Oral vitamin B12: a cost-effective alternative

Michael R. Kolber MD MSc CCFP **Sherilyn K.D. Houle** RPh PhD

On February 29, 2012, Sandoz Canada announced a disruption to the supply of its many injectable medications in Canada, including vitamin B12 (VB12) while it upgraded operations to meet US Food and Drug Administration standards.[1] This disruption forced Canadian physicians and pharmacists to find alternative sources or make therapeutic substitutions until the shortage was resolved. This shortage presented an opportunity to revisit an evidence-based therapeutic alternative for the treatment of VB12 deficiency.

Vitamin B12 deficiency is common, affecting approximately 5% of Canadian adults.[2] A diet low in animal products or malabsorption associated with increasing age could contribute to VB12 deficiency. Medications such as metformin and proton pump inhibitors have also been associated with VB12 deficiency.[3,4] Given Canada's aging population and the widespread use of these medications, the prevalence of VB12 deficiency is likely to increase. Because VB12 deficiency can present with subtle clinical symptoms, clinicians should consider testing for deficiency in at-risk patients, including the elderly, those who are malnourished, alcoholics, strict vegans, and those taking long-term metformin or proton pump inhibitor therapy.[3-5] In addition, VB12 levels should be measured in patients with hematologic or clinical symptoms that might be due to VB12 deficiency such as macrocytosis or pancytopenia, peripheral neuropathy or atypical neurologic symptoms, and dementia.[6] Initial testing should consist of measuring the serum cobalamin level. In situations where patients have low-normal cobalamin levels, or normal serum cobalamin levels despite the presence of unexplained neurologic symptoms, methylmalonic acid and homocysteine levels can be measured; these markers are more sensitive to early or borderline deficiency than is serum cobalamin.[7] Alternatively, given that patients could be physiologically deficient in VB12 at low-normal VB12 levels,[8,9] a more pragmatic option might be to treat patients who have low-normal VB12 levels and who are either at high risk of, or who have symptoms potentially compatible with, VB12 deficiency.

Role of oral VB12

Once deficiency has been diagnosed, evidence supports the use of oral VB12 supplementation. The use of oral therapy has been documented for more than 40 years.[10] Three recent randomized controlled trials and a well designed case series compared oral and intramuscular (IM) VB12 in patients with VB12 deficiency from various causes, including dietary restriction, pernicious anemia, or malabsorption secondary to gastrointestinal disease or resection.

The randomized controlled trials, although relatively short in duration (all fewer than 4 months) and of small sample size (N = 158), demonstrated that oral VB12 was as effective as IM therapy in improving VB12 levels and associated biochemical markers (total homocysteine and serum methylmalonic acid), anemia, and neurologic symptoms.[11-13] The case series enrolled 50 patients with VB12 deficiency and demonstrated that, for more than 18 months, no patient switching from parenteral to oral VB12 developed clinical or hematologic abnormalities that required a return to IM VB12 therapy.[14] A Cochrane review also concluded that oral VB12 was as effective as IM administration in obtaining short-term neurologic and hematologic responses in patients with VB12 deficiency.[15]

Oral therapy is also well accepted by patients. In the case series described above, all patients found oral therapy to be acceptable, with 83% preferring oral therapy to IM therapy.[14] A similar Canadian study of primary care patients taking IM VB12 found that 73% were willing to do a trial switch to oral VB12 therapy. After 6 months, 71% wished to remain on oral therapy permanently, citing convenience and decreased cost to the health system as contributing factors for their decision.[16]

Despite this evidence, most Canadian physicians recommend IM VB12 for their patients with deficiency.[6] Intramuscular injections burden patients' and caregivers' time to receive injections, cause unnecessary discomfort, and contribute considerable costs to the health system. A 2001 cost analysis estimated that up to $17.6 million could be saved over 5 years in Ontario alone if seniors using IM VB12 were switched to oral therapy.[17]

Absorption concerns of oral VB12

A common concern with oral VB12 therapy is absorption of the compound in the context of pernicious anemia or gastrointestinal disease or resection. While most dietary VB12 is absorbed actively via intrinsic factor, passive diffusion accounts for about 1% of VB12 absorption, with bioavailability unaffected in those with pernicious anemia or gastroduodenal surgical resection.[15] Therefore, an oral dose of 1000 µg daily is more than sufficient to meet the Canadian recommended dietary allowance of 1.8 to 2.4 µg daily.[18] Numerous studies have found oral therapy to be sufficient even in patients lacking intrinsic factor and those with gastrointestinal disease or bowel resections.[5,13,14]

While not extensively studied, the sublingual route might be another alternative in patients with gastrointestinal conditions potentially affecting the absorption

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of oral tablets. One study found no difference in effectiveness between the oral and sublingual route after 4 weeks of therapy.[19]

Because serum VB12 levels can be easily and inexpensively measured, concerns about absorption and clinical effectiveness of oral or sublingual therapy can be alleviated through follow-up laboratory testing. For clinicians not comfortable treating symptomatic VB12-deficient patients exclusively with oral therapy, a reasonable alternative would be to "load" initially with IM VB12 and switch to oral maintenance thereafter.

Access to oral VB12

Currently, IM VB12 is covered under almost all provincial health drug plans (except in Nova Scotia, where it has exception status), while oral VB12 is only covered in Nova Scotia, the Northwest Territories, and the Yukon, and is covered for all First Nations and Inuit individuals with Non-Insured Health Benefits status. However, even in jurisdictions where oral VB12 is not covered on provincial formularies, it is likely that patients would be willing to pay for the nonprescription tablets available in nearly all community pharmacies. Suggested retail prices indicate that the cost of oral VB12 therapy at a dose of one 1000 µg tablet daily is approximately equivalent to the cost of taking 500 mg of calcium and 1000 IU of vitamin D daily—a cost that, from our experience, many patients are currently willing to pay.

Conclusion

Oral VB12 is as effective as parenteral therapy in improving hematologic and neurologic outcomes, is preferred by most patients, and can be associated with substantial health care savings. We believe it should be the default treatment for VB12 deficiency and that VB12 oral tablets should be added to provincial drug plan formularies.

We hope physicians and pharmacists considered the recent supply chain disruption of injectable medications as an opportunity to implement this evidence-based clinical practice change and encourage oral VB12 therapy for their patients with VB12 deficiency.

Dr Kolber is Associate Professor with the Department of Family Medicine at the University of Alberta in Edmonton. **Ms Houle** is a registered pharmacist and is a doctoral candidate with the Department of Medicine at the University of Alberta.

Competing interests
None declared

Correspondence
Ms Sherilyn Houle, University of Alberta, Medicine, EPICORE Centre, 3rd Floor, Brain and Aging Research Building, University of Alberta, Edmonton, AB T6G 2M8; telephone 780 492-3454; fax 780 492-6059;
e-mail **sherilyn.houle@ualberta.ca**

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