

# Co-administration of equimolar doses of betaine may alleviate the hepatotoxic risk associated with niacin therapy

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**Summary** High-dose niacin has versatile and substantial efficacy for the treatment of hyperlipidemias, but its utility is compromised by various side effects, the most serious of which is liver damage. It is proposed that this hepatotoxicity reflects the high demand for methyl groups imposed by niacin catabolism, leading to a reduction in hepatic levels of S-adenosylmethionine (SAM). Depletion of the hepatic SAM pool has likewise been shown to mediate, at least in part, the hepatotoxic effects of ethanol, methotrexate, and niacinamide. If niacin does indeed decrease SAM, a likely consequence would be a counterproductive elevation of plasma homocysteine. Conceivably, methyl group deficiency, by altering membrane properties of skeletal muscle, also contributes to niacin-induced insulin resistance. Concurrent betaine supplementation – preferably administered as a complex with equimolar amounts of niacin – may represent the most cost-effective way to prevent niacin-mediated depletion of SAM and thus avoid hepatotoxicity (and possibly other adverse effects) while controlling homocysteine. Betaine also merits evaluation as an adjuvant to methotrexate and niacinamide therapies. © 2000 Harcourt Publishers Ltd

## NIACIN FOR HYPERLIPIDEMIAS – BENEFITS AND RISKS

High-dose niacin is a venerable and exceptionally effective therapy for hyperlipidemias (1). Like statin drugs, it reduces LDL cholesterol, but has the further advantage of decreasing elevated triglycerides while increasing HDL cholesterol. Niacin can also be used to decrease lipoprotein(a) and increase the size of small LDL particles. When combined with statin drugs or bile acid sequestrants, niacin potentiates the reduction in LDL cholesterol while improving lipid profiles in these other respects (2). A favorable impact of niacin therapy on fibrinolytic balance – reductions in both fibrinogen and plasminogen activator inhibitor-1 activity – has also been reported recently (3,4). A fifteen-year follow-up of participants in the

Coronary Project demonstrated a statistically significant 11% reduction in all-cause mortality in participants who had received niacin therapy (5).

Unfortunately, the feasibility of niacin therapy is compromised by significant side effects (6–10). The annoying flush reaction (attributable to acute dermal release of prostaglandins) is seen in all subjects who use high-dose rapid-acting niacin. The flush reaction can be minimized by use of time-release preparations of niacin, by taking niacin with meals (which slows its absorption), or by taking aspirin prior to the niacin dose. Fortunately, the intensity of the flush reaction tends to diminish with time as the body develops tolerance over weeks of continuing therapy. Gastrointestinal symptoms are not as common, but can be dose-limiting, especially with time-release preparations. High-dose niacin can exacerbate diabetes, gout, and peptic ulcer disease, and is contraindicated in patients suffering from these disorders. But the most potentially serious complication of high-dose niacin therapy is liver damage (7–10), which is seen more frequently in users of time-release niacin (8). Although in most cases this damage appears to be mild and of little evident

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clinical importance, it has the potential to progress to frank hepatic failure if niacin therapy is not discontinued. Because of this risk for liver damage, niacin therapy requires periodic physician monitoring of serum liver enzymes – which makes the therapy more expensive and inconvenient than it otherwise would be. Despite the fact that niacin therapy has been in use for decades, very little effort has been expended to elucidate the molecular basis of its potential hepatotoxicity.

### **DEPLETION OF HEPATIC SAM AS A MECHANISM FOR NIACIN HEPATOTOXICITY**

The catabolic pathways for niacin in humans have been determined (11–13). A portion of ingested niacin is conjugated to glycine, in a process involving nicotinyl-coA as an intermediate, and the resulting conjugate (nicotinuric acid) is excreted in the urine. This metabolic pathway is more prominent when niacin is administered in rapid-acting form rather than in time-release preparations (11). The remaining niacin is used for NAD synthesis; when this NAD is catabolized, most of the released free niacinamide is N-methylated, and a portion of this N-methylnicotinamide is oxidized to form N1-methyl-2-pyridone-5-carboxamide. These are the major end-products of niacin catabolism, and are excreted in the urine. It appears that NAD synthesis is the primary fate of niacin in humans; nicotinuric acid synthesis may only become prominent when high levels of niacin saturate the capacity for NAD production (11).

