BRONCHODILATOR
EFFECT OF $\Delta^1$-TETRAHYDROCANNABINOL

J.P.R. HARTLEY, S.G. NOGRADY & A. SEATON
Asthma Research Unit, Sully Department of
A/-trans-tetrahydrocannabinol ($\Delta^1$-THC) principal
The introduction activity bronchodilator by delivered
(Williams, Hartley dose A 1973; Vachon, discomfort in was
significant Al-THC of increase in reversibility demonstrate
They none had taken years) gave
Five in-patients who had recovered from attacks
asthma, and of discharge. awaiting cannabis previously
informed patients. To examine the total drug response over
6 h for the three doses of $\Delta^1$-THC.

Methods
Five asthmatic patients (female, age range 25–65 years) gave written informed consent to the study. None had taken cannabis previously in any form. They were in-patients who had recovered from attacks of asthma, and were in a relatively stable state awaiting discharge. Two patients were atopic. To demonstrate reversibility of the airways obstruction an increase in peak expiratory flow rate (PEFR) of at least 20% was established in each patient following the inhalation of 200 $\mu$g of salbutamol before inclusion in the study. All patients were on prednisone (10–15 mg/day), which was continued throughout the period of investigation. Bronchodilator drugs were withheld for 12 h before each test began.

Each patient was studied for four consecutive days, a different aerosol being administered double blind each morning according to an extended latin square design. Ventilatory function was measured by peak expiratory flow rate (PEFR) using a Wright Peak Flow Meter (Airmed) and forced expiratory volume in one second (FEV1) using a dry wedge spirometer (Vitalograph). On each occasion the best of three technically satisfactory readings was noted. Three sets of readings at 5 min intervals were recorded before administration of aerosol, the single best values for PEFR and FEV1 being used as baseline values. After one puff only of aerosol, measurements were made at 5, 15, 30, 45, 60, 90, 120, 240 and 360 min.

The results were analysed by three-way analysis of variance which compared the total drug response over 6 h for the three doses of $\Delta^1$-THC.

Drugs
The $\Delta^1$-THC was supplied in ethanol by the National Institute of Drug Abuse, U.S.A. and put up in identical canisters which were made as previously described (Williams et al., 1976). These delivered 63 $\mu$l per puff containing 50, 100 or 200 $\mu$g $\Delta^1$-THC in ethanol and propellant as placebo. They were labelled A–D respectively.

Results
All given doses of $\Delta^1$-THC caused bronchodilatation, as reflected by increases in both PEFR and FEV1. The
Figure 1 The mean ± s.e. mean for PEFR and FEV₁ for eleven observations on each of five subjects for placebo and 50, 100 and 200 μg of Δ¹-THC by aerosol.

The effect was dose related (Figure 1). The maximum improvement was seen at approximately 60 min and was sustained for at least 3 h. Thereafter the response to 50 μg declined sharply but that to the higher doses was maintained for at least one further hour (Figure 2). There was no difference in maximal response between 100 μg and 200 μg Δ¹-THC for PEFR from 1–4 h, but the maximal response to 50 μg Δ¹-THC was considerably less. A similar pattern was obtained for FEV₁. The effect of 100 and 200 μg Δ¹-THC was similar at 3 h. A marked improvement of FEV₁ persisted for more than 6 h after the higher doses. Analysis of variance for total drug response, eleven observations, showed that all doses of Δ¹-THC were significantly better than placebo with respect to PEFR (Table 1). Both 200 μg and 100 μg were better than 50 μg and 200 μg was more effective than 100 μg. Changes with respect to FEV₁ also showed all doses of Δ¹-THC were significantly better than placebo with respect to PEFR (Table 1). Both 200 μg and 100 μg were better than 50 μg and 200 μg was more effective than 100 μg. Changes with respect to FEV₁ also showed all doses of Δ¹-THC to be better

Table 1 Analysis of variance of PEFR and FEV₁ in five subjects, eleven observations each over 6 h after placebo or Δ¹-THC 50, 100 or 200 μg by aerosol

