BIOAVAILABILITY

Vitamin K2 Fact Sheet

Introduction

Vitamin K2 is important for bone and cardiovascular health. The vitamin K2s are essential co-factors for carboxylation of glutamate residues in certain proteins (Gla-proteins). Two important Gla-proteins are osteocalcin (OC) and matrix Gla-protein (MGP), involved in building of bone and prevention of calcification of blood vessel, respectively. Vitamin K is essential for their function (Schurgers et al. 2007, Cranenburg et al. 2007).

It has been demonstrated in clinical trials that vitamin K plays an important role for bone mineralization and may have a preventive effect on the development of osteoporosis (Review by Iwamoto et al. 2009). Vitamin K status is inversely associated with serum level of the inactive form of OC (undercarboxylated, ucOC).

Undercarboxylated osteocalcin ucOC is a recognized biomarker for vitamin K status. In the healthy adult population about 30% of the circulating osteocalcin occurs as ucOC (Knapen et al. 2007; Schurgers et al. 2004), and increased vitamin K intake results in a rapid decline of ucOC (Braam et al. 2003; Sokoll et al. 1997), suggesting subclinical vitamin K deficiency in "healthy" bone tissue. In a large prospective study among older men and women, high intake of vitamin K2 was associated with significantly lower degree of aortic calcification and lower incidence of coronary heart disease (the Rotterdam Study, Geleijnse et al. 2004).

Mainly two forms of vitamin K exist in food supplements today; synthetic phylloquinone (K1) and fermentation produced menaquinone-7 (K2 as MK-7); the latter based on *Bacillus subtilis natto* fermented soybeans. Studies have shown that MK-7 has superior bioavailability and better effects on the vitamin K dependent proteins, OC and MGP compared to K1 (Schurgers et al. 2007, Cranenburg et al. 2007). However, dietary intake of MK-7 in westernized populations is generally very low, and not optimal for bone or vascular health. (Booth and Sutti, 1998; Drevon et al. 2004). Supplementation with vitamin K2 as MK-7 may thus play a crucial role in preventing cardiovascular disease and poor bone health – the latter often related to development of osteoporosis (Shearer 1997; Cranenburg et al. 2007).

Kappa Bioscience is a pioneer in producing biologically active all-trans menaquinone-7 (K2VITAL®). Kappa Bioscience has carried out a clinical study in order to demonstrate bioequivalence between K2VITAL® and fermentation produced soy based MK-7.

Overall conclusion

K2VITAL® and fermentation produced soy based MK-7 are demonstrated to be bioequivalent.

Part I - Single Dose Bioavailability

In a cross-over study the objective was to compare the pharmacokinetics of MK-7 following intake of a single dose of 180 µg K2VITAL® versus fermentation produced based MK-7.

Sixteen subjects were given MK-7 either as fermentation produced based MK-7 or K2VITAL® with three weeks interval between the cross over. Large inter-individual variations were observed in MK-7 absorption from both products. Maximum average serum concentration of MK-7 was approx. 3 ng/mL at 5 to 6 hours after ingestion of fermentation produced based MK-7 and K2VITAL®. (This corresponds with data from Schurgers et al. (2007) taking the difference in dose into consideration.)

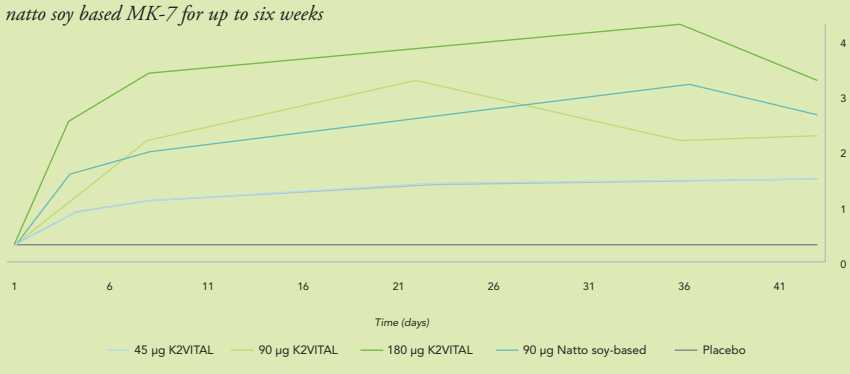
No significant difference in area under the concentration curve (AUC) could be demonstrated between fermentation produced based MK-7 and K2VITAL®, which implies that the same amount of MK-7 was absorbed over time for the two products.