Since time-release niacin is more hepatotoxic than the rapid-acting form, it seems likely that this hepatotoxicity is mediated by either the synthesis or catabolism of NAD, or by the derived products of these processes. It is immediately apparent that catabolism of NAD places a substantial strain on the methylating capacity of hepatocytes. If we assume that 80% of a 2 gram daily dose of time-release niacin will be methylated, this will require the methyl groups from about 2 grams of methionine (in the form of S-adenosylmethionine). Under ordinary circumstances, the lion's share of the liver's methylating capacity is used for creatine synthesis (14), since creatine turnover (in males) is about 2 grams daily (of which the diet provides a variable quantity, up to 1 gram) (15), it can be estimated that less than 2 grams of methionine are required for daily endogenous creatine production. Thus, the methylation requirements imposed by high daily doses of niacin are large compared to the liver's normal methylating activity. Fortunately, the methionine synthase reaction (in which 5-methyltetrahydrofolate donates a serine-derived methyl group to homocysteine with the assistance of vitamin B12) can 'recycle' methionine so that a limited dietary intake of methionine is often sufficient to support ordinary methylation requirements.

Theoretically, when methyl group demand is high, up-regulated activity of enzymes required for de-novo serine synthesis and folate pool turnover might be expected to maintain adequate methylating capacity; however, it seems likely that at least in some individuals these adaptive mechanisms would function suboptimally. Thus, the additional methyl requirements imposed by high-dose niacin therapy may have the potential to strain the capacity of the methionine synthase reaction, such that the hepatocyte pool of S-adenosylmethionine (SAM) becomes significantly depleted. As a result, other crucial methylation reactions in hepatocytes – such as synthesis of membrane phosphatidylcholine – will be underactive. I postulate that this is the chief metabolic mechanism whereby high-dose niacin therapy evokes hepatotoxicity. Furthermore, inasmuch as S-adenosylmethionine is a potent allosteric activator of the enzyme cystathionine-beta-synthase (16), required for the irreversible disposal of homocysteine, it is reasonable to expect that such therapy will tend to raise serum levels of homocysteine – a phenomenon that presumably would have a countervailing negative impact on the vascular benefits of niacin treatment.

This thesis is consistent with the fact that rapid-acting niacin, which is less prone to damage the liver, is more likely to be excreted as nicotinuric acid than is time-release niacin. Also consistent is the fact that niacinamide, which lacks the hypolipidemic and flush-inducing effects of niacin, but which requires methylation for its metabolism, can induce hepatic damage when administered in high doses (17–19). In rats consuming choline-deficient diets, high-dose niacinamide has been reported to diminish liver SAM levels, induce fatty liver and DNA single-strand breaks, and depress creatine synthesis (20–22), these effects are alleviated by administration of methyl donors. The absence of comparable reports concerning niacin may reflect the fact that, in rats, the predominant metabolite of high-dose niacin is nicotinuric acid (23) – a fact that may also account for the lack of evidence that niacin can be hepatotoxic in rats. Swendseid and colleagues recognized the possible relevance of their rodent niacinamide research to niacin therapy when, citing the potential toxicity of high-dose nicotinic acid, they advised that 'careful consideration should be given to the state of methyl pool of such patients...(19)'

The fact that methyl donors (namely choline and methionine) are reported to correct niacinamide hepatotoxicity in rats (21), can be viewed as confirmatory of the role of methyl depletion in niacin toxicity. While one could postulate that some other factor associated with accelerated NAD production was responsible for niacin/niacinamide toxicity – for example, depletion of the hepatic pool of phosphoribosylpyrophosphate or of ATP (24) – such a mechanism would appear inconsistent

with the ameliorative impact of lipotropes in niacin-amide-treated rats.

With respect to the effect of niacin therapy on homocysteine levels, Basu and Mann have recently reported that plasma levels of free homocysteine double in rats receiving 0.4% dietary niacin (25), no comparable clinical reports are currently available. Curiously, plasma pyridoxal phosphate was decreased in the niacin-treated rats and supplemental pyridoxine was shown to alleviate the homocysteine elevation, raising the possibility that, at least in rats, niacin can decrease hepatic pyridoxal phosphate levels.

