Original Paper

Chronic Respiratory Disease

Chronic Respiratory Disease
8(2) 109–118

DOI: 10.1177/1479972310391283
crd.sagepub.com
SAGE

Cannabinoid effects on ventilation and breathlessness: A pilot study of efficacy and safety

Elspeth E Pickering[1,2], Stephen J Semple[3], Muhummad S Nazir[4], Kevin Murphy[2], Thomas M Snow[1], Andrew R Cummin[2], Shakeeb H Moosavi[3], Abraham Guz[3], and Anita Holdcroft[4]

Abstract

Based on the neurophysiology of dyspnoea and the distribution of cannabinoid receptors within the central nervous system, we hypothesize that the unpleasantness of breathlessness will be ameliorated in humans by cannabinoids, without respiratory depression. Five normal and four chronic obstructive pulmonary disease (COPD) subjects entered a double blind, randomized, placebo-controlled crossover study with two test days. Subjects received sublingual cannabis extract or placebo. A maximum of 10.8 mg tetrahydrocannabinol and 10 mg cannabidiol were given. Breathlessness was simulated using fixed carbon dioxide loads. Measurements taken were of breathlessness (visual analogue scale [VAS] and breathlessness descriptors), mood and activation, end-tidal carbon dioxide tension and ventilatory parameters. These were measured at baseline and 2 hours post placebo and drug administration. Normal and COPD subjects showed no differences in breathlessness VAS scores and respiratory measurements before and after placebo or drug. After drug administration, COPD subjects picked 'air hunger' breathlessness descriptors less frequently compared to placebo. We have shown that breathlessness descriptors may detect an amelioration of the unpleasantness of breathlessness by cannabinoids without a change in conventional breathlessness ratings (VAS). A stimulus more specific for air hunger may be needed to demonstrate directly a drug effect on breathlessness. However, this study shows that the inclusion of respiratory descriptors may contribute to the assessment of drug effects on breathlessness.

Keywords

breathlessness, cannabinoids, carbon dioxide, COPD, human

Introduction

Breathlessness needs alleviation, particularly when the underlying condition cannot be cured and the maximum benefit has been achieved from current therapy. The only treatments that have some effect are benzodiazepines[1] and/or opiates,[2] but both cause morbidity and even mortality through central respiratory depression.

Several brain imaging studies have identified a link between dyspnoea, including air hunger, and the insular cortex, the limbic and paralimbic loci.[3-6] These anatomical connections may be susceptible to inhibition by endogenous cannabinoid mechanisms.[7]

The active cannabinoid tetrahydrocannabinol (THC) is a partial agonist at cannabinoid CB_1 receptors and can cause sedation and mood effects.[8] In humans, CB_1 receptors are virtually absent in the ponto-medullary area.[9] It is therefore unlikely that cannabinoids will cause respiratory compromise,

[1] North Thames West Region, London, UK
[2] Imperial College Healthcare, NHS Trust, London, UK
[3] National Heart and Lung Institute (NHLI), Imperial College London, Charing Cross Hospital Campus, London, UK
[4] Imperial College London, UK

Corresponding author:
Elspeth Pickering, Department of Anaesthesia, Northwick Park Hospital, The North West London Hospitals NHS Trust, Watford Road, Harrow, HA1 3UJ
Email: elspethpickering@yahoo.co.uk

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Male and female volunteers
	Age 40−75 years
	FEV_1 <60% and >40% predicted normal (COPD subjects)[a]
	FEV_1/FVC% of <70% (COPD subjects)
	FEV_1 ≥80% predicted normal (normal subjects)
	FEV_1/FVC ≥70% (normal subjects)
Exclusion criteria	Body mass index (BMI) >35 kg/m^2
	Breathless at rest
	Ischaemic heart disease
	Blood pressure >160/95 mmHg, heart rate >95 beats/min
	Recent COPD exacerbation requiring hospital admission[b]
	Hospital Anxiety and Depression scale score >10 in anxiety or depression or combined score >16[c]
	Psychiatric history or epilepsy
	Lung cancer or other clinically significant co-morbidity
	Fentanyl, sildenafil and cannabis use
	Cannabis, ethanol or peppermint oil allergy[d]
	Hepatic or renal impairment

Abbreviations: FEV_1: forced expiratory volume over 1 second, FVC: forced vital capacity, COPD: chronic obstructive pulmonary disease.

[a] FEV_1 and FEV_1/FVC values were taken as an average of grade IIa and IIb grading for COPD severity classification from the GOLD guidelines 2001.[17]

[b] Hospital admission within last 3 months.

