CLINICAL

Bio-availability

Hydroxocobalamin when used to treat vitamin B_{12} deficiency is better retained by the body than is cyanocobalamin. In a series of experiments, [redacted] compared the uptake and internalisation of hydroxocobalamin and cyanocobalamin bound to transcobalamin II, by a human cell model, the HeLa cell.

The hydroxocobalamin-transcobalamin II complex was taken up in larger amounts per unit time. The greater uptake was not a consequence of more effective attachment to receptors of transcobalamin II-cobalamin nor to a more rapid regeneration of receptors. The difference was expressed during the phase of internalisation of transcobalamin II-cobalamin. With cyanocobalamin, the stages of binding to receptors plus internalisation were more readily reversed. Larger amounts of hydroxocobalamin were internalised and converted to active coenzyme forms of cobalamin.

When injected into a healthy person, 200µg of hydroxocobalamin was better retained in the circulation than 200µg of cyanocobalamin. When added *in vitro* in equivalent amounts, more hydroxocobalamin was bound to non-specific plasma proteins. This greater and broader binding neither enhanced nor interfered with the uptake of cobalamin by cells, which was determined by the amount of cobalamin bound physiologically to transcobalamin II.

It was concluded that hydroxocobalamin is a more efficient form of treatment of the more common types of cobalamin deficiency, principally because of better retention which means less frequent injections, but also because of greater availability to cells.

[redacted] concurs in describing hydroxocobalamin as being better retained than cyanocobalamin; 90% of a 100µg dose and 30% of a 1mg dose are retained, a range believed to be sufficient for body requirements for 2 to 10 months.

It states the following:

- absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H_2-receptor antagonists and colchicine.
- serum concentrations may be decreased by concurrent administration of oral contraceptives.

but adds that many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.

- Parenteral chloramphenicol may attenuate the effect of vitamin B_{12} in anaemia.

Human Pharmacokinetics[2,4,8]

[redacted] states that normal individuals have plasma concentrations of vitamin B_{12} ranging from 150 to 660pM (pmol/l), approximately equivalent to 200 to 900 pg/ml, and that deficiency should be suspected whenever the concentration falls below 150pM.

Once absorbed, hydroxocobalamin is extensively bound to specific plasma proteins (transcobalamins); transcobalamin II appears to be involved in the rapid transport of cobalamins to tissues. In addition, hydroxocobalamin binds non-specifically to albumin and to a lesser extent to globulin fractions. Peak plasma levels are achieved after 8-10 hours.

Vitamin B_{12} bound to transcobalamin II is rapidly cleared from plasma and is preferentially distributed to hepatic parenchymal cells. Within the cell. cobalamin is freed promptly from transcobalamin II. In the normal adult, as much as 90% of the body's stores of Vitamin B_{12}, from 1 to 10mg, is in the liver. Hydroxocobalamin in liver undergoes extensive enterohepatic recycling by being re-excreted into bile. Intrinsic factor is required for its reabsorption. Approximately 3µg of cobalamins are secreted into bile each day, 50-60% of which is not reabsorbed.

Hydroxocobalamin readily converts into methylcobalamin (mecobalamin), and adenosylcobalamin (cobamamide). Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis and are essential for cell growth and replication. Methylcobalamin is concerned with the conversion of homocysteine to methionine, and adenosylcobalamin with the conversion of methylmalonyl-CoA to succinyl-CoA. Early biochemical evidence of cobalamin deficiency is the accumulation in plasma of homocysteine and methylmalonic acid. Both can be used diagnostically as an adjunct to reduction in circulating plasma levels of vitamin B_{12}. Mecobalamin is also closely involved with folic acid in several important metabolic pathways. As homocysteine also accumulates in deficiencies of folate or vitamin B_6, these causes need to be excluded. Assays in biological fluids measure all the cobalamins (cyanocobalamin, hydroxocoblamin, methylcobalamin, deoxyadenosylcobalamin).

Hydroxocobalamin diffuses across the placenta and also appears in breast milk.

Part of the dose (at least 30% after parenteral administration) is excreted in the urine, most of it in the first 8 hours.

Human Pharmacodynamics [redacted]

Vitamin B_{12} is a dietary essential. A deficiency, by its effect on intracellular folate metabolism, results in defective synthesis of DNA in any cell in which chromosomal replication and division are taking place. Since tissues with the greatest rate of cell turnover show the most dramatic changes, the haematopoietic system is especially sensitive. An early sign of deficiency is megaloblastic anaemia. Abnormal macrocytic red blood cells are produced, and the patient becomes severely anaemic.

