Introduction

This article describes the results of a research program that was set up to determine the dose-response relationship between marijuana and objectively and subjectively measured aspects of real world driving; and to determine whether it is possible to correlate driving performance impairment with plasma concentrations of the drug or a metabolite. The program consisted of three driving studies in which a variety of driving tasks were employed, including: maintenance of a constant speed and lateral position during uninterrupted highway travel, following a leading car with varying speed on a highway, and city driving. A laboratory study preceded the driving studies for identifying the highest THC dose to be administered in the subsequent studies.

General Procedures

Subjects in all studies were recreational users of marijuana or hashish, i.e., smoking the drug more than once a month, but not daily. They were all healthy, between 21 and 40 years of age, had normal weight and binocular acuity, and were licensed to drive an automobile. Furthermore, law enforcement authorities were contacted, with the volunteers’ consent, to verify that they had no previous arrests or convictions for drunken driving or drug trafficking.

Each subject was required to submit a urine sample immediately upon arrival at the test site. Samples were assayed qualitatively for the following common ‘street drugs’ (or metabolites): cannabinoids, benzodiazepines, opiates, cocaine, amphetamines and barbiturates. In addition a breath sample was analyzed for the presence of alcohol. Blood samples were repeatedly taken after smoking by venepuncture. Quantitative analysis of THC and THC-COOH in plasma was performed by gas chromatography/mass spectrometry (GC/MS) using deuterated cannabinoids as internal standards.

Marijuana and placebo marijuana cigarettes were supplied by the U.S. National Institute on Drug Abuse. The lowest and highest THC concentrations in the marijuana cigarettes used in the studies were 1.75% and 3.57%, respectively. Subjects smoked the administered cigarettes through a plastic holder in their customary fashion.

Subjects were accompanied during every driving test by a licensed driving instructor. A redundant control system in the test vehicle was available for controlling the car, should emergency situations arise.

In each study, subjects repeatedly performed certain simple laboratory tests (e.g. critical instability tracking, hand and posture stability), estimated their levels of intoxication and indicated their willingness to drive under several specified conditions of urgency. In addition, heart rate and blood pressure were measured. Results of these measurements are reported elsewhere (Robbe, 1994).

Laboratory Study
Methods
Twenty-four subjects, equally comprised of men and women, participated in this study. They were allowed to smoke part or all of the THC content in three cigarettes until achieving the desired psychological effect. The only requirement was to smoke for a period not exceeding 15 minutes. When subjects voluntarily stopped smoking, cigarettes were carefully extinguished and retained for subsequent gravimetric estimation of the amount of THC consumed.

Results
Six subjects consumed one cigarette, thirteen smoked two and four smoked three (data from one male subject were excluded from the results because no drug was found in his plasma after smoking). The average amount of THC consumed was 20.8 mg, after adjustment for body weight, 308 mg/kg. It should be noted that these amounts of THC represent both the inhaled dose and the portion that was lost through pyrolysis and sidestream smoke during the smoking process. There were no significant differences between males and females, nor between frequent and infrequent users, with respect to the weight adjusted preferred dose. It was decided that the maximum dose for subsequent driving studies would be 300 mg/kg.

Study 1: Driving on a Restricted Highway

Methods
The first driving study was conducted on a highway closed to other traffic. The same twelve men and twelve women who participated in the laboratory study served again as the subjects. They were treated on separate occasions with marijuana cigarettes containing THC doses of 0 (placebo), 100, 200, and 300 mg/kg. Treatments were administered double-blind and in a counterbalanced order. On each occasion, subjects performed a road-tracking test beginning 40 minutes after initiation of smoking and repeated one hour later. The test involved maintaining a constant speed at 90 km/h and a steady lateral position between the delineated boundaries of the traffic lane. Subjects drove 22 km on a primary highway and were accompanied by a licensed driving instructor. The primary dependent variable was the standard deviation of lateral position (SDLP), which has been shown to be both highly reliable and very sensitive to the influence of sedative medicinal drugs and alcohol. Other dependent variables were mean speed, and standard deviations of speed and steering wheel angle. Blood samples were taken 10 minutes before the driving tests (i.e. 30 and 90 minutes after initiation of smoking, respectively).
Results
All subjects were willing and able to finish the driving tests without great difficulty. Data from one male subject were excluded from the results because no drug was found in his plasma after smoking.

