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Caffeine intake in pregnancy: Relationship between internal intake and effect on birth weight

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ABSTRACT

We used a physiologically based kinetic model to simulate caffeine blood concentration-time profiles in non-pregnant and pregnant women. The model predicted concentration-time profile was in good accordance with experimental values. With 200 mg, the safe dose per occasion in non-pregnant women, AUC and peak concentration in pregnant women were nearly twice that of non-pregnant women. In order to derive a safe dose for the pregnant women we estimated the dose in the pregnant women model taken at once which would not exceed AUC and peak concentration in the non-pregnant women of 200 mg as single dose. The resulting dose is 100 mg caffeine per occasion which we recommend as safe.

The caffeine dose of 200 mg per day is declared as safe for pregnant women with respect to the foetus by EFSA based on results on reduced birth weight in epidemiological studies. We modelled AUC and peak concentration for different caffeine doses to investigate the relationship between internal caffeine exposure and risk measures of reduced birth weight from epidemiological studies. The graphical analysis revealed that the reduction in birth weight was related to AUC and peak concentration up to a dose of 250 mg caffeine.

1. Introduction

Caffeine is a constituent of beverages consumed worldwide in great amounts. Its effect is explained by its antagonistic action at adenosine A1 and A2A receptors, two of the four adenosine receptors (A1, A2A, A2B and A3) (Fisone et al., 2004; Ferre, 2008; Rieg et al., 2005). Acute effects raising the blood pressure are described. With doses of 200–250 mg caffeine, diastolic and systolic blood pressure increased by 4–13 mm Hg and by 3–14 mm Hg in normotensive subjects. The changes in blood pressure were related to the plasma concentration of caffeine (Nurminen et al., 1999). However, chronic intake of caffeine does not lead to permanent increase in blood pressure in non-pregnant subjects as demonstrated in a recent meta-analysis (Steffen et al., 2012) most probable by not yet fully understood mechanisms of tolerance development. Whether caffeine changes the perfusion of organs and in particular influences the perfusion of the placenta remains open. Polymorphism in adenosine receptors has been described and for some effects of caffeine the effect size might be related to the polymorphic state (Alsene et al., 2003).

The effects of coffee and other caffeine containing beverages on the outcome of pregnancy have been investigated in several studies. The CARE Study (2008), a prospective cohort study, in 2635 pregnant women, described increased odds ratios for fetal growth restriction. The study is remarkable as the caffeine intake was investigated by a questionnaire in each trimester separately and odds ratios were calculated also for the caffeine intake in the trimesters. In the Generation R Study, a population-based prospective cohort study in 7346 pregnant women in the Netherland, a tendency was observed for an association of caffeine intake and birth weight small for gestational age (Bakker et al., 2010). The same endpoint has been investigated in a prospective cohort study in 59,123 pregnant women from three Norwegian regions. The data showed that caffeine intake was related to the reduced weight of the babies corrected for gestational age (SGA) (Sengpiel et al., 2013). In addition, the results of a systematic review and meta-analysis published by Chen et al. (2014) demonstrated that maternal caffeine intake is associated with the risk of low birth weight.

After oral intake in humans caffeine is rapidly and to 100%

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absorbed (Blanchard and Sawers, 1983). Metabolism is via N-3 demethylation to 1,7-dimethylxanthine (70–80%), catalysed by CYP 1A2. Other metabolites are theophylline and theobromine. CYP1A2 accounts for about 95% of caffeine clearance, a smaller proportion is mediated by CYP3A4, xanthine oxidase and N-acetyltransferase 2 (Berthou et al., 1991; Miners and Birkett, 1996). In non-pregnant subjects, the half-life of caffeine ranges from 2 to 8 h (Knutti et al., 1981; Abernethy and Todd, 1985; Abernethy et al., 1985; Balogh et al., 1995) whereas in pregnant women the half-life increases to 6–16 h and returned to 2–8 h within 4–15 weeks after delivery (Knutti et al., 1982). In other studies the half-life of caffeine in non-smoking pregnant women was 11.5 h before pregnancy (Arnaud, 1993). It increased to 18 h (Aldridge et al., 1981) at the end of pregnancy. Further studies indicated that caffeine clearance decreases in the course of pregnancy by −32.8% ± 22.8% for weeks 14–18, by −48.1% ± 27% for weeks 24–28 and by −65.2% ± 15.3% for weeks 36–40 compared with the postpartum period (Tsutsumi et al., 2001; Tracy et al., 2005). The mechanism behind this observation is the finding that caffeine metabolism is inhibited by estrogens and gestagens as shown in studies in women taking oral contraceptives (Rietveld et al., 1984; Abernethy et al., 1985; Balogh et al., 1995; Haller et al., 2002). Caffeine readily crosses the placenta to reach the foetus. Given the prolonged half-life of caffeine during pregnancy and considering that neither foetus nor placenta can metabolize caffeine, the foetuses of caffeine consuming women are exposed to caffeine in increasing concentrations if the mother's intake does not decrease (Grosso et al., 2006).

Recently, EFSA (EFSA, 2015) issued an opinion on the safety of caffeine in which for the general population, excluding pregnant women, the safe daily dose is set at 400 mg caffeine per day and 200 mg caffeine per occasion. For pregnant women the daily dose is set at 200 mg caffeine.