[c] Hospital Anxiety and Depression scale.[18]

[d] Ethanol and peppermint oil are components of Sativex spray.

and this has been previously demonstrated in normal volunteers.[10-13]

The other main active cannabinoid in cannabis extract is cannabidiol (CBD), not active at CB_1 receptors, which may mitigate aversive behavioural effects of THC in humans.[14] CBD has anxiolytic properties in humans. Functional magnetic resonance imaging has shown CBD attenuated the responses in the amygdala and cingulate cortex to fearful stimuli.[15] Thus, we used a cannabinoid preparation containing an equivalent amount of cannabidiol as well as THC for its direct effects and because it may ameliorate THC effects promoting anxiety.[16]

We hypothesized that administration of THC combined with CBD ameliorates breathlessness by inhibiting neural activity in the cerebral neuroaxis for breathlessness without inducing respiratory depression or anxiety.

Methods

This pilot study was designed as a randomized, double blind, placebo-controlled crossover study of cannabis-based medicinal extract (CBME) on breathlessness induced by different loads of carbon dioxide (CO_2) in volunteers (normal subjects) and chronic obstructive pulmonary disease patients (COPD subjects). Ethics approval was granted from Riverside Research Ethics Committee (RREC), UK.

Subjects and screening

Recruitment was via advertisement or outpatient COPD clinics, followed by written informed consent. Lung function tests were available for COPD subjects. In normal subjects, forced expiratory volume over 1 second (FEV_1) and forced vital capacity (FVC) was measured.

Moderate severity COPD subjects were recruited with no breathlessness at rest. All subjects had a full history, examination and a 12-lead electrocardiogram (ECG). Exclusion and inclusion criteria are shown in Table 1.

Measurements

Subjects breathed through a mouth piece connected to a two-way valve (Hans Rudolph), with expired airflow measured using a Fleisch number 2 pneumotachometer with a differential pressure transducer (MP 45 ± 2 cm H_2O, Validyne, Northridge, California, USA). Expired gas was sampled from the connection between the mouthpiece and the two-way valve from which a continuous record of inspired and expired CO_2 was measured with a rapid response CO_2 meter

(Smith Medical PM Inc, Wisconsin, USA). All signals were recorded on a digital computer via an analogue-to-digital interface (model 1401 Plus, Cambridge Electronic Design, Cambridge, UK). Digital signals were then analyzed by the software Spike 2, Cambridge Electronic Design. This gave a continuous record of inspired CO_2 tension ($PiCO_2$), end-tidal PCO_2 ($P_{et}CO_2$), minute ventilation (MV), tidal volume (Vt) and respiratory rate (RR). The ECG and arterial oxygen saturation (via pulse oximetry) were continuously monitored. Blood pressure and heart rate were recorded intermittently throughout the course of the study days.

Breathlessness measurements

Subjects were asked to quantify their sensation of breathlessness by relating it to their experience of breathlessness during exercise. Subjects were asked to 'please rate your breathlessness' every 30 seconds whilst connected to breathing system.

Breathlessness rating was measured with two validated scales, a verbal rating scale (VRS) and a visual analogue scale (VAS).[6,19,20] The VRS was used with seven divisions of breathlessness from mild to severe. The VAS was used as an unmarked 10 cm line anchored at one end with 'not at all breathless' and at the other by 'extremely breathless.' As subjects were breathing CO_2 through a mouth-piece, subjects used finger-operated potentiometers to illuminate a light along the VRS and VAS scales at the location that best indicated their degree of breathlessness.

Immediately after each test, subjects picked one or more phrases to indicate which of these were applicable to their breathlessness. The list of nine phrases was derived from Lansing et al.[19] and included air hunger (AH) descriptors and breathing work/effort (WE) descriptors, see Table 2.

CO_2 administration

Breathlessness was induced by administration of an inhaled CO_2 load using the Fenn and Craig technique.[21] Subjects inspired room air from a wide bore tube (diameter 3.5 cm and length 60 cm) to which varying CO_2 loads ($mL.min^{-1}$) were added using a gas containing 79% CO_2 and 21% oxygen. The CO_2 loads used were determined from a rotameter (Cole-Parma Instrument Company, Vernon Hills, Illinois, USA). The loads used for each subject as determined on the pre-test days (see later) varied, but for each subject the same loads, identified as low, moderate and high, were repeated for the tests after the drug/placebo was administered.

Table 2. Respiratory descriptors

Air hunger (AH) descriptors	I felt the urge to breathe
	I had hunger for more air
	I felt like when I hold my breath
Work/effort (WE) descriptors	My breathing required more effort
	I felt my breaths were larger
	My breathing felt like when I exercise
Contradictory[a] phrases	My breaths felt too small
	My breaths felt too large
Non-specific phrase[b]	I was short of breath

[a] A contradictory pair of phrases were used to the judge reliability of individual selections.
[b] This phrase was included in the list, but was not analyzed with the AH or WE descriptors since the term is not specific to either.

Anxiety and arousal state

CBME can cause alterations in the level of arousal and anxiety and thus influence breathlessness rating.[16] To investigate this possibility, the Speilberger anxiety state[22,23] and the Thayer activation/deactivation scores[24] were recorded during tests.

