Menadione is a metabolite of oral vitamin K

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Phylloquinone is converted into menaquinone-4 and accumulates in extrahepatic tissues. Neither the route nor the function of the conversion is known. One possible metabolic route might be the release of menadione from phylloquinone by catabolic activity. In the present study we explored the presence of menadione in urine and the effect of vitamin K intake on its excretion. Menadione in urine was analysed by HPLC assay with fluorescence detection. Urine from healthy male volunteers was collected before and after administration of a single dose of K vitamins. Basal menadione excretion in non-supplemented subjects (n 6) was 5·4 (sd 3·2) µg/d. Urinary menadione excretion increased greatly after oral intake of the K vitamins, phylloquinone and menaquinone-4 and -7. This effect was apparent within 1–2 h and peaked at about 3 h after intake. Amounts of menadione excreted in 24 h after vitamin K intake ranged, on a molar basis, from 1 to 5 % of the administered dose, indicating that about 5–25 % of the ingested K vitamins had been catabolized to menadione. Menadione excretion was not enhanced by phylloquinone administered subcutaneously or by 2·3-dihydrophylloquinone administered orally. In archived samples from a depletion/repletion study (Booth et al. (2001) Am J Clin Nutr 74, 783–790), urinary menadione excretion mirrored dietary phylloquinone intake. The present study shows that menadione is a catabolic product of K vitamins formed after oral intake. The rapid appearance in urine after oral but not subcutaneous administration suggests that catabolism occurs during intestinal absorption. The observations make it likely that part of the menaquinone-4 in tissues results from uptake and prenylation of circulating menadione.

Menadione: Phyloquinone: Metabolism: Menaquinone-4: Vitamin K

Vitamin K is essential for the modification of glutamic acid residues of specific substrate proteins into γ-carboxyglutamatic acid (Gla) residues. Examples of Gla-containing proteins are the clotting factors II, VII, IX and X, which are synthesized in the liver. Other examples, synthesized by various tissues, are bone Gla-protein, matrix Gla-protein, protein S and gas-6 (Shearer, 2000; Berkner & Runge, 2005).

Two molecular forms of natural vitamin K can be distinguished that differ in the alkyl side chain at the 3-position of the common 2-methyl-1,4-naphthoquinone group: plant-derived phyloquinone (vitamin K1), which contains the phytol group as the side chain, and the bacterial-derived vitamin K2 group or menaquinones, with a polyisoprenyl side chain. The number of isoprenyl units may vary from six to thirteen (Conley & Stein, 1992). The daily dietary intake of vitamin K is mainly (>90 %) in the form of phyloquinone. Menaquinones may be present in low levels in food products, especially those whose processing contains fermentation steps (Schurgers & Vermeer, 2000). Absorption of dietary K vitamins from the proximal intestine occurs via the chylomicron and lymphatic pathway and, in the early postprandial state, is found largely associated with triacylglycerol-rich lipoproteins (Shearer et al. 1974; Kohlmeier et al. 1996; Schurgers & Vermeer, 2002). Absorption of bacterial menaquinones synthesized by the gut microflora may also occur, as evidenced by their presence in liver (Usui et al. 1989; Thijssen & Drittij-Reijnders, 1996).

A remarkable observation in vitamin K disposition is the conversion of phyloquinone into menaquinone-4, a non-bacterial menaquinone. The conversion, or at least the menaquinone-4 accumulation, appears to be localized mainly in extrahepatic tissues. Typically, tissues such as pancreas, salivary gland and brain contain menaquinone-4 levels exceeding those of phylloquinone (Thijssen & Drittij-Reijnders, 1994, 1996; Thijssen et al. 1996). This phyloquinone–menaquinone-4 conversion was first reported for birds (pigeon and chicken) in the early 1960s (Billetter & Martius, 1960). It was postulated that the side chain of phyloquinone is removed by metabolic activity of the gut flora and that the released menadione is then absorbed and converted into menaquinone-4 in tissues (Billetter et al. 1964). Menadione (vitamin K3) is known to be transformed into menaquinone-4, thereby exerting its vitamin K activity (Taggart and Matschiner, 1969). However, recent studies using germ-free rats showed that the conversion of phyloquinone to menaquinone-4 was independent of the gut flora (Davidson et al. 1998; Ronden et al. 1998).

