European Journal of Pediatrics
https://doi.org/10.1007/s00431-019-03519-0

SHORT COMMUNICATION

Intranasal treatment of vitamin B_{12} deficiency in children

G. Frederiek Estourgie-van Burk[1] · P. Hugo M. van der Kuy[2] · Tim G. de Meij[3] · Marc A. Benninga[4] · C. M. Frank Kneepkens[3]

Received: 11 July 2019 / Revised: 27 October 2019 / Accepted: 29 October 2019

Abstract

Vitamin B_{12} deficiency is traditionally treated with intramuscular injections of cobalamin, which are stressful events for children. In adults, studies have shown adequate absorption of intranasally administered vitamin B_{12}. To date, data concerning efficacy of intranasal administration of vitamin B_{12} in children are lacking. We report on ten cases of children with vitamin B_{12} deficiency who were successfully treated with intranasal administration of a spray containing hydroxocobalamin. The mean baseline vitamin B_{12} concentration increased from 126.3 pmol/l (SD 55.4) to 1914.7 pmol/l (SD 1509.7). No side effects were reported.

Conclusion: In children, intranasal application of vitamin B_{12} seems a safe and effective alternative to intramuscular injections, leading to higher compliance and less burden to patients.

What is Known:
- *Children with vitamin B_{12} deficiency are traditionally treated with intramuscular cobalamin injections, which are costly and painful.*
- *Studies in adults showed that intranasal application of hydroxocobalamin leads to normalisation of vitamin B_{12} levels.*

What is New:
- *The intranasal application of vitamin B_{12} resulted in a substantial increase of the mean baseline vitamin B_{12} levels without any side effect.*
- *These data encourage a systematic evaluation of intranasal treatment of vitamin B_{12} deficiency in order to define safety, optimal dosage and administration frequency.*

Keywords Cobalamin deficiency · Hydroxocobalamin · Nasal spray · Paediatric

Abbreviations
MMA Methylmalonic acid

Introduction

Vitamin B_{12} (cobalamin) is a coenzyme involved in homocysteine and methylmalonic acid (MMA) metabolism, which is important for bone marrow and central nervous system. The main source of vitamin B_{12} is food of animal origin, such as meat, eggs and milk products. Vitamin B_{12} deficiency may lead to megaloblastic anaemia and bone marrow failure [8]. In infants and children, vitamin B_{12} deficiency may result in developmental delay, feeding difficulties and neurological symptoms such as hypotonia and even demyelinating nervous

Communicated by Mario Bianchetti

✉ G. Frederiek Estourgie-van Burk
f.estourgie@antoniusziekenhuis.nl

P. Hugo M. van der Kuy
h.vanderkuy@erasmusmc.nl

Tim G. de Meij
t.demeij@amsterdamumc.nl

Marc A. Benninga
m.a.benninga@amsterdamumc.nl

C. M. Frank Kneepkens
cmf.kneepkens@amsterdamumc.nl

[1] Department of Paediatrics, St. Antonius Hospital, PB 2500, 3430 EM Nieuwegein, The Netherlands

[2] Department of Clinical Pharmacy, Erasmus Medical Centre, Rotterdam, The Netherlands

[3] Department of Paediatric Gastroenterology and Nutrition, Amsterdam University Medical Centres, Location VU Medical Centre, Amsterdam, The Netherlands

[4] Department of Paediatric Gastroenterology and Nutrition, Amsterdam University Medical Centres, Location Academic Medical Centre/Emma Children's Hospital, Amsterdam, The Netherlands

Published online: 22 November 2019

system disease and convulsions. The reported prevalences of vitamin B_{12} in children vary between 7.7 and 45% [2, 4, 6].

Vitamin B_{12} deficiency is traditionally treated with intramuscular injections of cobalamin. The monthly injections, which often have to be continued for several years, are commonly painful and stressful events, especially for children, and costly if given by a health care professional. This might affect patient compliance and result in discontinuation of therapy. Another route for treating vitamin B_{12} deficiency is by oral or sublingual supplementation with daily high-dose vitamin B_{12}, which has been shown to be effective and safe in adults [1, 11]. However, there are no data in children and insufficient data in patients with malabsorptive conditions, such as short bowel syndrome.

The administration of medication via the intranasal route is increasingly considered a non-invasive alternative for injections, particularly in emergency care and with procedural sedation. Intranasal application of agents such as midazolam is considered effective and safe [5]. Intranasal vitamin B_{12} administration has been demonstrated as effective in adults [7]. In vitamin B_{12}–deficient children as well, intranasal application of vitamin B_{12} seems a promising alternative to intramuscular injections. Therefore, we would like to share our first experience with intranasal treatment of vitamin B_{12} deficiency in children.

