Short-term oral cobalamin therapy for food-related cobalamin malabsorption

TO THE EDITOR: Oral cobalamin (vitamin B₁₂) therapy may be effective for treating patients with cobalamin deficiency, especially those with food–cobalamin malabsorption (FCM).² We have established that 3 months of oral cobalamin therapy is beneficial.² To date, however, the duration of treatment has not been determined.³

We report preliminary results of an open-label, non–placebo-controlled study on 30 patients with established cobalamin deficiency (serum vitamin B₁₂ <200 pg/mL ± homocysteine >13 µmol/L) related to FCM⁴ who received between 250 and 1000 µg of oral crystalline cyanocobalamin per day for at least 1 month.

**Methods.** All patients were white (mean age 72 ± 13 y); 20 were women. Clinical findings included alteration of cognitive function (impaired concentration, memory loss, disorientation) (n = 9), sensitive peripheral neuropathy (n = 7), and ischemic stroke (n = 2). The mean pretreatment vitamin B₁₂ and total homocysteine levels were 135 ± 32 pg/dL (range 82–192) and 20.2 ± 4.6 µmol/L (range 14–35), respectively (Table 1). All patients met the criteria for cobalamin deficiency related to FCM. No serum antibodies to intrinsic factor were detected. Schilling’s test results were normal in 10 of 10 patients who were tested (mean ± SD 57Co/58Co ratio 0.95 ± 0.1). Two patients also had mild deficiency due to low vitamin B₁₂ intake.

All the patients were treated with oral crystalline cyanocobalamin for >1 month. Oral cobalamin 250–1000 µg/d was administered. Compliance with therapy was good and no adverse events were reported.

**Results.** Response to treatment is indicated in Table 1. During the first month of treatment, 87% of the patients achieved normal serum cobalamin levels; all had increased serum cobalamin levels (mean 167 pg/dL; p < 0.001 compared with baseline), evidence of medullar regeneration, and corrected initial macrocytosis. Anemia was corrected in 54%. All patients had increased hemoglobin levels (mean 0.6 g/dL), reticulocyte count (mean 35 × 10³/mm³), and decreased erythrocyte cell volume (mean 3 fl) (all p < 0.05).

**Discussion.** These findings suggest that patients with cobalamin deficiency related to FCM promptly benefit from oral crystalline cyanocobalamin. In fact, during the first month of therapy, most patients had significant improvement in serum cobalamin levels as well as in blood cell counts. These results are consistent with those observed in larger studies that used long-term (3–6 mo) or higher doses (>2000 µg/d) parenteral cyanocobalamin.²⁴ We observed a dose–response effect of oral cyanocobalamin treatment.

Limitations of our study include the small population and lack of a control group. However, because of the apparent effectiveness of oral therapy and its possible benefits compared with intramuscular treatment (e.g., better compliance, lower cost), further studies with larger sample sizes that use different cyanocobalamin doses and duration are warranted.

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<table>
<thead>
<tr>
<th>Table 1. Pre- and Posttreatment Laboratory Values</th>
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<td><strong>Group</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>A (n = 16)</td>
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<tr>
<td>B (n = 8)</td>
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<tr>
<td>C (n = 6)</td>
</tr>
<tr>
<td>All patients (n = 30)</td>
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</table>

*MECV = mean erythrocyte corpuscular volume; ND = not determined.
*Mean po delivery dose.
*Complete data available for 20 patients.
*p < 0.05.
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REFERENCES

Commonly overlooked sources of vitamin K

TO THE EDITOR: An active 51-year-old woman was exhibiting what appeared to be warfarin resistance, requiring escalating doses of the drug to achieve a therapeutic international normalized ratio (INR). The patient had been stable on warfarin 5 mg/d, but eventually needed 7.5 alternating with 10 mg/d of warfarin to maintain a therapeutic INR. Interestingly, this change occurred somewhat abruptly during the spring and summer. Further investigation revealed that she had increased her exercise and was receiving a significant amount of vitamin K from Luna nutrition bars that she was eating on a regular basis, a sports bar marketed for active women to enhance exercise recovery. Upon discontinuation of these supplements, the patient’s warfarin requirements returned to the previous dose of 5 mg/d.