The hepatotoxicities of ethanol abuse, as well as of methotrexate, appear to be traceable, at least in part, to depletion of the hepatocyte SAM pool. With respect to ethanol, this depletion results from inhibition of methionine synthase (26). Methotrexate likewise reduces the effective activity of this enzyme, but by an indirect mechanism: it impedes production of 5-methyltetrahydrofolate by trapping much of the folate pool as dihydrofolate (27). (Methotrexate is a potent dihydrofolate reductase inhibitor.) Fortunately, the liver and kidneys have an alternative means of converting homocysteine to methionine; the enzyme betaine-homocysteine methyltransferase (BHMT) – as its name implies – transfers a methyl group from the choline metabolite betaine to homocysteine (28). Inclusion of adequate amounts of betaine in rodent diets has been shown to prevent and even reverse the hepatic steatosis induced by ethanol (29,30), while choline (converted to betaine by choline oxidase) and methionine supplements prevent methotrexate-induced hepatic steatosis in rats, without lessening methotrexate's cytostatic activity (31–33). Oral administration of SAM (which can be absorbed intact and taken up by tissues, including the liver) has been shown to protect baboons from ethanol-induced steatosis and necrosis (34). (Unfortunately, the excessive free radical generation associated with ethanol abuse has other hepatotoxic consequences – such as, in the long term, cirrhosis – that are less responsive to lipotrope supplementation (35)). It has been suggested that diminished hepatocyte production of phosphatidylcholine, leading to a disruption of membrane function, is responsible for the development of fatty liver in alcoholics and during methotrexate therapy (29). Whether or not this view is correct, the efficacy of lipotropes in these syndromes clearly points to depletion of hepatocyte SAM as the underlying pathogenic mechanism.

### **BETAINE MAY PREVENT NIACIN HEPATOTOXICITY**

The likelihood that the hepatic SAM pool is likewise depleted during high-dose niacin therapy prompts the

speculation that concurrent supplementation with adequate amounts of betaine would prevent the hepatotoxicity of niacin. Ideally, equimolar amounts of betaine could be administered, such that the additional methylation requirement imposed by the niacin could be entirely met by the co-administered betaine (assuming that the hepatic activity of betaine-homocysteine methyltransferase is adequate). Thus, a 1:1 complex of betaine and niacin would be an appropriate pharmaceutical agent. Co-supplementation with folic acid (to boost the capacity of methionine synthase) would also seem advisable. Creatine supplementation might offer an additional means of relieving the strain on the hepatic SAM pool, since dietary creatine has the potential to suppress endogenous creatine synthesis (via transcriptional repression of the rate-limiting enzyme, arginine-glycine transamidase) (36,37).

Although supplements of methionine or SAM presumably could be used to increase the hepatic SAM pool, this strategy would have the disadvantages of increasing daily homocysteine production and of promoting calciuria (38). SAM has the further drawback that it is very expensive. (However, in syndromes mediated by oxidative damage, SAM has the advantage of increasing hepatic glutathione levels) (34). With respect to choline, it is a poor source of labile methyl groups in humans owing to the fact that human hepatic choline oxidase activity is very low compared to that found in rodents (39) (in which choline is an effective lipotrope). Thus, while supplemental choline may aid phosphatidylcholine synthesis by the salvage pathway, it could not be expected to correct a deficit of SAM.

The impact of supplemental betaine on hepatic SAM levels in rats is rather extraordinary, in part because such supplementation has an inductive effect on BHMT activity (29,30). In rats not consuming alcohol, 0.5% dietary betaine was shown to double hepatic SAM; in alcohol-fed rats, betaine quadrupled SAM levels (29,30). (The greater response to betaine in the context of ethanol ingestion reflects ethanol-mediated induction of BHMT.) No comparable clinical data are available, and indeed few published clinical studies have assessed the physiological impact of betaine administration. However, significant BHMT activity has been demonstrated in human liver (40,41), and the efficacy of betaine therapy in homocystinuria resistant to pyridoxine and folate clearly demonstrates that betaine can be an effective source of methyl groups in humans (42,43). In addition, three German clinical groups during the 1970s published favorable evaluations of betaine citrate (5 g b.i.d.) as a treatment for various hepatopathies associated with steatosis (not including niacin toxicity); this therapy appeared to ameliorate liver histology, and in some instances improved serum parameters of liver function,

without any evident side effects (44–46). Of related interest are two recent reports that, in rats, betaine is both protective and therapeutic in carbon tetrachloride-induced liver injury (47,48).