Methods

We performed a retrospective chart review of paediatric patients with vitamin B_{12} deficiency, who were treated with intranasal hydroxocobalamin spray at the Amsterdam University Medical Centres since 2005. Clinical data were collected including age, sex, underlying medical condition, laboratory values, dosing regimen of intranasal hydroxocobalamin and side effects (Table 1). Plasma vitamin B_{12} (cobalamin) concentrations were determined through competitive immunoassay (Luminescence, Architect, Abbott Laboratories, Diagnostics Division, IL, USA). Intra- and inter-assay coefficients of variation (CV) with this technique are equal to or lower than 5% and 7%, respectively. Plasma MMA levels were measured using liquid chromatography electrospray ionisation tandem mass spectrometry [3], with intra- and inter-assay CV of less than 12%. Vitamin B_{12} deficiency was defined as a plasma cobalamin concentration below 200 pmol/l in combination with a MMA level above 0.32 μmol/l. Plasma cobalamin levels between 200 and 700 pmol/l were considered normal. Plasma cobalamin concentrations could be accurately determined up to 4400 pmol/l. For the intranasal application of vitamin B_{12}, a nasal spray was used containing per millilitre the following: 20 mg hydroxocobalamin, 2.7 mg sodium acetate, 5.5 mg sodium chloride, 1 mg sodium edetate and 0.1 mg benzalkonium chloride (US and EU patents). The solution has a pH of 4.5 and has a red colour. One puff of 100 μl results in the administration of 2 mg of hydroxocobalamin, with a bioavailability of 5.4% (Van der Kuy et al., unpublished). The hydroxocobalamin preparation used has not yet been approved by the European Medicines Agency or the Food and Drug Administration. The treatment schedules are listed in Table 1. Plasma vitamin B_{12} and MMA levels

Table 1 Patient characteristics and plasma vitamin B_{12} and MMA levels before and after start of treatment with intranasal hydroxocobalamin

Patient	Sex	Age (years)	Diagnosis	B_{12}* (pmol/l) Before	MMA (μmol/l)	Dose	B_{12}* (pmol/l) After	MMA (μmol/l)
1	M	14.7	Ulcerative colitis, deficient diet	72	NA	A	3433	NA
2	F	16.9	Vitamin B_{12} deficiency of unknown origin	140	NA	A	> 4400	NA
3	M	10	Short bowel syndrome	112	2.26	B	1000	NA
4	F	11.4	Pernicious anaemia (APECED syndrome)	251	2.13	B	4338	NA
5	F	16.2	Suspicion of pernicious anaemia	158	0.36	B	643	0.15
6	M	16.9	Crohn disease	129	NA	B	243	NA
7	F	7.2	Short bowel syndrome	61	NA	C	1071	NA
8	F	3.2	Short bowel syndrome	94	2.68	D	1476	0.10
9	F	17.3	Right-sided colitis	71	NA	D	456	NA
10	F	6	Short bowel syndrome	175	4.49	E	2060	0.18

M male, *F* female, *NA* not available

*Mean vitamin B_{12} level before and after start of treatment differ significantly (*t* test, $p = 0.008$)

Dose A one puff of the spray in both nostrils per day during 1 week, thereafter in one nostril per day. *Dose B* one puff in both nostrils once every week during 4 weeks, thereafter in one nostril per 2 weeks. *Dose C* one puff in one nostril per day during 4 weeks, thereafter in one nostril per week. *Dose D* one puff in both nostrils 2 days per week. *Dose E* one puff in both nostrils per week during 4 weeks, thereafter in one nostril per month

were checked at the next hospital visit. Descriptive analyses and paired t test were performed using Microsoft Office Excel, Microsoft, Redmond, WA. A value of $p < 0.05$ was considered a statistically significant difference.

Results

A total of 10 patients with vitamin B_{12} deficiency were treated with intranasal hydroxocobalamin (7 female; age 3–17 years). Clinical characteristics, underlying medical conditions, plasma vitamin B_{12} and MMA levels and treatment schedules are depicted in Table 1. The mean vitamin B_{12} concentration increased significantly from 126.3 pmol/l (SD 55.4) to 1914.7 pmol/l (SD 1509.7) (t test, $p = 0.008$). The time interval between measurements of vitamin B_{12} values before and after the start of treatment varied between patients from 47 to 266 days (median 101). Patients were treated with different dosing regimens, which were adapted in time according to the attained vitamin B_{12} levels. Length of follow-up ranged from 1 to 9 years (median 4). No side effects were reported. One patient switched to intramuscular therapy because the mother preferred intramuscular treatment (Table 1, patient 4). Compliance problems were documented in one case (Table 1, patient 6), which were reflected by the modest increase in vitamin B_{12} level after the start of treatment.

Discussion

To our knowledge, this is the first report to document paediatric data of intranasal treatment of vitamin B_{12} deficiency. We described results of 10 patients treated with hydroxocobalamin nose spray according to different dosing regimens. Vitamin B_{12} deficiency resolved in all patients without side effects.

Intranasal administration is thus a promising alternative for the stressful intramuscular injections to treat vitamin B_{12} deficiency in children. It seems preferable to the oral route because of the extremely low bioavailability of oral hydroxocobalamin requiring high doses during several months before the same effect is reached as with intramuscular therapy [11].

