

QUERY ANSWER REPORT

Alternatives to intramuscular administration of hydroxocobalamin

BACKGROUND

For a number of reasons, it may be necessary to consider whether there is an alternative to the intramuscular (IM) administration of hydroxocobalamin. Several options have been suggested:

- Oral administration of *cyanocobalamin*
- Subcutaneous (SC) administration of *hydroxocobalamin* (either by a healthcare professional, or self-administered by the patient)
- Subcutaneous administration of *cyanocobalamin* (either by a healthcare professional, or self-administered by the patient)
- Where IM injection is only undesirable in the short term, whether a dose can be skipped.

This document considers the evidence for the various options, and the circumstances in which each might be appropriate. The final decision in each case will be a clinical decision made by the prescriber. When prescribing an unlicensed or off-licence treatment, GMC guidance on unlicensed and off-licence prescribing should be followed.(1)

ANSWER: SUMMARY

OPTIONS

Omit hydroxocobalamin

- Hydroxocobalamin is stored in the body for several months. Optimal body stores of hydroxocobalamin are believed to be sufficient for 3-4 years; a single 1000 microgram (1mg) IM dose of hydroxocobalamin is believed to provide vitamin B12 sufficient for 2-10 months. It is therefore unlikely that skipping a single 3-monthly dose will result in significant deficiency in a patient whose levels are well within range.

Oral administration of *cyanocobalamin*

- There is relatively little evidence available for the efficacy of oral vitamin B12 in the treatment of vitamin B12 deficiency due to malabsorption. However, what evidence there is indicates that in adults, a cyanocobalamin dose of at least 500 micrograms daily is likely to be effective. There is some evidence that 1000 micrograms daily orally is as effective as intramuscular treatment.
- There is no UK-licensed medicinal product available that is suitable for oral treatment of vitamin B12 deficiency due to malabsorption. Therefore, a food supplement product (not a licensed medicine) will have to be used to achieve the required dose.

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- As there is no licensed medicinal product available that is suitable for treatment of vitamin B12 malabsorption-related deficiency, and therefore products marketed as food supplements must be used, it is not possible to evaluate cost compared to parenteral administration. However, it should be noted that for oral therapy, surgery appointments/home visits are not likely to be necessary.
- For dietary deficiency (e.g. in vegan patients), lower doses (e.g. 50-150 micrograms daily) of cyanocobalamin may be given using 50 microgram tablets which are a licensed medicine, but the formulation may not be acceptable to all patients. Individual formulations should be checked.
- We have no information regarding the efficacy of modified-release preparations of cyanocobalamin compared to immediate-release formulations. However, as higher plasma levels appear to trigger increased excretion, theoretically, modified-release preparations *might* provide an advantage by flattening the absorption curve, and providing a slightly lower plasma level for longer. However, we do not know whether this is correct, and if so, how significant it might be.

Subcutaneous administration of *hydroxocobalamin*

- There is very little information available regarding the subcutaneous administration of hydroxocobalamin, although it has been done. This should therefore be considered as an option only if other options are not available or not suitable.

Subcutaneous administration of *cyanocobalamin*

- The UK-licensed cyanocobalamin injection is only licensed for intramuscular administration. However, there is considerably more information available regarding the administration of cyanocobalamin via the subcutaneous route. If subcutaneous administration is necessary, it would be preferable to use cyanocobalamin rather than hydroxocobalamin. However, note that as cyanocobalamin is excreted more quickly, injections must be more frequent (monthly rather than every 3 months).

CHOICE

The most appropriate choice of treatment will depend on the patient's clinical situation.

Dietary Deficiency

- Patients whose vitamin B12 deficiency is of dietary origin are likely to be suitable for a switch to oral therapy at an appropriate dose (see the BNF). Be aware that not all products may be acceptable to all patients, e.g. vegans. Alternatively, skipping an IM dose may be appropriate.

