Clinical evidence for use of acetyl salicylic acid in control of flushing related to nicotinic acid treatment

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SUMMARY
Nicotinic acid (NA) is highly effective and widely used in the management of dyslipidaemia. For many patients, the side effect of flushing of the face and upper body leads to discontinuation. Flushing with NA is mediated by prostaglandins, and as acetyl salicylic acid (ASA, 'aspirin') is a highly effective inhibitor of prostaglandin synthesis, there is a rationale for its use to prevent or reduce the severity of NA-related flushing. This literature survey identified four studies specifically exploring the utility of ASA in preventing NA-related flushing in healthy volunteers. Twenty-three NA studies, where ASA was mandatory or optional within the protocol, and four studies, where background ASA therapy was reported in most participants, were also identified. Although the incidence of flushing in studies using ASA was often high, discontinuation rates due to flushing were low (mean 7.7%). This figure compares favourably with discontinuation rates with NA commonly reported in the literature (up to approximately 40%). There is good supportive evidence for the use of ASA in reducing the severity of NA-related flushing.

Keywords: Nicotinic acid; acetyl salicylic acid; flushing; discontinuation

NICOTINIC ACID USE AND PHARMACOLOGY
Nicotinic acid (NA) is a water-soluble B-complex vitamin, also known as niacin. Administration of NA in people with dyslipidaemia results in increased high-density lipoprotein (HDL)-cholesterol and decreased low-density lipoprotein (LDL)-cholesterol, triglycerides and lipoprotein(a) (1). The molecular mechanism of action of NA remained unknown before the recent identification of a high-affinity NA binding G-protein-coupled receptor that is expressed in adipose tissue (2–4).

Current hypotheses suggest that activation of the NA receptor induces an inhibitory G-protein signal that reduces adipocyte cAMP concentrations and thus inhibits lipolysis (5,6). This, in turn, reduces circulating nonesterified fatty acids. As these fatty acids are precursors for hepatic triacylglycerol synthesis, and thus of very low density lipoprotein (VLDL) production, a reduction of circulating nonesterified fatty acids could be expected to reduce hepatic VLDL output and therefore reduce circulating triglycerides.

Given the close inverse relation between plasma triglyceride and HDL concentrations, largely mediated by cholesteryl ester exchange between HDL and VLDL, activation of the NA receptor may cause the observed increase in HDL. Additionally, a direct HDL-raising effect of NA mediated by an increased cholesterol export from macrophages has also been suggested (7).

NICOTINIC ACID FLUSHING
Flushing of the face and upper body following administration of NA has been recorded since at least the 1960s (8) and can be unpleasant for patients. Thermographic studies in the late 1960s and 1970s established that flushing persisted as long as plasma concentrations of NA were rising but disappeared once a constant concentration was reached, ruling out any direct vasodilatory effect of NA (9,10). Findings from animal studies have subsequently suggested the involvement of prostaglandins (11,12). A study by Morrow and colleagues identified cutaneous release of prostaglandin D2 as the immediate cause of NA-induced flushing and established elevated levels of the prostaglandin D2 metabolite 9α,11β-PGF2 (13). Ex vivo data also showed significant elevations in prostaglandin E2, thromboxane B2 and leukotriene E2 synthesis following NA administration (2.5 g) (14). The involvement of G-protein-coupled receptor GPR109A in the flushing...
response to NA has recently been elegantly confirmed by studies in a variety of animal genetic models by Benyó and colleagues (15). Knockout mice lacking COX-1 demonstrated no flushing response to NA, while those lacking endothelial nitric oxide synthase (eNOS) retained the wild-type response, indicating that NA-related flushing depends on prostanooid synthesis and is unconnected to the production of endothelial nitric oxide. Mice lacking PUMA-G (the murine form of GPR109A) showed no flushing response to NA, although the response could be elicited using prostaglandin D₂. Interestingly, the role of immune cells in NA-related flushing was also shown by Benyó and colleagues using bone marrow chimaeric mice (15). Transplantation into irradiated PUMA-G-deficient mice of bone marrow from wild-type mice, but not of that from PUMA-G-deficient donors, was able to restore NA-related flushing. The cell type responsible for NA-related prostanoid formation remains, however, to be identified.

