Title: Oral versus Injectable Vitamin B12 Supplementation: Clinical and Cost-Effectiveness

Date: November 30, 2007

Context and policy issues:

Vitamin B12 (cobalamin) is essential for the formation of red blood cells and maintaining the integrity of the nervous system. Vitamin B12 deficiency causes megaloblastic anemia, loss of appetite, mood disturbances, and potentially irreversible neurological complications. Vitamin B12 deficiency has also been linked to an increased risk of myocardial infarction and stroke. Vitamin B12 deficiency may be due to poor dietary intake of meat and dairy products and inadequate absorption as a result of pernicious anemia, gastritis, bariatric surgery, ileal resection, inflammatory bowel disease, certain drugs (e.g. metformin or proton pump inhibitors), or food-cobalamin malabsorption (characterized by the inability to release vitamin B12 from food or from its binding proteins). The prevalence of vitamin B12 deficiency is not clear, but the incidence increases with age.

In North America, vitamin B12 deficiency is typically treated with intramuscular (IM) injections. The dose and duration of therapy is dependent on the severity and cause of deficiency, but injections every one to three months are usually required. Efficacy of therapy is monitored by the regression of neurological symptoms, levels of vitamin B12 in the blood, and formation of red blood cells (as indicated by hemoglobin level, the hematocrit, and the mean corpuscular volume). However, there are several drawbacks to IM administration including pain on injection, difficulty in patients with a tendency to bleed or in very thin patients, and the inconvenience and cost of frequent visits to health care professionals for injections. There is a growing body of evidence that vitamin B12 administered orally at doses greater than 500 μg may be efficacious for various types of vitamin B12 deficiency. Furthermore, there is evidence that switching patients from injection to oral therapy is both feasible and acceptable largely due to increased convenience. Vitamin B12 supplementation has not been associated with any serious adverse effects as amounts given in excess of need are excreted in the urine. Several single ingredient oral vitamin B12 preparations ranging in dose from 25 μg to 1200 μg are licensed by Health Canada as over the counter natural health products. This report will present the evidence evaluating the clinical and cost effectiveness of oral versus IM vitamin B12 supplementation.
Research questions:

1. What is the clinical effectiveness of oral Vitamin B12 supplementation compared to IM Vitamin B12 supplementation?

2. What is the cost-effectiveness of oral Vitamin B12 supplementation compared to IM Vitamin B12 supplementation?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1997 and the present, and are limited to English language publications only. Search filters were applied to limit the retrieval to systematic reviews, guidelines, economic studies, and randomized controlled trials. Internet links to full-text and abstracts are provided, where available. Bibliographies of reports were scanned to identify other relevant evidence.

Summary of findings:

A Cochrane systematic review published in 2005 was identified. The report compared the clinical effectiveness of oral versus IM vitamin B12 therapy in patients with vitamin B12 deficiency. Studies that included patients with primary folate deficiency, end stage renal disease, or those receiving treatment for cardiovascular disease were excluded. Meta-analysis was not performed because of study heterogeneity. Two randomized controlled trials (RCTs) conducted in outpatient hospital clinics met the inclusion criteria for the review (Table 1). Findings from the first study indicated statistically higher levels of serum cobalamin in the oral group at two months (p<0.001) and at four months (p<0.0005) compared with the IM group. The groups did not differ significantly in neurological response (improvement or clearing of paraesthesia, ataxia or memory loss). No timeframe was provided specifying how rapidly improvement in neurological symptoms occurred. Results from the second trial indicated significant differences (p<0.001) in serum cobalamin, hemoglobin level and mean corpuscular volume in both groups of participants from baseline. However, statistical analysis for between group comparisons were not conducted. The authors reported greater tolerability with oral vitamin B12 therapy but did not indicate how tolerability was evaluated. Improvements in cognitive function, sensory neuropathy and vibration sense were also reported but differences between the two groups were not statistically significant. Neither trial reported any adverse effects with the use of oral or IM vitamin B12 therapy. The studies did not analyze the effect of the intervention on the quality of life of the participants.