By modelling the kinetics of caffeine at various dose levels in pregnant women this study aimed to clarify the question, if the peak concentrations (C_{max}) or the area under the concentration time curve (AUC) of caffeine correlate with its effect on the birth weight of newborns as shown in epidemiological studies. In addition, we would find out which dose per occasion could be recommended as safe for pregnant women.

2. Material and methods

Two structurally different physiologically based human models (1) of a non-pregnant woman and (2) of a pregnant woman were used to represent the features relevant for simulating the concentration time profile of caffeine in the blood of the woman and in the pregnant woman model in the foetus after oral administration of caffeine. The details of the basic non-pregnant model and the physiological parameters used have been described elsewhere (Abraham et al., 2004; see Table 1a).

For the purpose of this evaluation the pregnant model has been adapted by introducing a foetal compartment, the physiological data of which were taken from data in ICRP (2009). In addition, the physiological data were taken for every trimester of pregnancy separately, i.e. weight and the volume of the foetal compartment increased during pregnancy according to the data given in ICRP (2009) (see Table 1a). The pregnant women model includes 7 organs/tissues as well as arterial and venous blood (Fig. 1).

The organs are connected via blood flows, and the circulation system is closed via the lung and the heart. Caffeine is a small lipophilic substance, and tissue membranes do not represent a significant barrier to distribution indicated by a volume of distribution which is 0.7 L/kg bw (Abernethy and Todd, 1985). Hence its distribution is best described by perfusion-rate-limited kinetics. The rate of change of concentration is described by the equation

Table 1a
Parameterisation of the models (non-pregnant and pregnant).

Physiological data[a,b]	Non-pregnant	Pregnant
Cardiac output (Qc) (l/h)	360	406
Body weight (bw) (kg)	65	64 (1. Trimester) 70 (2. Trimester) 73 (3. Trimester)
Blood flow through the organs (l/h)		
Fat	19.5	19.5
Liver	99.5	99.5
Brain	46.8	46.8
Kidney	74.1	74.1
Muscle	65.8	65.8
Foetus/Uterus	36	36
Vessel rich tissue	56.5	56.5
Skeleton	7.8	7.8
Organ volumes (l)		
Fat tissue	18.2	18.2
Liver	1.8	1.8
Brain	1.45	1.45
Kidney	0.31	0.31
Muscle	0.40*bw	0.40*bw
Foetus/Uterus	Not applicable.	0.16 (1. Trimester) 0.99 (2. Trimester) 2.70 (3. Trimester)
Vessel rich tissue	3.768	3.768
Skeleton	9.33	9.33
Substance specific data		
Molecular mass (g/mol)	194.19	
Partition coefficients[c]		
Fat/blood	0.9	0.9
Liver/blood	0.87	0.87
Brain/blood	0.95	0.95
Kidney/blood	0.91	0.91
Muscle/blood	0.88	0.88
Foetus/uterus/blood	Not applicable.	0.88[f]
Vessel rich/blood	0.73	0.73
Skeleton/blood	0.41	0.41
Metabolic constants		
V_{max} non-pregnant[d] (mg/h/kg bw)	6.29	Not applicable.
V_{max} pregnant (mg/h/L bw)	Not applicable.	0.485 of V_{max} non-pregnant[g]
V_{max} (mg/h/kg bw) 1. Trimester	Not applicable.	0.59 of V_{max} non-pregnant[g]
V_{max} (mg/h/kg bw) 2. Trimester	Not applicable.	0.485 of V_{max} non-pregnant[g]
V_{max} (mg/h/kg bw) 3. Trimester	Not applicable.	0.295 of Vmax non-pregnant[g]
K_m mg/L [d]	97	97[h]
Absorption half-life (min)[e]	20	20
Extent of absorption (% of the dose)[i]	100	100

[i] Blanchard and Sawers, 1983.
[a] Human data: see Abraham et al., 2004;
[b] Pregnant data see ICRP, 2002;
[c] Calculated according to Schmitt, 2008;
[d] According to Grant et al., 1987;
[e] Hildebrandt and Gundert-Remy, 1983,
[f] The partition coefficient of 0.88 refers to the ratio foetal to maternal blood.
[g] The values are the mean of data from Knutti et al. (1982) and Tracy et al. (2005),
[h] According to Tsutsumi et al., 2001, the changes in clearance are due to reduced activity of CYP1A2 which accounts to 95% of the clearanc (Berthou et al., 1991; Miners and Birkett, 1996), Hence K_m will not change with pregnancy.

$V_T \frac{d}{dt} C_T = Q_T(C_A - C_{VT})$ in non-metabolising tissues and by $V_T \frac{d}{dt} C_T = Q_T(C_A - C_{VT}) - RAM$ in metabolising tissues, where V_T denotes the volume of tissue T, C_T the concentration in tissue T, Q_T the blood flow through tissue T, C_A the concentration in the arterial blood, $C_{VT} = C_T/P_T$ the concentration in the venous blood leaving the tissue, and P_T the tissue:blood partition coefficient. Elimination of caffeine (RAM – Rate of Amount Metabolised) was modelled by metabolism in the liver via Michaelis–Menten kinetics with V_{max} being the maximum rate of elimination and K_m the concentration (in liver) at which half V_{max} is reached ($RAM = V_{max} \cdot C_L/P_L \cdot K_m + C_L$,