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Medicinal Δ⁹-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests

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ABSTRACT

Aims The acute and chronic effects of dronabinol [medicinal Δ⁹-tetrahydrocannabinol (THC)] on actual driving performance and the Standard Field Sobriety Test (SFST) were assessed. It was hypothesized that occasional users would be impaired on these tests and that heavy users would show less impairment due to tolerance. **Design, setting and participants** Double-blind, placebo-controlled, randomized, three-way cross-over study. Twelve occasional and 12 heavy cannabis users (14 males/10 females) received single doses of placebo, 10 and 20 mg dronabinol. **Measurements** Standard deviation of lateral position (SDLP; i.e. weaving) is the primary measure of road-tracking control. Time to speed adaptation (TSA) is the primary reaction-time measure in the car-following test. Percentage of impaired individuals on the SFST and subjective high on a visual analogue scale were secondary measures. **Findings** Superiority tests showed that SDLP ($P = 0.008$) and TSA ($P = 0.011$) increased after dronabinol in occasional users. Equivalence tests demonstrated that dronabinol-induced increments in SDLP were bigger than impairment associated with BAC of 0.5 mg/ml in occasional and heavy users, although the magnitude of driving impairment was generally less in heavy users. The SFST did not discriminate between conditions. Levels of subjective high were comparable in occasional and heavy users. **Conclusions** Dronabinol (medicinal tetrahydrocannabinol) impairs driving performance in occasional and heavy users in a dose-dependent way, but to a lesser degree in heavy users due possibly to tolerance. The Standard Field Sobriety Test is not sensitive to clinically relevant driving impairment caused by oral tetrahydrocannabinol.

Keywords Δ⁹-tetrahydrocannabinol, cannabis, driving, dronabinol, DUID, SFST, THC.

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INTRODUCTION

Cannabis is one of the most widely used drugs of abuse. Approximately 6% of the general US population aged 12 years and older admitted to recent cannabis use [1]. The widespread use of cannabis has also increased the prevalence of cannabis in the general driving population. Overall, 6.8% of drivers tested positive for Δ⁹-tetrahydrocannabinol (THC), the active ingredient of cannabis, in blood. The prevalence in young drivers aged 16–20 years was even higher, at 15.2% [2]. Moreover, 13% of drivers involved in fatal accidents were positive for THC [3]. High prevalence rates of THC among drivers may pose a serious problem, as experimental and epidemiological studies have demonstrated that THC increased driving impairment and crash risk in a dose-related manner [4–6].

The prevalence of drivers under the influence of THC is likely to increase even in countries that have passed laws to regulate medicinal cannabis distribution and

Nederlands Trial Register, NTR1903, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1903.

consumption. Pharmaceutical companies have developed synthetic cannabinoids, now available on the market as prescription drugs, for a number of medical indications. Dronabinol (Marinol®), a synthetic cannabinoid, is used to treat anorexia in AIDS and other wasting diseases, emesis in cancer patients undergoing chemotherapy and chronic pain. Therapeutic doses of orally administered dronabinol range between 2.5 and 20 mg/day. The pharmacokinetic profile of dronabinol differs markedly from smoked cannabis. After smoked cannabis, peak THC concentration (C_{max}) is reached within 5 minutes. This declines rapidly to about 10% of C_{max} within 1–2 hours. C_{max} is achieved within 2–4 hours after oral administration of dronabinol. Maximum concentrations are generally less than those observed after smoking, but remain on a plateau for up to 6 hours after administration [7–9]. Hence, oral administration of THC has a slower onset and blunted effect profile, but persists longer over time compared to smoked cannabis.

Similar effects of oral equipotent doses of THC to smoked THC on human performance are expected, yet only few studies have assessed the effects of oral THC on performance. Several studies have demonstrated that doses ranging from 5 to 15 mg THC produce subjective feelings of high [10–12]. Low doses (5–10 mg) did not produce impairments in a number of neuropsychological performance tests [10], but at higher doses (15–60 mg) memory and tracking impairment were reported in a driving simulator [11,13].

