REVIEW

Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin

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Niacin (nicotinic acid) is used frequently in the treatment of hypercholesteremia. It is available in both unmodified and time-release preparations. The latter were developed in attempts to minimize the skin-flushing reaction that affects virtually all users and may limit acceptance. Adverse effects on the liver from both unmodified and time-release preparations have been recognized for many years. We reviewed the literature on the hepatic toxicity of both types of niacin preparations. Adverse reactions in six patients resulted from the exclusive use of unmodified niacin and in two patients from the exclusive use of time-release preparations. In 10 additional patients, adverse reactions developed after an abrupt change from unmodified to time-release preparations. Many of these patients were ingesting time-release niacin at doses well above the usual therapeutic doses currently recommended. Signs of liver toxicity developed in less than 7 days in four of these 10 patients. In doses that achieve equivalent reductions in serum lipids, hepatic toxicity occurred more frequently with time-release preparations than with unmodified preparations. An awareness of toxicity associated with ingestion of high doses of time-release niacin preparations is important because of their widespread availability and the potential for self-prescribed, unmonitored use.

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Niacin has been used to lower plasma lipid concentrations for many years. It has been found to be efficacious and generally safe for long-term use. In one clinical trial, niacin treatment reduced the incidence of nonfatal myocardial infarctions [1]. Additionally, all-cause mortality 9 years after the conclusion of the trial was significantly lower in patients who had received nicotinic acid than in those who had received placebo [2]. In 1988, the Expert Panel of the National Cholesterol Education Program provided guidelines for the treatment of high blood cholesterol in adults 20 years of age and older [3]. Dietary therapy was recommended as the primary cholesterol-lowering treatment in most individuals. The Expert Panel further recommended that drug treatment should be considered if low-density lipoprotein (LDL)-cholesterol concentrations exceeded specified values after 6 months of intensive dietary therapy. Bile acid sequestrants and niacin (nicotinic acid; vitamin B_3) were recommended as first-choice drugs for patients without concurrent hypertriglyceridemia. Niacinamide is not therapeutically useful for treatment of hyperlipidemias.

Niacin therapy is generally begun with single doses of 100 to 250 mg/day. Frequency of dose and total daily dose are gradually increased until a first-level therapeutic dose of 1.5 to 2.0 g/day is reached. The dose is increased to 3 g/day (1.0 g three times per day) if the LDL-cholesterol is not lowered sufficiently by 1.5 to 2.0 g/day. Higher daily doses up to 6 g/day may occasionally be used in patients with marked elevations of plasma cholesterol. Since the Recommended Dietary Allowances for niacin as a vitamin are 13 to 19 mg/day for adult men and women aged 19 to 51+ years [4], doses of 2 g/day that are therapeutically useful for lowering serum cholesterol levels are approximately 100-fold higher than amounts of the vitamin required to meet normal adult nutritional needs.

Flushing, which has been recognized for half a century, is the commonest side effect of treatment with niacin and affects almost all patients using even low therapeutic doses of the compound. This side effect frequently limits acceptance, but tolerance to the flushing reaction usually develops over several weeks. Flushing can be significantly reduced in most patients by administration of aspirin

TABLE I

Incidence of Most Frequent Side Effects in a 6-Month Randomized Trial With 3.0 g/Day of Unmodified and Time-Release Preparations of Niacin*

Side Effect	Incidence (%)	
	Unmodified	Time-Release
Flushing	100	82
Diarrhea	22	45†
Nausea	8	38†
Fatigue	3	24†
Vomiting	0	18†
Indigestion	0	12†

*The patient populations consisted of 34 men and three women (unmodified niacin group; Nicolar tablets) and 31 men and three women (time-release niacin group; Nicobid capsules) between 18 and 65 years of age. The average daily dose for patients in the group taking the time-release preparation was decreased to 2.0 g/day after the second month of treatment because of side effects. Adapted from Knopp *et al* [9].
†$p < 0.05$ from other treatment group.

