INVITED COMMENTARY

Mysteries of Dosing Vitamin B12 and Much More!

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Tandon, et al. [1] studied the relative efficacy of high-dose oral and parenteral vitamin B12 in deficient children with macrocytic anemia, and found that in the short term, parenteral vitamin B12 was more effective in increasing their serum vitamin B12 and hemoglobin concentrations. This is not surprising, given the dosing routes. However, the issue is somewhat muddled by both groups getting a single parenteral vitamin B12 (1000 µg intramuscular) dose at the beginning of the trial [1], such that this was not a pure parenteral-oral dose comparison. Further, higher rates of attrition and concomitant iron therapy in the parenteral group weaken the interpretation. The difference in effect on hemoglobin after three months of treatment was dramatic: the hemoglobin increment in the parenteral group was nearly 2 g/dL greater than the oral group, in spite of other important causes of anemia not being ruled out [1]. The parenteral group possibly had greater baseline deficiency of vitamin B12 and hemoglobin, thereby suggesting regression to the mean as a partial explanation.

The relative benefits of oral vs parental dosing can be better understood through the prism of absorption. This requires effective gastric function: first acidity to release vitamin B12 from salivary haptocorrin and then intrinsic factor (IF) to bind and chaperone free vitamin B12 to the terminal ileum, where it is internalized by binding to finite numbers of Cubam receptors. Recently, a safe, stable isotope (^{13}C)-labelled vitamin B12 test became available, showing an average vitamin B12 bioavailability in normal Indian adults of ~50%, at an oral dose of 2.5 µg; with a 18 µg oral B12 dose, the absorption was 8% [2]. This is not surprising; since the number of transporters is finite, absorption follows zero-order kinetics, with a maximum of about 1 µg vitamin B12 absorption [2]. However, in addition, a passive absorption of about 1-5% of the dose was described, presumably following first-order kinetics. With a 500 µg oral dose, as in this trial, a substantive 5-25 µg could be passively absorbed, which is reflected in the increased serum vitamin B12 concentrations [1].

With effective passive absorption at high doses, the question remains whether oral or parenteral vitamin B12 is better for the treatment of deficiency anemia. Although Tandon, et al. [1] showed that sustained parenteral vitamin B12 resulted in significantly higher concen-trations of serum B12 and hemoglobin in deficient patients, the oral dose had a substantial effect on serum B12 concentrations (nearly 400 µg/mL; about two-third of the effect of the parenteral dose), but the confounding effect of the initial parenteral dose cannot be ruled out [1]. Other studies have also suggested that high oral doses are good enough, given the passive absorption, for pernicious anemia and food cobalamin malabsorption [3]. A Cochrane review has; however, highlighted the need for further clinical trials, as only low-quality evidence was available to suggest that oral doses (1000 µg/day vitamin B12) were as effective as parenteral in replenishing stores in a deficient elderly population [4]. These high resto-rative doses over 1000 µg are recommended because of the wide normal variation in absorption, by nearly four-fold in normal adults [2,5].

One additional finding from the present trial [1], that of the quite dramatic effect of parenteral dosing on hemoglobin, merits mention. The parenteral group started with a lower baseline hemoglobin and serum vitamin B12 (9.4 g/dL and 85 pg/mL) with particularly low hemoglobin values (lower IQR of hemoglobin: 6.5 g/dL) compared to the oral dose group (11.3 g/dL and 112 pg/mL). The 50% higher increase in serum vitamin B12 concentration in the parenteral group might be a reason for their better hemoglobin response, but this is unlikely. A weak but significant relation has been shown between hemoglobin and serum vitamin B12 in the range of <400 pg/mL [6] but this does not explain why a nearly 30% hemoglobin increment was observed in the parenteral group, particularly when the mean corpuscular volume change was similar between groups. A similar study in Turkish children younger than 18 years showed similar increments in serum vitamin B12, but much smaller changes in hemo-globin, similar between groups, one month after treatment [7]. Thus, there are still unanswered questions, and future dosing comparisons should include detailed characteri-

zation of the cause of anemia, sequential measurements of hemoglobin, along with functional biomarkers of vitamin B12 deficiency.

From a public health perspective, vitamin B12 deficiency, and macrocytic anemia should be rampant in India, given dietary habits, and the daily vitamin B12 requirement in 1-5-year-old children, which ranges from 1.2-2.2 µg [8]. However, a recent national survey of under-5 Indian children found only 13.8% prevalence of vitamin B12 deficiency [9], defined by serum vitamin B12 concentrations, with prevalence of macrocytic anemia due to folate or vitamin B12 deficiency of around 19% [10].

Thus, many questions about vitamin B12 remain: what is its daily requirement estimate in Indians; do adaptations in the conservation of vitamin B12 stores occur; why is the prevalence of its deficiency so low in apparently vegetarian populations; and in clinical defi-ciency, what should the appropriate dosing schedules be? We look forward to more studies to address these gaps in the literature.

Funding: HSS, AVK: recipients of the Wellcome Trust/Department of Biotechnology India Alliance Clinical/Public Health Research Centre Grant (IA/CRC/19/1/610006). *Competing interests*: none stated.

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