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Y Gweinidog Iechyd a Gwasanaethau Cymdeithasol
Minister for Health and Social Services

Llywodraeth Cymru
Welsh Government

Eich cyf/Your ref: P-04-571
Ein cyf/Our ref: MD/03175/14

William Powell AM
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Dear William,

24 February 2015

In my response to the Pernicious Anaemia Society's petition on 3 September, I said I would write again when advice had been received from the Haematology National Specialist Advisory Group (NSAG) on the treatment of this condition. I am sorry that it has taken longer than I expected to write back to you.

I am advised by the NSAG that a three monthly cycle of B12 injections is the British National Formulary's recommended therapeutic regime to provide more than adequate levels compared to that provided by a normal western diet (non vegetarian). Also, while there is increasing evidence to suggest that in the majority of cases, treatment with oral B12 supplements at adequate doses may provide effective replacement there is no licensed preparation of adequate dose in a single tablet in the UK.

In the absence of a clear definition of deficiency; the limitations of available tests; and the variable and non-specific symptoms that may be part of B12 deficiency, the clinical context in assessing and managing patients is key. It is important, therefore that those patients who feel they would benefit from an increased frequency of dosing need to discuss this with their clinician, usually the GP. During the consultation, the clinician and patient can take into account the specific symptoms; patient expectations of treatment and the available guidelines – all with a view to determining the appropriateness of an enhanced level of treatment.

In emphasising a collaborative approach, these discussions need to be based on a clinical assessment of the individual patient's circumstances and needs and also in line with best available evidence and expert advice. Clinicians would need to help patients understand that this collaborative approach does not signal a green light for requests/demands for inappropriate dosing – or that patients are to be referred automatically to haematology clinics should they be unhappy with the outcome of the discussion.

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The Chief Pharmaceutical Officer has advised that:

- the British National Formulary states that larger oral doses of B12 (1 – mg daily) are available but on an unlicensed basis;
- the consensus on treatment of choice is for intra-muscular B12;
- about half of people with pernicious anaemia have anti-intrinsic factor antibody and therefore are unlikely to absorb oral B12; and
- given the consensus position on intra-muscular B12, manufacturers may not view production of larger dose oral B12 a viable commercial decision.

I am supportive of efforts to facilitate a licensed product for use in the UK on the basis that tablet form may be a more acceptable therapy route for some eligible patients and there are benefits in reducing the burden on GP practice administration of intra-muscular injections and consequent additional cost to the NHS. My officials have asked that this be considered by the Department of Health's Medicines, Pharmacy and Industry Group and I am also writing to Jane Ellison, Parliamentary Under Secretary for Health to seek her support for rapid development of a licensed oral preparation.

In respect of the query about self-injection, the NSAG's advice is that intra-muscular injections are invasive and potentially harmful if not administered correctly in a sterile manner at an appropriate site.

In respect of private supplies, individuals must accept responsibility for sourcing and using products that may not have been formally evaluated by the regulatory authorities in the UK or in Europe.

I am pleased to include the NSAG's advice in full at the end of this letter. My officials will asking the NSAG to remind clinicians that treatment plans should be developed with the patient and appropriate to meet his/her individual medical needs.

The National Institute for Health and Care Excellence has not published a clinical guideline on pernicious anaemia. I am therefore going to ask that they give consideration to developing advice for clinicians.

Best wishes.

Mark.

Mark Drakeford AC/AM
Y Gweinidog Iechyd a Gwasanaethau Cymdeithasol
Minister for Health and Social Services

NSAG advice: November 2014

Request for specialist advice regarding the diagnosis and management of vitamin B12 (Cobalamin) deficiency

October 2014

Background

The prevalence of B12 deficiency especially amongst the elderly remains uncertain. Most studies quote rates of 1-10% and recognise that the incidence increases with age. However, the prevalence has varied substantially with different studies, largely because of inconsistent diagnostic criteria, with some studies suggesting 20% in those over 60 years of age (1). It can affect all age groups, particularly during times when supply may not be able to match increased demand such as active growth in children, adolescents and pregnancy. B12 is a water soluble vitamin, only found in animal sources such as meat, fish and dairy products. An adequate dietary supply along with normal stomach and small bowel function, is required to maintain a sufficient supply. However, body stores are usually high, of the order of 1-5mg, with daily requirements being 1-2 ug, and a varied daily western diet (non vegetarian) provides 1-5 ug of absorbable vitamin.(2,3,4), which under normal circumstances should be adequate to match supply with daily demands. The importance of a sufficient level of B12 arises because of its fundamental role in the process of DNA replication and general cell metabolism, both required for tissue growth and viability. This explains why clinical deficiency of B12 is usually associated with anaemia, (reduced haemoglobin concentration in the blood), as the production of red blood cells is a continual and extremely active process (3 million cells made every second).

However, nerve function also appears particularly susceptible to sub optimal B12 levels and neurological symptoms may occur in the absence of any obvious impact on bone marrow function or red cell production (anaemia), and in the absence of definable low serum levels of the vitamin.

Pernicious anaemia is a specific auto-immune disorder, and one important cause of clinical B12 deficiency associated with larger than normal red cells, low haemoglobin concentration and additional blood cell deficiencies. Specific anti-self proteins are made which act to block the absorption of B12 from the gut, and so treatment requires an alternative route of entry for B12, usually in the form of intra-muscular injections. B12 replacement with intramuscular injections of hydroxycobalamin 1mg x 6 to replace deficiency, followed by 1mg every 3 months as maintenance (standard treatment in the UK for Pernicious anaemia) should therefore provide more than adequate levels of available B12.