The present study was designed to assess the effects of orally administered, normal therapeutic doses of dronabinol (10 and 20 mg) on driving performance in a standardized on-the-road driving test performed in normal traffic. Previously this test was employed successfully to demonstrate dose-related impairments after smoked cannabis [6,14]. Occasional and heavy cannabis users participated to model acute THC effects in naive THC users and in chronic THC users who generally develop some behavioural tolerance to the impairing effects of THC [15,16]. A second objective was to determine whether THC-induced impairments, expected during on-the-road driving, could be assessed using Standardized Field Sobriety Tests (SFST). SFST consist of three tests administered and evaluated in a standardized manner to obtain validated indicators of impairment and establish probable cause for arrest. SFST are conducted routinely by the US police and several countries around the world to identify drivers under the influence.

METHODS

Subjects

Twelve occasional and 12 heavy cannabis users (14 males/10 females distributed evenly over both user groups) with mean [standard deviation (SE)] life-time use of 274.1 (89.6) and 2444.2 (708.8) times, respectively, and mean (SE) age 23.6 (0.6) years, participated. Almost all heavy users were daily smokers (range 7.7–23.1 joints per week), except subjects 21 and 23, who smoked on average 4.7 and 6.3 joints per week, respectively. Inclusion criteria were experience with cannabis (five to 36 times yearly for occasional users and >160 times yearly for heavy users); free from psychotrophic medication; good physical health; absence of any major medical condition; body mass index between 18 and 28; possession of valid driving licence; and written informed consent. Exclusion criteria were history of drug abuse or addiction to non-cannabinoids; pregnancy or lactation; cardiovascular abnormalities; excessive drinking; hypertension; history of or current psychiatric disorder; and allergy to sesame oil.

This study was conducted according to the Code of Ethics on Human Experimentation established by the declaration of Helsinki (1964) and amended in Seoul (2008). Approval for the study was obtained from the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University. A permit for obtaining, storing and administering THC was obtained from the Dutch drug enforcement administration.

Study design

The study was conducted according to a double-blind, placebo-controlled, randomized, three-way, cross-over design. Treatments consisted of single doses of placebo, 10 and 20 mg dronabinol and were administered orally in identically appearing capsules. Treatment orders were balanced over subjects and treatment periods. The washout period between treatments was at least 4 days, to prevent interference from preceding treatments.

Procedure

Subjects refrained from any drugs 1 week before the medical examination until study completion, except for heavy users, who continued their cannabis consumption. Subjects were not allowed to drink alcohol or caffeine during a 24-hour period prior to testing. Subjects were tested for alcohol in breath and drugs in urine upon arrival at the laboratory. Dronabinol and placebo were given only when occasional users tested negative and heavy users positive on THC and negative on other drugs. Subjective high was assessed and blood samples were taken at baseline (30 minutes before) and 1.5, 4.25 and 6 hours after drug administration. Driving tests were performed between 2 and 4 hours and SFST 4.5 and 5 hours post-drug. At the end of a testing day subjects were driven home.

Actual driving tests

The road-tracking test [17] consists of driving for approximately 1 hour in a specially instrumented car. Subjects have to maintain a constant speed of 95 km/hour (60 miles/hour) and drive as straight as possible on the right-hand lane of a primary highway. The dependent measure is the Standard Deviation of Lateral Position (SDLP), a measure of road-tracking control (i.e. weaving). Speed and standard deviation (SD) of speed are recorded as secondary control measures. This standardized test has been applied in more than 60 studies to determine drug effects on driving [18–20]. The road-tracking test has been calibrated for the effects of alcohol in such a manner that drug effects can be expressed in blood alcohol concentration (BAC) equivalents. A BAC of 0.5 mg/ml (0.05 g%) has been shown to increase SDLP by 2.4 cm [18]. Drug-induced changes in SDLP exceeding this alcohol criterion are qualified as a clinical relevant drug effect.