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PEFR</th>
<th>P</th>
<th>FEV₁</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plac/THC 50</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.001</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Plac/THC 100</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.001</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plac/THC 200</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.001</td>
<td>THC &gt; placebo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>THC 50/THC 100</td>
<td>100 &gt; 50</td>
<td>&lt; 0.001</td>
<td>100 &gt; 50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>THC 50/THC 200</td>
<td>200 &gt; 50</td>
<td>&lt; 0.001</td>
<td>200 &gt; 50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>THC 100/THC 200</td>
<td>200 &gt; 100</td>
<td>&lt; 0.05</td>
<td>100 &gt; 200</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>
than placebo. Both 200 μg and 100 μg were better than 50 μg. 100 μg was just significantly better than 200 μg. All the patients responded to Δ¹-THC in a similar fashion, although the degree of response varied between patients. Occasionally, cough was experienced after inhalation. There was no subjective response or tachycardia.

Discussion

Doses of Δ¹-THC which are large enough to cause bronchodilatation when taken orally are invariably associated with psychological effects, and direct bronchial administration of a smaller dose is, therefore, more appropriate. Smoking marhuana can cause bronchodilatation in asthmatic patients (Tashkin et al., 1974) and prevent experimentally-induced bronchospasm (Tashkin, Shapiro, Lee & Harper, 1975) but the dose is difficult to control, the smoke irritates the airways and long-term use can impair lung function (Henderson, Tennant & Guerry, 1972). More recently, therefore, aerosolized Δ¹-THC has been investigated. The smallest dose which has previously been shown to cause bronchodilatation when given by aerosol to asthmatic patients is 200 μg (Williams et al., 1976). Other workers have found larger doses given in this way to be effective, but not without psychological or local irritant effects (Tashkin, Reiss, Shapiro, Calvarese, Olsen & Lodge, 1977; Vachon, Robins & Gaensler, 1976).

The present study has demonstrated that small doses of Δ¹-THC given by aerosol can cause bronchodilatation as measured by improvement in PEFR and FEV₁. These tests were used because they give acceptable measure of clinically useful bronchodilatation. It is possible to construct an approximate dose-response curve for both PEFR and FEV₁. The optimal dose would appear to be 100 μg. The differences between 100 and 200 μg were small. We have found that doses higher than this commonly cause coughing and restrosternal discomfort, even in normal subjects, and this is more pronounced in asthmatics, in whom a transient increase in airways obstruction may be found. It is possible that the local irritant effect of Δ¹-THC even at 200 μg caused bronchoconstriction in all but the largest airways, which opposed the direct bronchodilator activity of the drug, and this may have been responsible for the inversion of the dose response effect with respect to FEV₁.

Our highest dose, 200 μg of Δ¹-THC was determined by practical considerations of patient tolerance. Reduction of the inhaled dose to 50 μg resulted in a significant loss of bronchodilator activity but no unpleasant respiratory symptoms. A dose of 100 μg delivered as two puffs of 50 μg each from a pressurized aerosol, would appear to be the most suitable one for further studies. At this dose, no measurable absorption from the lungs occurs, and neither psychological, nor cardiovascular effects are found (Williams et al., 1976).

The mechanism of action of the drug, though not as yet known, does not appear to be related to β-adrenoceptor stimulation or to cholinergic blockade (Shapiro, Tashkin & Frank, 1973; Davies, Radcliffe, Seaton & Graham, 1975). Naturally-occurring and synthetic cannabinoid compounds which are without psychological activity are now available, and may hold therapeutic potential if they can be shown to retain bronchodilator activity.

We thank Dr M. Braude of The National Institute on Drug Abuse, Maryland, U.S.A. and the Medical Research Council for the gift of Δ¹-THC; and Dr Anderson of the School of Pharmacy, U.W.I.S.T., Cardiff for the preparation of the aerosols. One of us (J.D.P.G.) holds Home Office Licence No. 984 under the Misuse of Drugs Act (1971).

References


(Received June 27, 1977)