During clinical use of NA, flushing, together with other less-common cutaneous side effects, including rash, tingling and itching, has been reported in up to 100% of patients who were using older formulations of the agent (16). Although tolerance to these side effects does develop with continued use, many patients discontinue NA treatment.

NA is rapidly and extensively absorbed after oral administration, with plasma concentrations reaching a maximum after 30–60 min with crystalline (‘immediate-release’) NA (17). Metabolism of NA occurs by two different pathways: a high-capacity conjugative pathway involving glycine and leading to the metabolite nicotinuric acid responsible for flush and a low-capacity amidation pathway, leading to nicotinamide adenine dinucleotide (NAD) and other nicotinamide derivatives responsible for hepatotoxicity (18–21). The relative importance of these two elimination pathways, and thus the amounts of each metabolite group, depend on the pharmacokinetics of the NA formulation used. Much attention has been paid to optimising NA delivery to achieve a balance between the two pathways and therefore to reduce flushing and avoid hepatotoxicity.

**EVIDENCE SUPPORTING ACETYLC SALICYLIC ACID USE TO CONTROL FLUSHING**

Because NA-related flushing appears to be a result of prostaglandin activity, and because acetylsalicylic acid (ASA) is a well-established inhibitor of prostaglandin synthesis, there is a rationale for use of this agent to control this troublesome side effect of NA therapy. The present literature review was undertaken to determine the strength of evidence supporting use of ASA, either NSAIDS or other COX-1-inhibiting agents to prevent NA-related flushing. A secondary objective was to seek evidence that low-dose ASA, such as that commonly used for prophylaxis in patients at high cardiovascular or cerebrovascular risk, counters NA-related flushing. Exploratory surveys were also undertaken to investigate evidence supporting the potential efficacy of cyclo-oxygenase inhibitors in general, and other compounds, in countering NA-related flushing.

**Search Methodology and Results**

A literature survey was performed to identify publications where nicotinic acid (in any presentation or formulation) was used in conjunction with ASA or ibuprofen. The primary search was carried out using MEDLINE, which was used to search for all documents with publication type listed as clinical trial, case report or letter and where niacin/nicotinic acid was used. This search yielded 338 documents from 1978 to 2005. Publications before 1978 were accessed with a free-text search for clinical trials using nicotinic acid/niacin during this time period, which yielded a further 80 candidate publications. Manual screening of abstracts within these 418 search results yielded 70 documents considered useful for further study. Main exclusions were nutritional studies, studies where NA was not part of a main treatment arm, case reports of no relevance, papers discussing hepatotoxicity of NA, studies in disease states unrelated to lipid lowering (e.g. schizophrenia) and articles with no abstract and where the title suggested little relevance. In addition, two articles were identified as extremely relevant (16,22). Related reference searches yielded an additional 11 publications of interest, giving a total of 81 shortlisted publications. References were included where any presentation or formulation of NA had been used, including those where the agent had been used in combination with other agents. A confirmatory search was carried out using EMBASE (with similar search criteria), which provided a further eight articles of possible interest.

Eighty-four shortlisted documents were obtained as full-text articles (comprising the 89 shortlisted articles from the MEDLINE and EMBASE searches, without the five articles that were unobtainable locally) and read. This reading yielded four articles specifically exploring the use of ASA to control NA flushing: 23 articles where NA was used in a study and where ASA was included in the protocol to control flushing (of which three also included ibuprofen or other NSAIDs as an alternative to ASA); four articles where NA was used in a study in patients, some or all of whom were reported to be already receiving ASA; nine articles exploring the mechanism of NA flushing without reference to ASA; 36 articles where NA was used in a study, but where the use of ASA was not reported; four articles were excluded because of suspected or explicit duplication of patient populations with other analysed articles, or where the article presented no original data; and four articles judged of no relevance for other reasons.