In the car-following test [21,22], subjects drive behind a leading vehicle on a primary highway for 25 minutes maintaining a constant distance between vehicles during a series of speed decelerations/acceleration initiated by the experimenter in the leading vehicle. The speed of the leading car is controlled by a cruise-control system, and is set to maintain a constant speed of ±100 km/hour (62 miles/hour). Sinusoidal speed changes reaching an amplitude of −10% and returning to the starting speed within 50 seconds are repeated six to 10 times. Time to speed adaptation (TSA), the primary measure, is calculated from the phase delay between speed signals from the leading and following vehicle. Secondary measures are gain, i.e. the amplification factor between both speed signals, and coherence, i.e. a measure for correspondence between both speed signals.

SFST

An investigator (W.M.B.) received extensive training by two SFST experts (W.K.J. and H.C.W.) to administer and evaluate the SFST in a standardized manner as defined in the training manuals used by all US police agencies and laboratory practice tests. The three tests of the SFST, i.e. horizontal gaze nystagmus (HGN), walk-and-turn (WAT) and one-leg stand (OLS), have been described and validated by Stuster & Burns [23]. A subject is impaired whenever he shows four of six signs of impairment on HGN, two of eight on WAT and two of four on OLS [23]. When a subject is impaired on two or more of these tests, he is classified as impaired overall by the SFST programme. Percentages of impaired subjects on each test, i.e. HGN, WAT, OLS and overall SFST, were the dependent variables.

Subjective measures

Subjective high was measured with a visual analogue scale (VAS). On a 100-mm line anchored 'not at all' and 'most ever', subjects indicated the effect of the drug by marking the line vertically.

Pharmacokinetic assessment

Blood samples (8 ml) were collected at baseline (heavy users only), 1.5, 4.25 and 6 hours post-drug. The blood sample was centrifuged and the resulting serum was frozen at −20°C until analysis. THC, 11-hydroxy THC (11-OH-THC) and nor-9-carboxy-THC (THCCOOH) concentrations were determined afterwards with limits of detection/limits of quantification of 0.24/0.73, 0.11/0.26 and 0.98/2.99 ng/ml, respectively.

Statistical analysis

All statistical analyses were performed using SPSS 18.0 for Mac. The analyses comprised two steps: (i) assessment of an overall dronabinol effect by means of superiority testing. Driving data entered a general linear model repeated-measures analysis of variance (ANOVA) procedure with dronabinol (three levels) as main within-subject factor and cannabis use history (two levels) as between-group factor. For subjective high an additional within-subject factor, time after drug administration (four levels) was added to the model to account for test repetitions. Following this overall analysis, the dronabinol (three levels) effects were tested separately in occasional and heavy users. If the sphericity assumption was violated, the Greenhouse–Geisser correction was used. (ii) Non-inferiority testing of dronabinol effects was based on difference scores from placebo relative to a predefined alcohol criterion [i.e. driving impairment equivalent to a BAC of 0.5 mg/ml (0.05 g%)] [18]. This analysis assessed whether the alcohol criterion value (2.4 cm), falls within the 95% confidence interval (CI) of the drug effect. If yes, then the drug effect was considered inferior, i.e. comparable to or greater than a BAC of 0.5 mg/ml (0.05 g%), and thus clinically relevant for traffic safety. If the upper limit of the 95% CI was below the alcohol criterion value then a drug effect was considered non-inferior, i.e. not clinically relevant. The sample size provided a power of at least 80% to detect a clinically relevant drug effect, given a mean population standard deviation of 4.0 cm, a test–retest correlation ≥0.70 and a non-inferiority margin of 2.4 cm at a two-sided α-level of 0.05.

The SFST were evaluated using χ^2 tests to determine whether a relationship existed between performance and THC dosing protocol. In case of a significant relationship, Spearman's coefficient (ρ) was calculated to determine strength and direction of the relationship [24].