Based on the RCTs identified, the authors of the systematic review concluded that doses between 1000-2000 μg of oral vitamin B12 therapy may be as effective as IM therapy in producing hematologic and neurologic responses. However, the length of follow-up in both trials was insufficient (ranging from 90 days to four months) since the biological half-life of body stores of vitamin B12 is greater than thirty months. Furthermore, neither study was conducted in a primary care setting where most vitamin B12 deficient patients are treated. There is also uncertainty regarding the long-term efficacy of oral vitamin B12 therapy in patients with malabsorption as no patients with inflammatory bowel disease were included in either study.
### Table 1: Details of Trials Included in Cochrane Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Kuziminski et al., 1998</td>
<td>RCT, open-label</td>
<td>Vitamin B12 Level (pg/mL) at 4 months:</td>
<td>Short follow-up, small sample size (5 withdrawals), method of randomization not clearly described, ITT analysis not reported.</td>
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<tr>
<td></td>
<td>Participants:</td>
<td>Oral B12: 1005 ± 595 IM B12: 325 ± 165 (p&lt;0.0005)</td>
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<td>Patients with chronic atrophic gastritis (17), pernicious anemia (7), ileal resection (3), poor dietary intake (4), gastric stapling (1), and omeprazole therapy (1)</td>
<td>Hematocrit (%) at 4 months:</td>
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<td></td>
<td>Intervention:</td>
<td>Oral B12: 40.5 ± 2.9 IM B12: 40.6 ± 4.4 (p value not reported)</td>
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<td>Oral B12: 2000 μg once daily for 120 days (n=18) vs. IM B12: 1000 μg on days 1,3,7,10,14,21,30,60 and 90 (n=15)</td>
<td>MCV (fL) at 4 months:</td>
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<td>IM B12: 1000 μg daily for 10 days (n=34)</td>
<td>Oral B12: 90 ± 7 IM B12: 91 ± 7 (p value not reported)</td>
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<td>Followed by both treatments administered once a week for four weeks then, once a month indefinitely</td>
<td>Neurologic Improvement at 4 months:</td>
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<td>Oral B12: 22.2% IM B12: 26.7% (p=NS)</td>
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<tr>
<td>Bolaman et al., 2003</td>
<td>RCT, open-label</td>
<td>Vitamin B12 Level (pg/mL):</td>
<td>Short follow-up, small sample size (10 withdrawals), ITT analysis not reported, authors did not analyze the differences between the oral and IM groups.</td>
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<td></td>
<td>Participants:</td>
<td>Oral B12: 72.9 ± 54.8 Day 0: 213.8 ± 30.2 (p&lt;0.001)</td>
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<td>Patients with megaloblastic anemia due to vitamin B12 deficiency</td>
<td>IM B12: 70.2 ± 59.1 Day 0: 225.5 ± 40.2 (p&lt;0.001)</td>
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<td>Intervention:</td>
<td>Hemoglobin level(g/dL):</td>
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<td></td>
<td>Oral B12*: 1000 μg once daily for 10 days (n=26) vs. IM B12: 1000 μg daily for 10 days (n=34)</td>
<td>Oral B12: 8.4 ± 2.1 Day 0: 13.8 ± 0.7 (p&lt;0.001)</td>
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<td>Followed by both treatments administered once a week for four weeks then, once a month indefinitely</td>
<td>IM B12: 8.3 ± 2.3 Day 0: 13.7 ± 0.9 (p&lt;0.001)</td>
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<td>Mean corpuscular volume(fL):</td>
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<td>Oral B12: 112.3 ± 11.4 Day 0: 86.9 ± 3.9 (p&lt;0.001)</td>
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<td>IM B12: 114.8 ± 10.9 Day 0: 86.7 ± 4.1 (p&lt;0.001)</td>
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RCT=Randomized Controlled Trial, IM=Intramuscular, NS=Non-significant, ITT=Intention-to-treat

* Oral cobalamin was administered as the contents of a 1000 μg ampule mixed with 20 mL of fruit juice since tablets were not available in Turkey at the time of the study.
Results from observational trials suggest comparable efficacy of the IM and oral route for treating vitamin B12 deficiency. A prospective case series of 50 patients with vitamin B12 deficiency in an out-patient setting was conducted to measure the effectiveness, safety and acceptability of oral vitamin B12 as a replacement therapy. Duration of oral therapy ranged from 3 to 18 months. At the beginning of the study, all patients received 1000 μg of vitamin B12 administered as an IM injection. When the patient’s serum level dropped to lower than 418 pg/mL, they were switched to 1000 μg of oral vitamin B12 daily. Results indicated that oral therapy was effective maintaining satisfactory serum B12 levels for all patients in the study and most patients (87%) demonstrated a preference for oral therapy compared with IM injections. Moreover, there were no significant changes in hemoglobin (p=0.4) or mean corpuscular volume (p=0.42), and no new neurological complications developed over the study period. This study did not indicate whether the length of oral vitamin B12 treatment had a significant impact on the overall clinical outcomes measured.