Thus, the survey revealed 31 articles of direct relevance to the use of ASA during NA therapy.
Exploratory Studies

Wilkin and co-workers evaluated the effect of ASA on NA-induced flushing intensity in a placebo-controlled study in 29 healthy volunteers (23). They found that pretreatment with ASA 975 mg [650 mg 60 min before and 325 mg 30 min before a single dose of ‘immediate-release’ NA (orally administered as an aqueous solution at doses of 0.71, 1.43, 2.86 and 5.71 mg/kg)] significantly reduced intensity of flushing, as determined by increase in malar temperature following NA doses of 2.86 and 5.71 mg/kg (Figure 1). All NA doses used in this study were below those routinely used in clinical practice (typically 1000–2000 mg/day). There was no significant effect of ASA on the much smaller flushing reactions following the two lowest NA doses in this study. With the highest dose of NA, pretreatment with 975 mg ASA reduced malar thermal circulation index (the measure of flushing used in this study, derived from changes in malar temperature relative to oral and ambient temperature) by approximately 40% (p < 0.01).

Wilkin and colleagues demonstrated that ASA was able to reduce NA-induced flushing intensity and also demonstrated that the degree of flushing showed a dose response, at least with the relatively small amounts of NA administered in this study (23).

The effect of ASA dose was investigated by Whelan and co-workers in a randomised, double-blind, placebo-controlled study in 31 healthy volunteers (16). This was a crossover study in which patients received placebo or ASA at 80 mg or 325 mg doses, followed by placebo or 500 mg NA after 30 min. In this study, there was only a small reduction in the number of patients reporting flushing following 325 mg ASA compared with placebo, and no reduction following 80 mg ASA (16). Patients in this study also rated the severity of their symptoms on a visual assessment scale, which suggested that the severity of reaction to NA was reduced by the higher dose of ASA but not by the lower 80 mg dose. When receiving 325 mg ASA, 60% of patients rated their reaction within the lowest two points on the scale vs. only 24% with placebo.

The authors of this small study concluded that 325 mg ASA given 30 min before NA administration was useful in reducing flushing but that there was no evidence for the use of an 80 mg dose (16).

Dose response to ASA was further investigated by Dunn and colleagues (24). In this double-blind study, 22 healthy volunteers were randomised to receive placebo, 325 mg or 160 mg ASA, or 200 mg ibuprofen, 30 min before taking a single 500 mg dose of NA ‘immediate release’ on an empty stomach. Both doses of ASA significantly reduced flushing compared with placebo, as did ibuprofen (all p < 0.05 for the number of patients reporting flushing in excess of 5 on a 10-point visual analogue scale; Figure 2). There was no significant difference in the response to 160 mg and 325 mg ASA, although the higher dose of ASA alone was superior to ibuprofen.

Dose response to ASA was further investigated by Jungnickel and co-workers (22). In this crossover study, 42 patients received extended pretreatment with 325 mg or 650 mg ASA, or placebo for 4 days, 30 min before

**Figure 1** Pretreatment with 975 mg ASA significantly reduces NA-induced flushing intensity. △MTCI, change in malar thermal circulation index; *p < 0.02, **p < 0.01 (23)

**Figure 2** Reductions in moderate–severe flushing with ASA and ibuprofen. IBU, ibuprofen; *p < 0.05 vs. placebo, **p < 0.05 vs. ibuprofen (24)
administering 500 mg NA ‘immediate release’. Symptom scores for flushing, as well as for other cutaneous reactions to NA, were significantly reduced by both ASA regimens compared with placebo (p < 0.05; Figure 3). There was no significant difference between the two doses of ASA; this finding was consistent for different methods of comparing symptom scores (total symptom score; peak score) and also when the proportion of patients experiencing a moderate or greater cutaneous reaction was considered. The investigators concluded that no additional benefit was gained by increasing the ASA pretreatment dose above 325 mg.

**NA Studies Using ASA to Control Flushing**

A total of 23 studies were identified in which NA was used as study medication and the study protocol was reported as including ASA as a mandatory medication, as a recommendation or on an ‘as-needed’ basis, specifically for the purpose of reducing NA-related flushing (Table 1) (25–47).