Protocol

Pre-test days. Subjects attended at least two pre-test practice sessions 7 to 10 days apart to familiarize them with breathing through the mouthpiece, CO_2 breathing and breathlessness ratings. When familiar with the equipment, the CO_2 load was increased until moderate to severe breathlessness was clearly reported; identified as the highest load (H). Then, in order to determine the relationship between CO_2 load, breathlessness and ventilation, two lower levels of load were chosen at about two-thirds (M, moderate load) and one third (L, low load) that of the highest load. The subjects were told which CO_2 load they were receiving.

Test days. Subjects attended at 09:00 hours after a light breakfast on two separate test days at least a week apart. Air (O) and CO_2 loads (L, M and H) were then presented in random order without verbal identification. Each load test period lasted 7 minutes and was separated by 5 minutes of breathing air so that the CO_2 load had been cleared prior to the next load delivery. Steady state measures of ventilation and breathlessness were determined from the last 2 minutes of

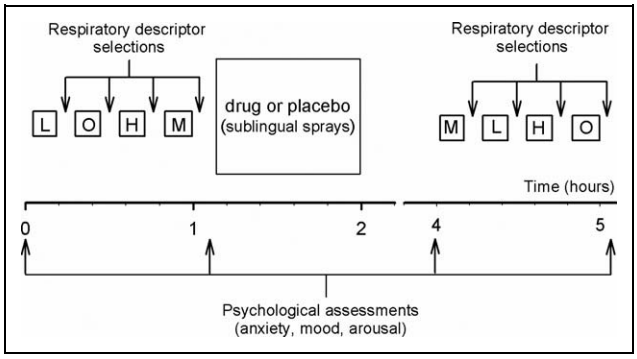

Figure 1. Diagrammatic illustration of test day protocol. O: air breathing, L: low CO_2 load breathing, M: medium CO_2 load breathing, H: high CO_2 load breathing.

each test period. The protocol for the test days is shown in Figure 1.

Throughout the day, a record of symptoms and signs of intoxication was kept. Food was kept to a minimum, but a small meal break was required after administration of drug/placebo. Subjects returned home with a carer about 4 hours after the last dose of drug/placebo, provided assessment of their cognitive and physical state was satisfactory.

Drug dosage and administration. The CBME (Sativex®) and its placebo (GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, UK) were supplied as a sublingual spray. After computer-generated randomization, double blinding was conducted through GW Pharmaceuticals.

The maximum single dose was four sprays. One spray contained 2.7 mg THC and 2.5 mg of CBD. Each spray was separated by a 20−30 minutes pause in order to observe for intoxication. If this occurred, no further sprays were given. The final measurements were made 2 hours after the last spray.

Data analysis

Ventilatory parameters, VRS and VAS scores were not normally distributed and were therefore treated as non-parametric data, with data presented as medians. The mean change in medians was determined from the individual change in medians. For paired samples, the Wilcoxon signed rank test was used, and for unpaired samples, the Wilcoxon Mann-Whitney rank sum test using SPSS15 software. The level of statistical significance was accepted at $p \leq 0.05$.

CO_2 sensitivity. The relationship between MV, VAS, VRS and $P_{et}CO_2$ was determined by normal linear regression analysis at four data points; air breathing, low, medium and high CO_2 inhalation. From the regression equation obtained, the slope and position of the CO_2 response was determined.

Analysis of respiratory descriptor selections. The quality of CO_2-related breathlessness was compared between patients and controls in the following way. For each subject, a descriptor was counted as chosen if the subject picked it following the M or H CO_2 load, both during the pre-placebo session and during the pre-drug session. Individual tallies for the air hunger cluster (AH) and for the WE cluster were summed and the total tallies for AH and for WE were compared between COPD and normal subjects. Fisher's exact test was used to determine statistical significance. To test whether changes after drug and placebo were statistically significant, AH and WE clusters were counted as picked for individual subjects if they selected two of the three descriptors. A significant drug effect was determined separately for COPD and normal subjects using the McNemar test.

Results

A total of 224 normal and 68 COPD subjects expressed interest in the study. On screening, 25 subjects fulfilled the inclusion criteria and were prepared or able to meet the time required for completion of the study; only 11 of 25 satisfactorily completed pre-test measurements. Of the 11, there were six normal and five COPD subjects; then one normal and one COPD subject dropped out.

Demographics

Subject demographics are shown in Table 3.

Active drug administration

At the request of our ethics committee, only 1 spray was given in the first two COPD subjects for safety. Summary of drug administration is shown in Table 4.

Anxiety and alertness

There was no difference in the Speilberger anxiety state and Thayer activation/de-activation scores in normal and COPD subjects, before and after CO_2 administration and before and after drug or placebo administration.