RESULTS

Actual driving performance

Overall, dronabinol increased SDLP significantly ($F_{2,40} = 7.812$, $P = 0.001$) during road-tracking and increased TSA almost significantly ($F_{2,24} = 3.083$, $P = 0.064$) during car-following. Cannabis use history and the interaction between dronabinol and cannabis use history did not affect SDLP and TSA significantly. Separate ANOVAs in occasional and heavy users revealed that the impairing effects of dronabinol on SDLP and TSA were prominent in occasional users (respectively, $F_{2,18} = 6.493$, $P = 0.008$; $F_{2,10} = 7.269$, $P = 0.011$), but less so in heavy users. Other driving measures were not affected by dronabinol. Means [standard error (SE)] for driving measures in the two driving tests in all treatment conditions are given in Table 1.

Mean (95% CI) changes in SDLP after dronabinol in occasional and heavy users are shown in Fig. 1. Non-inferiority tests demonstrated that the upper limit of the 95% CI associated with change SDLP relative to placebo exceeded the alcohol criterion limit after both dronabinol doses in occasional users. In heavy users mean change from placebo was relatively small, but the 95% CI associated with change in SDLP after both doses of dronabinol included the alcohol criterion value. Small mean changes and wide CIs indicate large inter-individual variation in response to dronabinol in heavy users. This was also demonstrated in plots of individual change scores, as shown in Fig. 2.

SFST

The analysis of the SFST did not reveal any significant effects of dronabinol or cannabis use history. Percentage of impaired individuals is shown in Table 2.

Subjective measures

Dronabinol increased subjective high significantly in occasional and heavy users to similar degrees (respectively, $F_{2,20} = 9.160$, $P = 0.001$; $F_{2,20} = 6.664$; $P = 0.006$). Subjective high decreased significantly as a function of time after dronabinol administration ($F_{3,60} = 15.780$, $P < 0.001$). Mean (SE) subjective high measurements are given in Fig. 3.

Pharmacokinetic assessment

Mean (SE) THC, 11-OH-THC and THCCOOH concentrations are displayed in Table 2. Baseline THC concentrations for heavy users did not differ significantly between treatment conditions ($F_{1.086,8.686} = 1.971$, $P = 0.196$). Overall, a significant difference in drug concentrations between the drug conditions was shown ($F_{1.430,22.881} = 10.567$, $P = 0.001$) as well as a significant drug effect of time after dosing ($F_{1.152,18.433} = 7.015$, $P = 0.013$).

DISCUSSION

This study was designed to assess the effects of typical dosing of dronabinol on driving performance in occasional and heavy cannabis users.

Superiority tests revealed an overall effect of dronabinol on SDLP, independent of cannabis use history. ANOVAs in occasional and heavy users indicated separately that dronabinol's impairing effects were most prominent in occasional users. Mean SDLP increased 2.5 and 4.2 cm, respectively, after 10 and 20 mg dronabinol. Non-inferiority tests demonstrated that 95% CIs of the mean SDLP change included equivalent BAC effects of 0.8 and 1.0 mg/ml (0.08 and 0.1 g%). These data suggest that road-tracking impairments after dronabinol were of clinical relevance and comparable to impairments observed in drivers operating their vehicles at a BAC > 0.8 mg/ml (0.08 g%). Dronabinol also increased TSA during car-following of occasional users, indicating that drivers under the influence of dronabinol needed more time to react and adjust to speed changes of a leading vehicle. The present data confirm previous driving studies assessing the effects of smoked cannabis in occasional users and dose-related significant increases in SDLP [5,6,9].

