AN INVESTIGATION OF THE CLEARANCE OF ^{14}C-LABELLED VITAMIN K IN CONTROL AND MCCP-TREATED FEMALE CD RATS

Robert H. Powrie,[1] David G. Farrar,[2] and Clifford R. Elcombe[1].

[1]CXR Biosciences Ltd, Dundee, Scotland, UK and [2]Ineos Chlor Ltd, Runcorn, United Kingdom.

Introduction

Previous studies have shown that the oral administration of medium chain chlorinated paraffins (MCCPs) to female rats prior to pregnancy and during gestation markedly decreased the maternal plasma and milk concentrations of Vitamin K. This in turn contributed to Vitamin K deficiency in the neonatal pup and increased mortality due to internal haemorrhaging.

The study presented here was aimed at determining the effect of MCCPs on the disposition of Vitamin K in female rats.

Methods

Female Sprague Dawley rats (4 rats per group, 9-11 weeks old) were administered corn oil (control) or Cereclor S52 (MCCP, 1000 mg/kg) for 14 consecutive days by oral gavage. 24 hours after the last dose the rats received a single oral dose or a single intraperitoneal dose of ^{14}C-Vitamin K_1 at 5 mg/kg body weight (ring labelled, approx. 100µCi/kg bwt.).

The animals were transferred to all glass metabolism cages and blood was sampled at timed intervals over a 24 hour period. Urine and faeces were collected at 24 hour intervals. Total ^{14}C was determined by scintillation counting. Values displayed are Mean ± SD (n=4).

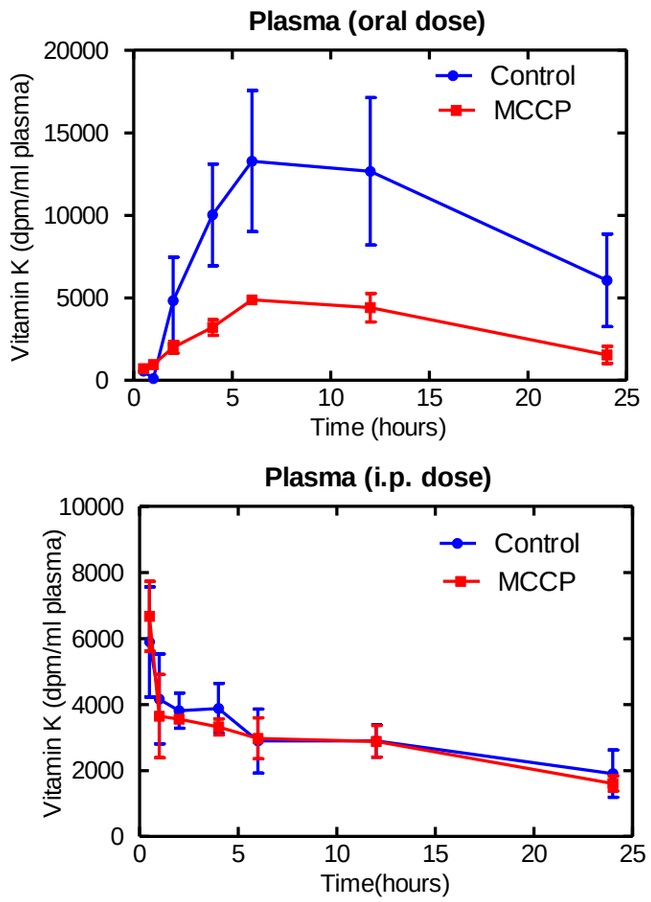
Results

Pretreatment of rats with MCCPs greatly decreased the peak plasma concentration and AUC of radiolabelled material following the oral administration of ^{14}C-Vitamin K (Figure 1).

This decrease in plasma concentrations was not seen after the i.p. administration of ^{14}C-Vitamin K (Figure 1).

Approximately 10% of the total administered radioactivity was excreted in the urine of rats administered vitamin K orally. Pretreatment with MCCPs diminished this by about 50% (Figure 2). Following the i.p. administration of Vitamin K only around 1% of the administered dose was recovered in the urine. MCCP pretreament appeared to have no effect.

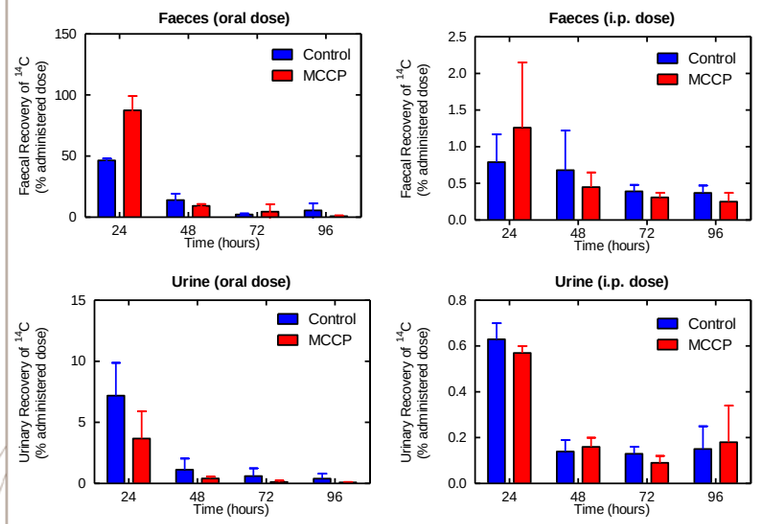
Figure 1: Total ^{14}C measurements in plasma following oral and intraperitoneal administration of ^{14}C-Vitamin K: Effect of 14 days MCCP-pretreatment



Faecal excretion was high in the orally dosed groups (~100% in MCCP group and ~60% in control group), but low (~1-2%) in the i.p. dosed groups. This suggests that the majority of the i.p. administered Vitamin K remained unexcreted after 5 days, the duration of the experiment.

Research supported by Eurochlor

Figure 2: Radioactivity recovered from faeces and urine of control and MCCP-treated rats



Conclusion

The observations following the oral administration of Vitamin K suggest that that prior treatment of rats with MCCPs, either increases the metabolism and elimination of ^{14}C Vitamin K *via* the bile into the faeces, or decreases the intestinal uptake of ^{14}C Vitamin K.

However, following i.p. administration of Vitamin K, MCCP pretreatment did not increase the elimination of Vitamin K into the faeces.

Hence, these observations suggest that prior treatment of rats with MCCPs decreases the intestinal uptake of orally administered ^{14}C Vitamin K.

It is likely that the neonatal haemorrhagic lesions and mortality, observed in pups from dams that had been administered MCCPs before and during gestation, was due to the inhibition of intestinal absorption of Vitamin K and consequential Vitamin K deficiency in the pups, due to decreased secretion of the vitamin during lactation.