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ORIGINAL PAPER

Acceptance of two liquid vitamin D_3 formulations among mothers with newborn infants: a randomized, single-blind trial

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Abstract In Switzerland, children are prescribed 7.5–12.5 μg per day of vitamin D_3 dissolved in alcohol, but many families do not adhere to the recommendation. The aim of the trial was to compare the acceptance of vitamin D_3 dissolved in alcohol or in medium-chain triglycerides among mothers of Swiss newborn infants. The acceptance was tested in 42 healthy newborn infants (20 girls and 22 boys) aged between 2 and 7 days. Their neonatal body weight ranged between 2.225 and 4.150 kg, and the gestational age between 36 1/7 and 41 3/7 weeks. The blinded mothers rated the facial reaction of their children by pointing on a facial hedonic scale. Thirty eight of the 41 mothers, who brought the comparison to completion, assigned a better score to the oily preparation with no difference in the remaining three cases ($P<0.0001$). The acceptance for the oily preparation was significantly better both among mothers whose babies were initially presented the alcoholic preparation and among mothers whose babies were initially presented the oily preparation. Furthermore, the acceptance for the oily preparation was better irrespective of gender of the infant or parity of the mother. In conclusion, from the perspective of mothers, Swiss newborn infants prefer the taste of the oily vitamin D_3 preparation over the alcoholic preparation.

Keywords Newborn · Palatability · Preference · Vitamin D

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Introduction

Vitamin D deficiency rickets is an ancient disease, which was thought to have been cured in the early twentieth century [14]. However, despite the availability of vitamin D and demonstration of its usefulness in preventing rickets, vitamin D deficiency rickets still exists as a major health problem with significant morbidity in developing countries all over the world including Africa and South America, and has been reported with increasing prevalence in minority groups in North America and in immigrant populations in Australia, New Zealand, and Europe [14]. In many countries, there are reports of a high prevalence of subclinical vitamin D deficiency in childhood [8].

In addition to rickets and other possible consequences of disturbed calcium homeostasis, vitamin D deficiency in infancy and early childhood might increase the incidence of diabetes mellitus and the risk of tuberculosis, pneumonia, influenza, and other respiratory tract infections [1, 8, 16].

Finally, vitamin D deficiency predisposes to further disease states including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and perhaps some forms of cancer [1, 8].

In the USA, to prevent vitamin D deficiency, it is currently recommended that all children receive 10.0 μg[1] per day of vitamin D from their first days of life through adolescence [18]. In Switzerland, children receive 7.5 to 12.5 μg of vitamin D_3 in an alcoholic solution beginning during the first month of life [11]. Unfortunately, in Switzerland, approximately 50% of the families do not adhere to the recommendation, either because they consider unsatisfactory the palatability of the alcoholic vitamin D_3 preparation or because they oppose "alcoholic drugs" for socio-cultural reasons [3, 7, 13].

The purpose of the present study with healthy newborn infants and their mothers was to compare the acceptance of the standard alcoholic vitamin D_3 preparation with that of a new preparation that contains vitamin D_3 dissolved in medium-chain triglycerides.

Subjects and methods

The single-blind test was performed with 42 Swiss singleton newborn infants with gestational age of $36^{0/7}$ weeks or more and neonatal body weight of 2.000 kg or more and their mothers. None of them had been previously exposed to a vitamin D_3 preparation. The infants were recruited and tested immediately before discharge from the well baby nursery, Ospedale della Beata Vergine, Mendrisio (Switzerland), from 1 March through to 30 April 2010.

Gestational age was assessed from the mother's last menstrual period, unless the mother's dates were in doubt, when gestational age was assigned postnatally using the New Ballard Score [2]. The body weight was considered appropriate for gestational age in newborn infants with a birth weight between the 10th and the 90th percentiles according to the birth weight-for-gestational age charts. An umbilical cord artery pH of 7.15 or more and a neonatal Apgar sum score of 7 or more at 1 and 5 min were used to indicate a newborn infant in good condition.