Table 3. Patient demographics

	Age (years)	Sex	BMI (kg/m^2)	FEV_1 (% predicted)	FEV_1/FVC (%)
C1	66	M	23.6	2.08 (58.6)	46
C2	67	F	28.1	1.49 (51.9)	56
C3	68	F	23.1	1.32 (56.9)	43
C4	67	M	27.4	1.90 (52.2)	36
N1	59	M	22.8	2.90 (81.5)	73
N2	51	M	29.6	3.80 (98.7)	84
N3	55	M	24.8	3.85 (95.1)	77
N4	67	F	23.9	2.50 (113.1)	70
N5	59	M	27.3	3.45 (88.7)	78

Abbreviations: BMI: body mass index, C: COPD subject, FEV_1: forced expiratory volume over 1 second, FVC: forced vital capacity, N: normal subject, M: Male, F: female.

Table 4. Active drug administration[a]

Normal subjects	Active drug sprays	Day of administration
1	3	1
2	4	2
3	4	2
4	4	1
5	4	1
COPD subjects	**Active drug sprays**	**Day of Administration**
1	1	2
2	1	1
3	2	2
4	3	2

Abbreviation: C: COPD subject.

[a] Table shows number of active sprays of cannabinoid-containing drug administered to subjects and on which test day they received it.

Resting $P_{et}CO_2$

We observed no increase in the $P_{et}CO_2$ breathing air before each CO_2 load on both test days pre and post drug or placebo. Thus, there was no evidence of CO_2 retention between CO_2 loads with a 5-minute break of breathing air.

Ventilation and breathlessness

Table 4 records the MV, $PetCO_2$ and VAS before and after placebo or drug.

For clarity, only three variables have been included in Table 4. Respiratory rate, Vt and VRS are considered in text below. Results are expressed as medians and changes from baseline median with 25th and 75th percentiles.

Ventilation and breathlessness pre placebo and drug. Consistent increases in MV, Pet CO_2 and VAS with inhaled CO_2 are shown in Table 5. There was no statistically significant difference in these three variables before placebo and drug. This was also true for Vt, RR and VRS.

Ventilation and breathlessness post placebo and drug. The changes in $P_{et}CO_2$, MV and VAS following placebo and drug are shown in Table 4. There were consistent rises in the medians and 25th percentiles for $P_{et}CO_2$ after placebo and drug; only three of the eight individual rises in medians after placebo and drug were statistically significant. However, when the results of air and CO_2 breathing were combined, the rise in $P_{et}CO_2$ after placebo and drug were highly significantly different ($p < 0.001$).There were no consistent changes in MV and VAS. The 75% percentiles of MV fell after placebo and drug and the median decreased with medium and high inspired CO_2. These changes in MV suggest, although not statistically significant, that they could be responsible for the rise in $P_{et}CO_2$.There was no significant difference between the changes in $P_{et}CO_2$, MV, VAS, Vt, RR and VRS after placebo compared with those after drug, that is there was no drug effect.

Effect of cannabinoids on respiratory descriptor selection

Normal subjects selected two of the three respiratory descriptors comprising the AH cluster and all three respiratory descriptors comprising the WE cluster, with a frequency of greater than 75%, to describe their breathlessness during CO_2 loaded runs before any drug or placebo administration. COPD subjects made similar choices but with a lower frequency of the first and third WE descriptors (see Figure 2).

In all subjects, there was no change in the selection of AH and WE descriptors between before and after placebo. In normal subjects, there was also no change in selection frequency before and after drug. In contrast, all COPD subjects made a change in their choice of descriptors, leading to a lower selection frequency of AH and higher selection frequency of WE descriptors following cannabinoids (see Figure 3). Because of the small number of subjects, these changes failed to reach statistical significance.

Table 5. MV, $PetCO_2$ and VAS before and after placebo or drug at zero, low, medium and high CO_2 load breathing[a]

	CO_2 load	Pre placebo Median (25%, 75%)	Post placebo Change in medians (25%, 75%)	Pre drug Median (25%, 75%)	Post drug Change in medians (25%, 75%)
$PetCO_2$ (kPa)	0	5.00 (4.55, 5.46)	0.13 (0.27, 0.00)	5.11 (4.72, 5.40)	0.25[b] (0.31, 0.00)
	L	6.20 (5.47, 6.99)	0.00 (0.251,0.00)	5.91 (5.24, 7.04)	0.08 (0.56, −0.15)
	M	6.65 (5.65, 7.65)	0.08[b](0.28, −0.04)	6.15 (5.81, 7.51)	0.23 (0.37, −0.08)
	H	6.97 (5.88, 8.45)	0.13 (0.24, −0.04)	6.69 (5.97, 7.87)	0.25[b] (0.33, 0.00)
MV (L/min)	0	9.6 (6.0, 12.1)	0.4 (1.6, −1.2)	10.8 (6.9, 13.1)	−0.1 (1.7, −1.4)
	L	17.7 (16.0, 22.5)	0.6 (2.7, −2.4)	19.7 (17.8, 24.5)	0.5 (0.7, −1.7)
	M	26.8 (21.2, 29.1)	−1.2 (0.4, −2.1)	24.6 (21.7, 28.3)	−0.3 (2.2, −4.0)
	H	29.8 (23.6, 34.0)	−0.8 (0.1, −1.9)	31.5 (23.3, 34.2)	−2.0 (2.2, −4.8)
VAS (cm)	0	0.0 (0.0, 0.5)	0.0 (0.0, −0.4)	0.0 (0.0, 2.6)	0.0 (0.0, −0.5)
	L	0.7 (0.4, 2.3)	0.1 (0.5, −0.2)	0.9 (0.6, 2.6)	0.0 (0.0, −0.6)
	M	1.8 (1.0, 4.2)	0.2 (0.8, −0.5)	2.5 (1.1, 3.4)	−0.5 (0.2, −1.1)
	H	4.5 (2.0, 5.8)	0.1 (1.3, −0.9)	3.9 (1.6, 4.3)	0.6 (1.4, −0.3)