Abbreviation: Gla, γ-carboxyglutamatic acid.

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The pathway of the conversion is unclear but at least two routes can be postulated: first, desaturation of the phytol side chain to produce the geranylgeranyl group of menaquinone-4; second, removal of the phytol side chain to release menadione, which is subsequently prenylated. One possibility is that both side-chain removal as well as the subsequent prenylation is a concerted metabolic activity specific to certain tissues. Cell cultures were reported to convert phylloquinone into menaquinone-4 (Davidson et al. 1998; see also p. 262). A second possibility is that the removal of the phytol group is a catabolic activity of a central compartment in the body (e.g. the liver) from which menadione is released into the circulation and prenylated by the target tissue. In the latter scenario it is to be expected that menadione will also be excreted, in the form of conjugates, in urine. The experiments reported herein demonstrate that the intake of K vitamins stimulates the urinary excretion of menadione, strongly indicating that the alkyl side chain of both phylloquinone and menaquinones is removed during their uptake and distribution in the body. Furthermore, basal menadione excretion was found to reflect dietary phylloquinone intake.

Materials and methods

Menadione assay

Menadione is excreted in urine in the form of conjugates, glucuronides and sulfates, of menadione, the reduced form of K vitamins (Losito et al. 1967). To hydrolyse the conjugates and to oxidize the released menadionol to menadione, urine was treated with a sulfuric acid–dichromate mixture. To 0·5 ml urine was added 0·035 ml potassium dichromate, 0·1 mol/l, in sulfuric acid, 0·35 mol/l. The mixture was heated for 30 min at 60°C. After cooling to room temperature and neutralizing with 0·045 ml sodium carbonate buffer (1 mol/l, pH 9·0), 0·020 ml internal standard (7-ethoxycoumarin, 20 nmol/ml in isopropanol) was added. For the analysis of high urine menadione concentrations (after supplementation with K vitamins) urine was diluted 1:4 with water. The mixture was extracted with 4 ml diethyl ether. The diethyl ether extract was carried over in a conical glass tube containing 0·050 ml 50% ethylene glycol in water. The 50% ethylene glycol served to prevent menadione from evaporation/sublimation (Hu et al. 1995) during the removal of diethyl ether under a gentle stream of N₂ at room temperature. The compounds of interest in the remaining ethylene glycol phase were analysed by fluorescence detection following HPLC separation and post-column reduction with Zn. The HPLC system consisted of a reverse-phase C₁₈ column (ChromSpher, 100 mm × 3 mm; Varian, Bergen op Zoom, The Netherlands) with a mobile phase of acetonitrile–water (30:70, v/v), which also contained, per 100 ml, 0·05 ml glacial acetic acid and 0·5 ml of a solution of zinc acetate in water (0·22 g/ml). The flow rate was 0·7 ml/min. The Zn column was a 50 mm × 2 mm poly(ether ether ketone) tube filled with granular Zn (>160 mesh; Haroon et al. 1987). Fluorescence was recorded at 430 nm emission wavelength with 243 nm excitation wavelength. Calibration points were routinely included in sample analysis.

Method validation. The efficiency of the oxidation of menadiol to menadione with potassium dichromate was confirmed by the complete oxidation of borohydride-reduced menadione (checked by HPLC). The efficiency of the acid-catalysed (sulfuric acid) hydrolysis of conjugates of menadiol was verified by comparing the menadione recovery in urine following deconjugation via either sulfuric acid or enzymatic (glucuronidase/sulfatase) hydrolysis. The results showed equal recovery of menadione.

The extraction recovery of menadione was >80%. The intra-assay CV of the menadione assay was determined by analyses of urine from a non-vitamin K-supplemented healthy subject, with the following results (menadione, μmol/l): 0·016 (SD 0·002; n 5, CV 15%) and 0·079 (SD 0·009; n 5, CV 12%) for ‘blank’ urine and after spiking the urine with menadione at an additional concentration of 0·06 μmol/l, respectively.