Whether betaine supplementation per se would influence serum lipids in humans – or influence the efficacy of niacin in this regard – is unclear. It is interesting to note, however, a Russian-language study concluding that dietary betaine lowers serum lipids and prevents atherosclerosis in cholesterol-fed rabbits (49). It seems unlikely that methyl group depletion is crucial to niacin's hypolipidemic activity – niacinamide, which is not hypolipidemic, requires at least as much methylation for its metabolism as does niacin.

Chronic high-dose intakes of both niacin and niacinamide have the potential to provoke insulin resistance (50–52), thus, many authorities consider niacin contraindicated for diabetics (53). Even in non-diabetics, it seems likely that an adverse impact of niacin on insulin sensitivity – like the postulated effect on homocysteine – could lessen the net cardiovascular protection afforded. The mechanistic basis of this effect is not known; since it is evoked by both niacin and niacinamide, we can once again conclude that synthesis or catabolism of NAD is responsible. Inasmuch as modulation of membrane structure can regulate the number, affinity, and post-binding activity of insulin receptors – greater unsaturation of membrane lipids and greater membrane fluidity being associated with more efficient insulin action (54–57) – and phosphatidylcholine synthesis is reported to increase membrane fluidity (58), it may be credible to speculate that a deficit of methyl group availability in skeletal muscle contributes to the insulin resistance associated with niacin/niacinamide therapy. In rats, choline deficiency is associated with a marked reduction of insulin receptor expression in hepatocytes – although these receptors have a higher affinity for insulin (59). Such a mechanism would be consistent with the fact that many days of niacin therapy are required to induce insulin resistance – whereas the rapid-acting antilipolytic action of niacin (and of its analogue acipimox) is favorable to insulin function (50,60–62).

The basis of the gastrointestinal upset often seen with time-release niacin therapy – which frequently is dose-limiting – is not known, but some authorities believe that it is somehow reflective of liver damage (63). If concurrent betaine supplementation alleviated the GI side effects (as well as protecting the liver), it might be feasible to administer higher doses of time-release niacin. The hypolipidemic response to niacin is dose-dependent within the ordinary therapeutic range; most practitioners currently recommend no more than 1.5 g of time-release niacin daily, whereas the common dose of rapid-acting niacin is at least 3 g per day. The clinical benefits

observed at the 3 g dose are decidedly more impressive than those achievable with 1.5 g (64).

One side effect of niacin not likely to respond to betaine is hyperuricemia. This presumably is reflective of increased synthesis and subsequent catabolism of NAD.

The considerations cited above likewise imply that betaine should be administered in conjunction with methotrexate therapy – a possibility suggested by Barak and Tuma fifteen years ago (27). Although methotrexate is often the most effective agent for treating severe rheumatoid arthritis, hepatotoxicity is a frequent complication of long-term methotrexate therapy, and can force discontinuation of this drug (65–67). Nonetheless, one searches the medical literature in vain for any indication that betaine has been studied as an adjuvant to methotrexate therapy. In light of increasing clinical use of high-dose niacinamide for prevention of autoimmune diabetes (68) or treatment of osteoarthritis (69), adjunctive use of betaine with nicotinamide therapy would also appear to be prudent. The previous use of betaine in alcoholic steatosis has been cited above.

Betaine, lacking major pharmaceutical sponsorship, has never received adequate clinical evaluation as an hepatoprotective strategy. (In this respect, it is analogous to soy phosphatidylcholine and the antioxidant flavonoid silymarin – natural hepatoprotective agents used for decades in German clinical practice, yet almost totally neglected in North America.) The relative disinterest in betaine may also reflect the fact that past disappointing clinical experience with choline supplementation in liver disorders led physicians to conclude that 'lipotropes' were not clinically useful. In fact, choline is a very poor methyl donor in humans (unlike rats), whereas betaine appears to be quite efficient in this regard.

Whether or not the speculations offered here prove valid, this essay will have served its purpose if it underlines the desirability of clarifying the mechanisms responsible for the adverse effects of niacin. Such an understanding may enable us to devise countermeasures that could render niacin safer, better tolerated, and possibly more effective for promoting vascular health. In light of the exceptional versatility and potency of this agent with respect to beneficial modulation of many cardiovascular risk factors – and its proven positive impact on mortality – significant improvements in the feasibility of high-dose niacin therapy could be of great practical importance.

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