In heavy users, mean SDLP did not differ between treatments according to superiority tests. However, non-inferiority tests demonstrated that the 95% CI associated with change in SDLP after both doses of dronabinol included the criterion value equivalent to a BAC of 0.5 mg/ml (0.05 g%). These 95% CIs were relatively wide due to large inter-individual variations in change SDLP after both doses. Individual data indicated that approximately 25% of heavy users demonstrated impairment in road-tracking performance equivalent to or worse than that observed in drivers with a BAC of 0.5 mg/ml (0.05 g%). Thus, THC-induced impairments of road-tracking performance in heavy cannabis were fewer compared to occasional users. This reduction in sensitivity to the impairing effects of THC in heavy users has been reported previously, and has been suggested to result from the development of behavioural tolerance after repeated cannabis use [9,10,15,16,25]. This study, however, also demonstrated that behavioural tolerance was not complete in every heavy cannabis user, as indicated by large inter-individual differences in driving impairments.

SFST did not differentiate between treatments. The absence of any observable impairment in SFST appears to indicate that these tests are not sensitive to the impairing

Table 1 Mean (standard error) performance on road-tracking test and car-following test and percentage of subjects impaired on Standard Field Sobriety Test (SFST) in every treatment condition. Significance indicated by *P*-value.

		Drug			*ANOVA (overall)*	
Test	*Cannabis use history*	*Placebo*	*10 mg dronabinol*	*20 mg dronabinol*	*Dronabinol × cannabis use history*	*Dronabinol*
Road-tracking						
SDLP (cm)	Occasional	17.9 (0.8)	20.4 (1.2)	22.1 (1.4)	NS	0.008
	Heavy	19.7 (1.3)	21.0 (1.2)	21.4 (1.2)		NS
Mean speed (km/hour)	Occasional	96.1 (0.4)	95.9 (0.3)	96.1 (0.6)	NS	NS
	Heavy	95.8 (0.2)	95.8 (0.4)	95.6 (0.3)		NS
SD speed (km/hour)	Occasional	2.1 (0.1)	2.2 (0.2)	2.1 (0.1)	NS	NS
	Heavy	2.2 (0.2)	2.3 (0.2)	2.3 (0.2)		NS
Car following						
TSA (second)	Occasional	2.5 (0.4)	4.1 (0.3)	2.9 (0.3)	NS	0.011
	Heavy	3.1 (0.1)	3.6 (0.4)	3.8 (0.8)		NS
Coherence	Occasional	0.9 (0.01)	0.9 (0.02)	0.9 (0.01)	NS	NS
	Heavy	0.9 (0.01)	0.9 (0.02)	0.9 (0.01)		NS
Gain	Occasional	1.2 (0.07)	1.2 (0.05)	1.2 (0.07)	NS	NS
	Heavy	1.2 (0.06)	1.2 (0.04)	1.4 (0.10)		NS
SFST					χ^2	
Overall SFST (% impaired)	Occasional	8.3	8.3	8.3	NS	
	Heavy	0.0	16.7	16.7	NS	
HGN (% impaired)	Occasional	0.0	8.3	0.0	NS	
	Heavy	0.0	0.0	0.0	NS	
WAT (% impaired)	Occasional	8.3	33.3	33.3	NS	
	Heavy	16.7	41.7	50.0	NS	
OLS (% impaired)	Occasional	16.7	16.7	25.0	NS	
	Heavy	8.3	25.0	16.7	NS	

ANOVA: analysis of variance; NS: not significant; SDLP: standard deviation of lateral position; TSA: time to speed adaptation; HGN: horizontal gaze nystagmus; WAT: walk and turn; OLS: one-leg stand; SD: standard deviation.