For adults, the daily requirement of vitamin B_{12}, a water-soluble vitamin, is between 1 and 3µg and this amount is present in most normal Western diets (vitamin B_{12} content: 10-30µg daily [redacted] Vitamin B_{12} occurs only in animal products; meats, especially liver and kidney, fish, milk, eggs and other dairy products are good sources. It does not occur in vegetables, therefore strict vegetarian (vegan) diets that exclude dairy products may provide an inadequate amount, although it may be many years before a deficiency is produced, the enterohepatic circulation being intact in vegans so vitamin B_{12} stores are conserved. Absorption of vitamin B_{12} is via the ileum following binding to intrinsic factor in the stomach.

Dietary vitamin B_{12}, in the presence of gastric acid and pancreatic proteases, is released from food and salivary binding protein, and binds to intrinsic factor secreted by the parietal cells of the stomach. When this factor complex reaches the ileum, it interacts with a receptor on the mucosal cell surface and is actively transported into the circulation. Absorption is limited to 2-3µg daily.

Vitamin B_{12} deficiency in adults is rarely the result of a deficient diet per se; rather, it usually reflects a defect in one or other aspect of this sequence of absorption. An autoimmune gastritis which results in achlorhydria (reduced or absent acid production) and decreased secretion of intrinsic factor by parietal cells, secondary to gastric atrophy or gastric surgery, is a common cause. Auto-antibodies to parietal cells or intrinsic factor complex can play a prominent role in producing a deficiency. A specific anaemia, pernicious anaemia, develops in patients with an absence of intrinsic factor. In pernicious anaemia, intrinsic factor antibodies are present in the plasma of 50% of patients and parietal cell antibodies in 90% of patients.

Deficiency may also occur in patients with metabolic disorders, nitrous oxide-induced megaloblastosis, or following gastrectomy or extensive ileal resection.

Deficiency leads not only to the development of megaloblastic anaemias, but also to demyelination and other neurological damage.

Vitamin B_{12} deficiency or folate deficiency accounts for the vast majority of cases of megaloblastic (macrocytic) anaemias. Deficiency of either produces similar clinical and haematological effects.

Macrocytosis is a rise in the mean cell volume (MCV) above the normal range which in adults is 80-95 femtolitres (fl). The causes of macrocytosis fall into two groups: deficiency of vitamin B_{12} (cobalamin) or folate in which the bone marrow is megaloblastic; other causes, in which the bone marrow is usually normoblastic. Megaloblastic bone marrow is exemplified by developing red blood cells (reticulocytes) that are larger than normal, with nuclei more immature than their cytoplasm. The underlying mechanism is defective DNA synthesis.

The blood film shows oval macrocytes and hypersegmented neutrophil nuclei (with six lobes). In severe cases, the white cell count and platelet count fall (pancytopenia). The bone marrow shows characteristic megaloblastic erythroblasts and giant metamyelocytes (early granulocyte precursors). Biochemically, there is an increase in plasma of unconjugated bilirubin and serum lactic dehydrogenase. These changes, including jaundice, are due to increased destruction of red cell precursors in the marrow (ineffective erythropoesis).

In the UK, vitamin B_{12} deficiency is usually due to pernicious anaemia, which accounts for up to 80% of all cases of megaloblastic anaemia. The incidence of the disease is 1:10,000 in northern Europe, and the disease occurs in all races. It peaks at age 60; the condition has a female:male incidence of 1.6:1.0 and is more common in those with early greying, blue eyes and blood group A, and in those with a family history of the disease or of diseases which may be associated with it, for example, vitiligo, myxoedema, Hashimoto's disease, Addison's disease and hypoparathyroidism.

Symptoms are slow to develop but are typically fatigue, breathlessness, anorexia and weight loss, indigestion or episodic diarrhoea or both, reversible sterility and neuropathy – numbness, unsteadiness, muscular weakness, difficulty in walking, visual problems and psychiatric disturbance – ranging from mild neurosis to severe organic dementia.

Signs are pallor, mild jaundice, atrophic glossitis and angular cheilosis, mild pyrexia, paraesthesia, ataxia or mental disturbance, tachycardia, murmurs, cardiac enlargement and heart failure.