The study design had been approved by the Institutional Review Board, and informed consent was obtained from the mothers of the infants. Acceptance was determined by the single administration of two liquid cholecalciferol formulations commercialized by Wild AG, Basel, Switzerland: (a) one drop of the standard preparation Vi-De3® ("alcoholic vitamin D_3"), which contains vitamin D_3 dissolved in 65% ethanol (113 μg/mL, corresponding to 2.5 μg per drop) and (b) one drop of Vitamin D3 Wild® ("oily vitamin D_3"), which is available since 2009 and contains vitamin D_3 dissolved in medium-chain triglycerides (500 μg/mL, corresponding to 12.5 μg per drop). After the mother gave informed consent, the interviewer took the enrolled newborn baby and the mother to the test area. Each study consisted of a session lasting approximately 5–10 min. The acceptance was determined by a single-blind taste test of one drop of both the alcoholic and the oily vitamin D_3 formulations. Immediately thereafter, the blinded mother was asked to rate the hedonic facial reaction of the infant by pointing on a scale that depicts 4 degrees of pleasure: 4="good," 3="not sure," 2="bad," 1="really bad" [6, 9]. Between the tasting of the two formulations, the baby received some milk to rinse its mouth (the time between the tasting of the two formulations was at least 3 min).

An independent statistician had generated a randomization list to balance the order of presentation of the preparations so that each preparation was tasted first an equal number of times and prepared 42 sequentially numbered, opaque sealed envelopes containing the assignment. The envelopes were opened in sequence after accompanying the infant with the mother to the test area.

Since a sample size of 20 is considered appropriate for this type of study [6], we performed *ad abundantiam* the test in 42 newborns and their mothers. The scores from the hedonic scales were analyzed using the Wilcoxon matched paired signed rank test. Significance was assumed when $P<0.05$ (two tailed).

Results

The 42 Caucasian mothers recruited for the comparison had born 20 girls and 22 boys with a neonatal body weight ranging between 2.225 and 4.150 kg and a gestational age ranging between $36^{1/7}$ and $41^{3/7}$ weeks (Table 1). Eighty-three percent of the infants had been delivered vaginally, and the neonatal body weight was appropriate for gestational age in 88% of them. The umbilical cord artery pH and the neonatal Apgar sum score failed to detect perinatal or neonatal alarm indicators in 98% and 88% of them, respectively.

The 42 children were between 2 and 7 days of age when the acceptance test was performed. The secundiparous mother of a vaginally born, breastfed boy with a neonatal body weight of 2.845 kg and a gestational age of $37^{5/7}$ weeks initially offered the alcoholic vitamin D_3 preparation was not able to rate the facial reaction of her baby. Thirty eight of the 41 mothers, who brought the comparison to completion, assigned a better facial score to the oily vitamin D_3 preparation, with no difference

[1] Multiply the number of micrograms by 40 to convert micrograms to international units.

Table 1 Characteristics of 42 Caucasian newborn infants recruited for the present study

Variable	
Gender, ♀/♂	20:22
Age, days	4 (3–5)
Mother nulliparous, *N*	14 (33%)
Vaginal delivery, *N*	35 (83%)
Gestational age	
Duration, weeks	$39^{0/7}$ ($37^{6/7}$–$39^{5/7}$)
Duration, $37^{1/7}$ weeks or more, *N*	38 (90%)
Neonatal body weight	
Absolute value, kg	3.125 (2.850–3.470)
Appropriate for gestational age, *N*	37 (88%)
Umbilical cord artery pH ≥7.15, *N*	41 (98%)
Apgar score ≥7 at 1 and 5 min, *N*	37 (88%)
Breastfeeding, *N*	38 (90%)

The results are given either as median with interquartile range, which includes half of the data points, or as relative frequency with percentage

between the two preparations in the remaining three cases. From the perspective of the mothers, none of the infants preferred the alcoholic preparation. The difference between the two preparations was highly significant ($P<0.0001$, Fig. 1). Moreover, the mothers never evaluated the alcoholic vitamin D_3 preparation as "good" or "not sure."

The test preference was similar among 20 mothers whose babies were initially presented the alcoholic vitamin D_3 preparation (better score for oily vitamin D_3, $N=18$; no difference, $N=2$; $P<0.0002$) and among 21 mothers whose babies were initially presented the oily vitamin D_3 preparation (better score for oily vitamin D_3, $N=20$; no difference, $N=1$; $P<0.0001$). Furthermore, the acceptance for the oily vitamin D_3 preparation was significantly higher both among mothers of 21 boys (better score for oily vitamin D_3, $N=20$; no difference, $N=1$; $P<0.0001$) and among mothers of 20 girls (better score for oily vitamin D_3, $N=18$; no difference, $N=2$; $P<0.0002$). Finally, the acceptance for the oily vitamin D_3 preparation was significantly better both among 14 nulliparous (better score for oily vitamin D_3, $N=13$; no difference, $N=1$; $P<0.0002$) and among 27 non-nulliparous (better score for oily vitamin D_3, $N=25$; no difference, $N=2$; $P<0.0001$) mothers.