The most common recommendation in these studies was for patients to take a 325 mg tablet ‘as needed’ if NA flushing was a problem. Two studies specified lower doses of ASA [100 mg (27); 150 mg (28)]. A number of study reports failed to specify the ASA dose used.

The incidence of NA-induced flushing, where reported, varied from 18 to 100%, with a mean overall report of approximately 29%. However, since many study protocols advised the use of ASA ‘as needed’ in response to flushing, the incidence of flushing cannot be taken as a measure of the efficacy of ASA in preventing flushing, as the reaction would have occurred before ASA use was indicated under these protocols. For this reason, discontinuation rates due to flushing may be a better guide to the utility of ASA; presumably few patients would discontinue after only a single flushing event if they had the possibility of trying ASA before the next dose of NA.

Discontinuation rates were reported in all but two studies, although in some cases, no specific indication was given of the number of discontinuations attributable to flushing as distinct from other adverse reactions. However, taking published discontinuation rates due to flushing where reported, and taking discontinuation due to all adverse reactions where no specific data were available, yielded an overall discontinuation rate of 7.7% (575/7495 patients). The flushing-specific discontinuation rate, for those studies where such rates were reported, was 6.5% (430/6635 patients).

No pattern is evident relating discontinuation rates or incidence of flushing where reported to duration of treatment or dose of NA. There is, however, also some evidence for the effect of NA formulation in influencing flushing. Discontinuation rates (flushing-specific where reported) were 18.2% overall in studies using ‘immediate-release’ formulations of NA and 8.3% in studies using the newer ‘extended-release’ formulation (extended-release formulation is also called ‘prolonged-release’ formulation).

Aims and design of particular studies may also have played a part in highlighting the reporting of NA-related flushing. The highest discontinuation rates and flushing incidences were seen in three studies using ‘immediate-release’ formulations of NA: Knopp and colleagues (25) (in which ‘special attention was paid to obtaining information on the quality of the flushing symptoms’, perhaps encouraging high report rate); Tsalamandris and colleagues (28) (a comparative trial in support of combination therapy with pravastatin, perhaps again paying particular attention to adverse reactions of NA); and Rindone and Arriola (31) (a cohort study in secondary care where discontinuation rates may be higher as physicians were free to switch patients to alternative therapies for any reason).

Conversely, an unusually low incidence of flushing was reported in the large IMPACT Study with the ‘extended-release’ NA formulation (45). The investigators suggest that the low rate of flushing in their study reflected good patient education before and during the study and the relatively short follow-up (which was, however, no shorter than several other studies in Table 1). The IMPACT Study was designed to identify trends in adherence according to geographical region in the USA and medical subspeciality. And the fact that the discontinuation rate due to flushing in IMPACT was similar to the mean across the other studies excluding IMPACT (6.0 vs. 8.0%) suggests that the difference in flushing incidence reflects differing priorities in data collection rather than an underlying difference in NA tolerability.