Fig. 1 demonstrates that marijuana impairs driving performance as measured by an increase in lateral position variability: all three THC doses significantly affected SDLP relative to placebo (p<.012, .001 & .001, for the 100, 200 & 300 mg/kg conditions, respectively. The Dose by Time effect was not significant indicating that impairment after marijuana was the same in both trials. Marijuana’s effects on SDLP were compared to those of alcohol obtained in a very similar study by Louwerens et al. (1987). It appeared that the effects of the various administered THC doses (100-300 mg/kg) on SDLP were equivalent to those associated with BACs in the range of 0.03-0.07 g%. Other driving performance measures were not significantly affected by THC. Plasma concentrations of the drug were clearly related to the administered dose and time of blood sampling but unrelated to driving performance impairment.

Study 2: Driving on a Normal Highway in Traffic

Methods
The second driving study was conducted on a highway in the presence of other traffic and involved both a road-tracking and a car-following test. A new group of sixteen subjects, equally comprised of men and women, participated in this study. A conservative approach was chosen in designing the present study in order to satisfy the strictest safety requirements. That is, the study was conducted according to an ascending dose series design where both active drug and placebo conditions were administered, double-blind, at each of three THC dose levels. THC doses were the same as those used in the previous study, namely 100, 200, and 300 mg/kg. Cigarettes appeared identical at each level of treatment conditions. If any subject would have reacted in an unacceptable manner to a lower dose, he/she would not have been permitted to receive a higher dose.

The subjects began the car-following test 45 minutes after smoking. The test was performed on a 16 km segment of the highway and lasted about 15 minutes. After the conclusion of this test, subjects performed a 64-km road-tracking test on the same highway which lasted about 50 minutes. At the conclusion of this test, they participated again in the car-following test. Blood samples were taken both before the first and after the last driving test (i.e. 35 and 190 minutes after initiation of smoking, respectively).
The road-tracking test was the same as in the previous study except for its duration and the presence of other traffic. The car-following test involved attempting to match velocity with, and maintain a constant distance from a preceding vehicle as it executed a series of deceleration/acceleration maneuvers. The preceding vehicle's speed would vary between 80 and 100 km/h and the subject was instructed to maintain a 50 m distance however the preceding vehicle's speed might vary. The duration of one deceleration and acceleration maneuver was approximately 50 seconds and six to eight of these maneuvers were executed during one test, depending upon traffic density. The subject's average reaction time to the movements of the preceding vehicle, mean distance and coefficient of variation of distance during maneuvers were taken as the dependent variables from this.

**Results**

All subjects were able to complete the series without suffering any untoward reaction while driving. Data from one female subject were excluded from the results because no drug was found in her plasma after smoking.

Road-tracking performance in the standard test was impaired in a dose-related manner by THC and confirmed the results obtained in the previous closed highway study (Fig. 2). The 100 mg/kg dose produced a slight elevation in mean SDLP, albeit not statistically significant (p<.13). The 200 mg/kg dose produced a significant (p<.023) elevation, of dubious practical relevance. The 300 mg/kg dose produced a highly significant (p<.007) elevation which may be viewed as practically relevant. After marijuana smoking, subjects drove with an average speed that was only slightly lower than after placebo and very close to the prescribed level.

In the car-following test, subjects maintained a distance of 45-50 m while driving in the successive placebo conditions. They lengthened mean distance by 8, 6 and 2 m in the corresponding THC conditions after 100, 200 and 300 mg/kg, respectively. The initially large drug-placebo difference and its subsequent decline is a surprising result. Our explanation for this observation is that the subjects' caution was greatest the first time they undertook the test under the influence of THC and progressively less thereafter.