As B12 is a necessary requirement for all cell metabolism and 'cell health' then any relative lack of B12 may well give rise to a range of non-specific and ill defined symptoms in an individual. Deficiency is therefore usually identified and managed in primary care, with only a fraction of patients in whom the diagnosis may be less clear, or where the response to treatment is not ideal, being referred for specialist opinion, usually to haematology because of the association with anaemia, although specialist neurological input may be required in severe cognitive impairment (6)

Diagnostic challenges, potential for sub clinical B12 deficiency

There are however, diagnostic difficulties as there is no clearly defined robust test for assessing functional, or active B12 levels, or actual clinical deficiency in the absence of megaloblastic anaemia, and 'normal' ranges are by their nature somewhat arbitrarily defined around assay method and target population (5). In addition serum B12 levels can be affected by many variables such as diet, pregnancy, hormones (oral contraceptive use), drugs eg metformin. In Wales all laboratories currently perform serum cobalamin assay as the standard initial diagnostic test, as per UK guidelines (5). This quantitates the inactive transcobalamin I and III bound forms and the active transcobalamin II bound form, but lacks both specificity and sensitivity and there is no standardised clearly defined cut-off point which confirms clinical deficiency. Other tests may help as indicators of deficiency, such as a raised plasma total homocysteine, which is a sensitive, but not specific indicator of B12 deficiency. In addition measurement of total homocystene varies between laboratories, and sample collection and processing require special measures which are critical for valid results. Plasma Methylmalonic Acid is also raised in B12 deficiency and is regarded as having a good level of sensitivity, but again is not specific, is of limited availability for routine testing, and is a high cost test.

Current Recommendations

Recently revised and published guidelines from the British Committee for Standards in Haematology (BCSH) (5), highlight these diagnostic difficulties and the lack of evidence from randomized controlled trials to inform appropriate diagnostic tests and treatment strategies.

The recommendations are as follows:

1. The significance of test results for B12 levels should be assessed in the clinical context, because there is no 'gold standard' test to define deficiency.
2. Serum cobalamin should remain as the first line test. There are some second line tests which may be of help in cases of significant diagnostic difficulty.
3. Definitive cut off points to define clinical and subclinical deficiency states are not possible.
4. Treatment should not be delayed in the presence of strong clinical features of deficiency, regardless of test results.
5. Treatment of cobalamin deficiency should be in line with recommendations in BNF. Oral therapy may be suitable provided appropriate doses are taken, and compliance is not an issue.

Reflections on questions raised by patient group

1. The inflexibility of the usual regimen of vitamin B12 injections on a three monthly cycle to respond to individual health needs;

   This is the recommended therapeutic regime for B12 replacement on a maintenance basis in the presence of absent or abnormal B12 absorption from the gut, as per the BNF. The delivery of these pharmacological doses of B12 should provide more than adequate active vitamin levels as compared to normal daily dietary availability and as the route of administration bypasses any potential abnormal entry pathway. There is no evidence to demonstrate that such a dosing regime provides inadequate in vivo levels of B12, and the anaemia associated with B12 deficiency resolves completely on this regime. However, in some patients, for whom non specific symptoms persist despite resolution of anaemia, it is possible that some functional deficiency of active B12 may be present although there is no clinical way of confirming this. It is also possible that resolution of symptoms may be related to a placebo effect rather than any biochemical requirement. The important aspect for clinicians to address in such situations is the possibility of alternative diagnosis or pathology, to ensure that a different clinical problem, requiring a different therapy, is not the cause of the symptoms. If alternative diagnoses are excluded, and symptoms persist despite normal haemoglobin and biochemical evidence of adequate B12 replacement, and in the absence of a robust method to absolutely exclude functional B12 deficiency, it would seem reasonable for the treating clinician and patient to develop a collaborative management plan. This might include consideration of shorter dosing intervals, particularly if despite standard replacement regimes, measurable B12 levels remain in the low normal range. There is increasing evidence to suggest that in the majority of cases, treatment with oral B12 supplements, at adequate doses, may provide effective B12 replacement even in Pernicious anaemia (7). The current difficulty in the UK is the lack of an oral preparation of adequate dose as a single tablet, to make this route of administration feasible. It would be appropriate to support initiatives to enable such a licensed product to be available in the UK.

2. The ability of current blood testing to pick up the different types of B12 (active and inactive)

   There are no currently available robust tests to address this issue satisfactorily, as highlighted in the recently revised BCSH guidance. As such serum Cobalamin as currently undertaken across Wales, in conjunction with appropriate clinical assessment is the recommended method for diagnosis.

3. The potential risk to patients – and possibly the NHS if things go awry – if they purchase products privately that may not have been formally evaluated by appropriate bodies

   Individuals must accept responsibility for sourcing and using any products from any source, as with any herbal or dietary supplement. However, a strong case for ensuring that larger

dose oral B12 tablets are available on formulary in the UK would be a welcome addition to therapeutic options for the management of B12 deficiency.

References

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NSAG advice – February 2015

Re - B12 deficiency and replacement therapy, 'the issue of self-injection needs to be addressed'

Consideration of 'self injection' in this context relates to comments from patient groups that individuals may be inclined to source unlicensed and unregulated products for intramuscular self injection in the belief that symptoms they are experiencing are caused by inadequate levels of B12, despite receiving regular replacement therapy on prescription as advised by, and administered through, appropriately trained clinical support from the general practitioner surgery.

Intramuscular injections are invasive and potentially harmful if not administered correctly in a sterile manner at an appropriate site. Such intervention cannot be endorsed or supported, particularly in the absence of evidence of clinical need or benefit from the therapy, as the potential risk of harm from treatment cannot be justified.

As previously indicated, a suitable oral formulation for B12 replacement therapy is recommended.