed to niacin. Such a

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Table 1. Treatment Groups and Treatment Regimen Received by Subjects at Each Visit

Visit	Group 1 (n = 7)	Group 2 (n = 4)	Group 3 (n = 6)	Group 4 (n = 8)
1	Pl–Pl	80–N	325–N	Pl–N
2	80–N	325–N	Pl–N	Pl–Pl
3	325–N	Pl–N	Pl–Pl	80–N
4	Pl–N	Pl–Pl	80–N	325–N

Pl–Pl denotes placebo–placebo; 80–N, 80 mg of aspirin–500 mg of niacin; 325–N, 325 mg aspirin–500 mg niacin; and Pl–N, placebo–500 mg niacin.

paucity of data led to this randomized, double-blind, placebo-controlled study, which evaluated the relative efficacy of 80 mg of aspirin and 325 mg of aspirin in reducing the cutaneous reactions associated with niacin therapy. These two doses of aspirin were chosen because, as indicated above, small doses of aspirin are being empirically recommended with virtually no scientific data for support.

Methods

Men and women between 18 and 50 years of age were enrolled in the study if they met the entry criteria. All pregnant, lactating, and menopausal women were excluded. Subjects with any known sensitivity to aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), niacin, or lactose were ineligible for inclusion. Also excluded were patients with active peptic ulcer disease, hepatic dysfunction, hypotension, diabetes mellitus, or gout. Subjects gave written informed consent for this study, which was approved by the Institutional Review Board for Human Research at this institution.

Subjects were randomly assigned to one of four treatment groups to which four treatment regimens were administered: placebo followed by placebo; 80 mg of aspirin followed by 500 mg of niacin; 325 mg of aspirin followed by 500 mg of niacin; placebo followed by 500 mg of niacin (Table 1). Each group began its series of four regimens at a different point in the sequence, but the sequence remained the same for each group. The contents of the placebo, the aspirin, and the niacin were all repackaged into identical, opaque capsules. The placebo–placebo regimen was administered only to determine if a placebo effect was present. Each subject received each treatment regimen on four separate visits that were at least 24 hours apart. Subjects, as well as the investigators, were blinded as to what group the subject was in and, therefore, what regimen was being received.

On the day of each visit, the subjects were asked to refrain from smoking, eating, or drinking alcohol or any hot beverages for at least 2 hours before starting the study. At time zero, skin temperature (using a strip fever thermometer) and room temperature were recorded. The first drug in the regimen (placebo or aspirin 80 mg or aspirin 325 mg) was given. Thirty minutes later, skin and room temperatures were once again recorded, and the second drug was given (placebo or niacin 500 mg). Within 1 hour, the subject's temperature and the room temperature were once again documented. Subjects were asked to complete a questionnaire concerning the intensity, and onset after administration of the second drug, of the adverse reactions being studied: flushing, warmth, itching, and tingling. Subjects then rated these reactions using a 10-cm visual analog scale (VAS). Opposing adjectives (nonexistent, intolerable) were placed at each end of the 10-cm straight-line visual scale. Subjects were asked to mark the spot on the line between the two extremes that they believed best reflected the tolerability of their reaction. Subjects also rated the severity of their reactions using an intensity rating scale (0 = no reaction, 1 = mild, 2 = moderate, 3 = severe). On the last visit, subjects were asked to rank each visit from one (most severe) to four (least severe). Subjects were asked at each visit to record any other adverse reactions experienced from the treatment.

The VAS data were analyzed using the Friedman two-way analysis of variance by ranks, while the intensity rating scale data were analyzed using a nonparametric test for independence. Statistically, it was determined that 23 subjects would be needed to detect a difference between the treatments with a power of 90 and a level of significance of .10. Twenty-eight subjects would be needed to obtain a power of .90 and a level of significance of .05.[21]

Results

Thirty-one subjects meeting entry criteria were enrolled in the study. The mean age of the subjects was 29 years (range 24 to 41 years). Of the 31 patients enrolled, complete data are available for 25 subjects. Two subjects were unable to complete the study owing to unforeseen work obligations, and four chose to drop out after experiencing adverse effects (one had a syncopal episode, one had difficulty swallowing, and two had nausea and dizziness).

The number of cutaneous reactions that the 25 remaining subjects experienced with each treatment regimen are listed in Table 2. Only one subject experienced mild flushing, warmth, and tingling with the placebo–placebo regimen. Therefore, as no significant placebo effect was demonstrated, data from this regimen were excluded from further analysis. Room temperatures did not change significantly at any time during the study and were not considered to have influenced the outcome. Skin temperatures did change in some subjects; however, the fever strip used was not sufficiently sensitive to detect

Table 2. Number of Cutaneous Reactions Reported by Subjects for Each Treatment Regimen (N = 25)

Reaction	Placebo–Placebo No. (%)	80 mg Aspirin–Niacin No. (%)	325 mg Aspirin–Niacin No. (%)	Placebo–Niacin No. (%)
Flushing	1 (4)	21 (84)	18 (72)	20 (80)
Warmth	1 (4)	21 (84)	18 (72)	20 (80)
Itching	0	18 (72)	15 (60)	17 (68)
Tingling	1 (4)	18 (72)	17 (68)	16 (64)

small changes, and these data therefore were not used in the final analysis.

Data from the VAS showed that 325 mg of aspirin was more effective ($P < .10$) than 80 mg of aspirin or a placebo in reducing the intolerability associated with the cutaneous reactions induced by niacin. There was no significant difference between the effect of the placebo and 80 mg of aspirin. Analysis of data from the intensity rating score indicated that the 325 mg of aspirin reduced warmth and flushing but not itching or tingling.