Experiments

Urine samples were collected from healthy male volunteers before and after single oral doses of menadione (10 mg in 100 ml tap water; n 2), phylloquinone (10 mg, Konakion chewable tablets; Roche, Woerden, The Netherlands; n 3), menadione-4 (15 mg, Glakay capsules; Eisai Co., Amsterdam, The Netherlands; n 3), and 2,3'-dihydrophylloquinone (10 mg in 1 ml maize oil; n 2), and before and after subcutaneous administration of phylloquinone (5 mg Konakion in mixed micelles; Roche; n 2). Also analysed were archived urine samples collected before and after the intake of menadione-7 (1 mg in capsules; Natural ASA, Lysaker, Norway; n 3) in a study executed to estimate lipoprotein distribution of menadione-7 (L Schurgers, unpublished results). To measure basal excretion of menadione, cumulative 24 h urine samples (07.00 hours–07.00 hours) were collected from non-supplemented subjects (n 6). The oral vitamin K preparations were taken between 08.00 and 10.00 hours on an empty stomach. Subcutaneous injections of phylloquinone were administered at 13.00 hours. Aliquots of all urine collections were stored at −20°C until analysis. The experiments had the approval of the Medical Ethical Committee of the University Hospital, Maastricht, The Netherlands.

To investigate if urinary menadione excretion follows dietary vitamin K intake, archived urine samples from a controlled vitamin K dietary study were analysed for menadione excretion. The study, from Dr Booth’s laboratory of Tufts University, Boston, MA, USA and published earlier (Booth et al. 2001), had a cross-over design containing a 5-d control period of 100 μg dietary phylloquinone daily followed by a 14 d depletion period of 10 μg phylloquinone daily. In the repletion period, lasting 10 d, the volunteers were served a diet containing either 200 μg phylloquinone or 200 μg 2,3'-dihydrophylloquinone. The urine samples analysed were those collected over 24 h at the end of each period.

Cell cultures

Cells were cultured in Dubelco’s modified Eagle medium (Sigma Chemical, Zwijndrecht, The Netherlands) with 10% fetal calf serum (Sigma Chemical) and penicillin/streptomycin. Cells were seeded 1:3 to 1:4 from 25 ml flask cultures into six-well plates. Incubation was at 37°C in humidified 5% CO₂. When >90% confluent the medium was changed to medium containing phylloquinone (0·1–0·5 μM) or...
menadione (1-µM). After 20 h (menadione) or 20 and 44 h (phyloquinone) of incubation, cells were washed with PBS. Cells were sonicated in 0·5 ml 1 % Triton X-100 in PBS. A 0·4 ml aliquot of the cell lysate was used for vitamin K analysis (Thijssen et al. 1996), the remainder for protein assay (BSA protein assay reagent; Pierce/Perbio Science, Ettenleur, The Netherlands). The cell-lines tested were Hep-G2, HEK-293, Panc-I, AR-42J (all from American Type Culture Collection, Rockeville, MD, USA) and rat vascular smooth muscle cells (isolated from rat aorta).

**Results**

A pilot experiment showed that the urine of a volunteer collected 0–8 h after the oral intake of phylloquinone (10 mg Konakion chewable tablet) contained a chromatographic peak with the same retention time as menadione. The peak was much higher than that seen in the urine sample voided before the intake of phylloquinone. Further evidence that this peak was menadione was obtained by showing that it was barely detectable without sulfuric acid–dichromate treatment of urine and was completely abolished in the absence of post-column reduction with Zn. Taken together, the phenomena strongly indicated that the chromatographic peak indeed represented menadione. These initial findings initiated the experiments described.