This reaction led us to examine the vitamin K content of other health and sports bars and some other common supplements. We found that many of them contain significant amounts of vitamin K. For example, Viactiv soft calcium chews, labeled as “a unique blend of vitamins D & K,” contain 40 µg of vitamin K in each chew. Since the recommended dose for a postmenopausal woman is 3 chews daily, an individual taking the recommended amount of this supplement will receive 120 µg of vitamin K intake (roughly equivalent to 1/2 cup broccoli). Likewise, 8 fluid ounces of Boost or Ensure nutritional supplement will provide 30 µg. Some energy/protein bars such as Balance or Clif bars may deliver as much as 40 µg of vitamin K per bar, while each Luna bar contains up to 65 µg. The recommended daily allowance of vitamin K, based on a 2000-calorie daily diet, is 60–65 µg for women or 70–80 µg for men. This recommended daily allowance is met or exceeded by some available supplements and health bars.

It is important to note that not all sports bars contain vitamin K. Some, such as Met-Rx, Power Bars, and Power Harvest Bars, do not include vitamin K. Nevertheless, as the use of nutritional supplements continues to grow across all age groups, practitioners who monitor anticoagulation therapy must be aware of the impact that these products may have on their patients. While patients receiving anticoagulation are routinely encouraged to maintain a stable diet low in vitamin K, they are rarely counseled about significant nontraditional sources of vitamin K they may unknowingly ingest.

We recommend that, as part of their routine warfarin education, clinicians also advise their patients that many of these products are significant sources of vitamin K, and periods of increased intake may result in unstable INR values. Furthermore, when a patient with a previously stable INR appears to require escalating doses of warfarin, clinicians should remember to inquire about intake of nutritional supplements and/or health or sports bars in addition to their routine questions about recent dietary changes.

Ballism associated with bupropion use

TO THE EDITOR: In December 1999, the Netherlands was the first country in Europe to grant a marketing authorization for bupropion (Zyban) as an aid in smoking cessation. In the US, bupropion has also been approved as an antidepressant (Wellbutrin). It is chemically and pharmacologically unrelated to other marketed antidepressants. Bupropion selectively inhibits the reuptake of norepinephrine and dopamine, 2 monoamines. It has minimal effects on the reuptake of serotonin and no anticholinergic properties or effects on monoamine oxidase-A- and B-activity.

Recently, the Netherlands Pharmacovigilance Centre received a report concerning an extrapyramidal disorder possibly related to the use of bupropion.

Case Report. A 42-year-old white woman used bupropion in the recommend- ed dose of 150 mg once daily, increased to 150 mg twice a day on the fourth day. Eight days after initiation of therapy, she suddenly developed an involuntary urge to move: she made gross flexion movements with her torso (Salama) and slapping moves with her arms and, in a lesser degree, with her legs. The movements occurred in short attacks of 5-10 seconds, 10–15 times each hour, and were diagnosed as ballism. During these attacks, she was conscious and had no cognitive disturbances. There was no rigidity, no cogwheel phenomenon, and no hypertonia of the extremities. Additional neurologic examination revealed no abnormalities. Additional investigations (hematologic and chemical examination of blood, computed tomography scan of the brain, electroencephalogram) revealed no abnormalities. Since the movement disorder was thought to be related to the use of bupropion, therapy was discontinued. Treatment with haloperidol 5 mg twice a day and oxazepam 10 mg 3 times a day was initiated, after which the extrapyramidal symptoms diminished.

The patient had no history of neurologic disorders besides migraine without aura, and she used no concomitant medication other than sumatriptan; she took the last sumatriptan tablet 4 days prior to the onset of symptoms. As far as we know, sumatriptan (5-HT1-receptor agonists are not known to induce extrapyramidal disord-

Discussion. According to the Naranjo probability scale, this adverse reaction can be classified as probable. The fact that the movement disorder diminished after discontinuation of bupropion and no new episodes have occurred since then supports a causal relationship between bupropi-
on and the extrapyramidal symptoms. Moreover, related extrapyramidal disorders such as acute dyskinesia can be explained from the dopaminergic activity of bupropion. So far, 4 cases of extrapyramidal disorders associated with the use of bupropion have been published: orofacial dyskinesia and tremor in a 70-year-old woman, retropulsion in 2 geriatric patients (aged 85 and 72 y), and rigidity of the trunk and extremities, amnnesia, and roving eye movements in a 60-year-old man. All patients used bupropion as an antidepressant.

The ability of other dopaminergic drugs such as levodopa and bromocriptine to induce acute dyskinesia is substantiated in the literature. Extrapyramidal disorders are described in relation to amphetamines and other central nervous system stimulants, but it is unclear whether the structural relationship between bupropion and amphetamines contributes to the occurrence of dyskinesia. This case report shows that acute dyskinesia due to the use of bupropion can manifest itself as ballism, even at low doses.

