

Elimination of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (CTHC) and formation and elimination of its acyl-glucuronide (CTHC-Glu) in serum after intravenous application of 5 mg

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AIMS: Little is known about the metabolic fate of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (CTHC) after being formed by breakdown functions. As one important parameter which needs to be known for pharmacokinetics is the body burden, our approach uses the intravenous application of this metabolite. The parent compound delta 9-tetrahydrocannabinol (THC) does not have influence on the CTHC pharmacokinetics under these conditions. Better knowledge of CTHC-pharmacokinetics should help to understand the varying concentration profiles of THC and its metabolite with special regard to cumulating of CTHC in serum and urine in relation to the consumption behaviour.

METHODS: In the present study the pharmacokinetics of CTHC was investigated in absence of the precursor THC, after i.v. administration (10 min) of 5 mg CTHC in 10 healthy male individuals. Serum was collected over a period of 96 hours. All samples were extracted before and after enzymatic (serum) deglucuronidation and were analysed using GC/MS. Non-parametric pharmacokinetic analysis were carried out using WinNonlin 4.0.

RESULTS: Mean C_{\max} of free CTHC was 337 ± 62 ng/ml. Serum concentration curves of free CTHC showed only slight variations between subjects. The mean AUC was 968 ± 268 h \times μ g/L. An unexpected long distribution phase of about 12 h was observed, V_z equals 140 ± 52 L, systemic clearance was 5.5 ± 1.4 L/h with a resulting elimination half-life of 17.6 ± 5.2 h. These shortest serum half-life of CTHC observed (A. Glaz-Sandberg et. al., Pharmacokinetics of 11-nor-9-carboxy- Δ 9-tetrahydro-cannabinol after intravenous administration in healthy human subjects, Eur J Clin Pharmacol 61: 684, 2005) is in contrast to data in frequent or infrequent cannabis users. The formation and elimination of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol glucuronide (CTHC-Glu), was also studied. During the observation period, CTHC-Glu arose with a half-life of approximately 15 min and was eliminated with slightly shorter half-life than its precursor ($14,9$ h. \pm $6,4$ hours). The CTHC-Glu concentration exceeded CTHC concentration at 0,8 hours and peaked after 1,66 hours, indicating that glucuronide conjugation further decreases the volume of distribution of CTC. Serum concentration curves of CTHC-Glu differed between subjects. Yet, the AUC values were within a moderate range (2804 ± 915 h \times μ g/L).

CONCLUSIONS: Due to splitting into a renal and a faecal excretion pathway, both, the percentage of formation of CTHC-Glu and its volume of distribution is difficult to estimate from the above data. Similar AUCs of CTHC-Glu indicate that, after intravenous application of CTHC and biotransformation without formation of 11-hydroxy-THC as a precursor, a relatively constant portion of CTHC-Glu reaches the bloodstream. A rough estimation using the volume of the extra cellular water (25 L) as it is seen for other water-soluble glucuronides would lead to a CTHC-Glu body burden of approximately 69 % of the administered dose.

KEYWORDS: *Elimination, Formation, 11-nor-9-carboxy-delta 9-tetrahydrocannabinol, CTHC, Glucuronide, Pharmacokinetics*

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