A minority of patients with vitamin B_{12} deficiency develop a neuropathy due to symmetrical damage to the peripheral nerves and posterior and lateral columns of the spinal cord, the legs being more affected than the arms. Psychiatric abnormalities and visual disturbance may also occur. Men are more commonly affected than women. The neuropathy may occur in the absence of anaemia.

Damage to the nervous system can be irreversible. Progressive swelling of myelinated neurones, demyelination and neuronal cell death are seen in the spinal column and cerebral cortex. This causes a wide range of neurological signs and symptoms, including paraesthesias of the hands and feet, diminution of vibration and position senses with resultant unsteadiness, decreased deep tendon reflexes, and, in the later stages, confusion, moodiness, loss of memory and even a loss of central vision. The patient may exhibit delusions, hallucinations and even an overt psychosis. Since the neurological damage can be dissociated from the changes in the haematopoietic system, vitamin B_{12} deficiency should be considered a possibility in elderly patients with dementia and psychiatric disorders even if they are not anaemic.

Deficiency of vitamin B_{12} may cause sterility, which is reversible with appropriate vitamin supplementation. The tongue (glossitis) and other epithelial surfaces may show cytological abnormalities. Raised serum homocysteine concentrations have been associated with arterial obstruction and venous thrombosis.

As most megaloblastic (macrocytic) anaemias result from a lack of either vitamin B_{12} or folate, it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, where delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test, while plasma assay results are awaited. Normally, however, appropriate treatment should be instituted only when the results of tests are available.

Efficacy and Safety Studies[1,2,4]

The purpose of treatment with hydroxocobalamin is to correct a deficiency state and this entails rebuilding stores, which are then normally long-lasting, with relapse on cessation of injections taking years rather than weeks to evolve. With a 1mg dose, an average of 700µg is retained so that such a dose will suffice if injections are given at 8- to 12- weekly intervals. In the early stages of therapy, it is desirable to attempt to replenish cobalamin stores which are of the order of 3mg in an adult taking a mixed diet. This is done by giving a series of about 10 injections of 1mg, either daily or on alternate days. Patients with treated pernicious anaemia who die of unrelated causes, are found to have liver cobalamin stores well below those in healthy subjects, although significantly greater than in the untreated case.

The response to treatment should be monitored by regular red cell and reticulocyte counts over the first two weeks. An optimal response is shown by an increase in reticulocytes, which reach a peak on days 5 to 7. The red cell count should exceed 3×10^6 in the third week in more anaemic patients. Preceding these blood changes, there is a gratifying return of well-being and appetite.

Addisonian pernicious anaemia is the classical cobalamin deficiency state. It is the result of severe atrophic gastritis. It is apparent that some elderly subjects have a gastric atrophy that impairs the absorption of cobalamin from food. This is caused by impaired release of cobalamin even though intrinsic factor is present. Vitamin B_{12} is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia which inactivates the vitamin.

Total gastrectomy, though not now a common operation, removes all intrinsic factor-secreting tissue (parietal cells) and hence prophylactic cobalamin therapy in maintenance dosage should be instituted immediately and continued for the duration of the patient's life; also after partial gastrectomy if a vitamin B_{12} absorption test shows vitamin B_{12} malabsorption. Resection of the ileum may prevent absorption of cobalamin, but a deficiency is unlikely unless substantially more than 60cm is removed. Abnormalities of the small gut can produce stasis of contents and hence a permanent bacterial flora which can abstract cobalamin from the luminal fluid to such an extent that deficiency occurs in the long term.

Other indications are nutritional deficiency, congenital cobalamin malabsorption, congenital intrinsic factor deficiency and the rare syndrome of congenital transcobalamin II deficiency. There is the unusual situation in the latter, of normal serum cobalamin levels but with profound cellular deficiency. A severe megaloblastic anaemia presents between the second and fourth month of life and requires treatment with 1mg twice weekly or more to prevent irreversible mental deficiency.

Rare indications for immediate, but not ongoing treatment, are methylmalonylaciduria – seen in children with a defect in the metabolism of methylmalonate to succinate, and infants born to cobalamin-deficient mothers.

Vitamin B_{12} treatment usually results in rapid haematological improvement and a striking clinical response. Neurological symptoms respond more slowly and in some cases remission may not be complete.

Hydroxocobalamin is the form of vitamin B_{12} of choice for therapy. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted.