Abbreviations: O: air breathing, L: low, M: medium and H: high load of inspired CO_2, $PetCO_2$: end-tidal PCO_2, MV: minute ventilation, VAS: visual analogue scale.

[a] The medians and change in medians (with their 25th and 75th percentiles of the inter-quartile range in brackets) pre and post placebo and drug for $P_{et}CO_2$, MV and VAS. The mean (SD) of the loads (mL/min) were 0 = no load, L = 963 (292), M = 1424 (304) and H = 1881 (384).

[b] Statistically significant $p < 0.05$.

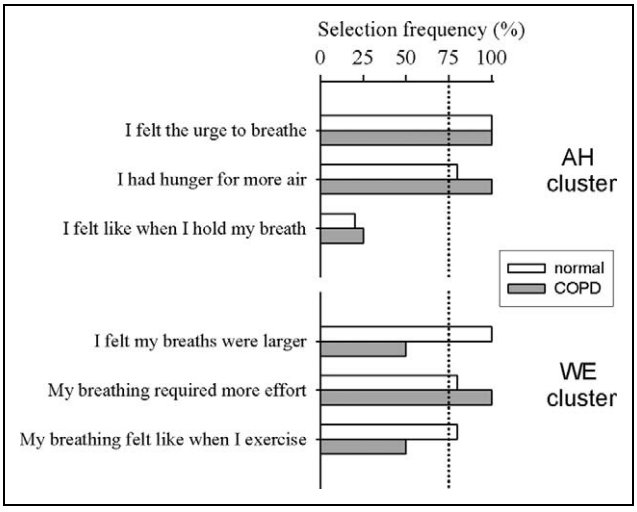

Figure 2. Quality of breathlessness associated with CO_2-loaded breathing. The frequency of selecting the descriptors making up the air hunger (AH) cluster and the work/effort (WE) cluster in four patients (closed bars) and five normal subjects (open bars) to describe the breathlessness experienced during CO_2 loaded breathing periods prior to any drug or placebo administrations. Descriptor choices pertaining only to moderate or high CO_2 loads are included in the selection tallies. Individual bars represent total selection frequency for the group expressed as percentage of highest possible selection frequency. An arbitrary threshold of 75% is indicated to identify a high selection frequency.

CO_2 sensitivity

There was no change in the slopes of the CO_2 sensitivity curves except for one COPD subject; there was no respiratory failure in this subject as their $P_{et}CO_2$ breathing air remained within the normal range. In 3 of the normal subjects, there was a small shift in the curve to the right (see supplemental data).

Adverse events and missing data

There were four adverse events, and after the study, cardiac investigations were performed as indicated.

Intoxication. One normal subject received four active sprays; 2 hours after the last spray, the subject was too drowsy to proceed, thus measurements after drug are missing. Another COPD subject received two active sprays after which mild intoxication developed so that during the High CO_2 load, the subject became confused and was unable to rate their breathlessness.

Cardiac dysrhythmias. One of the COPD subjects, after only one active spray, developed Wenckebach block phenomenon (Mobitz type 1) during the final CO_2 load breathing. There was no cardiovascular impairment so measurements were completed.