Typical urinary excretion patterns of menadione with time following the oral intake of menadione and K vitamins are presented in Fig 1. The data clearly show the stimulation of urinary menadione excretion following oral intake of phylloquinone, menaquinone-4 and menaquinone-7. Moreover, the data show that the stimulatory effect was rapid, with enhanced urinary excretion of menadione detectable within 1 h and the maximal excretion rate occurring about 3 h after vitamin K intake. One possibility to consider was that the rapid appearance of menadione in urine may have resulted from menadione contamination in the preparations. To exclude this possibility, we measured the menadione content of the administered vitamin K preparations. The Konakion chewable tablets contained no detectable menadione contamination. On the other hand, pure phylloquinone (Roche) was found to contain about 0·03 % and menaquinone-4 of the Glakay capsules about 0·05 % (on a molar basis) menadione. This would mean that the amounts of menadione ingested with the 10 mg phylloquinone and 15 mg menaquinone-4 preparations were about 2 and 5 µg, respectively. These ingested amounts of menadione, however, could not explain the stimulated menadione excretion.

Remarkably, subcutaneous administration of phylloquinone did not raise menadione excretion over the 24 h period following administration (Fig. 2(A)). Plasma phylloquinone levels in the two volunteers 3 h after administration were 6·7 and 25·2 ng/ml, thus proving that the phylloquinone had been released from the subcutaneous depot. No significant rise in menadione excretion was found after oral intake of hydrogenated phylloquinone (2,3',5'-dihydrophylloquinone), the urinary excretion rate at all times being < 1 µg/h (Fig. 2(B)).

![Graphs](https://www.cambridge.org/core/journals/british-journal-of-nephrology/issue/10.1079/BJN20051630/004935/fig1)

**Fig. 1.** Typical examples of urinary excretion of menadione. Menadione excretion is presented as the average excretion rate (µg/h) during the urine collection period before and after oral intake of: (A) menadione, 10 mg; (B) phylloquinone, 10 mg; (C) menaquinone-4, 15 mg; (D) menaquinone-7, 1 mg.
Table 1. Urinary excretion of menadione following vitamin K intake

<table>
<thead>
<tr>
<th>K vitamin</th>
<th>Dose</th>
<th>Mean</th>
<th>SD</th>
<th>% of dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phylloquinone (n 3)</td>
<td>10 mg</td>
<td>160</td>
<td>95</td>
<td>16–56</td>
</tr>
<tr>
<td>Menaquinone-4 (n 3)</td>
<td>15 mg</td>
<td>102</td>
<td>45</td>
<td>1–2.5</td>
</tr>
<tr>
<td>Menadione (n 2)</td>
<td>10 mg</td>
<td>1984</td>
<td>361</td>
<td>17–22</td>
</tr>
</tbody>
</table>

*On a molar basis.

The amounts of menadione excreted in 24 h after oral administration of different forms of vitamin K are summarized in Table 1. After the administration of menadione itself, about 20% of a 10 mg dose was excreted in urine within 24 h. For 10 and 15 mg doses of phylloquinone and menaquinone-4, respectively, the 24 h recoveries ranged from 1 to 5% (on a molar basis) of the administered dose. Assuming complete bioavailability of the pharmaceutical K vitamin preparations and 20% urinary recovery of the menadione formed, the results indicate that some 5–25% of the ingested K vitamins were catabolized to release menadione.

Mean basal menadione excretion, the daily excretion of menadione in unsupplemented subjects, all of whom were taking their normal diet, was found to be 5-4 (SD 3.2) μg (range 1.6–9.1 μg or 9.3–52.3 nmol, n 6).

Fig. 3 summarizes the results of the urinary menadione excretion in the depletion/repletion study. The results clearly show that the pattern of menadione excretion followed the daily phylloquinone intake. The mean 24 h amounts of menadione excreted were 5.79 (SD 2.54), 3.16 (SD 1.68) and 7.75 (SD 1.68) μg at the end of the control, depletion and phylloquinone repletion periods, respectively. The differences between the control (n 16) and depletion (n 16) periods, and between the depletion (n 8) and phylloquinone repletion (n 8) periods, were highly significant (P < 0.001 and < 0.01, respectively, paired t test). Mean menadione excretion at the end of the 2,3-dihydrophylloquinone repletion period (4.10 (SD 2.00) μg) was not statistically different from that in the preceding depletion period (P = 0.067).

Of the cell lines tested, i.e. the hepatic cell line HepG-2, the pancreatic cell lines Panc-I and AR-24J, the kidney cell line HEK-293 and rat vascular smooth muscle cells, none was found to contain menaquinone-4 when cultured in the presence of phylloquinone. However, all of the cells were found to form menaquinone-4 in the presence of menadione (Table 2).