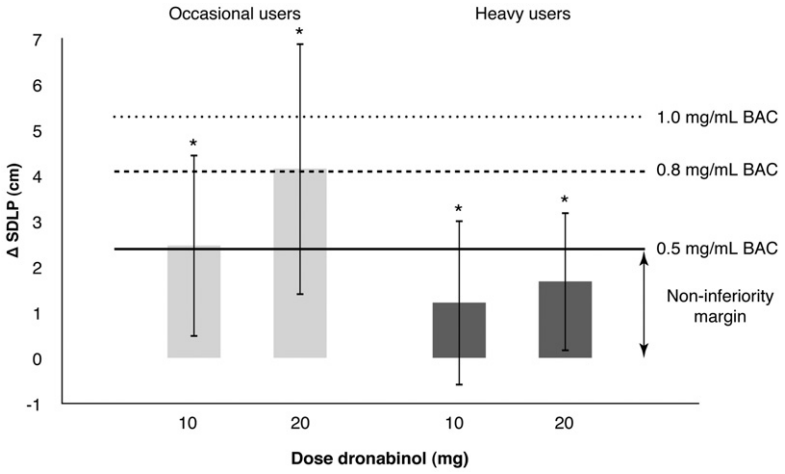

Figure 1 Mean [95% confidence interval (CI)] change in standard deviation of lateral position (SDLP) after single doses of dronabinol in occasional and heavy users. *Non-inferiority not shown, upper bound of the 95% CI is above the non-inferiority margin of 2.4 cm. BAC: blood alcohol concentration

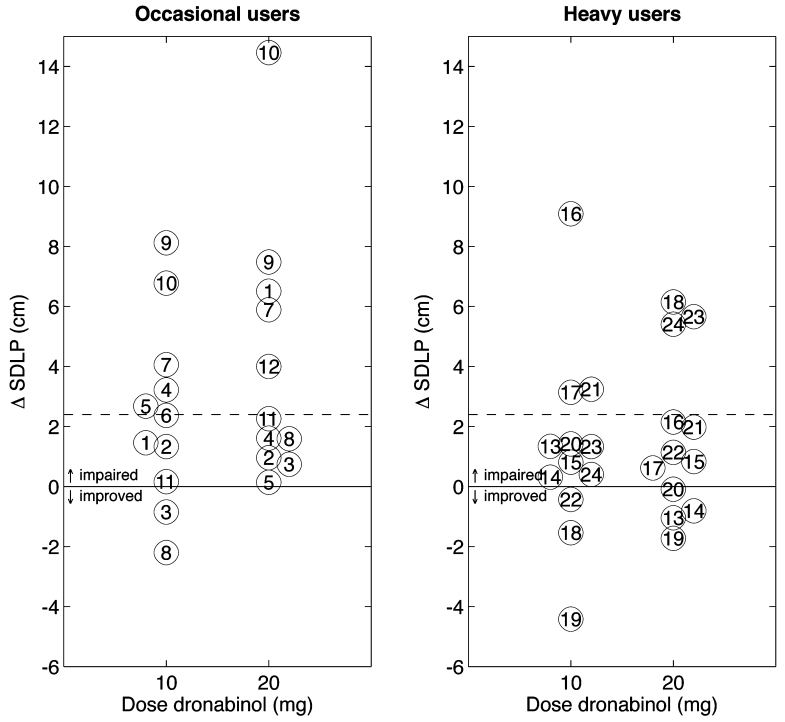

Figure 2 Individual data of change change in standard deviation of lateral position (SDLP) in occasional and heavy users after single doses of dronabinol. Change score >0 indicates impairment, change score <0 indicates improvement. The dotted horizontal line represents impairment equivalent to blood alcohol concentration of 0.5 mg/ml

effects of THC, even when objective impairment levels are comparable to BAC > 0.8 mg/ml (0.08 g%). These findings confirm results from a previous placebo-controlled study, demonstrating that the number of impaired subjects during THC intoxication was comparable to placebo [26]. SFST have been validated against alcohol impaired drivers at various BACs, which might explain the low propensity of SFST to discriminate between THC use and placebo [23]. The present results underscore this notion, and demonstrate that current SFST are insufficiently sensitive to detect THC-induced driving impairment following oral administration of dronabinol. Therefore, more indicators of impairment besides the three SFST are included in the Drug Recognition and Evaluation Program in North America to detect driving impairment, which may be indicative of drug use.

Both dronabinol doses produced dose-related increments in subjective high that were extremely comparable in both groups. The latter confirms that dronabinol doses were centrally active in users from both groups. It is noteworthy that the driving impairments after dronabinol use were evident, even though THC plasma concentrations were relatively low. Overall, mean THC concentrations varied between 10 and 2 ng/ml during onset and completion of the road driving tests. This finding confirms the results from a previous report showing that impairment of neurocognitive functions can be observed when THC in plasma ranges between 2 and 5 ng/ml [8]. For patients

Table 2 Mean (standard error) serum concentrations (ng/ml) for tetrahydrocannabinol (THC), 11-hydroxy THC (11-OH-THC) and nor-9-carboxy-THC (THCCOOH) in occasional and heavy users for every treatment and measurement time.

		Occasional users			*Heavy users*		
	Time post-drug (hour)	*THC*	*11-OH-THC*	*THCCOOH*	*THC*	*11-OH-THC*	*THCCOOH*
Placebo	–0.5	–	–	–	15.3 (8.5)	5.6 (2.4)	58.2 (17.5)
	1.5	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	6.4 (2.7)	2.8 (0.9)	37.4 (9.9)
	4.25	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	4.9 (1.7)	2.0 (0.6)	37.2 (11.6)
	6	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	4.4 (1.6)	1.6 (0.5)	31.2 (9.4)
10 mg dronabinol	–0.5	–	–	–	7.6 (3.6)	2.9 (1.2)	41.8 (11.2)
	1.5	3.2 (0.8)	4.2 (0.6)	22.6 (5.6)	9.2 (2.1)	6.2 (0.9)	54.4 (8.8)
	4.25	2.1 (0.7)	1.8 (0.3)	18.5 (2.8)	4.6 (1.1)	3.1 (0.4)	43.4 (7.4)
	6	1.2 (0.3)	1.7 (0.3)	16.8 (1.3)	4.2 (1.0)	2.3 (0.4)	37.2 (7.6)
20 mg dronabinol	–0.5	–	–	–	10.3 (4.9)	3.6 (1.5)	46.2 (12.7)
	1.5	6.2 (1.3)	6.9 (1.4)	37.2 (11.4)	10.2 (2.2)	7.1 (1.1)	54.0 (10.1)
	4.25	1.8 (0.3)	2.6 (0.5)	24.0 (3.7)	6.3 (1.2)	4.5 (0.5)	52.0 (8.9)
	6	2.8 (0.6)	3.1 (0.5)	30.2 (4.3)	5.7 (1.1)	3.9 (0.5)	56.2 (9.1)

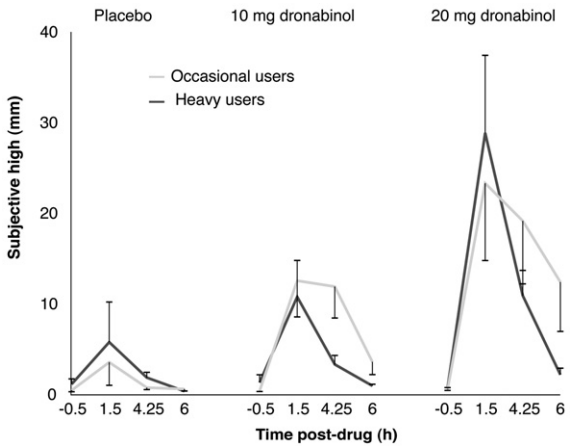

Figure 3 Mean (standard error) subjective rating of high as a function of time after drug administration in all treatment conditions

using dronabinol, this means that risk of driving impairment is present at any therapeutic dose, independent of THC concentration.

It is concluded that a single dose of dronabinol severely impairs driving performance of drivers with a history of occasional cannabis use. Behavioural tolerance to the impairing effects of dronabinol was observable in heavy cannabis users, although not in every individual. About 25% of heavy users still displayed driving impairments comparable to or worse than a BAC of 0.5 mg/ml (0.05 g%). The advice to patients using dronabinol is not to drive, irrespective of dose, serum concentration or THC use history. This study points clearly to the need for development of field tests to detect drug (e.g. THC)-induced impairment.

Declarations of interest

None.

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