The reaction time of the subjects to changes in the preceding vehicle's speed increased following THC treatment, relative to placebo. The administered THC dose was inversely related to the change in reaction time, as it was to distance. However, increased reaction times were partly due to longer distance (i.e. the longer the distance to the preceding vehicle, the more difficult it is to perceive changes in its speed). Statistical adjustment for
this confounding variable resulted in smaller and non-significant increases in reaction time following marijuana treatment, the greatest impairment (0.32 s) being observed in the first test following the lowest THC dose (Fig. 3). Distance variability followed a similar pattern as mean distance and reaction time; the greatest impairment was found following the lowest dose. As in the previous study, plasma concentrations of the drug were not related to driving impairment.

Study 3: Driving in Urban Traffic

Methods
The program proceeded into the third driving study, which involved tests conducted in high-density urban traffic. There were logical and safety reasons for restricting the THC dose to 100 mg/kg. It was given to a new group of 16 regular marijuana (or hashish) users, along with a placebo. For comparative purposes, another group of 16 regular users of alcohol, but not marijuana, were treated with a modest dose of their preferred recreational drug, ethanol, and again placebo, before undertaking the same city driving test. Both groups were equally comprised of men and women.

Marijuana was administered to deliver 100 mg/kg THC. The driving test commenced 30 minutes after smoking. The alcohol dose was chosen to yield a BAC approaching 0.05 g% when the driving test commenced 45 minutes after onset of drinking. Active drug and placebo conditions were administered double-blind and in a counterbalanced order in each group. Blood samples were taken immediately prior to and following all placebo and drug driving tests (i.e. 20 and 80 minutes after initiation of smoking, or 35 and 95 minutes after initiation of drinking).

Driving tests were conducted in daylight over a constant 17.5 km route within the city limits of Maastricht. Subjects drove their placebo and active-drug rides through heavy, medium and low density traffic on the same day of the week, and at the same time of day. Two scoring methods were employed in the present study. The first, a 'molecular' approach adopted from Jones (1978), involved the employment of a specially trained observer who applied simple and strict criteria for recording when the driver made or failed to make each in a series of observable responses at predetermined points along a chosen route. The second, a 'molar' approach, required the driving instructor acting as the safety controller during the tests to retrospectively rate the driver's performance using a shortened version of the Royal Dutch Tourist Association's Driving Proficiency...
Test. In total, 108 items were dichotomously scored, as either pass or fail. Total test performance was measured by the percentage items scored as ‘pass’. Subscores were calculated for vehicle checks, vehicle handling, traffic maneuvers, observation and understanding of traffic, and turning. This method has been applied previously to show the impairing effects of alcohol and diazepam (De Gier, 1979; De Gier et al., 1981).

Results
Data from two male subjects in the marijuana group were excluded from the results because neither THC nor THC-COOH was found in their plasma after smoking.

Neither alcohol nor marijuana significantly affected driving performance measures obtained by the molecular approach, indicating that it may be relatively insensitive to drug-induced changes. The molar approach was more sensitive. Table 1 shows that a modest dose of alcohol (BAC=0.034 g%) produced a significant impairment in city driving, relative to placebo. More specifically, alcohol impaired both vehicle handling and traffic maneuvers. Marijuana, administered in a dose of 100 mg/kg THC, on the other hand, did not significantly change mean driving performance as measured by this approach.

Subjects' ratings of driving quality and effort to accomplish the task were strikingly different from the driving instructor's ratings. Both groups rated their driving performance following placebo as somewhat better than ‘normal’. Following the active drug, ratings were significantly lower (35%, p<.009) in the marijuana, but not (5%, ns) in the alcohol group. Perceived effort to accomplish the driving test was about the same in both groups following placebo. Following the active drug, a significant (p<.033) increase in perceived effort was reported by the marijuana, but not the alcohol group.

Table 1 Mean (±SED) changes in driving performance scores measured by the molar approach for the marijuana (N=14) and alcohol (N=16) group; and, the significance of each change and difference between changes.