Discussion

The present study shows, for the first time, menadione as a urinary excretion product in healthy subjects taking their normal standard diet. Furthermore, the study provides unequivocal evidence that pharmacological dosages of phylloquinone...
and menaquinones (at least, menaquinone-4 and -7) are catalyzed to release menadione. The metabolic efficiency of the side-chain removal must be high since urinary menadione excretion was found to be enhanced as early as 1 h after intake of K vitamins. Menaadione as a possible product of phylloquinone catalysis was first reported in the 1960s, and its release was attributed to gut flora activity (Billette et al. 1964). The main basis for that conclusion was studies in pigeons, which showed that the conversion was not seen when radiolabelled phylloquinone was given parenterally, together with evidence that a faecal culture over time (anaerobic incubation for several days) was able to form menadione from phylloquinone.

As our results in human volunteers also show that menadione release was confined to the oral route (Figs 1(B) and 2(A)), the involvement of the gut flora cannot entirely be ruled out. However, the rapid appearance of menadione in urine intuitively argues against this explanation. Moreover, two recent and independent studies have clearly shown that the conversion of dietary or supplemental phylloquinone into menaquinone-4 is as efficient in germ-free rats as in normal rats (Davidson et al. 1998; Ronden et al. 1998). Therefore, it is more likely that the side-chain removal is an intrinsic catalytic activity of the body. Since menadione release occurred only after the oral route of vitamin K administration, we suggest that side-chain cleavage occurs during the uptake from the gastrointestinal tract. An obvious alternative site for this metabolic activity would be the liver. However, it would be necessary to speculate that the conversion can occur only when vitamin K enters the liver via the oral route and not after subcutaneous injection. In the early phase of intestinal absorption, about 90% of absorbed phylloquinone is associated with triacylglycerol-rich lipoproteins and probably enters the liver via chylemicron remnants (Shearer et al. 1974; Lamon-Fava et al. 1998). After intramuscular injection the majority of phylloquinone is distributed between LDL and HDL fractions (Hagstrom et al. 1995). Whether this transport difference can explain the metabolic differences between oral and parenteral routes, i.e. only the chylomicron remnant pathway delivers vitamin K to the intracellular site of menadione release, must remain conjectural and further studies are needed to define the tissue sites of menadione release. Based on the available evidence, the intestinal enterocytes are likely candidate cells for the vitamin K dealkylating activity.

A known metabolic route for side-chain metabolism of phylloquinone and menaquinones is via the stepwise shortening β-oxidation (Shearer et al. 1974). For both vitamin K and ubiquinones, the terminal product of β-oxidation has a side-chain length of five carbon atoms and the theoretically possible two-carbon side-chain product has not been found (Imada et al. 1970; Shearer et al. 1974; Harrington et al. 2005). The resistance of the five-carbon side-chain metabolite of ubiquinone to further β-oxidative shortening has been attributed to steric hindrance from the bulky benzoquinone nucleus (Imada et al. 1970) and the same explanation would apply to the naphthoquinone nucleus of the K vitamins.

In fact, studies in pigeons using side-chain 14C-labelled phylloquinone reported recovery of the complete side chain as phytic acid (Billette et al. 1964). Therefore, we believe that the menadione release resulted from integral side-chain removal via an as yet unknown pathway. The 2,3'-double bond of the side chain appears to be essential for removal as oral 2,3'-dihydrophylloquinone did not stimulate menadione excretion (Figs 2 and 3). This fits in with the previous observation that 2,3'-dihydrophylloquinone-supplemented rats did not show the formation and accumulation of tissue menaquinone-4 (Sato et al. 2003).

Basal urinary menadione excretion follows dietary phylloquinone intake as shown by the results of the depletion/repletion study (Fig. 3). However, excretion was not linearly related to intake; the intake of 200 mg phylloquinone during the repletion period increased menadione excretion by only 2.4-fold compared with the daily intake of 10 mg during the depletion period. This may point to additional sources for the excreted menadione, such as that liberated during the absorption of menaquinones (dietary and microfloral origin) or by metabolism of liver stores.

