PERINATAL DIOXIN EXPOSURE AND CYTOCHROME P-450 ACTIVITY AND LIVER FUNCTIONS AT FOLLOW-UP AFTER 7 – 12 YEARS: EVIDENCE FOR TRANSIENT EFFECTS ON LIVER FUNCTIONS

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Objective

Perinatal exposure to Dutch "background" dioxin levels is rather high but not much higher than other industrialised countries. Previous studies of our cohort revealed elevated ALAT levels in the perinatal period[1], which was no longer evident at follow-up at the age of 2½ years[2]. However, dioxins may cause health effects spanning many years. Therefore we determined plasma ALAT and ASAT levels amongst our longitudinal cohort, as was done previously. Furthermore, the children underwent a caffeine provocation test to determine CYP1A2 activity.

Study design

The longitudinal cohort consisted of 37 healthy children (7 - 12, mean 8.2 years), with documented perinatal dioxin exposure. The children refrained from caffeine intake for 48 hours prior to the ingestion of a single dose (3 mg/kg body weight) caffeine. The caffeine was dissolved in 'AA'® soda drink, which contains no caffeine, but to which the caffeine was added. Six hours later blood was drawn and later analysed in the laboratory of the AMC Clinical Pharmacy Department (Amsterdam, The Netherlands).

The venapuncture was performed by an experienced clinical laboratory worker. The blood was centrifuged within two hours and thereafter cooled at 4° C until analysis. Paraxanthine and caffeine concentrations were determined in the blood samples, and the paraxanthine/caffeine molar ratio was calculated. This was done making use of a HPLC assay for simultaneous determination of paraxanthine and caffeine, which we developed and validated before the current study was performed[3]. Caffeine and paraxanthine in plasma was quantitated with a 'reversed-phase'-HPLC using UV-detection.

ASAT and ALAT were determined using routine determinations.

The prenatal exposure ranged from 8.74 to 88.80 (mean 34.6) ng TEQ dioxin/kg milk fat. The postnatal exposure ranged from 4.34 to 384.51 (mean 75.4) ng TEQ dioxin.

Results

All the children had normal aspartate aminotransferase levels. Linear regression showed no correlation between ASAT and prenatal or postnatal dioxin exposure.

Similarly, all the children had normal alanine aminotransferase levels. Linear regression also showed no correlation between ALAT and prenatal or postnatal dioxin exposure.

Linear regression of the paraxanthine/caffeine molar ratio, indicative of the CYP1A2 activity, versus prenatal and postnatal dioxin exposure revealed no significant linear correlation

Conclusion

Follow-up of 7 to 12 year old children with documented prenatal and postnatal dioxin exposure has shown a normalisation of previously increased ALAT levels, seen during the perinatal period. These results point to a transient effect of the toxic influences of Dutch background levels of dioxins on the liver. This may be a result of the combination of body composition (less adipose tissue) in the perinatal period and decreasing exposure from the relatively high perinatal to the much lower later childhood background exposure, and from a dilutional effect (more adipose tissue). The cytochrome P-450 1A2 activity, measured by means of a caffeine-provocation test revealed no correlation with the pre- and postnatal dioxin exposures.

References

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