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Effect of Administration Route on the Pharmacokinetics of Cobalamin in Elderly Patients: A Randomized Controlled Trial

Monique P.H. Tillemans, PharmD[1,*], Eline M.V.J. Donders, MD[2], Sjoerd L. Verweij, PharmD[1], Ruud T.M. Van der Hoeven, PharmD[1], Kees J. Kalisvaart, MD, PhD[2]

[1] Stichting Apotheek der Haarlemse Ziekenhuizen, Haarlem, The Netherlands
[2] Department of Geriatric Medicine, Kennemer Gasthuis, Haarlem, The Netherlands

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ABSTRACT

Background: The gold standard for cobalamin deficiency treatment is administration of cobalamin by intramuscular injection. The injection is painful and inconvenient, particularly for elderly persons. Cobalamin might also be administered intranasally. Previous studies do not provide insight into the pharmacokinetics of intranasal cobalamin administration in comparison with cobalamin injection.
Aim: To quantify the pharmacokinetics of intranasally and intramuscularly administered cobalamin to determine if intranasal administration might be an alternative for intramuscular administration.
Methods: Ten inpatients and outpatients of a geriatrics unit were recruited and randomly assigned to receive a single dose of 1000 μg cobalamin administered either by intranasal spray or intramuscular injection (5 per group). Inclusion criteria were written informed consent, age >65 years, and a cobalamin serum concentration <200 pmol/L. Total cobalamin serum concentrations were determined 10 times within 48 hours after administration. The differences in C_{max}, T_{max}, and $AUC_{0-48\ h}$ per administration route were statistically compared using ANOVA.
Results: The average C_{max} was 1 nmol/L after intranasal and 38.5 nmol/L after intramuscular administration. The average T_{max} for intranasal and intramuscular administration was 42 minutes versus 342 minutes, respectively, and the $AUC_{0-48\ h}$ was 1.3 μmol/L/min versus 45.4 μmol/L/min, respectively. These values also differed significantly ($P<0.05$). The estimated bioavailability of the intranasal administration was 2%.
Conclusions: The pharmacokinetics of intranasal and intramuscular cobalamin administration in elderly, cobalamin-deficient patients differ significantly. However, the estimated 2% bioavailability of cobalamin after intranasal administration makes intranasal cobalamin administration a potentially interesting administration route for elderly patients. Netherlands Trial Registry identifier: NTR 3005.

Introduction

Cobalamin deficiency in human beings may take 3 to 4 years to develop due to the large cobalamin stores in the liver. Nevertheless, approximately 10% to 15% of the population aged 65 years and older has cobalamin (vitamin B_{12}) deficiency. An even higher prevalence of 30% to 40% is reported for malnourished and sick elderly people.[1] Cobalamin serves as a cofactor for methionine synthase and L-methylmalonyl-coA mutase. People with cobalamin deficiency may experience megaloblastic anemia, subacute combined degeneration of the spinal cord, peripheral polyneuropathy, cognitive impairment, and mental changes.[2] Cobalamin deficiency is due to malabsorption of food-bound cobalamin and/or insufficient dietary intake. Food-bound cobalamin is released by pepsin in the acidic environment in the stomach. Subsequently, cobalamin is bound to intrinsic factor in the duodenum. The cobalamin-intrinsic factor complex then binds to the ileal endocytic cubam receptor. The cubam receptor consists of 2 proteins: cubulin and amnionless. Together these proteins take part in the endocytosis of the intrinsic factor-cobalamin complex, which is followed by degradation of intrinsic factor in lysosomes and the release of cobalamin into plasma in complex with transcobalamin II. Cobalamin malabsorption can therefore be caused by lack of intrinsic factor, decreased pepsin or acid secretion, or other defects in the cobalamin uptake system.[3,4]

Repeated administration of cobalamin by way of intramuscular injection has been the gold standard for cobalamin deficiency

* Address correspondence to: Monique Tillemans, PharmD, Stichting Apotheek der Haarlemse Ziekenhuizen (SAHZ), Boerhaavelaan 22, 2035 RC Haarlem, The Netherlands.
E-mail address: mtillemans@sahz.nl (M.P.H. Tillemans).

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treatment for many years. These intramuscular injections have several disadvantages. Injections are painful; injection-related adverse reactions (such as intramuscular hematoma) may occur, especially in elderly persons who are frequently treated with anticoagulant medication; and health care professionals are usually needed to administer the injections. The latter increases the burden of the treatment considerably. A more convenient and safer treatment would be advantageous to both patients and the health care system in general.[5]

Food-bound cobalamin is actively absorbed. In contrast, crystalline cyanocobalamin administered via capsules is absorbed by way of passive diffusion. Although approximately only 1% of an oral dose of crystalline cyanocobalamin is absorbed, oral administration of cyanocobalamin is effective in normalizing serum cobalamin levels.[6,7] Oral treatment might not be an option in patients who have an absorption disorder or are unable to take oral medication.[8–10] Intranasal administration of cobalamin could be a suitable alternative to both cobalamin injections and oral administration in elderly patients.