![Figure 3](image-url) Timecourse of flushing after administration of NA 500 mg, comparing two ASA doses and placebo (22)
<table>
<thead>
<tr>
<th>Author</th>
<th>Duration</th>
<th>Patients</th>
<th>ASA regimen</th>
<th>NA max. dose (mg)/regimen</th>
<th>Formulation</th>
<th>n</th>
<th>Incidence of flushing (%)</th>
<th>Discontinuation due to flushing (%)</th>
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<td>Knopp et al. (25)</td>
<td>6 months</td>
<td>Hypercholesterolaemia</td>
<td>Regimen not specified</td>
<td>1500–3000</td>
<td>IR</td>
<td>37</td>
<td>100</td>
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<td>ER (Nicobid)</td>
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<td>Hypercholesterolaemia</td>
<td>Regimen not specified</td>
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<td>SR (wax-matrix)</td>
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<td>53</td>
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<td>Dyslipidaemia</td>
<td>ASA 100</td>
<td>100–3000 ± FVS</td>
<td>IR</td>
<td>42</td>
<td>100</td>
<td>&lt;2.1*</td>
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<td>78</td>
<td>31</td>
<td>&lt;5.1*</td>
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<td>Hypercholesterolaemia</td>
<td>ASA EC</td>
<td>1500 then 1000/PVS 20</td>
<td>IR</td>
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<td>(NR)</td>
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<td>34</td>
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<td>Hypercholesterolaemia + diabetes</td>
<td>ASA 325 as needed</td>
<td>100–1500 + PVS</td>
<td>IR</td>
<td>23</td>
<td>(NR)</td>
<td>13.0</td>
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<td>Secondary care cohort</td>
<td>ASA 160 or IBU 200</td>
<td>100–2250</td>
<td>IR</td>
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<td>(NR)</td>
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<td>75</td>
<td>(NR)</td>
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<td>ASA 325 as needed</td>
<td>3000</td>
<td>ER (Niaspan)</td>
<td>517</td>
<td>75</td>
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<td>1500</td>
<td>ER (Niaspan)</td>
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<td>ASA 325 as needed</td>
<td>325–3000 ± statin ± BAS</td>
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<td>PAD</td>
<td>ASA 325 EC</td>
<td>750–3000 ± PVS ± warfarin ± antioxidants</td>
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<td>78</td>
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<td>87</td>
<td>22–68</td>
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<td>Hypercholesterolaemia</td>
<td>ASA 325 as needed</td>
<td>375–3000</td>
<td>ER (Niaspan)</td>
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<td>22–68</td>
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<td>22–68</td>
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<td>ASA 325 as needed</td>
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<td>ER (Niaspan)</td>
<td>87</td>
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<td>9.1</td>
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<td>ER (Niaspan)</td>
<td>97</td>
<td>ca. 67</td>
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<td>Dyslipidaemia</td>
<td>ASA 325 or NSAID</td>
<td>1000, 1500</td>
<td>ER (Niaspan)</td>
<td>97</td>
<td>ca. 67</td>
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<td>ASA 325 as needed</td>
<td>1000, 2000</td>
<td>ER, ER + LVS</td>
<td>104</td>
<td>(NR)</td>
<td>11.5</td>
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<td>ASA 325 as needed</td>
<td>1000, 2000</td>
<td>ER, ER + LVS</td>
<td>104</td>
<td>(NR)</td>
<td>11.5</td>
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<td>Rubenfire et al. (45)</td>
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<td>Dyslipidaemia</td>
<td>ASA or NSAID as needed</td>
<td>1000, 2000</td>
<td>ER, ER + LVS</td>
<td>104</td>
<td>(NR)</td>
<td>11.5</td>
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<td>Dyslipidaemia</td>
<td>ASA 325 as needed</td>
<td>1000, 2000</td>
<td>ER, ER + LVS</td>
<td>104</td>
<td>(NR)</td>
<td>11.5</td>
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<td>Zhao et al. (47)</td>
<td>2 years</td>
<td>Dyslipidaemia and CAD</td>
<td>Regimen not specified</td>
<td>2000</td>
<td>+ SVS</td>
<td>80</td>
<td>30</td>
<td>6.0</td>
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BAS, bile-acid sequestrant; CAD, coronary artery disease; EC, enteric-coated; ER, extended release, also called prolonged release; FVS, fluvastatin; IBU, ibuprofen; IR, immediate release; LVS, lovastatin; NR, not reported; PAD, peripheral arterial disease; PVS, pravastatin; SR, sustained release; SVS, simvastatin. *Quoted discontinuation rate due to all adverse reactions where flushing not specified (25–47).
Studies in People Using ASA as Concomitant Medication

Two NA studies were performed in individuals receiving ASA as part of background therapy.

In a study by Wink and co-workers (48), 50 patients receiving statin therapy were randomised to receive a very low dose of ‘immediate-release’ 100 mg NA or placebo for 3 months. Of the 22 patients receiving NA, 64% had hypertension and 50% had known coronary artery disease. Mean total cholesterol at baseline in this group was 191 mg/dl. The relatively high-risk profile of these patients was reflected in a baseline usage of ASA in 64% of patients in the NA group.

