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Effects of chlormadinone acetate, acetazolamide and oxygen on awake and asleep gas exchange in patients with chronic obstructive pulmonary disease (COPD)

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ABSTRACT: The purpose of this study was to assess the short-term effects of chlormadinone acetate (CMA), a synthetic progestogen, acetazolamide (ACET) and oxygen on awake and asleep blood gas values.

The study was conducted according to a randomized, double-blind and placebo-controlled design in 53 hypoxaemic patients with chronic obstructive pulmonary disease. On the first two consecutive nights, all patients received either room air or oxygen, *via* a nasal cannula, in random order. They then received either CMA (25 mg), ACET (250 mg) or placebo twice a day, all in identical capsules. On the third study night, after one week of drug treatment, the patients were tested breathing room air.

CMA and ACET therapy decreased mean daytime arterial carbon dioxide tension (Pa_{CO_2}) by 0.7 and 0.5 kPa, respectively, and night-time end-tidal carbon dioxide tension (P_{ETCO_2}) by 0.5 and 0.3 kPa, respectively. Supplemental oxygen caused increased CO_2 retention during the day and night (0.6 and 0.3 kPa, respectively. Daytime arterial oxygen tension (Pa_{O_2}) increased to the same extent during ACET (1.9 kPa) and oxygen (2.5 kPa). Asleep oxygen saturation improved most with oxygen supplementation (7%), although ACET also caused significant improvement (4%). CMA administration had virtually no effect on mean awake and asleep hypoxaemia. ACET therapy significantly improved subjective sleep quality. On CMA, minute ventilation increased in association with an augmentation of the hypercapnic ventilatory response. ACET treatment increased both hypercapnic and hypoxic ventilatory responses.

We conclude from the group of patients with COPD studied, that the short-term effects of ACET treatment on gas exchange compare favourably with those of CMA. Oxygen therapy improves oxygenation slightly more than ACET, but aggravates CO_2 retention.

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Hypoxaemic patients with chronic obstructive pulmonary disease (COPD) may develop more profound oxygen desaturations during sleep [1]. Treatment of hypoxaemia is beneficial, since hypoxaemia leads to pulmonary hypertension, cor pulmonale, secondary polycythaemia, and cardiac arrhythmias [1]. Indeed, it has been shown that long-term oxygen supplementation, for at lease 18 $h \cdot day^{-1}$, can increase life expectancy in these patients [2].

Drugs that stimulate ventilation may ameliorate hypoxaemia as well as carbon dioxide retention in certain patients with COPD [3], and may, thus, provide an additional treatment to oxygen supplementation.

Synthetic progestogens, such as medroxyprogesterone and chlormadinone acetate (CMA), raise arterial oxygen tension and reduce carbon dioxide tension during wakefulness by central stimulating effects [3–7]. The effects on hypoxaemia during sleep were beneficial [3, 4, 6], or absent [5, 7].

Another respiratory stimulant is acetazolamide (ACET). It is a carbonic anhydrase inhibitor, which increases ventilation by inducing a metabolic acidosis, which possibly stimulates both the peripheral and the central chemoreceptors [8]. It diminishes nocturnal hypoxaemia and periodic breathing at high altitude [9]. ACET has been shown to improve blood gas values during the day and at night, in a few patients with COPD [4].

The aim of the current study was to determine whether CMA and ACET affect hypoxaemia and hypercapnia, and to compare the results with those derived during oxygen therapy. Therefore, the effects of CMA, ACET and oxygen on arterial blood gas values during wakefulness

and sleep were studied in a group of hypoxaemic patients with COPD. Furthermore, the effects on subjective sleep quality, on patients' subjective feeling of well-being, and on control of breathing were measured.

Patients

Fifty three out-patients with COPD, as defined by the American Thoracic Society, participated in this study [10]. Inclusion criteria were: forced expiratory volume in one second (FEV_1) less than 65% of predicted value [11], and daytime arterial oxygen tension (Pa_{O_2}) of ≤8.5 kPa. At the time of the study, all patients had been in a stable clinical condition for at least four weeks and were receiving optimal bronchodilator treatment. Exclusion criteria were: thromboembolic events in the past, and factors suggesting possible obstructive sleep apnoea, such as complaints of excessive daytime sleepiness or anomalies of the oropharyngeal area. All medication was continued and remained unchanged during the study period. Patients already treated with supplemental home oxygen were allowed to continue this during the one week's pharmacological treatment. Patient characteristics are shown in table 1.

Methods

Daytime measurements

Hypercapnic ventilatory response was assessed by the steady-state method [12, 13]. The patient was connected to a closed spirometric circuit *via* a mouthpiece. The end-tidal carbon dioxide tension (P_{ETCO_2}) level could be increased by adjusting a three-way valve, partially short-circuiting the CO_2 absorber in the inspiratory limb of the circuit. Two different levels of P_{ETCO_2} were studied. Oxygen was added to the system to keep the arterial oxygen saturation (Sa_{O_2}) level at 93–95%. Sa_{O_2} was measured with an oximeter.

