Single-dose pharmacokinetics and tolerability of oral delta-9- tetrahydrocannabinol in patients with amyotrophic lateral sclerosis

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BACKGROUND
Cannabinoids exert neuroprotective and symptomatic effects in amyotrophic lateral sclerosis (ALS). We assessed the pharmacokinetics (PK) and tolerability of delta-9-tetrahydrocannabinol (THC) in ALS patients.

METHODS
Nine patients received THC single oral doses of 5mg and 10mg, separated by a wash-out period of two weeks. Blood samples for the determination of THC, 11-nor-9-carboxy-THC (THC-COOH) and hydroxy-THC (THC-OH) were taken up to 8 hours after intake. Adverse events were assessed by visual analogue scales (VAS). Plasma concentrations of the active metabolite THC-OH were submitted to sequential pharmacokinetic-pharmacodynamic population modeling on individual heart rate as a proxy for THC's cardiovasculatory effects.

RESULTS
Drowsiness, euphoria, orthostasis, sleepiness, vertigo and weakness were significantly more frequent in patients receiving 10mg compared to 5 mg THC. A marked interindividual variability was found for the absorption of oral THC (84%) and elimination of THC-COOH (45%). PK data did not support any clinically relevant deviation from linear PK in the investigated range of concentrations. Plasma concentrations of THC-OH were positively correlated with the individual heart rate. An E(max-model) was successfully fitted to individual heart rate, with a THC-OH plasma concentration of 3.2 x 10(-4) μmol/L for EC(50) and an E(max) of 93 bpm for heart rate.

CONCLUSIONS
The higher 10mg dose of THC was dose-limiting in patients with ALS. High interindividuell PK variability requires individuell titration of THC for potential therapeutic use in patients with ALS.