Another study conducted in a community setting analyzed retrospective data from 60 patients with vitamin B12 deficiency who were switched from IM to oral therapy. The dosing range for oral vitamin B12 supplementation was not specified. After three years of oral therapy there was no significant difference in vitamin B12 levels (p=0.62), hemoglobin levels (p=0.67) or mean corpuscular volume (p=0.44) between IM and oral vitamin B12 supplementation. Two cohort studies also indicate similar efficacy in correcting serum B12 levels and hematological abnormalities in patients with food-cobalamin malabsorption.

Economic evaluations:

Two costing studies were retrieved in the search. The first study estimated the cost savings that would be achieved if all elderly patients were switched from IM injections to a 1000 μg tablet. A third-party perspective was adopted. Patients over 65 years old who received IM vitamin B12 during 1995 and 1996 were identified using population-based administrative databases in Ontario. The cost for each patient included drugs, injections, pharmacists' fees and injection-associated physician visits and was estimated in Canadian dollars. Potential savings to the provincial healthcare system from switching was estimated to be substantial (between $2.9 and $17.6 million) over five years in Ontario alone, depending on the number of injection visits avoided.

Another study conducted in the UK also examined whether savings could be made by changing patients from IM injections to high doses of oral vitamin B12 in a primary care setting. The dose for oral vitamin B12 supplementation was not reported. The analysis was carried out from the perspective of the third-party payer but the price year was not defined. Data obtained from a literature review and expert opinion were used to determine the costs associated with the drug (including the needle and syringe) and administration (mainly the costs of nursing time). The cost of the resources used to administer IM vitamin B12 was calculated at between £56 and £100 per patient per year. Initial conversion costs arising from frequent monitoring (increased laboratory tests and visits to a health care professional) considerably increased the cost of switching patients to high-dose oral vitamin B12. Home visits had the highest impact on conversion costs. These costs were estimated to be between £126 and £249 but were only applicable during the first year, and were not necessary in newly diagnosed patients started on oral treatment from the outset. However, once patients receiving IM treatment had been converted to oral treatment, or in new patients treated orally from the outset, the cost was £36 per patient per year. These savings were mainly the result of a decrease in nursing time required with oral therapy. These results suggest that switching patients from IM to oral therapy and treating newly diagnosed patients with oral vitamin B12 from the outset could save health care resources in the long term.
Guidelines:

Guidelines from the British Columbia Medical Association (2003) recommend that oral supplementation of vitamin B12 is the treatment of choice in most cases including pernicious anemia. However, the guidelines state that in patients with significant neurological complications IM injections at a dose of 1000 μg should be used to help prevent irreversible complications followed by oral doses of 1000-2000 μg per day.

Conclusions and implications for decision or policy making:

Overall, evidence to suggest that oral supplementation may be as effective as IM therapy for vitamin B12 deficiency is limited. Results from economic evaluations suggest that potential savings made by switching patients from IM to oral vitamin B12 could be substantial but may not be realized immediately due to high conversion costs. Although oral therapy is more convenient, symptoms and laboratory measurements would need to be monitored closely, especially during the first months of therapy to ensure efficacy and compliance. IM administration is more appropriate for patients unable to take medications by mouth, those presenting with severe neurological symptoms, and when compliance to a daily dosage regimen is a concern. Caution is particularly warranted when using timed-release preparations (whose dissolution can take up to 6 hours) when prompt treatment is required to prevent progressive, irreversible neurologic and cognitive impairment.

Further research is needed to confirm long-term efficacy for clinically important outcomes, dosing and treatment duration for different causes of deficiency, and economic benefit of oral vitamin B12 supplementation in order to help establish guidelines for use in primary care settings.

Prepared by:

Sarah Ndegwa, BScPharm, Research Officer
Kelly Farrah, MLIS, Information Specialist
Health Technology Inquiry Service (HTIS)
E-mail: HTIS@cadth.ca
Toll free phone: 1-866-898-8439
References:


