European Neuropsychopharmacology (2014) **24**, 1475–1482

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Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial

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Received 3 March 2014; received in revised form 6 June 2014; accepted 20 June 2014

KEYWORDS
Elderly;
Safety;
Pharmacokinetics;
Delta-9-tetrahydrocannabinol;
Cannabinoids

Abstract
There is a great concern about the safety of THC-based drugs in older people ($\geq$65 years), as most of THC-trials did not include such group. In this phase 1, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial, we evaluated the safety and pharmacokinetics of three oral doses of Namisol®, a novel THC in tablet form, in older subjects. Twelve healthy older subjects (6 male; mean age 72$\pm$5 years) randomly received a single oral dose of 3 mg, 5 mg, or 6.5 mg of THC or matching placebo, in a crossover manner, on each intervention day. The data for 11 subjects were included in the analysis. The data of 1 subject were excluded due to non-compliance to study medication. THC was safe and well tolerated. The most frequently reported adverse events (AEs) were drowsiness (27%) and dry mouth (11%). Subjects reported more AEs with THC 6.5 mg than with 3 mg (p=0.048), 5 mg (p=0.034) and placebo (p=0.013). There was a wide inter-individual variability in plasma concentrations of THC. Subjects for whom the C_{max} fell within the sampling period (over 2 h), C_{max} was 1.42-4.57 ng/mL and T_{max} was 67-92 min. The $AUC_{0\text{-}2\ h}$ (n=11) was 1.67-3.51 ng/mL. Overall, the pharmacodynamic effects of THC were smaller than effects previously reported in young adults.

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http://dx.doi.org/10.1016/j.euroneuro.2014.06.007

In conclusion, THC appeared to be safe and well tolerated by healthy older individuals. Data on safety and effectiveness of THC in frail older persons are urgently required, as this population could benefit from the therapeutic applications of THC.

1. Introduction

The cannabis plant (*Cannabis sativa L.*) has been used to treat a range of symptoms and diseases for more than 4000 years (Li and Lin, 1974; Touw, 1981). Its broad therapeutic applications reflect the various pharmacological and physiological effects of cannabinoids, the bioactive components of the cannabis plant (Ashton, 2001). The plant contains more than 60 cannabinoids, such as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol, and cannabichromene (Ashton, 2001). While the pharmacological effects of most cannabinoids are still not known, THC appears to be responsible for most of the physical and psychoactive effects of cannabis (Ashton, 2001). Cannabinoids exert their effects by binding to two cannabinoid receptors, i.e. CB1, which is expressed primarily in the central nervous system, and CB2, which is found primarily in the immune system and hematopoietic cells (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993).

In recent years, cannabinoid-based drugs and non-smoking routes of drug administration have been investigated in clinical trials. To date, there are only two oral cannabis-based medicines (dronabinol and nabilone) available by prescription in some countries, and one available as an oromucosal mouth spray (nabiximols). Dronabinol (synthetic THC) and nabilone (THC analog), are approved by the United States Food and Drug Administration, and in some European countries, for appetite stimulation in AIDS-related anorexia and chemotherapy-induced nausea and vomiting. Nabiximols (Sativex®), which contains both THC and CBD, is approved in the United Kingdom and in some other European countries and Canada, but not in the USA, for the management of pain and spasticity in patients with multiple sclerosis.

Growing interest in the medical use of cannabis has recently led to the development of Namisol®. Namisol® is a novel cannabinoid-based drug formulation that contains THC ($\geq$ 98%) in tablet form. It was developed using a novel drug delivery technology, Alitra™ to improve its absorption and bioavailability (Klumpers et al., 2012). The results of the first trial in humans investigating the optimal route of administration, safety, pharmacokinetics, and pharmacodynamics of the drug showed that Namisol® (5 mg, 6.5 mg, and 8 mg) might have more favorable pharmacokinetics and pharmacodynamics than currently available cannabinoid-based drugs (Klumpers et al., 2012). This is because Namisol® showed 1) a faster absorption and a shorter time to reach the maximal THC concentrations; 2) a smaller variability in T_{max} (time to maximum plasma concentration) and plasma concentrations; and 3) faster pharmacodynamic effects, which are important for achieving a rapid clinical effect (Klumpers et al., 2012). Klumpers et al. (2012) also reported that namisol was safe and well tolerated by subjects. However, their study involved only young adults (mean age 21.4 years, range 18–27 years), and so findings cannot directly be extrapolated to older population (65 years and older). Older people are in general more likely to experience adverse drug events, due to a combination of age-related physiological changes (such as a decrease in lean body mass, diminished renal and hepatic clearance) and a high prevalence of comorbidities, which can lead to polypharmacy and drug–drug interactions (Hilmer et al., 2007; Shi et al., 2008; Corsonello et al., 2010). The aims of this trial were first, to assess the safety and tolerability of three oral doses of THC (3 mg, 5 mg, and 6.5 mg) in healthy older subjects. Second, to evaluate the pharmacokinetics of THC in older people and to investigate the relationship between the drug's pharmacodynamic effects and the plasma concentrations of THC and its active metabolites 11-hydroxy-delta 9-THC (11-OH-THC) and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THC-COOH).

2. Experimental procedures

2.1. Study design and participants

This phase 1, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial (ClinicalTrials.gov ID NCT01740960) was approved by the local ethics committee (Registration number: NL 40591.091.12) and carried out at the Radboud University Medical Center, Nijmegen, The Netherlands. The trial was performed according to the International Conference on Harmonization guideline for good clinical practice, the ethical principles of the Declaration of Helsinki, and the related Dutch laws and regulations.

The subjects were healthy elderly volunteers who were recruited between August and November 2012 through personal contacts and word of mouth. All subjects provided written informed consent before they were screened for eligibility. Inclusion criteria were age 65 years or older; physically healthy, based on a medical history, physical examination, electrocardiography (ECG), results of hematological and biochemical blood tests on screening; and body mass index between 18.0 and 30 kg/m^2. Main exclusion criteria were high falls risk (based on body sway test); regular cannabis use (defined as smoking one or more cannabis cigarettes per week); history of sensitivity/idiosyncrasy to cannabis; history of drug or alcohol abuse; smoking more than ten cigarettes a day; history of severe comorbidities (e.g. COPD GOLD III or IV; heart failure NYHA III or IV) or diabetes mellitus; history of psychiatric or cognitive disorders; consumption of more than six units of (methyl)xanthine products per day (e.g. coffee, tea, cola, chocolate); use of drugs that inhibit CYP2C9, CYP2C19 and CYP3A4, and was not possible to discontinue the use of the drugs during the study period.

2.2. Randomization and masking

Subjects were randomly allocated to receive a single dose of 3 mg (two 1.5 mg tablets), 5 mg (one tablet), or 6.5 mg (one 5 mg and one 1.5 mg tablet) of Namisol® or matching placebo in a double-blind,