Fibrates plus betaine: a winning combination?

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Abstract

Because most of the cardiac risk remains despite successful statin therapy there has been renewed interest in fibrate therapy for persisting hyperlipidaemia. Fibrate therapy lowers triglycerides but causes the urinary loss of betaine, which is an essential metabolite that is involved in osmoregulation, in methyl group metabolism, and which also affects lipid partitioning in the body. Loss of betaine is associated with an elevation of homocysteine and may compromise the potential benefits of fibrate therapy. However, betaine deficiency could be easily and inexpensively corrected by concurrent betaine supplementation. Clinical trials of combinations of betaine and fibrate, to complement statin therapy, are needed to determine the value of these agents in reducing the residual cardiovascular disease risk.

In a 2007 viewpoint article in this Journal, Benatar and Stewart\(^1\) posed the question “Is it time to stop treating dyslipidaemia with fibrates?” Their main points were that the success of statin therapy for dyslipidaemia made fibrates redundant, and that there was only equivocal evidence for decreased mortality with fibrate therapy.

Although they did not question the safety of fibrates, others have; this safety has been reviewed and affirmed\(^2,3\) and the case made for the use of fibrates in conjunction with statins, especially for the treatment of combined dyslipidaemia in patients with the metabolic syndrome or Type 2 diabetes, elevated plasma triglycerides and low HDL-cholesterol.\(^4-8\)

Statins are well-known to be highly effective, but despite optimal treatment with statins and while achieving LDL-cholesterol treatment goals, 65–75% of the cardiovascular disease risk persists.\(^8,9\) It is now accepted that fibrates reduce the risk in patients with persistent elevated triglyceride and low HDL-cholesterol which persist even with high doses of statins.\(^4,6,9\) Prospective studies to quantify the clinical value of these agents are still in progress.

One of the concerns raised about fibrate therapy is the apparent effect on renal function, and in particular the elevation of plasma homocysteine. The commonly observed rise in plasma creatinine and homocysteine has been interpreted to indicate the apparent impairment of renal function, although these changes may not be associated with a change in the glomerular filtration rate.\(^10\)

In the FIELD study (on patients with Type 2 diabetes) fenofibrate was found to reduce the incidence of renal complications,\(^11\) and fibrates decrease microalbuminuria.\(^12\) Nevertheless the elevation in homocysteine has been suggested as a limitation on the effectiveness of fibrates\(^13\) although the implied causal connection has been questioned.\(^14\)
We have shown that the elevation of homocysteine by bezafibrate is associated with a greatly increased excretion of betaine in the urine. A probable primary renal effect of fibrates is to increase betaine excretion. The fractional clearance of betaine in these patients is often in excess of 100%, implying an active process, and this contrasts with normal betaine excretion which is minimal even after a betaine load (< 2% of dose).

It is likely that the effect on betaine excretion is particularly pronounced in patients with dyslipidaemia or other features of the metabolic syndrome, many of whom may lose excessive betaine without drug treatment, and since this population is the one that is most likely to be prescribed fibrates, it is not surprising that New Zealand patients being treated with bezafibrate are losing so much betaine. Although betaine loss from fibrates is variable the daily loss through the urine exceeds the normal dietary intake of betaine in some patients; the median intake of the New Zealand population is about 220 mg/day.

Betaine is probably the most important osmolyte used by tissues for cell volume regulation, and additionally it functions as a store of methyl groups which are needed for the synthesis of creatine phosphate, phospholipids and for the epigenetic control of gene expression. Excessive betaine loss means that more choline must be oxidized to betaine to correct the betaine deficit, thus placing stress on the supply of choline, which in itself is an essential nutrient with many important biological functions.

Betaine can be easily replaced by supplementation. It is a natural by-product of the sugar beet industry, and long-term betaine supplementation is safe and socially acceptable. Health food shops often market betaine, also called “trimethylglycine” (TMG), as a nutritional supplement with extravagant claims for its benefits in a wide range of diseases and although most of these have not been substantiated by controlled trials, there are good grounds for believing that the supply of betaine is relevant to health.

Betaine is widely used in the animal industries as a long-term additive to animal feeds because this decreases body fat and increases the proportion of lean meat. Comparable long-term supplementation data is not available for any human population, but there is cross-sectional evidence that plasma betaine negatively correlates with important lipid cardiovascular risk factors such as plasma triglycerides, percent body fat and especially non-HDL cholesterol.

Betaine appears to affect the partitioning of lipids between tissues and blood, and limitations in the supply of betaine are probably a feature of the metabolic syndrome. It is also well-established that modest betaine supplementation lowers plasma homocysteine in humans. The betaine supply is the main determinant of non-fasting homocysteine, and we believe that the loss caused by fibrates is the main reason why fibrate therapy is associated with elevations in plasma homocysteine.

The interaction between betaine and lipids means that the loss of betaine induces a betaine deficiency which will also compromise the effectiveness of the fibrate in improving the lipid profile. Therefore, we conclude that fibrate therapy combined with betaine supplementation should be an attractive therapeutic option.

The level of supplementation that is added to pig and poultry feed corresponds to about 2 gm betaine a day in a human population, or about ten times the median daily
New Zealand intake. Although the dietary betaine intake can be raised by increasing the consumption of whole wheat products and high betaine vegetables of the beet family, long-term intakes of more than about 850 mg/day cannot be achieved by dietary modification alone (Elmslie, unpublished data).

Large increases in dietary betaine intake are likely to be associated with substantial increases in total energy intakes, but we have shown that dietary betaine and betaine supplied in the form of supplements have similar effects.\(^\text{20}\) Much higher levels of supplementation than those proposed have been used in human populations without ill effects.\(^\text{16,19}\) Such modest supplementation would be easy to achieve, and is close to that which has been shown recently to improve athletic performance.\(^\text{28,29}\) The cost of supplementation would be less than $NZ0.50 per day. This level of supplementation may be beneficial by itself, but if combined with fibrate it would be expected to completely compensate for the increased betaine loss.

A predicted marker of compensation should be lowered plasma homocysteine, which in many of these patients is presumed to be a marker of betaine deficiency. This should remove one of the concerns about using fibrates, and could be recommended on the basis of present evidence, however there will still be a need for prospective studies to see if the combination of fibrate and betaine delivers the long-term health outcomes that fibrate treatment would be expected to achieve, but without the equivocation in the results of previous trials. The combination should offer benefits that are complementary to those of statins, and answer the question posed in 2007 by Benatar and Stewart.\(^\text{1}\)

**Competing interests:** None.

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