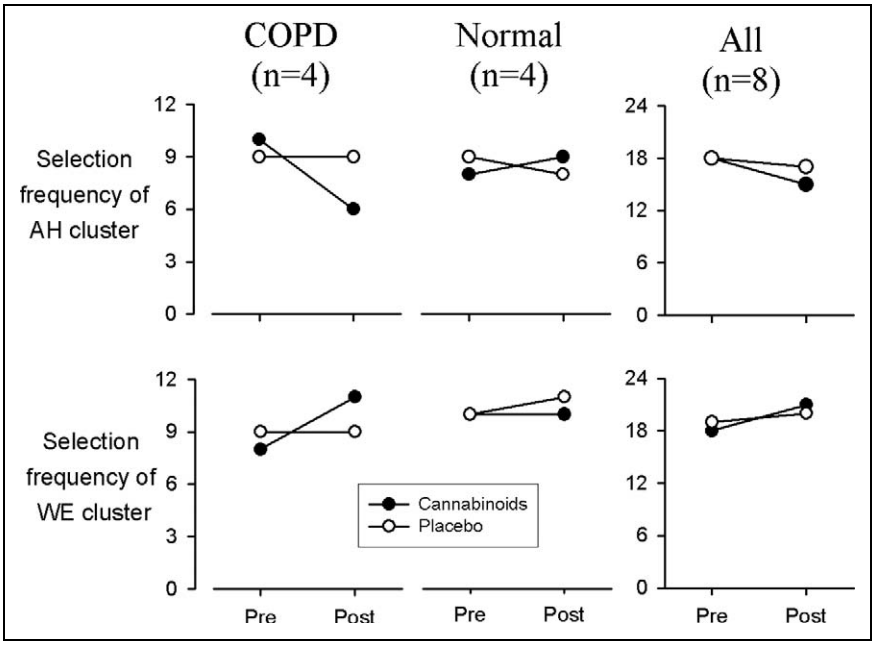

Figure 3. Effect of cannabinoids and placebo on breathlessness quality. Change in pooled selection frequency of the three descriptors comprising the air hunger (AH) cluster and the change in pooled selection frequency of the three descriptors comprising the work/effort (WE) cluster following cannabinoid administration (closed circles) and placebo administration (open circles) shown separately for COPD patients, normal subjects and all subjects combined.

The dysrhythmia spontaneously terminated after completion of the test. At a subsequent 24-hour ambulatory ECG, no bradycardia or heart block occurred.

A second COPD subject who received three active sprays showed four beats of ventricular tachycardia during air breathing and medium CO_2 load breathing. No further CO_2 was given so measurements at low and high loads are missing. A 24-hour ambulatory ECG revealed isolated multifocal ventricular ectopics, ventricular bigeminy and several couplets, but no sustained ventricular tachycardia.

Discussion

We have shown that our method for producing breathlessness with CO_2 inhalation is reproducible and credible in normal and COPD subjects. Over a week, the control values were reproducible and allowed a direct comparison of the effects of placebo with that of CBME. We found no significant effect of CBME on ventilation, $P_{et}CO_2$, sensitivity to CO_2 and breathlessness in response to inhaled CO_2. Interestingly, we found no changes in anxiety or arousal levels. However, although our original hypothesis that CBME would reduce breathlessness was not confirmed, our analysis of respiratory descriptors suggests amelioration of the unpleasantness of breathlessness in COPD subjects.

Other clinical trials of cannabinoids in patients with lung disease are scarce. A brief dose escalation and safety study in breathless COPD patients reported improvement in breathlessness with CBME using VAS scores.[25]

Recruitment

We encountered considerable difficulties in recruiting subjects. Primarily this was due to co-morbidity, but also the time commitment was demanding. Initial recruiting advertisement did not include details that the drug to be investigated was cannabis extract, as we did not want to attract regular cannabis users. On screening for recruitment, we disclosed that the drug was cannabis extract and a few subjects declined for this reason. On pre-testing, some subjects' breathing became unstable or they were unable to provide consistent breathlessness ratings.

CO_2 sensitivity

Although there was no statistically significant change in CO_2 sensitivity during the study, there was a consistent drug-independent rise in $P_{et}CO_2$ during the

day, which was statistically significant. This increase is consistent with the findings of Spengler et al., 2000, who found an endogenous circadian rhythm of respiratory control in humans.[26]

In previous studies on the ventilatory response to CO_2 in normal subjects after THC (oral doses up to 22.5 mg), no change in slope was observed, but there was a shift in intercept to the right, that is reduction in ventilatory response to CO_2.[10,12] This is in agreement with our results as the same change occurred in six of the eight subjects.

CBME administration and adverse events

The time course of the absorption of orally administered THC and CBD varies between subjects. However, on the basis of unpublished data of blood levels and clinical observations after sublingual CBME, it was anticipated that therapeutic levels would be reached at 2 hours (Personal correspondence with Dr Philip Robson Medical Director GW Pharmaceuticals, 2006), thus we tested our second set of CO_2 loads at that time.

After unblinding, we identified that intoxication and cardiac dysrhythmias occurred in relation to active drug administration. In order to attempt to prevent adverse events, sprays were given at 20 minutes intervals and administration stopped if intoxication appeared. In retrospect, these measures were inadequate. Not all subjects required the full dose prior to the onset of mild intoxication. In fact, one of the COPD subjects allocated to have only one spray described intoxication and no further sprays would have been administered even if desired.