The release of menadione shown in the present study raises questions about current concepts of the conversion of phylloquinone into menaquinone-4 and how it accumulates in extrahepatic tissues. This conversion has generally been interpreted as a metabolic and functional route that takes place in tissues themselves, implicating the presence of the enzymatic machinery to remove or to convert the side chain (Thijssen et al. 1996; Davidson et al. 1998). A strong argument for this route is the observed conversion of phylloquinone into menaquinone-4 epoxide in HEK-293 cells (Davidson et al. 1998). In our laboratory, however, we have been unable to demonstrate any conversion from phylloquinone into any of the various cell lines we have tested. These cell cultures include pancreatic cell lines (Panc-1 and AR-24J), which, based on the very high capacity of the pancreas to accumulate menaquinone-4 (Thijssen & Drittit-Reijnders, 1994, 1996), would seem to be a likely cellular model in which we would be able to demonstrate menaquinone-4 synthesis. A possible explanation for the contradictory results may be that the previous study (Davidson et al. 1998) used much higher phylloquinone concentrations in the cell cultures, 2–22 μM, vs. 0.1–0.5 μM in our studies. As was found in the present study, commercially available phylloquinone (and menaquinone-4) contains traces of menadione. On the other hand, most of the cells were able to synthesize menaquinone-4 from menadione (Table 2). Although our results are not definite proof, we are inclined to believe that menaquinone-4 is synthesized in tissues from circulating menadione that is released from phylloquinone (and menaquinones). Further support of this route of tissue menaquinone-4 synthesis is the absence of menadione formation from both subcutaneously administered phylloquinone and oral 2,3'-dihydrophylloquinone (present

### Table 2. Menaquinone-4 formation from menadione in cell cultures (Mean values and standard deviations for three wells)

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Menaquinone-4 (pmol/mg cellular protein per 20h incubation)</th>
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<tbody>
<tr>
<td>HepG-2</td>
<td>4.76 ± 0.17</td>
</tr>
<tr>
<td>Panc-1</td>
<td>3.61 ± 0.35</td>
</tr>
<tr>
<td>HEK-293</td>
<td>1.72 ± 0.22</td>
</tr>
<tr>
<td>VSMC</td>
<td>0.73 ± 0.24</td>
</tr>
</tbody>
</table>

HepG-2, hepatic cell line; Panc-1, pancreatic cell line; HEK-293, kidney cell line; VSMC, rat vascular smooth muscle cells.
dependent carboxylase in non-hepatic tissues as was inferred quinone, there seems no reason for menaquinone-4 synthesis menadione. For other tissues, which may readily take up phyllo- may derive benefit from the menaquinone-4 synthesis from vitamin K-dependent carboxylase activity but with a relative there is a physiological reason for the high menaquinone-4 syn- thesis in various non-hepatic tissues. Tissues with a need for vitamin K-dependent carboxylase activity but with a relative transfer barrier to phylloquinone, such as the brain and placenta, may derive benefit from the menaquinone-4 synthesis from menadione. For other tissues, which may readily take up phyllo- quinone, there seems no reason for menaquinone-4 synthesis unless the latter is the preferred cofactor for the vitamin K-dependent carboxylase in non-hepatic tissues as was inferred from rat data (Thijssen et al. 1996). However, there may be other possible functions of K vitamins that are specific to mena- quinone-4. Recent studies showed that sulfatide metabolism and sphingolipid concentrations in rat brain were correlated with brain menaquinone-4 concentrations (Sundaram et al. 1996; Carrie et al. 2004), and pancreatic juice was recently reported to contain high levels of menaquinone-4 suggesting a physio- logical role in digestive enzyme synthesis and or processing (Thomas et al. 2004).

In summary, the present study shows that menadione is a product of vitamin K catalysis, both of phylloquinone as well as menaquinones. The menadione released from phyllo- quinone occurs early and possibly during intestinal absorption within the enterocyte. We suggest that the menadione released may be the source of the menaquinone-4 that is known to accumulate in various target tissues.

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References


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