The dose for adults and children by intramuscular injection in pernicious anaemia and other macrocytic anaemias without neurological involvement is 1mg three times a week for two weeks initially followed by 1mg every three months. Where there is neurological involvement, 1mg should be given on alternate days until there is no further improvement, followed by 1mg every two months. For the prophylaxis of macrocytic anaemias associated with vitamin B_{12} deficiency, 1mg every 2-3 months and for tobacco amblyopia and Leber's optic atrophy, initially 1mg daily for two weeks, then 1mg twice weekly until no further improvement, thereafter 1mg every 1-3 months.

Side effects comprise itching, exanthema; fever, chills, hot flushes; nausea, dizziness; initial hypokalaemia; rarely acneiform and bullous eruptions; anaphylaxis.

1. Pernicious anaemia and other macrocytic anaemias without neurological involvement.

[redacted] treated 17 patients for vitamin B_{12} deficiency by intramuscular injection of hydroxocobalamin: initial depot treatment of one or two series of five x 1mg injections on alternate days followed by maintenance therapy of 1mg every three months for eight to 20 years.

In three of four patients given two depot series less than or equal to three months apart, and with no antibody to transcobalamin II detected previously, abnormally high values of serum cobalamins were measured at the end of injection periods of seven to 12 years.

In contrast, no increase in unsaturated B_{12} binding capacity was found in patients given identical therapy, in whom an early increase above the normal level occurred in association with antibody to transcobalamin II.

One depot series followed by intramuscular injection of 1mg of hydroxocobalamin every third month secured values within the normal range for serum cobalamin, unsaturated B_{12} binding capacity and total B_{12} binding capacity.

2. Addisonian pernicious anaemia and other macrocytic anaemias with neurological involvement

[redacted] reported a male infant with methylcobalamin deficiency presenting at 6 weeks of age with lethargy, staring spells and vomiting. The baby later became hypotonic and unresponsive to stimuli and required intubation and ventilation. He had homocystinuria and hypomethioninaemia with megaloblastic anaemia, but normal serum folate and vitamin B_{12} concentrations. Methylcobalamin content of fibroblasts was low while the adenosylcobalamin content was normal.

The patient responded dramatically to hydroxocobalamin treatment. Homocystinuria disappeared after 10 days of therapy and methionine was normalised after three weeks. Psychometric testing at 15 months showed a developmental age of nine months.

[redacted] reported a 51-year old woman with vitamin B_{12} deficiency who presented with slight megaloblastic anaemia and severe neurological deficits associated with multiple focal and confluent T2-weighted white matter hyperintensity on brain MRI.

Forty-four months after initiation of hydroxocobalamin therapy, there was clinical improvement and striking reduction in the MRI abnormalities. B_{12} deficiency should be considered in the differential diagnosis of neurological disorders.

[redacted] describe a male presenting in early infancy with megaloblastic anaemia, who was treated with folinic acid from six weeks of age. The diagnosis of transcobalamin II deficiency was not made until he was 2 years old when he showed severely retarded intellectual development, ataxia and pyramidal deficit in the limbs.

Following treatment with hydroxoxcobalamin, his condition slowly improved but he remained with a severe neurological deficit.

3. Prophylaxis of macrocytic anaemia associated with Vitamin B_{12} deficiency resulting from gastrectomy, some malabsorption syndromes and strict vegetarianism

[redacted] investigated five patients presenting clinically with a form of B_{12} deficiency neuromyelopathy, with cord involvement in all of them and proximal muscle weakness in one, for their neurological, haematological and vitamin status.

Megaloblastosis and achlorhydria were present in all, and impaired absorption of ^{57}Co vitamin B_{12} was detected in four. In those tested for serum levels of other B group vitamins, riboflavin (B_2), total vitamin B_6 and pyridoxal were reduced.

All five responded to injections of hydroxocobalamin. Markedly elevated initial serum folate levels fell with B_{12} treatment. Vitamin B_2 and B_6 levels also corrected themselves on B_{12} therapy.

The B-vitamin deficiencies in these patients probably resulted from intestinal malabsorption with a possible factor of malnutrition consequent to their strictly vegetarian diet.

In a single-blind, placebo-controlled intervention study conducted by [redacted][15], 16 healthy community-dwelling elderly subjects with low plasma cobalamin concentrations and no cognitive impairments underwent one month of treatment with placebo, followed by five months of treatment with intramuscular injections of hydroxocobalamin. Before and after measurements of plasma cobalamin, total homocysteine and methylmalonic acid were carried out, as well as a quantitative electroencephalograph and psychometric tests.