Reported incidence of flushing was low, occurring in 24% of individuals in the NA group. No patients discontinued therapy as a result of NA-related flushing (48). However, the dose of NA used in this study was unusually low (but was nevertheless associated with favourable effects on HDL-cholesterol).

Extensive use of ASA was also reported in the recent Armed Forces Regression Study by Whitney and colleagues (49). This study of 143 people, with low HDL-cholesterol and angiographically confirmed coronary artery disease, compared combination therapy with NA plus gemfibrozil and colestyramine vs. placebo during 30 months. The risk profile and medical history of the patient population (history of angina in 65% of the treatment group and myocardial infarction in 45%; 72% with history of hypertension and more than 85% previous or current smokers) were reflected in use of ASA in 89% of patients in the treatment group.

Unlike the study by Wink and co-workers, dose of ‘immediate-release’ NA was titrated by Whitney and colleagues to a maximum of 3000 mg/day. As might be expected with this higher dose of NA, flushing was reported more frequently, occurring in 91% of patients in the treatment group (49). Flushing was, however, also reported by 16 patients (25%) in the placebo group and only seven patients in the treatment group (10%) were unable to tolerate NA. Drug therapy, including NA, in this study achieved a 46% reduction in triglycerides and a 38% increase in HDL-cholesterol, reflected in a significant 52% reduction (p = 0.039) in a composite clinical endpoint, including hospitalisation for angina, myocardial infarction, transient ischaemic attack or stroke; percutaneous coronary angioplasty, coronary artery bypass graft or death.

The ARBITER 2 Study, reported by Taylor and colleagues, examined the effect of extended-release NA on atherosclerosis progression in patients with known coronary disease (50). Eighty-six per cent of patients in this study were receiving ASA and were advised to continue their existing ASA dose, to be taken concomitantly with NA. Flushing was reported during this 12-month study in 69% of patients treated with NA, and in 13% of those treated with placebo. Only two patients in the NA group withdrew due to adverse drug effects.

In the earlier Familial Atherosclerosis Treatment Study, reported by Brown and colleagues, 56% of 146 men with documented coronary disease used ASA at some time during the 2.5-year study, including 80% of those experiencing a cardiovascular event during the trial (51). Incidence of flushing was not reported, but five of the 36 patients assigned to NA–colestipol therapy withdrew due to NA intolerance.

NA Studies not Reporting Use of ASA

Some 36 studies using NA were identified that, on inspection, did not report the use of ASA in the protocol as a measure to reduce flushing or ASA as background therapy for the study population. As these studies provide no information on the potential value of ASA in countering NA-related flushing, they are not analysed in detail in this report.

However, the nature of the patient populations of a number of these studies, especially those performed in recent years, means that it is extremely likely that ASA therapy was being used to reduce cardiovascular risk in many patients. For example, Ryan and co-workers performed a study in 417 patients, 62% of whom had established coronary heart disease (CHD) and 48% of whom had diabetes (52). Brown and colleagues, in the HDL-Atherosclerosis Treatment Study (HATS), studied 160 patients who had established CHD and advanced coronary stenoses (53). Elam and co-workers, in the Arterial Disease Multiple Intervention Trial (ADMIT), studied 468 patients who had peripheral arterial disease, 41% and 18% of whom had a history of CHD and cerebrovascular accident, respectively (54).

Other Agents

Although most attention has focused on use of ASA in the management of NA-related flushing, data are available on the efficacy of a number of other agents in relation to the NA-related flushing response. Indomethacin, 100 mg, was shown to significantly reduce the incidence of flushing following intravenous NA in patients, and healthy volunteers, undergoing testing for Gilbert’s syndrome (55). It has also been shown that topical application of cream containing ibuprofen, 5%, produced a 74% inhibition of flushing after methyl nicotinate application, compared to control (56).

A number of other topical agents were also evaluated in this study, with marked inhibitory effects also being demonstrated with nilfumic acid, indomethacin and diclofenac.