Deficiency due to Malabsorption (Low Risk)

- Patients whose vitamin B12 deficiency is due to malabsorption but whose levels tend to run in the top half of the range (where known) and have never had neurological symptoms may be suitable for either skipping a single dose or switching to oral treatment.
 - If oral treatment is used, the higher dose should be prescribed (500 micrograms – 1mg daily).
 - If a dose is to be skipped, counsel the patient regarding symptoms of vitamin B12 deficiency so that oral treatment can be instituted if these occur.

Deficiency due to Malabsorption (High Risk)

- This includes patients whose vitamin B12 deficiency is due to malabsorption and whose levels tend to run near the bottom of the range (where known), or have had neurological symptoms of vitamin B12 deficiency, or are regarded as high-risk for any other reason. These patients should probably not skip a dose, so oral cyanocobalamin (500 micrograms – 1mg daily) is likely to be the preferred option. Patients should be counselled regarding the symptoms of vitamin B12 deficiency so that IM treatment can be re-instituted if these occur.

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Subcutaneous administration

- This is almost never likely to be the best option. There is little information regarding subcutaneous administration of hydroxocobalamin, so it should be avoided if possible. As cyanocobalamin requires more frequent administration, it is also unlikely to be a useful option unless oral treatment is not possible and skipping a dose not appropriate.
- Although it may be possible to teach patients to self-administer subcutaneous injections, this will require face-to-face training and support. As there is no vitamin B12 preparation licensed for SC administration in the UK, such administration would also be off-licence. Such a course of action should therefore be embarked upon with extreme caution, and only when there are no viable alternatives.

ANSWER: DETAIL

HYDROXOCOBALAMIN

PHARMACOKINETICS OF HYDROXOCOBALAMIN

A short review in 1984 noted that after injection of *cyanocobalamin* a large proportion was excreted in the urine within 24 hours; the body retained only 55% of a 100-microgram dose and 15% of a 1000-microgram dose. Body stores of vitamin B12 amounted to 2000 to 3000 micrograms which was believed to be enough for 3 to 4 years. If 1000 micrograms is injected monthly, the 150 micrograms retained lasts for about 1 month.(2)

Hydroxocobalamin was better retained than cyanocobalamin; the review stated that 90% of a 100-microgram dose and 30% of a 1000-microgram dose were retained which was believed to be enough for 2 to 10 months. While UK licensed product information supports these figures, it has been pointed out that the latter figure was misquoted by the review from its original source, which claimed that 30% of a 1000 microgram-dose was excreted and 70% retained, hence allowing for the longer dosing interval.(2)

ADMINISTRATION OF HYDROXOCOBALAMIN SUBCUTANEOUSLY

The UK formulations of hydroxocobalamin are only licensed for IM administration.(3) Martindale(2) states:

Cyanocobalamin and hydroxocobalamin are generally given by the intramuscular route, although cyanocobalamin may be given orally or subcutaneously, or intranasally.

None of our usual reference sources refer to hydroxocobalamin being given subcutaneously,(4,5) although we are aware of one website which does quote doses for subcutaneous hydroxocobalamin.(6) However, we are not sure how reliable it is.

A literature search reveals very few references to the subcutaneous administration of hydroxocobalamin. The most significant is a conference abstract describing a study in three children investigating whether hydroxocobalamin administered subcutaneously via a pen device would be effective and more acceptable than intramuscular hydroxocobalamin.(7) Other references to subcutaneous administration of hydroxocobalamin are made in passing, in case reports,(8,9) and a study in end-stage renal disease.(10)

CYANOCOBALAMIN

PHARMACOKINETICS OF CYANOCOBALAMIN

The oral bioavailability of cyanocobalamin is poor. The presence of intrinsic factor, calcium and the proper pH influence the absorption of vitamin B12. Binding to intrinsic factor occurs during passage through the gastrointestinal tract, and the intrinsic factor-vitamin B12 complex is absorbed in the ileum in the presence of

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calcium. Intrinsic factor, bile, and sodium bicarbonate are required for ileal transport of vitamin B12. Small amounts of vitamin B12 can also be absorbed independent of intrinsic factor via simple diffusion.(4)