After cobalamin supplementation, plasma cobalamin concentrations increased and plasma total homocysteine and methylmalonic acid concentrations decreased. The performance on the Verbal Word Learning Test, Verbal Fluency and Similarities improved. The quantitative EEG showed more fast activity and less slow activity. Lower plasma total homocysteine concentrations were related to increased fast activity on the quantitative EEG and improved performance on the Verbal Word Learning Test and Similarities. Increased fast or decreased slow activity on the quantitative EEG was associated with improved performance on the Verbal Word Learning Test, Similarities and Verbal Fluency.

It was concluded that electroencephalographic signs of improved cerebral function and improved cognitive function were found after cobalamin supplementation in older subjects with low plasma cobalamin concentrations who were free of significant cognitive impairment. These improvements were related to a reduction of plasma total homocysteine concentration.

[redacted][16], studied prospectively 472 consecutive referrals to a geriatric medical unit. Fifty-six (13%) had a low serum vitamin B_{12} level (< 175 pmol/l), of whom 19 (34%) also had evidence of iron deficiency. Low vitamin B_{12} was associated with a raised mean erythrocyte volume (MCV: mean 96.0 fl [SD 6.7]) compared with a control group (91.7 fl [SD 6.0], P = 0.001). However, only 13 (23%) of the 56 patients with a low vitamin B_{12} had an MCV ≥ 100 fl. Mean haemoglobin (Hb) levels were not significantly reduced in those with a low vitamin B_{12}.

In their subsequent study, the haematological response to intramuscular hydroxocobalamin was examined in 34 patients with a low serum vitamin B_{12}.

Treatment resulted in a significant fall in MCV and rise in Hb. These effects could be detected both in those patients with an initially normal full blood count (change in MCV: – 1.2 fl [SD 1.2]; Hb: + 0.5 [SD 0.6]; P < 0.01) and in those with macrocytosis and/or anaemia (MCV: - 9.1 fl [SD 11.8]; Hb: + 0.8 [SD1.2]; P < 0.05).

The authors conclude that a low serum vitamin B_{12} is common in geriatric medical patients. This is usually associated with an upset in erythropoiesis, although the abnormalities are often subtle and may not be apparent on inspection of the full blood count. Elderly patients with serum vitamin B_{12} < 175 pmol/l should be assumed to have vitamin deficiency even if their full blood count is normal.

[redacted]7 reported widespread soreness and focal ulceration of the oral mucosa developing in a woman with vitamin B_{12} deficiency shortly after hydroxocobalamin therapy had commenced. An oral mucosal biopsy showed disordered epithelial maturation with marked cytologic atypia.

During the next month of treatment, the patient's oral mucosa became clinically and histologically normal.

The authors consider that pathologists should be aware that vitamin B_{12} deficiency may be associated with epithelial changes similar to those associated with premalignancy.

4. Tobacco amblyopia and Leber's optic atrophy

[redacted]18 recorded in seven recently diagnosed and untreated patients with tobacco amblyopia, light and dark adapted electroretinograms (ERG), together with visual acuity, central fields and the Farnsworth-Munsell 100-Hue test.

After three months of treatment with injections of hydroxocobalamin, these tests were repeated. An improvement in visual acuity resulted in all cases. A significant reduction in the Farnsworth-Munsell total error score of the seven patients was noted (P < 0.01) and a significant increase in the amplitude of the light adapted b-wave of the ERG was found (0.01 < P < 0.02). No other significant changes in the ERG were demonstrated.

[redacted]19 reported three patients presenting with painless bilateral visual failure due to tobacco amblyopia. The whole blood cyanide levels were raised above those predicted from their high tobacco consumption, approaching the lethal levels reported from acute inhalation of cyanide. Each patient had an excessive alcohol intake with biochemical evidence of hepatic dysfunction, the elevated whole blood cyanide levels being attributed to the associated impairment of cyanide detoxification.

In each case, the improvement in visual acuity following abstinence and hydroxoxcobalamin therapy was accompanied by a reduction in the whole blood cyanide level to within the normal range. Serial measurements of whole blood cyanide, serum alcohol and the detection of urinary nicotine provided valuable indices of the patients' subsequent compliance and clinical progress.