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REFERENCES

Slowing the progression of renal disease in patients with diabetes mellitus

TO THE EDITOR: Since publication of the review entitled “Slowing the Progression of Renal Disease in Diabetic Patients,” 3 long-term studies have been published that demonstrate that the angiotensin–receptor blockers (ARBs) decrease urinary albumin excretion (UAE) in patients with type 2 diabetes mellitus. Brenner et al.2 evaluated the effects of losartan on renal and cardiovascular outcomes in 1513 type 2 diabetics with nephropathy. The primary composite endpoint of a doubling of the serum creatinine concentration, endstage renal disease, or death occurred in 43.5% (327) of patients treated with losartan, compared with 47.1% (359) of patients in the placebo treatment arm. Losartan also decreased the risk of endstage renal disease by 28% (p = 0.002).

Lewis et al.3 randomized 1715 hypertensive diabetic patients with nephropathy to 1 of 3 treatment arms: irbesartan,amlodipine, or placebo. Patients treated with irbesartan had a risk of reaching the primary point that was 20% lower than those in the placebo treatment arm (p = 0.02).

and 23% lower than those in the amlodipine treatment arm (p = 0.006). Patients in the amlodipine group had poorer renal outcomes when compared with those taking irbesartan, although there was equal control of blood pressure in both groups. The MARVEL (Microalbuminuria Reduction with Valsartan) study4 compared the effectiveness of valsartan with that of the calcium-channel blocker amlodipine in the reduction of UAE in 332 patients with type 2 diabetes mellitus and evidence of microalbuminuria. At the end of the 24-week study period, valsartan had a UAE reduction of 56% (95% CI 49.6% to 63.0%) from baseline that was a 44% reduction in UAE. Treatment with amlodipine resulted in a 92% (95% CI 81.7% to 103.7%) baseline reduction of UAE, an 8% reduction in UAE. No significant differences in blood pressure control between the groups were reported.

ARBs may play a role in attenuating the progression of diabetic nephropathy by reducing systemic blood pressure and slowing UAE. The American Diabetes Association (ADA)5 now recommends ARBs as initial agents of choice for hypertensive type 2 diabetic patients with microalbuminuria or clinical albuminuria. The ADA still supports the use of angiotensin-converting enzyme (ACE) inhibitors as first-line treatment for normotensive and hypertensive type 1 diabetic patients with evidence of microalbuminuria or clinical albuminuria.

It is reasonable to postulate that interruption of the renin–angiotensin system is a key factor in attenuating the progression of nephropathy. However, we cannot conclude that ACE inhibitors and ARBs are equivalent in the treatment of nephropathy in patients with type 2 diabetes, due to the complex pharmacologic activity of these agents. Until there are long-term studies that directly compare ARBs with ACE inhibitors in these patients, the use of both agents in normotensive as well as hypertensive type 2 diabetics with microalbuminuria or clinical albuminuria is warranted. Since the dihydropyridine calcium-channel blockers may have detrimental effects in some patients, these agents should be used with caution in patients at risk of developing diabetic nephropathy when other options are available.

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Comment: hospital admissions resulting from preventable adverse drug reactions

TO THE EDITOR: We would like to comment on the article, “Hospital Admissions Resulting from Preventable Adverse Drug Reactions,” by Mc-

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.
Donnell and Jacobs, who retrospectively reviewed adverse drug reactions (ADRs) reported at their hospital and found that 62.3% were preventable.\(^1\) Antineoplastics posed the greatest risk, causing 16% of events, 21% of which were preventable. It is paramount that there is qualification of the degree of preventability when assessments are made; otherwise, interpretation of results such as these can lead to inappropriate conclusions.

In a study at the Peter MacCallum Cancer Institute (February 28–June 2, 2000), we randomly selected admissions for review of patient medical records and further selected a subset for interviews about ADRs. All adverse events were assessed for relationship to drugs using the Naranjo algorithm.\(^2\) A total of 577 ADRs were identified.

To realistically assess preventability, we modified the criteria of Schumock and Thornton\(^3\) to categorize ADRs into definitely, probably, and not preventable (Table 1). Where a history of allergy or adverse reaction to a drug is present or the drug, dose, route, or frequency of administration is inappropriate, an ADR was regarded as definitely preventable (Section A).

We omitted the factor of toxic serum drug concentration. With advances in cancer supportive therapy and transplant technology, antineoplastics are increasingly administered at high dosages, often resulting in blood concentrations beyond traditionally recognized toxic levels. This factor, therefore, does not necessarily identify preventability.