In the absence of intrinsic factor (pernicious anaemia), large oral doses of cyanocobalamin (1000 mcg or more) have been effective in achieving therapeutic vitamin B12 plasma levels as sufficient vitamin is absorbed via passive diffusion. The oral bioavailability of cyanocobalamin in pernicious anaemia is reportedly 1.2%.(4)

When administered parenterally, with larger injections of cyanocobalamin there is increasing loss of free cobalamin into the urine with 25 micrograms 5% is lost, 50 micrograms 17%, 100 micrograms 45%, 200 micrograms 60%, 500 micrograms 70%, and 1000 micrograms 85%. With doses of 50 micrograms, excretion is complete in 8 h, but with larger doses (500 micrograms and more) the bulk is excreted in 24 h and smaller amounts in the subsequent 48 h. The range of excretion of an injection of 1000 mcg cyanocobalamin is 33 to 85% of the dose in the next 24 h.(11)

ADMINISTRATION OF CYANOCOBALAMIN SUBCUTANEOUSLY

Although the subcutaneous route is a known route of administration for cyanocobalamin injection,(2,4,5) the UK-licensed formulation is not licensed for use in this way.(3)

ADMINISTRATION OF CYANOCOBALAMIN ORALLY

Guidelines

The current UK guidelines on B12 deficiency from the British Committee on Standards in Haematology(12) recommend the BNF approach as first line, but add "Oral therapy may be suitable and acceptable provided appropriate doses are taken and compliance is not an issue."

A Canadian guideline (latest update 2013) has recommended oral B12 for most patients since at least 2006.(13)

Efficacy

One study found that the lowest dose of oral cyanocobalamin required to normalise vitamin B12 levels in deficient patients was 500micrograms daily.(14) A recent Cochrane Review(15) concluded that low quality evidence showed oral (1000 micrograms daily) and IM vitamin B12 having similar effects in terms of normalising serum vitamin B12 levels. They found very low-quality evidence that oral vitamin B12 appears as safe as IM vitamin B12. The authors recommended that further trials should conduct better randomisation and blinding procedures, recruit more participants, and provide adequate reporting, and that future trials should also measure important outcomes such as the clinical signs and symptoms of vitamin B12 deficiency, health related-quality of life, socioeconomic effects, and report adverse events adequately, preferably in a primary care setting.

There has been little additional research since the publication of the Cochrane review. A larger trial of oral vs IM vitamin B12 treatment (320 patients in total; 160 on oral treatment and 160 on intramuscular) was completed in November 2017, but the results are not yet available.(16) A study of treatment of vitamin B12 deficiency in children found that treatment with oral cyanocobalamin 1mg daily for a month was as effective as IM cyanocobalamin 1mg daily for a week, then on alternate days for a week, then twice weekly for a week, then once weekly for a week (children unable to swallow the tablets were given the injection orally, on the same schedule as the injection arm of the trial).(17)

There appears to be no published evidence for the use of cyanocobalamin MR rather than plain tablets.

Availability

Cyanocobalamin 50 microgram tablets are available as a licensed medicine,(3) but although these are suitable for the treatment of dietary vitamin B12 deficiency, which requires 50-150 micrograms daily, they are not generally suitable for the treatment of deficiency due to malabsorption as this tends to require higher doses, as described above.

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Higher strength tablets (e.g. 1000 micrograms) are available in the UK as food supplements.

Cost

The latest Cochrane review(15) concluded that oral vitamin B12 replacement is cheaper than IM, but this was based on one study including 60 patients in the oral treatment group and 34 in the IM group. The study only lasted for 90 days, and took place in Turkey in 2003.(18) The results may therefore not be generalizable to the UK – particularly since there is no standard price for high-strength cyanocobalamin tablets.

Oral vitamin B12 and vegans

To check whether a product is suitable for vegans, contact the manufacturer directly as formulations may differ between products. For instance, Advanz Pharma state that their cyanocobalamin 50 microgram tablets are not suitable for vegans as they contain lactose of animal origin.(19)

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