The half life of MK-7 could not be determined accurately since most subjects still had MK-7 in their blood after 72 hours. This is in accordance with results from Schurgers et al. 2007. They estimated the half life of MK-7 to be approximatly three days. This is in strong contrast to vitamin K1 and menaquinone- 4 (MK-4), which both have half-lives of only 1-3hrs (Schurgers et al. 2002 and 2007).

Conclusion

K2VITAL® was shown to be bioequivalent with fermentation produced based MK-7 when comparing plasma level of MK-7 after administration of a single dose. Moreover, no significant difference was demonstrated between the two products for the parameters; area under the concentration curve (AUC), concentration maximum (Cmax) and time maximum (Tmax).

Figure 1: Plasma level of vitamin K2 (MK-7), after administration of different doses of K2VITAL® and natto soy based MK-7 for up to six weeks



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Part II - Biological function at steady state

MK 7 concentration in plasma after 6 weeks

In the biological function study, healthy subjects were divided into five groups and given three doses (45 µg, 90 µg and 180 µg) of K2VITAL®, 90 µg fermentation produced based MK-7 or placebo for six weeks. The results are presented in Figure 1. The plasma concentration increased in time with a plateau after approx. 3 weeks (The variations observed were partly due to some subjects forgetting to take the daily capsules at some time points).

Conclusion

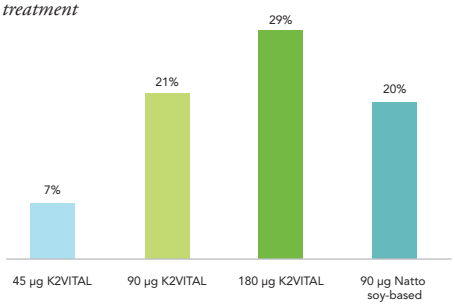
A close to linear dose-response relationship was observed for plasma concentration of MK-7 after administration of three different dosages of K2VITAL® for six weeks; supported by statistical significant increase of the AUC between the different dosages.

Furthermore, no significant difference in AUC was observed between K2VITAL® and natto based MK-7 after administration of 90 µg of MK-7 over six weeks.

Effect of intake of MK 7 on biomarkers in blood

Since vitamin K status is inversely associated with ucOC level in blood, serum values of ucOC were measured as sensitive biomarkers for human vitamin K status during the six weeks period. The results are presented in Figure 2.

Figure 2: Relative reduction in ucOC concentration in blood samples compared to baseline after 6 weeks of treatment



Conclusion

In the group receiving 180 µg K2VITAL®, a statistically significant increase in cOC and a corresponding decrease in ucOC were observed at all time points compared to baseline. No difference was observed between K2VITAL® and fermentation produced based MK-7 regarding the ability to reduce ucOC level in blood after six weeks.

K2VITAL® - The Vitamin of Tomorrow

K2VITAL® is currently the only product based on pure MK-7 to facilitate the optimal bioavailability and effect in non-activated GLA proteins such as osteocalcin and MGP.

Application Field	K2VITAL® MCC Microcrystalline cellulose powder	K2VITAL® MCT OIL Medium chain triglyceride oil	K2VITAL® DELTA Microencapsulated powder
Food based (low fat basis)			✓
Food based (adequate fat basis)		✓	
Beverages (no fat base)*			✓
Beverages (with fat base, eg Dairy)		✓	
Powdered Beverage Formulation			✓
Compressed Tablets (without minerals)	✓		
Compressed Tablets (with minerals)			✓
Soft Gel Capsules		✓	
Hard Gel Capsules	✓		✓
Dietary Powder Formulation			✓

**Stability tests are ongoing*

Country of origin: USA & Europe

References: *For Appendix information, please go to: www.kappabio.com/references*

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ABOUT KAPPA BIOSCIENCE

Kappa Bioscience AS, a Norwegian entity, is the innovative leader and first mover with its patent protected high purity, all-trans vitamin K2 as menaquinone-7 (MK-7). Driven by our core vision to make Vitamin K2 MK-7 available for everyone, we own and manage the whole value chain - from production to sales. Kappa Bioscience has substantial resources and knowledge about vitamins and vitamin K2 in particular. We deliver our vitamin K2, branded as K2VITAL® on various commercially suitable carriers, such as MCC, MCT & microencapsulated powder.