or other nonsteroidal anti-inflammatory agents [3]. Elevations in serum levels of prostaglandin E_2 have been shown to correlate with nicotinic acid-induced flushing, and these levels can be reduced by concomitant administration of aspirin [5]. The flushing reaction may also be partially controlled or reduced by avoiding ingestion of niacin when the stomach is empty and by gradually increasing daily doses during initiation of therapy. Since rapid gastrointestinal absorption of niacin seems to be related to the flushing reaction, time-release preparations have been developed and marketed with the expectation that such formulations would minimize or eliminate this side effect.

Time-release preparations consist of nicotinic acid formulated to provide slow release of the active ingredient. For example, slow-release forms may be very highly compressed tablets containing nicotinic acid, combinations of nicotinic acid in an inert resinous base, or plastic sponge-like matrices filled with nicotinic acid. Another time-release preparation is an ester of pentaerythritol containing four residues of nicotinic acid [5]. Rates of absorption and metabolic transformation and frequency of side effects may vary among different time-release formulations. For example, Figge *et al* [6] found significant differences in cumulative urinary excretion of nicotinic acid and nicotinuric acid in patients following ingestion of 500 mg of either of two time-release preparations.

Liver toxicity is a potentially serious effect of treatment with niacin. Rivin [7] first reported elevated serum transaminase levels in a patient treated with unmodified niacin. Liver toxicity of time-release niacin preparations has also been recognized for many years [8].

Additional cases of adverse hepatic effects of therapy with unmodified and time-release niacin preparations have been reported recently [9–14]. Typically, the patient experiences nausea and vomiting, and, in some cases, is jaundiced. In more severe cases, elevation of serum bilirubin and ammonia concentrations and a prolonged prothrombin time are observed. The most severe cases [10,11,13] have resulted in fulminant hepatic failure and hepatic encephalopathy.

Knopp *et al* [9] conducted a randomized trial of effects of unmodified and time-release forms of niacin in hyperlipidemic patients with no prior histories of diabetes, peptic ulcer, liver disease, or hypersensitivity to niacin. Their report apparently represents the only clinical trial conducted to date that systematically measured therapeutic effectiveness and adverse side effects of these two types of preparations. The frequencies of commonly reported side effects are listed in **Table I.** Adherence to regimens of either unmodified or time-release preparations at a dose of 1.5 g/day for 1 month was excellent [9]. When the dose was raised to 3 g/day, however, side effects were serious enough among users of time-release niacin preparations to necessitate a reduction in average daily intake to 2.0 g daily (64% of the targeted dose). A slight but not statistically significant reduction in flushing was reported among users of the time-release preparation. Frequencies of other reported adverse effects such as nausea, indigestion, diarrhea, vomiting, and fatigue were significantly higher among users of the time-release preparation. Since the patients taking the time-release niacin ingested only two thirds of the targeted dose, it was not possible to make direct comparisons of the therapeutic effectiveness of the two types of preparations. Knopp *et al* [9] concluded that the reductions in LDL-cholesterol observed with both the unmodified and time-release preparations were in approximate proportion to the amounts of compound taken. High-density lipoprotein cholesterol (HDL-C) and HDL_2-C were increased significantly in patients treated with unmodified niacin but were not significantly changed in those taking the time-release preparation [9].

Reports of liver dysfunction associated with ingestion of unmodified niacin exclusively indicate adverse effects after 1 to 18 months (**Table II**). Most patients were taking usual doses of 3 to 4.5 g/day for control of hyperlipidemia. One patient taking niacinamide for schizophrenia (a disorder for which the drug is not useful [15]) increased his dosage to 9 g/day on several occasions and experienced repeated episodes of adverse reactions [16]. Toxicity from a niacin dose of 0.75 g/day for less than 3 months occurred in a man who had attempted suicide by carbon monoxide asphyxiation 3 days