Studies of cannabinoids in humans have not shown any life-threatening adverse cardiac events in subjects without cardiac disease.[11,27] We consider that the results of our trial are in accord with CBME being safe because the adverse effects may have been related to acute single dose administration that was part of our study design but is not recommended in clinical practice. Unwanted adverse effects can be avoided or reduced by small doses with gradual increments over weeks rather than as a single administration. In this study, we considered that prolonged administration might lead to inconsistent baseline results. It is probable that we encountered more adverse events than would have occurred in clinical practice, but we consider that we used an effective dosage regimen for the study.

Respiratory descriptors

Recent evidence suggests that AH is the dominant component of breathlessness in COPD patients[28] and is a more unpleasant component than WE.[29] In the current study, the instructions for VAS and VRS ratings of breathlessness required subjects to only consider the intensity of sensation irrespective of the constituent components or its 'unpleasantness.' Our analysis of the respiratory descriptor selections, although preliminary, does suggest that the experience of breathlessness in COPD subjects shifts away from AH to that of WE after cannabinoids. Thus, a reduction in unpleasantness of breathlessness by CBME cannot be excluded from the absence of a change in VAS or VRS ratings in the current study.

Since the start of this study, there has been considerable development in the use of respiratory descriptors that take into account the multiple components of dyspnoea namely intensity, quality and emotional response.[30] It is anticipated that the specific selection of descriptors to assess the quality and emotional components of dyspnoea[28,31] will make the evaluation of dyspnoea more comprehensive and consistent than that of the present study.

How can we explain the discrepancy in the results between COPD subjects and normal subjects with regard to changes in respiratory descriptor selections after cannabinoid administration? The increase in the sense of WE in the COPD subjects was due predominantly to an increase in selection of 'I felt my breaths were larger.' The patients may have perceived relatively larger breaths after cannabinoids as a result of changes in airway resistance. Cannabinoids are known to reduce airways resistance specially when administered by inhalation,[32] but a small and inconsistent effect has also been reported with oral doses.[33] No such effect will be expected in normal subjects as they already have a low airways resistance at baseline.

With regard to the reduced sense of AH after cannabinoids, the chronic experience of high levels of AH in the patients may make them more sensitive to a change in AH than the normal subjects. Furthermore, the patients' ventilation may have been limited as a consequence of their pathology, giving them a greater sense of AH for a given CO_2 load. The same breathlessness stimulus in the healthy subjects may not have generated enough of a sense of AH for an appreciable relief to be manifested by the cannabinoid treatment. These are speculative explanations that need to be explored further.

Method for producing laboratory-based dyspnoea

The induction of breathlessness with CO_2, which allows a free breathing response, as used in the present study, is not the best method for eliciting AH as it increases WE at the same time. If air hunger is the dominant component of breathlessness in patients with COPD, then the conclusion from our study is that a more appropriate stimulus is required. This can be achieved by using a breathing circuit that limits the ventilatory response to CO_2, a potent stimulus of air hunger.[29]

Conclusions

We have demonstrated a lack of effect of cannabinoids on simulated breathlessness using CO_2 loads in normal and COPD subjects when its intensity is rated on unidimensional VAS or VRS scales. However, we have shown that breathlessness descriptors may detect an amelioration of the unpleasantness of breathlessness by cannabinoids. To our knowledge, this is the first time that respiratory descriptors have been used to assess the unpleasantness of breathlessness in COPD subjects after a drug administration. We predict that a stimulus more specific for air hunger may demonstrate cannabinoid modulation of the unpleasantness of breathlessness.

This study reports the difficulties of cannabinoid administration in humans using one of the present generation of drugs and provides safety data under controlled conditions. This clinical study contributes to the choice of methodology for the assessment of drug therapy for breathlessness in patients with COPD.

Acknowledgements

We particularly thank Professor Martyn Partridge, the late Dr Mangalam Kumaraswamy Sridhar and Dr Mark Palazzo for their encouragement, and our advisors Dr Philip Robson Medical Director GW Pharmaceuticals, Dr Nicola R Roberts, Lecturer in Respiratory Health Care Delivery, and Dr Elena Kulinskaya, Director of the Statistical Advisory Service Imperial College London.

Competing interests

None.

Funding

This project was funded in part by the Breathlessness Research Charitable Trust and the researcher by the Cromwell Hospital, London. The study drug, CBME and placebo were provided without cost by GW Pharmaceuticals.

Ethics

Ethics approval was granted from Riverside Research Ethics Committee (RREC) UK: number 3329. MHRA CTA 21388/0006/001.