The vitamin B_{12} levels after the start of treatment vary greatly reflected by the high standard deviation of the mean, with levels above the upper limit of normal in seven out of ten cases. The different dosing regimens can explain part of the widespread in vitamin B_{12} levels. Furthermore, differences in nasal mucociliary clearance and variations in spraying technique may lead to intersubject differences. Remarkably, one patient switched to intramuscular therapy despite a large increase in serum vitamin B_{12} level after intranasal treatment, because the mother believed that intramuscular treatment is more effective.

This report carries several strengths. It describes an innovative and child-friendly way to treat vitamin B_{12} deficiency. Moreover, there was a long follow-up and vitamin B_{12} levels were assessed in a standardised way. However, there clearly are also some limitations. First, it is a retrospective study with a small group size. A further limitation is that patients were treated according to different dosing regimens, as the appropriate dosing protocol was not yet established. In addition, no pharmacokinetic data were assessed and there was no standardised assessment of compliance and follow-up.

The plasma vitamin B_{12} concentrations achieved after intranasally administered hydroxocobalamin were above the therapeutic range in part of our patients. This could simply be addressed by lowering the administration frequency. No side effects were reported in our patients, nor in adults treated with intranasal vitamin B_{12} [7, 9]. Toxicity is rare, although symptoms such as diarrhoea and skin reactions have been described after the *intramuscular* administration of hydroxocobalamin [10]. It should be noted that intramuscular injection of hydroxocobalamin results in much higher plasma vitamin B_{12} levels than intranasal administration [9]. There are no studies available on pharmacokinetics of vitamin B_{12} supplementation in children. Further research is needed to provide information on the optimal dosage and administration frequency and the minimal age of children who qualify for this treatment, and to assess patient compliance and possible adverse effects. Treatment of vitamin B_{12} deficiency in children, either by the intramuscular or intranasal route, should take place under medical supervision to check plasma vitamin B_{12} levels and adjust, if necessary, the dosing regimen. Patients should be informed about the non-licensed status of the product and the red colour of the solution, which may result in red-coloured nasal discharge.

Notwithstanding the theoretical advantages of intranasal application of cobalamin in terms of costs and burden on patients, the number of studies is surprisingly limited and confined to adults. Our preliminary data should encourage the systematic evaluation of intranasal treatment and follow-up of vitamin B_{12} deficiency in children.

Authors' contributions All authors contributed to the study conception and design. Acquisition of the data was performed by FE, TdM, MB and FK. FE, HvdK and FK were involved in data interpretation. The first draft of the manuscript was written by FE. FE and FK wrote the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all participants.

References

1. Bensky MJ, Ayalon-Dangur I, Ayalon-Dangur R, Naamany E, Gafter-Gvili A, Koren G, Shiber S (2019) Comparison of sublingual vs. intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency. Drug Deliv Transl Res 9:625–630. https://doi.org/10.1007/s13346-018-00613
2. Benson J, Phillips C, Kay M, Webber MT, Ratcliff AJ, Correa-Velez I, Lorimer MF (2013) Low vitamin B12 levels among newly-arrived refugees from Bhutan, Iran and Afghanistan: a multicentre Australian study. PLoS One 8:e57998. https://doi.org/10.1371/journal.pone.0057998
3. Blom HJ, van Rooij A, Hogeveen M (2007) A simple high-throughput method for the determination of plasma methylmalonic acid by liquid chromatography-tandem mass spectrometry. Clin Chem Lab Med 45:645–650. https://doi.org/10.1515/CCLM.2007.117
4. Cuevas-Nasu L, Mundo-Rosas V, Shamah-Levy T, Méndez-Gómez Humaran I, Avila-Arcos MA, Rebollar-Campos Mdel R, Villalpando S (2012) Prevalence of folate and vitamin B12 deficiency in Mexican children aged 1 to 6 years in a population-based survey. Salud Publica Mex 54:116–124
5. Miller JL, Capino AC, Thomas A, Couloures K, Johnson PN (2018) Sedation and analgesia using medications delivered via the extravascular route in children undergoing laceration repair. J Pediatr Pharmacol Ther 23:72–83. https://doi.org/10.5863/1551-6776-23.2.72
6. Pawlak R, Lester SE, Babatunde T (2014) The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. Eur J Clin Nutr 68:541–548. https://doi.org/10.1038/ejcn.2014.46
7. Slot WB, Merkus FW, Van Deventer SJ, Tytgat GN (1997) Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. Gastroenterology 113:430–433. https://doi.org/10.1053/gast.1997.v113.pm9247460
8. Stabler SP (2013) Clinical practice. Vitamin B12 deficiency. N Engl J Med 368:149–160. https://doi.org/10.1056/NEJMcp1113996
9. Tillemans MP, Donders EM, Verweij SL, Van der Hoeven RT, Kalisvaart KJ (2014) Effect of administration route on the pharmacokinetics of cobalamin in elderly patients: a randomized controlled trial. Curr Ther Res Clin Exp 76:21–25. https://doi.org/10.1016/j.curtheres.2014.01.001
10. U.S. National Library of Medicine. TOXNET Toxicology Data Network. Hydroxocobalamin. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~rpdPVM:3. Accessed 26 Oct 2019
11. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH (2018) Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency. Cochrane Database Syst Rev 3:CD004655. https://doi.org/10.1002/14651858.CD004655.pub3