TABLE II

Hepatic Toxicity Associated with Ingestion of Niacin (Nicotinic Acid) and Niacinamide (Nicotinamide) in Unmodified or Time-Release Forms

Form*	Dose (g/day)	Therapy (months)	Patient Age (years)	Patient Sex	Clinical Features	Reference
Unmodified niacin and niacinamide						
NA	3.0	14	23	M	Jaundice; increased AST, alk phos, bilirubin. Normalization within 20 days after cessation of NA.	[7]
NA	3.0	6	58	M	Peripheral edema; increased AST, alk phos; decreased serum albumin; increased SBP retention. Rapid resolution on cessation of NA.	[21]
ND	3.0–9.0	18	35	M	Nausea, vomiting; increased AST, ALT, bilirubin; prolonged PT; liver biopsy: increased portal fibrosis, a number of canalicular bile plugs were observed. Liver chemistries normalized within 3 weeks of cessation of ND. Patient was taking ND for schizophrenia. He had increased his dosage to 9 g/day several days before each of four episodes of nausea and vomiting.	[16]
NA	0.75	<3	69	M	Jaundice that deepened for 3 weeks after cessation of NA; increased ALT, alk phos, bilirubin. Liver biopsy: cholestatic hepatitis with minimal lymphocytic infiltration, increased bile stasis. Jaundice disappeared gradually during subsequent several months. Patient had attempted suicide by carbon monoxide inhalation 3 days prior to start of NA therapy.	[17]
NA	0.9–4.5	6	41	M	Nausea, vomiting, anorexia, weakness, jaundice; increased AST, ALT, alk phos. Rapid resolution following cessation of NA.	[22]
NA + ND	4.5 + 3.0	18			Nausea, vomiting, jaundice; increased AST, ALT, alk phos; prolonged PT. Liver biopsy: focal hepatic fibrosis and lobular collapse, cholestasis with canalicular plugging. Biochemical indices normalized within 1 month after cessation of medication. Patient self-prescribed increasing doses of vitamin B complex for depression.	
NA	3.0	1	46	M	Nausea, vomiting; increased AST, ALT. Serum chemistries normalized within 6 weeks of cessation of NA therapy.	[13]
NA	3.0	2.5			Jaundice; increased AST, ALT, alk phos, bilirubin, ammonia; prolonged PT; hepatic encephalopathy. Encephalopathy resolved in <10 days. Serum chemistries were normal at 4 months.	
Time-release nicotinic acid						
NA	3.0	48	54	M	Edema, ascites, jaundice; increased AST, ALT, alk phos. Liver biopsy: intrahepatic cholestasis with chronic portal inflammation and fibrosis. Resolution within 3 months after cessation of therapy. Patient was ingesting aluminum nicotinate (Nicalex). Longest reported exposure to either type of nicotinic acid before toxicity developed.	[18]
NA	0.5	2	32	M	Abdominal pain, nausea, vomiting, anorexia; elevated AST, ALT, alk phos; fulminant liver failure; hepatic encephalopathy. Encephalopathy resolved within 7 days; complete recovery within 2 months. Patient was taking "super timed-release" tablets for health effects.	[10]

NA = nicotinic acid; ND = nicotinamide; AST (SGOT) = aspartate aminotransferase; ALT (SGPT) = alanine aminotransferase; alk phos = alkaline phosphatase; PT = prothrombin time; SBP = sulfobromophthalein.

*The names of preparations of NA and/or ND taken by patients described in [7,10,13,16,17,21,22] were not reported.

before the start of niacin therapy [17]. Liver damage may have resulted from this prior incident, perhaps potentiating the effects of niacin on the liver.

There are two reports of adverse effects associated with ingestion of time-release niacin exclusively (Table II). One involved a very long-term exposure (48 months) to a dosage of 3 g/day of aluminum nicotinate [18], whereas the other involved a severe adverse response to a dosage of 0.5 g/day for 2 months [10]. The clinical profile in the report of Kohn and Montes [18] suggests that the patient may have been experiencing toxic effects of the time-release preparation well before the diagnosis of niacin toxicity was made.