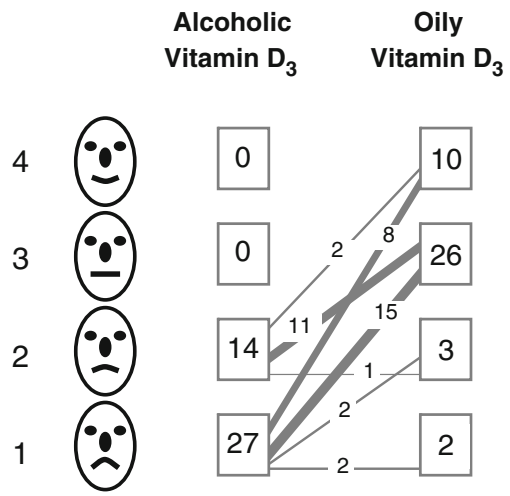

Fig. 1 Acceptance of alcoholic vitamin D_3 and oily vitamin D_3 among mothers of 41 Caucasian newborn infants (20 girls and 21 boys), who brought the trial to completion. The difference between the two preparations was highly significant ($P<0.0001$). The reaction of the child was rated using a facial hedonic scale depicting the following degrees of pleasure: 4="good," 3="not sure," 2="bad," 1="really bad." The figure indicates among others that 27 mothers graded oily vitamin D_3 as "really bad" and 10 graded oily vitamin D_3 as "good"

Discussion

The present study tested the acceptance of two liquid preparations that contain vitamin D_3 dissolved either in alcohol or in medium-chain triglycerides among mothers of healthy newborn infants. The results demonstrate that the acceptance for the oily vitamin D_3 preparation is significantly superior to that of the alcoholic preparation.

In this trial, the acceptance of the two vitamin D_3 formulations among mothers of newborn infants was assessed with 2.5 μg of alcoholic and 12.5 μg of oily vitamin D_3. The use of identical doses, obviously a situation closer to reality, might have further advantaged the oily preparation.

Facial hedonic scales have achieved a large popularity to determine the degree of liking for foods and beverages [4, 5, 12]. Three- to 5-point facial hedonic scales like those used in the present trial have been widely used to evaluate the acceptance for drug suspensions and for crushed drugs with children 4 years or more of age [6]. The scales were also used to assess the taste of liquid drugs in newborns and small infants [6, 9]. Like in other trials performed with children 3 years or less of age, in the present study, infant facial reactions following drug administration were interpreted by the parents to score acceptance [6, 9].

The major limitation of the study resides in the fact that facial hedonic scales, albeit frequently used and very popular, still are unvalidated tools for assessing acceptance of drug formulation or measuring pain among newborn infants [6, 17].

The clear-cut preference for oily vitamin D_3 observed in the present trial might be related to the burning sensation in the throat that is caused by 65% ethanol [9]. This has generated the impression that alcohol has a strong taste [3]. The poor palatability of alcoholic vitamin D_3 is not associated with some toxic potential. As a matter of fact, the daily dose of this preparation contains an insignificant amount of ethanol.

Nonetheless, unfounded concerns related to the alcohol content of vitamin D preparations are not rare [3].

Most Swiss infants are currently prescribed either 10.0 μg per day of vitamin D_3, i.e., four drops of the standard alcoholic preparation, or 12.5 μg per day, i.e., one drop of the new oily preparation. In some cases, switching from the standard alcoholic to the new alcoholic preparation resulted in an excessive intake of 50.0 μg per day of vitamin D_3 [15].

The results of the present report are supported by those of a study which indicates that in newborn infants the acceptance for vitamin D_3 dissolved in peanut oil is superior to that of vitamin D_3 dissolved in ethanol [9]. Since the prevalence of peanut allergy is increasing in recent years, some authorities currently recommend not to introduce peanuts for the first 6 months of life [10]. This advice is based on the findings of studies which suggest that exposure to peanuts in early life may increase the risk of peanut allergy [10].

Conclusion

Appreciating the preference for drug preparations in childhood is of great value [6]. This small trial indicates that from the perspective of mothers of Swiss newborn infants, the taste of oily vitamin D_3 is significantly better than that of alcoholic vitamin D_3.

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