<table>
<thead>
<tr>
<th>dependent variable</th>
<th>marijuana group</th>
<th>alcohol group</th>
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<tr>
<td></td>
<td>marijuana v alcohol</td>
<td></td>
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<tr>
<td>total score</td>
<td>-0.7 (±2.7)</td>
<td>-6.8 (±1.8)</td>
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<tr>
<td></td>
<td>ns</td>
<td>.002</td>
</tr>
<tr>
<td>vehicle checks</td>
<td>-0.6 (±1.5)</td>
<td>+0.5 (±1.3)</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>vehicle handling</td>
<td>+3.7 (±2.8)</td>
<td>-8.4 (±2.2)</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>.002</td>
</tr>
<tr>
<td>traffic maneuvers</td>
<td>-2.7 (±3.1)</td>
<td>-8.4 (±2.3)</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>.003</td>
</tr>
<tr>
<td>observation and understanding of traffic</td>
<td>+1.8 (±8.7)</td>
<td>-6.3 (±7.0)</td>
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<td></td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>turning</td>
<td>-1.8 (±4.9)</td>
<td>+3.1 (±7.5)</td>
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Thus, there is evidence that subjects in the marijuana group were not only aware of their intoxicated condition, but were also attempting to compensate for it. These seem to be important findings. They support both the common belief that drivers become overconfident after drinking alcohol and investigators’ suspicions that they become more cautious and self-critical after consuming low doses of THC, as smoked marijuana.

Drug plasma concentrations were neither related to absolute driving performance scores nor to the changes that occurred from placebo to drug conditions. With respect to THC, these results confirm the findings in previous studies. They are somewhat surprising for alcohol but may be due to the restricted range of ethanol concentrations in the plasma of different subjects.

Discussion

The results of the studies corroborate those of previous driving simulator and closed-course tests by indicating that THC in inhaled doses up to 300 mg/kg has significant, yet not dramatic, dose-related impairing effects on driving performance (cf. Smiley, 1986). Standard deviation of lateral position in the road-tracking test was the most sensitive measure for revealing THC’s adverse effects. This is because road-tracking is primarily controlled by an automatic information processing system which operates outside of conscious control. The process is relatively impervious to environmental changes but highly vulnerable to internal factors that retard the flow of information through the system. THC and many other drugs are among these factors. When they interfere with the process that restricts road-tracking error, there is little the afflicted individual can do by way of compensation to restore the situation. Car-following and, to a greater extent, city driving performance depend more on controlled information processing and are therefore more accessible for compensatory mechanisms that reduce the decrements or abolish them entirely.

THC’s effects on road-tracking after doses up to 300 mg/kg never exceeded alcohol’s at BACs of 0.08 g%; and, were in no way unusual compared to many medicinal drugs’ (Robbe, 1994; Robbe and O’Hanlon, 1995; O’Hanlon et al., 1995). Yet, THC’s effects differ qualitatively from many other drugs, especially alcohol. Evidence from the present and previous studies strongly suggests that alcohol encourages risky driving whereas THC encourages greater caution, at least in experiments. Another way THC seems to differ qualitatively from many other drugs is that the former’s users seem better able to compensate for its adverse effects while driving under the influence.

Inter-subject correlations between plasma concentrations of the drug and driving performance after every dose were essentially nil, partly due to the peculiar kinetics of THC. It enters the brain relatively rapidly, although with a perceptible delay relative to plasma concentrations. Once there, it remains even at a time when plasma concentrations approach or reach zero. As a result, performance may still be impaired at the time that plasma concentrations of the drug are near the detection limit. This is exactly what happened in the first driving study. Therefore an important practical implications of the study is that is not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentrations of THC and THC-COOH determined in a single sample.

Although THC’s adverse effects on driving performance appeared relatively small in the tests employed in this program, one can still easily imagine situations where the influence of marijuana smoking might have a dangerous effect; i.e., emergency
situations which put high demands on the driver's information processing capacity, prolonged monotonous driving, and after THC has been taken with other drugs, especially alcohol. Because these possibilities are real, the results of the present studies should not be considered as the final word. They should, however, serve as the point of departure for subsequent studies that will ultimately complete the picture of THC's effects on driving performance.

References