[redacted]decribes an unusual case of a 15-year old Chinese boy diagnosed as having Leber's hereditary optic neuropathy, as he manifested typical symptoms of bilateral severe vision loss and telangiectasia at the optic disc. However, no family history was elicited and an interval of more than five years separated visual loss in the two eyes.

Visual improvement was rapid and marked after instituting intramuscular hydroxocobalamin, 5mg weekly. Bilateral improvement of Snellen acuity to 6/9 was achieved within six months, the eye with a longer history of poor vision responding to therapy first.

[redacted] evaluated the safety, efficacy and pharmacokinetic parameters of 5g hydroxocobalamin given intravenously, alone or in combination with 12.5g of sodium thiosulphate, in healthy adult men who were heavy smokers.

Sodium thiosulphate caused nausea and vomiting, and localised burning, muscle cramping or twitching at the infusion site. Hydroxocobalamin was associated with a transient reddish discolouration of the skin, mucous membranes and urine, and when administered alone produced mean elevations of 13.6% in systolic and 25.9% in diastolic, blood pressures, with a concomitant 16.3% decrease in heart rate. No other clinically adverse effects were noted. Hydroxocobalamin alone decreased whole blood cyanide levels by 59% and increased urinary cyanide excretion. Figures for pharmacokinetic parameters are given for the group who received both antidotes.

The authors concluded that hydroxocobalamin is safe when administered in a 5g intravenous dose, and effectively decreases the low whole blood cyanide levels found in heavy smokers.

Adverse Effects

[redacted]states the following:

- Two examples of anaphylactic reactions to injections of hydroxocobalamin have been reported.

- Patients sensitive to cobalt may show reactions caused by the cobalt content of cobalamin.

- Aggravation of symptoms and acidosis followed therapeutic administration of hydroxocobalamin in a 4-week-old infant with methylmalonicacidemia.

- Hypokalaemia may occur during initial therapy. Monitoring of plasma potassium is recommended to avert secondary cardiac arrhythmia.

- A single excessive dose is unlikely to have any ill effect; no high risk groups are known; no potentially hazardous (or useful) interactions have been described.

and [redacted]:

- Allergic hypersensitivity reactions have occurred rarely following the parenteral administration of hydroxocobalamin.

- Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy.

- Arrythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin.

- Hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable.

- Administration of doses greater than 10µg daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B_{12} deficiency.

[redacted] describe how hydroxocobalamin interferes with the determination of some biochemical parameters. Plasma pools were spiked with two concentrations of hydroxocobalamin and eight parameters (CK, SGOT, SGPT, ALP, lactic acid, creatinine, glucose and bilirubin) were assayed.

The two parameters affected by the presence of hydroxocobalamin were creatinine kinase and bilirubin.

Post-marketing Experience
The dates of some of the references found and the date of the earliest reported adverse reaction (see below) indicate that injectable preparations of hydroxocobalamin have been commercially available and used with regular application in patients for the last 30 years.

The volume of sales for the last three years is shown in the table below.

Year	NHS Hospital Sales No. of ampoules	Retail Sales No. of ampoules
2000	160,000	3,225,000
2001	160,000	3,270,000
2002	160,000	3,320,500

From the *MCA Adroit service*[23], extraction period: 01/07/63 to 26/03/03, the reported numbers of adverse reactions by body system for hydroxocobalamin single constituent products (intramuscular administration) are tabulated below (from 207 reports). The earliest reaction date was 04 August 1973.

Body System	**No. of reported reactions**
Cardiovascular disorders	13
Disorders of the ear	1
Disorders of the eye	5
Disorders of the immune system	22
Gastrointestinal disorders:	42
Nausea	16
Vomiting	10
General disorders:	84
Dizziness	14
Pain in limb	13
Flushing	12
Malaise	10
Haemopoietic disorders	1
Hepato-biliary disorders	1
Musculoskeletal, connective tissue and bone disorders	15
Neurological disorders	29
Peripheral vascular disorders	1
Psychiatric disorders	7
Renal and urinary disorders	1
Respiratory disorders	20
Skin/subcutaneous tissue disorders:	133
Injection site pain	30
Rash (not otherwise specified)	16
Urticaria	18
TOTAL REACTIONS FOR DRUG	**375**

It can be seen from the table that local injection site reactions and skin rashes had the greatest incidence. No adverse reaction had a fatal outcome.

All redactions in the document are made under sections 41 and 43 of the FOI Act