Folic Acid Supplementation and Riboflavin Status

To the Editor:

Flour in the US is fortified with folic acid and riboflavin. Folic acid reduces mean plasma total homocysteine (tHcy) concentration (1). Riboflavin has been associated with reduced tHcy in homozygotes for the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism (2).

In a study that investigated the effect of riboflavin status on the tHcy-lowering response of folate interventions, Moat el al. (3) reported that riboflavin status is compromised after folic acid supplementation. Subjects were assigned to three interventions (each lasting 4 months) using a crossover design: (a) usual diet but avoiding folic acid-fortified foods, plus a daily placebo tablet; (b) usual diet plus additional folic-acid-fortified and folate-rich foods to achieve at least 400 µg of folic acid/day; (c) usual diet but avoiding folic-acid-fortified foods, plus a folic acid supplement of 400 µg/day.

Moat et al. (3) reported that suboptimal riboflavin status [erythrocyte glutathione reductase activation coefficient (EGRAC) ≥1.4] increased from 52% at baseline to 62% after intervention 3. The authors suggested that this was attributable to supplementation with folic acid and proposed two possible mechanisms in which circulating flavins would be reduced as a consequence of the effect of enhanced folate status on MTHFR activity. However, their data show that circulating flavins remained similar to baseline levels following intervention 3.

Riboflavin status may have been affected by the study design. As the authors (3) pointed out, avoiding folic-acid-fortified foods in interventions 1 and 3 also implied a reduction in riboflavin intake because the two vitamins are often present together in fortified foods. Thus, for 8 of the 12 study months, volunteers had reduced riboflavin intake. Because there was no washout period between interventions, this implied up to 8 consecutive months of reduced riboflavin intake in 84 subjects (4). Because 52% of the population already had suboptimal riboflavin status at baseline, it is not surprising that this percentage increased after the dietary interventions. The authors (3) defined suboptimal riboflavin status as EGRAC ≥1.4, but previous studies have defined it as EGRAC ≥1.2 (5). Therefore, by other standards, suboptimal riboflavin status at baseline was actually higher.

The absence of a washout period between interventions may also explain the increase in the proportion of individuals with EGRAC ≥1.4 after intervention 3. Minimizing the repetition of intervention sequence by assigning subjects to 1 of 6 possible patterns may have reduced the carryover effect in plasma determinations. However, it would have been inadequate for the erythrocyte variables on which the authors (3) based their conclusion with respect to riboflavin status. Also, the effects of each intervention should have been evaluated by comparisons with measurements at the beginning of each intervention. Comparison with baseline measurements inevitably consisted of an accumulative reduction in riboflavin status from baseline, before beginning intervention 3 in at least half of the subjects. To determine whether folic acid supplementation negatively affects riboflavin status, riboflavin intake should have been identical in all three intervention groups.

Moat et al. (3) reported that riboflavin status was negatively associated with EGRAC, which, in turn, was significantly negatively associated with tHcy concentrations. N Engl J Med 1999;340: 1449–54.

References
otide showed a relationship with dietary riboflavin, neither were they related to EGRAC or plasma riboflavin. This supports the use of EGRAC, and, to a lesser extent, plasma riboflavin, as a marker of riboflavin status that reflects dietary intake.

We do not agree with the suggestion that the improvement in folate status in the folate-rich diet should have compromised riboflavin status, as it did in the folic acid supplementation period, because riboflavin intake after this intervention increased significantly from 1.45 ± 0.51 mg/day at baseline to 1.85 ± 0.61 mg/day (P < 0.001). This is to be expected because the folate-rich cereals consumed are also good sources of riboflavin. We do, however, accept that a decrease in riboflavin intake might have contributed to the observed effect of folate supplementation on measures of riboflavin status.

The study design incorporated 4-month intervention periods without any washout period. Subjects were considered to have reached a “steady state” by the end of each intervention; a comparison was made between measurements at the end of each intervention; a comparison with baseline was also made before any intervention. Justification for this design was established on the basis of known characteristics of erythrocyte turnover, which is ~120 days. Concerns in this regard are fewer for riboflavin, which, unlike folates, readily enters circulating erythrocytes from the plasma. For this reason, and as has been known for many years, EGRAC is sensitive in the short term to dietary intake of riboflavin (4).

We do not accept the suggestion that we have underestimated the prevalence of riboflavin deficiency. The most common measure of riboflavin status in current use is EGRAC. It is accepted that there is a discrepancy between estimates of riboflavin deficiency through the use of EGRAC and estimates made from dietary intakes, such as to suggest either an overestimate of bioavailability or an inappropriately low EGRAC threshold for normality. After using an established analytical method over many years, it is our experience, and that of others, that a cutoff value >1.4 more adequately reflects the distribution of values in a human population and has more functional relevance than a lower cutoff value (5–7).

References

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Sample Preparation in Patients Receiving Uric Acid Oxidase (Rasburicase) Therapy

To the Editor:

With the advances in medicine and the development of newer therapeutic agents, the laboratory needs to be constantly aware of the potential analytical interferences from these medications. Here we demonstrate a potential analytical interference with a case report of a patient who received the recombinant uric acid oxidase Rasburicase (Sanofi-Synthelabo) and the sample handling requirements for uric acid analysis. Rasburicase is a potent uricolytic agent that catalyzes the enzymatic oxidation of uric acid to allantoin, a water soluble metabolite that is readily excreted by the kidney (1). It is used in the treatment and prevention of hyperuricemia, predominantly in patients with hematologic malignancies (1–5). The half-life of Rasburicase is estimated to be between 16 and 22 h (2).

A 28-year-old man presented with ascites to the emergency department at Sir Charles Gairdner Hospital, a tertiary teaching hospital in Western Australia. The patient was subsequently diagnosed with B-cell non-Hodgkin lymphoma 7 days postadmission. The day before commencement of the patient’s scheduled chemotherapy (day 8 of admission), he developed tumor lysis syndrome. The patient