BIOEQUIVALENCE STUDY 2010 Comparison of the absorption of MK-7 after intake of 3 different existing MK-7 supplements

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The primary objective of the study is to compare the absorption of MK-7 after intake of 3 different MK-7 supplements.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vitamin related disorders
Study type	Interventional

Summary

ID

NL-OMON34781

Source
ToetsingOnline

Brief title
BIOEQUIVALENCE STUDY 2010

Condition

- Vitamin related disorders

Synonym
Vitamin K2 deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Nattopharma,VitaK BV

Intervention

Keyword: Absorption, Menaquinone-7, Vitamin K2

Outcome measures

Primary outcome

Circulating MK-7 levels will be measured at the various points in time: at

baseline (before sampling), and 2, 4, 6, 8, 24, 48 and 96 hours after MK-7

supplementation to determine the MK-7 absorption profiles.

Secondary outcome

NVT

Study description

Background summary

Vitamin K is a group name for a family of related compounds, generally divided into the naturally occurring phylloquinone (vitamin K1) and menaquinones (MK-n; K2 vitamins). The latter can be subdivided into the short-chain menaquinones (e.g. MK-4) and the long-chain menaquinones (e.g. MK-7, MK-8, and MK-9). All K vitamins share a common 2-methyl-1,4-naphthoquinone nucleus, substituted at the 3-position with different polyisoprenoids. Vitamin K1 (K1) is distributed in green leafy vegetables and vegetable oils. K2 vitamins (K2) make up about 10% of vitamin K consumption and are found in animal products, such as meat, egg yolk, and dairy products. The higher menaquinones can also be synthesized by gut bacteria; however the vitamin K contribution from this source to general health is not fully understood. Natto, a Japanese fermented (using Bacillus subtilis natto) soybean product, contains substantial amounts of MK-7, the most bioavailable form of K2.
New research showed that increased K2 intake strongly reduced the risk of coronary heart disease (CHD). In contrast, consumption of K1 had no effect on vascular health. The reduction in CHD risk was tied to the higher menaquinones. Higher menaquinones are more efficiently absorbed than K1, suggesting that K1 and K2 may contribute similarly to the body*s vitamin K supply. Most of K1 is carried by the triacylglycerol-rich lipoproteins (chylomicrons and VLDL) in the circulation and rapidly cleared to tissue (mainly liver); a small amount is also carried by LDL and HDL. The higher menaquinones are observed in the same classes of lipoprotein particles as K1, but appear to have a different

distribution (predominantly LDL). Since LDL has a long half-life time in the circulation, these menaquinones may have better bioavailability for extra-hepatic tissue uptake compared to K1. Consumption of higher menaquinones may therefore be important for vitamin K functions not related to blood coagulation, such as regulation of calcium deposition in bone and prevention of arterial calcification.
As the Western diet is likely deficient in vitamin K, supplementation or enrichment with these higher menaquinones is an obvious choice. At present, MK-7 is the only natural vitamin K2 on the market; the potential market size for MK-7 is considered to be extremely large. We are interested to compare the absorption of MK-7 after intake of 3 different MK-7 products that are already on the market.

Study objective

The primary objective of the study is to compare the absorption of MK-7 after intake of 3 different MK-7 supplements.

Study design

After meeting the inclusion criteria, study participants will be randomized into six groups and will receive three different types of capsules as a single dose (75 µg of MK-7/day): MenaQ7 M-1500 capsule, Gnosis P-1000 capsule, and Gnosis M-1500 capsule. Every two weeks, participants switch to another type of capsule; the washout period (WO) will therefore be two weeks. Each group will consist of four volunteers with (approximately) equal numbers of men and women. After meeting the inclusion criteria, 3x four intervention days (for each MK-7 product four visits) will be planned during a period of 9 weeks. On the first intervention day, the first blood sample will be taken at 08.00 AM. Immediately after sampling, participants will receive a standardized breakfast [three slices of brown bread with chocolate paste or margarine&jam, and two glasses of juice (orange juice or fruit&milk beverage)] and take the first type of MK-7 capsule. Subsequently, blood will be sampled at 10.00 AM, 12.00 PM, 14.00 PM, 16.00 PM, and at 08.00 AM on Tuesday, Wednesday, and Friday. After the sampling at 12.00 PM, participants will receive a standardized lunch (similar as the standardized breakfast).

Intervention

After meeting the inclusion criteria, 3x four intervention days (for each MK-7 product four visits) will be planned during a period of 9 weeks. On the first intervention day, the first blood sample will be taken at 08.00 AM. Immediately after sampling, participants will receive a standardized breakfast [three slices of brown bread with chocolate paste or margarine&jam, and two glasses of juice (orange juice or fruit&milk beverage)] and take the first type of MK-7 capsule. Subsequently, blood will be sampled at 10.00 AM, 12.00 PM, 14.00 PM,

16.00 PM, and at 08.00 AM on Tuesday, Wednesday, and Friday. After the sampling at 12.00 PM, participants will receive a standardized lunch (similar as the standardized breakfast).
Two weeks before the start of the study and during the study, subjects will be asked to refrain from consuming foods rich in K1 (spinach, kale, broccoli, Brussels sprouts) and rich in K2 (curd cheese, cheese, natto). The subjects will also be instructed to report any signs of illness, medication used, and any deviations from the study protocol.

Study burden and risks

No adverse effects are to be expected from supplementing MK-7.
The major burden for the subjects will be the 25 venapunctions.
Participants will be asked to arrive for each study visit after a fast of at least 8 hours. On the morning of sampling, subjects are not allowed to eat or to drink (except water). In addition, subjects are not allowed to drink alcohol 24 hours before sampling. All venipunctures will be performed by experienced researchers. The risks for the subjects are minimal. Another major burden is the abstaining from foods rich in K1 (spinach, green kale, broccoli, Brussels sprouts) and rich in K2 (curd cheese, cheese, natto) during 9 weeks.
Other minor restrictions:
• Replication of smoking schedule at all sampling visits
• Standardization of physical activity during the 24 hours prior to each study visit

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Healthy men and women, aged between 20 and 40 years
* Normal body weight and height (18.5 kg/m2 < BMI <30 kg/m2)
* Stable body weight (weight gain or loss <3 kg in past 3 mo)
* Written consent to take part in the study
* Agreement to adhere to dietary restrictions required by the protocol

Exclusion criteria

* Abuse of drugs and/or alcohol
* Use of vitamin supplements containing vitamin K
* Soy allergy
* Pregnancy
* (a history of) metabolic or gastrointestinal diseases including hepatic disorders
* Chronic degenerative and/or inflammatory diseases, e.g. diabetes mellitus, renal failure
* Use of oral anticoagulants
* Corticoid treatment
* Subjects with anaemia or subjects who recently donated blood or plasma
* Systemic treatment or topical treatment likely to interfere with coagulation metabolism (salicylates, antibiotics)
* Chronic degenerative and/or inflammatory diseases
* Use of oral anticoagulants
* Corticoid treatment
* Systemic treatment or topical treatment likely to interfere with evaluation of the study parameters

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2010
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	08-11-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL31496.068.10
Other	Zal geregistreerd worden