Absorption of intranasally administered cobalamin has been demonstrated in studies.[11–14] However the results of those studies do not provide insight into the pharmacokinetics of intranasally administered cobalamin in elderly, cobalamin-deficient patients or in comparison with cobalamin injection. Insight into the pharmacokinetics is necessary to determine if intranasal administration could be an alternative to intramuscular administration in elderly patients. Also, insight into the pharmacokinetics could be used to develop a dosing regimen. The objective of our pilot study was to quantify the pharmacokinetics of intranasally and intramuscularly administered cobalamin in elderly, cobalamin-deficient patients to determine if intranasal administration might be an alternative for intramuscular administration.

Materials and Methods

Design, setting, and study population

Ours was a randomized, open, comparative pilot study conducted between September 2011 and January 2012 in Haarlem, the Netherlands. Patients were recruited from the in- and outpatient geriatrics department of the Kennemer Gasthuis, a teaching hospital with a total of 450 beds of which 15 are geriatrics beds (3250 geriatric outpatient visits a year). Cobalamin serum concentration measurements are part of standard care at this clinic. Eligible patients were aged 65 years or older who had a cobalamin serum concentration < 200 pmol/L. Patients also had to be able to give written informed consent. Patients with chronic rhinitis, a running nose, or concomitant use of intranasally administered medication were excluded from study participation to minimize possible influences on intranasal absorption. In addition, patients who were hemodynamically instable, had clinically significant infections, or were severely malnourished were excluded from participation for ethical reasons. Simplified Nutritional Appetite Questionnaire was used to determine a patient's nutritional status.[15] Patients with a score of 3 were excluded. Patients with a glomerular filtration rate ≤ 20 mL/min/1.73 m^2 were also excluded from study participation, because cobalamin is exclusively excreted through the kidneys. The study protocol (NL33450.029.11) was approved by the Medical Ethics Committee of the Vrije Universiteit Amsterdam and the Kennemer Gasthuis Haarlem.

Randomization and intervention

Patients were randomly assigned to 1 of the 2 study groups, to receive a single dose of 1000 μg cobalamin administered by intranasal spray or by intramuscular injection. A research nurse administered either 2 mL of a 500 μg/mL hydroxocobalamin solution for injection (Hydrocobamin, Nycomed BV, Hoofddorp, the Netherlands) in the muscle of the upper left or right arm, or 1 puff (0.1 mL) 500 μg cyanocobalamine (Nascobal, Par Pharmaceutical Companies Inc, Woodcliff Lake, New Jersey) in each nostril. The intranasal spray was primed before each administration. Blood samples were obtained at 0, 15, 30, 60, 120, 240, 480, 1440 (24 hours), and 2880 minutes (48 hours) following administration. These blood samples were drawn using an intravenous cannula inserted into a forearm vein. The cannula was inserted in the arm not used for injection if the patient received the cobalamin by way of intramuscular injection.

Analysis

Total cobalamin serum concentrations were determined using a competitive immunoassay vitamin B_{12} kit with a measuring range between 22 and 1476 pmol/L (Roche Diagnostics GmbH, Mannheim, Germany) on a Roche Modular Analytics E170 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The mean coefficient of variation in human serum of this assay is 1.9% for repeatability and 4.7% for intermediate precision. Samples were diluted with Elecsys Diluent Universal (Roche Diagnostics GmbH, Mannheim, Germany) in case the cobalamin serum concentration exceeded the upper range of the assay.

A concentration-time graph was constructed for each patient using PK Solutions (version 2.0, Summit Research Services, Montrose, California). For each patient C_{max}, T_{max}, and $AUC_{0–48\ h}$ were determined using PK Solutions. The average of C_{max}, T_{max}, and $AUC_{0–48\ h}$ for the group receiving cobalamin intranasally and the group receiving cobalamin intramuscularly were also calculated using PK Solutions. Bioavailability of the intranasal administration was estimated by dividing the mean $AUC_{0–48\ h}$ after intranasal administration by the mean $AUC_{0–48\ h}$ after intramuscular administration.

In our pilot study a sample size of 10 was presumed sufficient to establish if intranasal administration could be a potential alternative for intramuscular administration in elderly patients. Data were tested for deviations from a normal distribution. Subsequently differences between both groups of patients in C_{max}, T_{max}, and $AUC_{0–48\ h}$ were tested for significance using ANOVA. The ANOVA was done using PASW Statistics (version 18, IBM-SPSS Inc, Armonk, NY). A P value ≤ 0.05 was considered statistically significant.

Results

Thirteen patients gave written informed consent. Three patients were excluded from the final analysis. One patient did not receive the study medication because the intravenous cannula could not be inserted. Analyses of blood samples of 2 patients failed due to incorrect handling. Ten patients were therefore included in the final analysis. The mean age of patients was 81 years (range = 70–91 years), the mean weight was 76 kg (range = 60–93 kg), and the mean baseline cobalamin serum concentration was 165 pmol/L (range = 100–250 pmol/L). Five patients received cobalamin by way of intranasal spray and 5 patients by way of intramuscular injection. Between the intranasal and intramuscular groups there were no significant differences in mean baseline cobalamin serum concentration, body mass index, and age (Table I).

The concentration-time graphs of the different patients following intranasal and intramuscular administration are presented in Figure 1. Similar overall changes in serum cobalamin concentration over time were determined among patients in the intranasal administration group (Figure 1A). The C_{max} varied between 0.5 and