Studies in vitro and ex vivo by Saareks and colleagues suggest that modulators of the arachidonic acid pathway such as pyridoxine or leukotriene B4 antagonists may have potential to suppress the effect of NA on prostaglandin synthesis (14,57).
DISCUSSION

Flushing after NA administration is an important limitation to the utility of an agent that has clinically important and beneficial effects on lipids and lipoproteins. Significant advances have been made in recent years with newer formulations of NA; for example, the ‘prolonged-release’ NA reduced the incidence of flushing within the first 2 weeks of treatment by more than 50% compared with ‘immediate-release’ NA (33). The incidence of flushing further decreases with continued therapy; in a 96-week study using NA, the incidence of flushing decreased from 1.9 episodes/patient/month during the first 4 weeks to 0.19 episodes/patient/month at the end of the study (32).

There is good supportive evidence for the value of ASA in reducing the severity of NA-related flushing, and the degree to which this is acknowledged is reflected not only in long-standing NCEP recommendations (58) but also in the relatively large number of studies reporting the inclusion of ASA in the treatment regimen and in advice given to patients to take ASA ‘as needed’ to reduce flushing.

Studies in which ASA was used to reduce flushing reported discontinuation rates due to flushing that were much lower than those commonly cited for NA: less than 8% in the studies reviewed here, compared with up to 40% in other published studies using older formulations of NA (Table 2) (59–64).

However, although several studies that did not report the use of ASA were identified, quantitative comparison is unsound because there may be extensive unreported use of ASA in the treatment populations.

While a recommendation to use ASA is supported by both pharmacological evidence and experience from clinical studies, it is more difficult to deduce a relationship between ASA dose and the efficacy in reducing the intensity and/or frequency of flushing. Findings from one small study suggested that a dose as low as 80 mg might be ineffective (49). A subsequent study, however, found that a 160 mg dose was as effective as a 325 mg dose. Meanwhile, most studies using ASA in the protocol used a 325 mg dose (where specified).

The two prospective studies using lower doses (100 and 150 mg) provided no evidence from discontinuation rates that these lower doses of ASA were less effective than the higher 325 mg dose (27,28). Discontinuation rates due to flushing were probably higher in a cohort study using 160 mg ASA, but no details are provided in the report of the study (31).

Nicotinic acid is a highly effective agent in dyslipidaemia management. Its use is well established in guidelines, especially as add-on treatment to statins, for patients with a high CHD risk. However, the main disadvantage of NA remains its common side effect of flushing. Discontinuation rates (flushing-specific where reported) are reduced with the new formulation (18.2% overall in studies using ‘immediate-release’ formulations and 8.3% in studies using ‘extended-release’ formulations). In addition to the advantages offered by new formulations of NA, it is critical to recognise that flushing is a frequent event that can be managed with adequate physician and patient education. Administration guidelines for ‘extended-release’ NA indicate that the impact of flushing can be minimised by careful dose escalation, administering ‘extended-release’ NA at bedtime, administering ASA 30 min before ‘extended-release’ NA and avoiding alcohol or hot drinks near the time of administration (KOS Pharmaceuticals Inc.; US prescribing information on line) (65).

Ultimately, the barrier of flushing can be overcome if the physician is convinced of the significant added value of NA in reducing cardiovascular risk in a given patient. This motivates the physician to invest the necessary time and effort to initiate an appropriate NA formulation and encourage its continued use despite flushing.

Table 2 Representative discontinuation rates from studies using NA in older formulations (59–64)

<table>
<thead>
<tr>
<th>Author</th>
<th>NA dosage (mg)</th>
<th>n</th>
<th>Discontinuation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug</td>
<td>616</td>
<td>3000</td>
<td>11</td>
</tr>
<tr>
<td>Research Group (59)</td>
<td>1000</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>Luria (60)</td>
<td>1500</td>
<td>99</td>
<td>28</td>
</tr>
<tr>
<td>Schectman et al. (61)</td>
<td>4500</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>Illingworth et al. (62)</td>
<td>23</td>
<td>3000</td>
<td>39</td>
</tr>
<tr>
<td>McKenney et al. (63)</td>
<td>1500</td>
<td>44</td>
<td>16</td>
</tr>
</tbody>
</table>

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