References

1. Mitchell-Heggs P, Murphy K, Minty K, et al. Diazepam in the treatment of dyspnoea in the 'pink puffer' syndrome. *Q J Med* 1980; 49: 9-20.
2. Muers MF. Opioids for dyspnoea. *Thorax* 2002; 57: 92–923.
3. Banzett RB, Henrietta E, Mulnier HE, et al. Breathlessness in humans activates insular cortex. *Brain Imaging* 2000; 11: 2117–2120.
4. Peiffer C, Poline J, Thivard L, Aubier M, and Samson Y. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med* 2001; 163: 951–957.
5. Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RSJ, and Corfield DR. fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *J Neurophysiol* 2002; 88: 1500–1511.
6. Von Leupoldt A, Sommer T, Kegat et al. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. *Am J Respir Crit Care Med* 2008; 177: 1026–1032.
7. Robbe D, Kopf M, Remaury A, Bockaett J, and Manzoni OJ. Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *PNAS* 2002; 99: 8384–8388.
8. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. *Pharmacol Ther* 1997; 74: 129–180.
9. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *PNAS* 1990; 87: 1932–1936.
10. Bellville JW, Swanson GD, and Aqleh KA. Respiratory effects of delta-9-tetrahydrocannabinol. *Clin Pharm Ther* 1975; 17: 541–548.
11. Johnstone RE, Lief PL, Kulp RA, and Smith TC. Combination of delta-9-tetrahydrocannabinol with oxymorphone or pentobarbital: effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 1975; 42: 674–684.
12. Malit LA, Johnstone RE, Bourke DI, et al. Intravenous delta-9-Tetrahydrocannabinol: effects on ventilatory control and cardiovascular dynamics. *Anesthesiology* 1973; 42: 666–673.

13. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, and Wiethe KE. Regional cerebral blood flow after marijuana smoking. *J Cereb Blood Flow Metab* 1992; 12: 750–758.
14. Karniol IG and Carlini EA. Pharmacological interaction between cannabidiol and delta-9-tetrahydrocannabinol. *Psychopharmacologia* 1973; 33: 53–70.
15. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with widespread spectrum of action. *Rev Bras Psiquiatr*. 2008; 30: 271–280.
16. Zuardi AW, Shirakawa I, Finkelarb E, and Karanol IG. Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. *Psychopharmacology* 1982; 76: 245–250.
17. Lefant C and Khaltaev N. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO workshop report. National Institutes of health and National Heart, Lung, and Blood Institute. Publication Number 2701, 2001: 14.
18. Zigmond AS and Snaith RP. The Hospital Anxiety and Depression scale. *Acta Psychiatr Scand* 1983; 67: 361–370.
19. Lansing RW, Moosavi SH, and Banzett RB. Measurement of dyspnea: word labelled visual analogue scale vs. verbal ordinal scale. *Resp Phys Neurobiol* 2003; 134: 77–83.
20. Banzett RB, Lansing RW, Brown R, et al. 'Air hunger' from increased PCO_2 persists after complete neuromuscular block in humans. *Respir Physiol* 1990; 81: 1–17.
21. Fenn WO and Craig JR. Effect of CO_2 administration using a new method of administrating CO_2. *J Appl Physiol* 1963; 18: 1023–1024.
22. Speilberger CD. *State-trait anxiety inventory for adults*. Palo Alto, CA: Mind-Garden, 1983.
23. Speilberger CD, Gorsuch RL, and Lushene R. *Test for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press, 1970.
24. Thayer RE. *The biopsychology of mood and arousal*. New York: Oxford University Press, 1989.
25. Hartung TK, Rolfe S, Wilson AM, Al-Khairalla MZH, and Winter JH. Dose-escalation and safety study of cannabis based medicinal extract in patients with severe COPD [Abstract]. *Proc Am Thorac Soc* 2005; 2: A544.
26. Spengler CM, Czeisler CA, and Shea SA. An endogenous circadian rhythm of respiratory control in humans. *J Physiol* 2000; 526: 683–684.
27. Holdcroft A, Maze M, Dore C, Tebbs S, and Tompson S. A multidose-escalation study of the analgesic and adverse effects of an oral cannabis extract (cannador) for post-operative pain management. *Anaesthesiology* 2006; 104: 1040–1046.
28. Smith J, Albert P, Bertella E, Lester J, and Calverley P. Qualitative aspects of breathlessness in health and disease. *Thorax* 2009; 64: 713–718.
29. Banzett RB, Pedersen SH, Schwartzstein RM, and Lansing RW. The affective dimensions of laboratory dyspnea. Air hunger is more unpleasant than work/effort. *Amer J Respir Crit Care Med* 2008; 177: 1384–1390.
30. Lansing RW, Gracely RH, and Banzett RB. The multiple dimensions of dyspnoea: Review and hypotheses. *Respiratory Physiology and Neurobiology* 2009; 167: 53–60.
31. Yorke J, Moosavi SH, Shuldham C, and Jones PW. Quantification of dyspnoea using descriptors: Dyspnoea-12. *Thorax* 2010; 65: 21–26.
32. Laviolette M and Belanger J. Role of prostaglandins in marihuana-induced bronchodilation. *Respiration* 1986; 49: 10–15.
33. Abboud RT and Sanders HD. Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. *Chest* 1976; 70: 480–485.