Onset of cutaneous reactions ranged from 5 to 90 minutes after drug 2 of the regimens (placebo or niacin) was administered. Average onset of reaction in all subjects was 21 minutes. The adverse effects (aside from those being evaluated in the study) experienced by the 25 subjects are shown in Table 3. Nausea was the most frequently reported adverse effect.

Discussion

The results of this study indicate that 325 mg of aspirin is better than 80 mg of aspirin in decreasing the intolerability of the cutaneous reactions associated with a 500-mg dose of niacin at a P value $< .10$. The larger dose of aspirin did not necessarily prevent the reaction completely but did lessen the severity. There was no difference between the 80 mg of aspirin and the placebo. In fact, more subjects ranked the regimen of 80 mg of aspirin followed by niacin as causing more severe adverse effects than the regimen of the placebo followed by niacin (Table 4). The regimen of placebo only was ranked least severe, and the regimen of 325 mg of aspirin followed by niacin ranked close behind.

Table 3. Number and Type of Adverse Effects Experienced by Subjects with Each Treatment Regimen

Effect	Placebo–Placebo	80 mg Aspirin–Niacin	325 mg Aspirin–Niacin	Placebo–Niacin
Nausea	0	1	0	3
Metallic taste	0	0	0	1
Eye irritation	0	1	1	1
Nasal congestion	0	1	0	2
Facial edema	0	0	0	1
Ear pressure	0	0	1	0

Table 4. Subjects' Ranking of the Overall Severity of Adverse Reactions With Each Treatment Regimen

Severity of Reaction*	Placebo–Placebo No. (%)	80 mg Aspirin–Niacin No. (%)	325 mg Aspirin–Niacin No. (%)	Placebo–Niacin No. (%)
1	0	14 (56)	4 (16)	7 (28)
2	1 (4)	5 (20)	6 (24)	12 (48)
3	3 (12)	4 (16)	13 (52)	4 (16)
4	21 (84)	2 (8)	2 (8)	2 (8)

**Subjects ranked overall severity at last visit after all four treatment regimens had been received. Rank 1 = most severe reaction; rank 4 = least severe reaction.*

The apparent lack of effectiveness of the 80 mg of aspirin may be explained in part by a study[22] that examined the pharmacokinetics of the co-administration of niacin and aspirin. Aspirin administration caused a rise in nicotinic acid concentrations by saturating the glycine elimination pathway shared by the two agents. Studies have shown that the flushing reaction appears to correlate more with the rise of plasma niacin levels rather than with the height of the peak.[23,24] Therefore, in this study, administration of aspirin would cause plasma niacin levels to rise. It appears that the lower dose of aspirin was not sufficient to inhibit the synthesis of prostaglandins associated with the flushing, and that co-administration resulted only in worsening the reaction. However, even though the 325 mg of aspirin probably caused a rise in plasma niacin levels, the aspirin dose may have been high enough to overwhelm the production of prostaglandins, and, hence, severe cutaneous reactions.

Aspirin appeared to be most effective at decreasing the intensity of the flushing and warmth, while not significantly affecting itching and tingling. While studies have shown that flushing and warmth are definitely prostaglandin mediated, it is unknown whether prostaglandins are responsible for the itching and tingling reactions.[6–11]

Analysis of the data indicated that the order in which the subjects received the different regimens may have affected the outcome. Subjects in group 3, who were the first to receive the regimen of 325 mg of aspirin followed by niacin, reported it to be the least effective regimen. However, group 3 subjects did not find the other regimens to be much better. The other three groups all ranked the regimen of 325 mg of aspirin followed by niacin as the best (most tolerable) treatment regimen. This may indicate the subject's apprehension of taking niacin for the first time, regardless of the dose of aspirin accompanying it. This may have biased the subject's ranking of intensity and intolerability of reactions at subsequent visits. Randomization of the sequence in

which the regimens were received within a group might not have relieved this problem. Perhaps the best way to offset this problem would have been to give each subject a prestudy dose of niacin so that subjects would know what to expect during the study.

Although several studies used NSAIDS or aspirin when attempting to determine if niacin-induced flushing was prostaglandin mediated, it was not until 1977 that Svedmyr and colleagues[25] actually tried to determine clinically if an NSAID (indomethacin) could reduce this adverse reaction. Ten healthy male volunteers were pretreated with indomethacin for 9 days before being given a predetermined submaximal flushing dose of niacin. Intensity of the flush, as measured by ear temperature, was significantly reduced by the pretreatment with indomethacin. Twenty-nine subjects participated in the only study assessing the effects of aspirin in blocking niacin-induced flushing.[18] All subjects were given 650 mg of aspirin 1 hour before and 325 mg of aspirin 30 minutes before receiving a niacin dose. Four different doses of niacin were administered (0.71, 1.43, 2.86, and 5.71 mg/kg). Pretreatment with the 975 mg of aspirin decreased the intensity of the flush induced by the two larger doses of niacin. Two studies[19,20] have evaluated the effects of aspirin on the flushing reaction induced by niceritrol, an agent hydrolyzed to nicotinic acid. Although the flushing induced by niceritrol appears to be milder than that seen with niacin, some patients still find it intolerable. In both studies, aspirin reduced the flushing reaction.

Conclusions

Results from this pilot study provide further clinical evidence that preceding the dose of niacin with 325 mg of aspirin is effective in reducing the intensity of the cutaneous reactions. Results from this study also indicate that 80 mg of aspirin is not effective in offsetting these reactions. Further study, with a larger sample size done in patients with hyperlipidemia, is warranted. As previously mentioned, it is recommended by the National Cholesterol Education Program that a dose of niacin be preceded by aspirin. Based on the results of this study, 325 mg of aspirin given 30 minutes before a dose of niacin should help to decrease the severity of niacin-induced cutaneous reactions.

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