We added 2 questions (4, 5; Section B) on the use of preventive measures because many ADRs are predictable and preventable.\(^4\) When a predictable ADR occurs, questions should be raised about whether known prevention has been used in an appropriate, adequate, and timely manner.

Where an ADR could have been avoided if there had been laboratory monitoring, no drug interaction or compliance problems, or appropriate and adequate prevention, it was regarded as probably preventable (Section B).

Like Schumock and Thornton,\(^3\) we agree that there will ultimately be ADRs that occur, even with all necessary precautions. These were regarded as not preventable (Section C).

Using the modified scale, we found that <2% of ADRs were definitely preventable, less than half were probably preventable, and just over half were not preventable.

In oncology practice, where a patient’s general health status is heavily compromised, many factors and influences determine patient management. More often than not, there is little choice between giving a life-preserving drug that would likely elicit an undesirable reaction and not giving it at all. The challenge in these circumstances becomes how well we can prevent predictable ADRs. Our results show that few ADRs in oncology practice are definitely preventable. There are, however, many occasions where improved use of preventive measures has the potential to reduce the incidence and severity of ADRs. The vigilant prevention of ADRs is therefore an important issue in the quality use of medicine.

Conclusions regarding the preventability of adverse events in oncology must be qualified with the degree of preventability to enable robust estimations or extrapolations of potential impacts of intervention strategies.

### Table 1. Criteria for Determining Preventability of an ADR*

<table>
<thead>
<tr>
<th>Section A</th>
<th>Answering “yes” to one or more of the following implies that an ADR is definitely preventable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Was there a history of allergy or previous reactions to the drug?</td>
</tr>
<tr>
<td>2.</td>
<td>Was the drug involved inappropriate for the patient’s clinical condition?</td>
</tr>
<tr>
<td>3.</td>
<td>Was the dose, route, or frequency of administration inappropriate for the patient’s age, weight, or disease state?</td>
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<tr>
<td></td>
<td>If answers are all negative to the above, then proceed to Section B.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section B</th>
<th>Answering “yes” to one or more of the following implies that an ADR is PROBABLY preventable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Was required therapeutic drug monitoring or other necessary laboratory tests not performed?</td>
</tr>
<tr>
<td>2.</td>
<td>Was a documented drug interaction involved in the ADR?</td>
</tr>
<tr>
<td>3.</td>
<td>Was poor compliance involved in the ADR?</td>
</tr>
<tr>
<td>4.</td>
<td>Was a preventative measure not administered to the patient?</td>
</tr>
<tr>
<td>5.</td>
<td>If a preventative measure was administered, was it inadequate and/or inappropriate? Answer “no” if this question is non-applicable.</td>
</tr>
<tr>
<td></td>
<td>If answers are all negative to the above, then proceed to Section C.</td>
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</tbody>
</table>

| Section C | The ADR is NOT preventable. |

ADR = adverse drug reaction.

*Modified from reference 3.

AUTHORS’ REPLY: We appreciate the comments by Lau et al. regarding concerns of stratifying adverse drug reactions (ADRs) to chemotherapy as being preventable. Although the preventability factors as published by Schumock and Thornton\(^3\) were the primary parameters used in our report, a “modified” concept was used when evaluating the preventability of ADRs as applied to antineoplastic therapy. This was not implied in the report, but was very similar to what Lau et al. have described.

In our report, 5 of 24 ADRs (21%) secondary to antineoplastic therapy were considered to be potentially preventable. One of these cases was considered to be definitely preventable. These events included the following:

Two cases involved patients with repeat admissions with neutropenic fever from antineoplastic therapy for nonmyelogenous malignancies. One may categorize the events as being potentially preventable if prophylactic granulocyte-colony–stimulating factor was administered after subsequent cycles of chemotherapy due to the patients’ histories of myelosuppression that required hospitalization.

Two cases involved patients who were admitted with fecal impaction/bowel obstruction related to vincristine. When these cases were reviewed, it was discovered that these patients did not receive medications (i.e., stool softeners, laxatives) that may have potentially prevented this reaction.

One case involved methotrexate. The use was for ectopic pregnancy versus cancer, in which this patient with end-stage renal disease received this agent. She was subsequently admitted with manifestations of methotrexate toxicity. This, of course, would be classified as preventable, as this patient had an absolute contraindication to methotrexate for this particular indication.
All of the ADRs that were included in our report were also reviewed at multidisciplinary health system meetings (Medication Practices; Pharmacy & Therapeutics) to discuss items such as probability and severity, as well as preventability.

We thank Lau et al. for sharing their comments as well as their criteria for determining preventability of ADRs due to antineoplastic therapies.

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