Pharmacokinetic and Pharmacodynamic Effects of Caffeine

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Absorption and distribution

- Rapid (t_{max} 30 - 120 min) and complete absorption
- Crosses freely blood-brain, placental and testicular barrier
- Volume of distribution (~ 0.67 L/kg bw)
- No specific tissue accumulation

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➢ Metabolism / Excretion - General

- Main route of metabolism in humans (70-80 %): N-3 demethylation to paraxanthine (1,7-dimethylxanthine, 17X) catalysed by cytochrome (CYP) 1A2 in the liver.
- Other primary metabolites are theophylline and theobromine.
- Smaller proportion is metabolised by CYP3A4, xanthine oxidase and N-acetyltransferase 2.
- Plasma half-life in adults about 2 - 8 hrs
- Linear kinetic up to at least 7.1 mg/kg in adult
- Paraxanthine, theophylline and theobromine are further metabolized and then excreted in the urine.

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- **Metabolism – variability factors**
- **minor**

- Age
- Genetic factors:
  - Men with higher CYP1A2 enzyme activity than women
  - genetic polymorphism of CYP1A2
- Life-style factors
  - caffeine intake (>2 cups of coffee/d) > CYP1A2 activity ↑
  - smoking > CYP1A2 activity ↑
  - Contraceptives > CYP1A2 activity ↓

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- **Metabolism – variability factors**
- **Major**
- Pregnancy > CYP1A2 activity ↓

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➢ Metabolism – genetic polymorphism of CYP1A2

- Single nucleotide polymorphism “rs762551” (= also referred to as “CYP1A2*1F” or “-163C>A”);
  - AA genotype => so-called *“fast metaboliser”* phenotype
  - AC and CC genotypes => *“slow metaboliser”* phenotype
  - Prevalence of AA *vs.* AC+CC about 50:50 (± 10%) > thus phenotypes are well represented in larger cohort studies considered in this opinion.

- Adjusted for smoking and caffeine intake > no difference between the CYP1A2 genotypes ⇒ polymorphism affects inducibility, but not directly linked with fast/slow metabolism

- A study (McMahon et al., 2014) suggests that genetic polymorphisms at three different loci (CYP1A1, CYP1A2 and aryl-hydrocarbon receptor) cannot be accounted to any relevant degree for variability of caffeine intake.

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Pregnancy

- Estrogenes and gestages inhibit CYP1A2 activity (like oral contraceptives)
- Half-life time increases progressively during pregnancy up to 16 hours (3-4 times longer than in non-pregnant women)

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Fetus

- Caffeine readily crosses the placenta into the fetus.
- Neither fetus nor placenta can metabolise caffeine.

➢ Given the prolonged half-life of caffeine during pregnancy, fetus of caffeine consuming women are exposed to caffeine and its metabolites for a significantly prolonged time.

➢ Amniotic fluid and maternal serum concentrations of caffeine are considered to be reliable indicators of fetal serum concentration.

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Pregnancy

	Non pregnant		pregnant		fetus	
Dose (mg)	C_{max} blood (mg/kg blood)	AUC blood (mg/kg x h)	C_{max} blood (mg/kg blood)	AUC blood (mg/kg x h)	C_{max} fetus (mg/kg)	AUC fetus (mg/kg x h)
50	1.2	52.6	2.1	98.4	1.9	86.4
150	3.6	160.3	6.7	303.5	5.9	266.9
200 morning plus 150 mg afternoon	6.3	367.7	12.1	710.1	10.7	624.1

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Breast fed infants

• intervention study with 150 mg caffeine in nursing women: caffeine entered breast milk with ratio of about 0.8 to the mothers plasma concentration > low caffeine intake by infants (0.03 to 0.2 mg/kg). Infants saliva peak caffeine concentration (proxy for infants plasma concentration) was about 1/8 of the mothers plasma peak concentration.

• neonates have very low CYP1A2 activity with half-life times reported of 50-100 h; activity develops quickly ($t_{1/2} \approx$ 14 h at 3-4 mon; 2-3 h at 5-6 mon, stable in childhood, in adolescence increasing to values of adults).

• *Side effects* of **high** (3, 15, 30 mg/kg bw) caffeine dose (data from preterm neonates from clinical study): tachycardia (19/379) and jitterness (6/379).

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Conclusions

- Several genetic and non-genetic factors have been reported that significantly affect caffeine metabolism by CYP1A2 for various population groups.
- Considering the reduced maternal clearance and prolonged half-life during pregnancy and the fetus' exposure to maternal caffeine plasma levels, the Panel considers the **unborn child** to be the most vulnerable group for adverse effects of caffeine among the general population.

PHARMADYNAMIC EFFECTS

General

- Predominantly through its antagonistic activity at adenosine receptors.
- Four adenosine receptors (A1, A2A, A2B and A3) known in human; presence and distribution and thus effects vary among organs and tissues, even among vessel types.
- E.g: A1 and A2A receptors expressed in the CNS, in particular at basal ganglia, which are involved in motor activity; psychomotor stimulant effect of caffeine is generated by affecting a particular group of projection neurons located in the striatum (high levels of adenosine A2A receptors).
- Caffeine acts, at least in part, by facilitating dopamine D2 receptor transmission.

PHARMADYNAMIC EFFECTS

General

- Caffeine acts, at least in part, by facilitating dopamine D_2 receptor transmission.
- Agonist of the SR Ca^{2+} release channel ryanodine receptor (maximal effect in vitro 10 mM = 1.94 g/L)
- Beating rate increased in vitro 100 µM = 19.4 mg/L

PHARMADYNAMIC EFFECTS

Tolerance development

- Develops after repeated administration; mechanism not fully understood; it has been attributed to the upregulation (number) of adenosine receptors.
- Differs for organ systems; eg: fast tolerance development (within days) has been observed concerning the pressor effects of caffeine; slow or no tolerance to other effects; high variable among the population.
- Unclear whether the development of tolerance may explain the difference in the sensitivity to the effects of caffeine on sleep.

PHARMADYNAMIC EFFECTS

Withdrawal symptoms

Headache, fatigue, decreased energy and activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and not clear headed are observed 12 - 24 h after abstinence.

METHODOLOGY AND CONCLUSIONS

OPEN FOR DISCUSSION