Cases most useful for evaluating the toxicity of time-release niacin preparations are summarized in **Table III.** A number of adverse reactions have been reported in patients after an abrupt change from

TABLE III

Hepatic Toxicity Associated with Intentional or Inadvertent Changes from Unmodified to Time-Release Niacin (Nicotinic Acid) Preparations

Form*	Dose (g/day)	Therapy (months)	Patient Age (years)	Patient Sex	Clinical Features	Reference
NA or ND†	3.0	19	42	M	Increased SBP retention.	[19]
	3.0	1			Increased SBP retention. Liver biopsy result normal.	
	3.0	11			Mild general malaise; increased SBP retention; increased AST. Liver biopsy: increase in fibrous connective tissue, cirrhosis. Patient had used a time-release preparation of NA (Klestrol B) at 20 months into therapy with resultant increased SBP retention only.	
NA or ND‡	3–4.5	16	46	M	Jaundice; increased SBP retention; increased AST, alk phos. Patient had used a time-release form of NA (Nicospan) for 4 weeks before first abnormal liver function test results. Resolution of jaundice within 4 to 5 days of cessation of treatment. Serum chemistries were normal within 2 months.	[19]
NA or ND§	3–4.5	26	47	M	Nausea, vomiting; increased SBP retention; increased AST, alk phos. Liver biopsy: inflammatory infiltrate around bile ducts, connective tissue proliferation, cholestasis. Patient had two injections of prochlorperazine prior to liver abnormalities. Patient had used a time-release preparation of NA (Nicospan) for 5 weeks before first abnormal liver function test results. Serum chemistries were normal 22 weeks after cessation of therapy.	[19]
NA	3.0	24	56	M	No adverse reactions.	[8]
TR NA-a‖	3.0–1.6	3			Moderate anorexia, nausea, abdominal pain, cramping while taking Gradumet formulation. Dose reduced from 3.0 to 1.6 g/day.	
TR NA-b‖	1.6	4 days			Anorexia, nausea, pain, vomiting, general malaise; jaundice, elevated AST, alk phos while taking Nicospan formulation. Patient received one injection (10 mg) of prochlorperazine. All test results were normal within 8 weeks of discontinuation of therapy.	
NA	3.0	>12	51	M	No adverse effects.	[8]
TR NA	3.0	<7 days			Jaundice, increased SBP retention, increased AST, alk phos; prolonged PT while taking Nicospan formulation. Liver biopsy: marked parenchymal injury, centrolobular bile stasis. Jaundice cleared within 1 week. Serum chemistries were normal within 7 weeks of discontinuation of therapy.	
NA	¶	¶	67	M	Prior toleration of NA for an unspecified interval.	[14]
TR NA	¶	18 days			Gastrointestinal upset, fatigue, increased AST, ALT. Inadvertent change to time-release niacin 18 days before symptoms. Resolution with discontinuation of treatment.	
NA	6	16	44	M	No adverse effects; liver enzymes normal.	[11]
TR NA	6	3 days			Nausea, vomiting, abdominal pain, jaundice, elevated AST, ALT; prolonged PT; increased ammonia; fulminant hepatic failure, hepatic encephalopathy, hepatic necrosis; required liver transplant.	
NA	3–4	5	62	M	Normal liver function indices at 4 months.	[12]
TR NA	4	5 days			Nausea, elevated AST, ALT; serum chemistries returned to normal during 4 weeks following cessation of therapy. Therapy successfully reinstituted with unmodified NA (below).	
NA	4	>6			Normal serum chemistries, asymptomatic.	
TR NA	1.5	5	50	F	Elevated AST after 5 months of treatment with Nicobid.	[12]
	1.5	4			Elevated AST 4 months after reinstitution of therapy with Nicobid.	
	2.0	6			Atypical chest pain; increased AST, ALT, alk phos, bilirubin 6 months after reinstitution of therapy with time-release preparation. Serum chemistries normalized within 6 weeks of discontinuation of therapy with time-release preparation. Therapy successfully reinstituted with unmodified NA (below).	
NA	2.5	10			Normal serum chemistries; asymptomatic.	
NA	0.5	0.5	47	M	Flushing.	[12]
TR NA	2.0	2			Elevated AST, ALT, alk phos 2 months after beginning treatment with Slo-Niacin caplets. Patient returned to use of unmodified preparation.	
NA	4.0	6			Normal serum chemistries.	

NA = nicotinic acid; ND = nicotinamide; AST (SGOT) = aspartate aminotransferase; ALT (SGPT) = alanine aminotransferase; alk phos = alkaline phosphatase; PT = prothrombin time; SBP = sulfobromophthalein; TR = time-release.

*The names of slow-release preparations taken by patients described in [11,14] and in one case reported in [12] were not reported.

†Patient received 3 g NA/day except for Months 8 to 10, during which he received 3 g/day of ND. Patient had occupational exposure to carbon tetrachloride.

‡Patient received 3 to 4.5 g of NA daily except during Months 8 to 10, when he received 4.5 g/day of ND.

§Patient received 3 to 4.5 g/day of NA except during Months 9 to 11, during which he received 4.5 g/day of ND.

‖NA-a and NA-b were two time-release preparations differing in ingredients used to provide slow release.

¶Identity of preparation, dosage, and time were not specified.

unmodified niacin to time-release preparations. In some cases, the change to a time-release preparation was made inadvertently, whereas in others, the change was intentional. In the cases reported by Parsons [19], patients were apparently taking the same daily dosages of the time-release preparations as they had previously been taking of the unmodified niacin. This is also true of the 51-year-old man reported by Christensen *et al* [8], the 44-year-old man reported by Mullin *et al* [11], and the 62-year-old man reported by Henkin *et al* [12]. The dosages reported to cause adverse effects in these patients, as well as in most other cases summarized in Table III, were well above the usual doses of 0.25 to 1.0 g/day of time-release niacin recommended in recent reference manuals [15,20]. There is a six-fold difference in the upper limits of recommended dosages for time-release niacin (1 g/day) and unmodified niacin (6 g/day) [15,20].

The *U.S. Pharmacopeia Drug Information for the Health Care Professional* states that: "(1) niacin (nicotinic acid) tablets or niacin tablets USP: usual adult maintenance dose for antihyperlipidemic effect: 1 g to 2 g three times per day (maximum of 6 g/day); (2) niacin extended-release tablets: usual adult dose for antihyperlipidemic effect: 150 mg to 400 mg two times per day, morning and evening; (3) niacin extended-release capsules: usual adult dose for antihyperlipidemic effect: 125 mg to 500 mg two times per day, morning and evening" [15]. The *Physicians' Desk Reference* recommends 250 mg to 1,000 mg/day for sustained-release niacin preparations with the added comment: "before exceeding usual adult dose, consult a physician" [20].

The onset of toxicity related to a change from unmodified niacin to a time-release preparation was rapid: time to onset was less than 7 days in four of 10 cases reported (Table III). Current information is not sufficient to determine the contribution, if any, of the prior treatment with unmodified niacin to the toxicity observed on changing to a time-release form.

In conclusion, time-release niacin preparations appear to have significantly lower therapeutic indices than unmodified niacin with regard to liver toxicity. In dosages that achieve the same reduction in serum lipids, the likelihood of hepatic toxicity appears to be greater with the sustained-release preparations than with the unmodified form. Both unmodified and time-release preparations are widely available over-the-counter in the United States. An increased awareness of toxicities associated with niacin, especially those associated with effects of ingestion of high doses of time-release preparations, is needed because of the widespread availability of these preparations and the considerable potential for self-prescribed, unmonitored use.

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