The hypoxic ventilatory response was performed by inducing progressive isocapnic hypoxia [14]. P_{ETCO_2} was maintained at the initial resting level. All patients started the test at an Sa_{O_2} level of 90–93%, by adding supplemental oxygen to the system. The hypoxic ventilatory response was stopped when the Sa_{O_2} reached 80%.

Furthermore, the capability of the ventilatory pump to lower P_{ETCO_2} was assessed by means of a voluntary hyperventilation test.

Night-time measurements

Oxygen saturation was measured by a pulse-oximeter (Oxyshuttle, Sensormedics). Data of a whole night were stored, digitized and analysed by a computer (Apple IIe) to provide mean and standard deviation as well as lowest saturation of each night. Nocturnal Pa_{O_2} was calculated from the measured Sa_{O_2} using the (Hill equation). The awake and asleep baseline Sa_{O_2} were defined as the mean saturation 15 min before falling asleep and whilst sleeping, respectively. Desaturation was defined as a decrease in oxygen saturation of more than 4% from the asleep baseline value. The total desaturation time was calculated. Thoraco-abdominal movement was assessed by respiratory inductance plethysmography (Vitalog or Respitrace).

P_{ETCO_2} was determined by introducing a cannula through the nose into the nasopharyngeal cavity. An air sample was taken *via* a perma-pure drying tube connected to a sampling capnograph (Mijnhart capnolyser). No P_{ETCO_2} signal and, thus, no air movement for a least 10 s, was considered to indicate apnoea. Baseline P_{ETCO_2} awake and asleep were defined as the mean P_{ETCO_2} value 15 min before falling asleep and whilst sleeping, respectively. P_{ETCO_2} was not considered to be representative of arterial or alveolar carbon dioxide tension (P_{CO_2}).

Study protocol

Prior to the study, pulmonary function tests were performed and an arterial blood gas sample was taken.

Table 1. – Patient characteristics

	Whole group	CMA group	ACET group	Placebo group
Sex M/F	39/14	14/4	11/6	14/4
Age yrs	65 (9)	64 (9)	64 (6)	65 (9)
FEV_1 % pred	30 (10)	31 (11)	31 (9)	29 (9)
IVC % pred	75 (14)	78 (14)	75 (14)	70 (10)
TLC % pred	101 (18)	99 (14)	100 (18)	103 (21)
FRC % pred	132 (30)	129 (26)	131 (31)	135 (33)
RV % pred	151 (46)	142 (38)	146 (41)	163 (57)
Pa_{O_2} daytime kPa	7.4 (1.0)	7.2 (1.1)	7.5 (1.1)	7.5 (0.8)
Pa_{CO_2} daytime kPa	6.4 (1.2)	6.5 (1.3)	6.4 (1.3)	6.3 (0.8)
HCVR $l \cdot min^{-1} \cdot kPa$	2.4 (1.7)	2.3 (1.5)	2.7 (2.4)	2.2 (1.2)
HVR $l \cdot min^{-1} \cdot \%$	0.20 (0.15)	0.20 (0.20)	0.22 (0.16)	0.19 (0.10)
Body mass index	24 (4)	23 (4)	23 (4)	25 (5)
Mean Sa_{O_2} night %	84 (10)	82 (11)	85 (11)	86 (4)

Data are presented as mean and SD in parenthesis. None of the characteristics is significantly different between the CMA, ACET and placebo groups. The fall in Pa_{O_2} was calculated from fall in Sa_{O_2} using the Hill equation. FEV_1: forced expiratory volume in one second; IVC: inspiratory vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response; Sa_{O_2}: arterial oxygen saturation; CMA: chlormadinone; ACET: acetazolamide.

Naso- and orpharyngeal areas were examined and the neck circumference was measured.

All patients were studied during three nights. For two consecutive nights they received either room air or oxygen in a random order. On the third night, after one week of drug administration, the patients were studied receiving room air. Room air as well as oxygen was administered *via* a nasal cannula at 1 $l \cdot min^{-1}$, in a single-blind fashion. The part of the study with the pharmacological respiratory stimulants was randomized, double-blind and placebo-controlled. After the first two study nights the patients ingested either CMA (25 mg), ACET (250 mg) or placebo, all in identical capsules (8 a.m. and 8 p.m.) for a period of one week. The patients were randomized within each of the four subgroups, defined according to FEV_1 value (above or below 35% of predicted value) and daytime Pa_{O_2} (above or below 7.5 kPa).

After each study night, arterial blood gas samples were taken at 10 a.m., after 15 min of rest. These blood gas values were compared to the sample taken 2–4 weeks before the start of the study, in order to confirm the stability of the disease. Furthermore, after each study night, the patients answered the St Mary's Hospital Sleep Questionnaire concerning subjective sleep quality [15]. After the first night and after one week of "drug treatment", plasma-testosterone levels, white blood cells, sodium, potassium and creatinine concentration were measured. On these two days, the ventilatory responses to hypercapnia and hypoxia were also measured.

Informed consent was obtained from all patients, and the study was approved by the Hospital Ethics Committee.

Statistical analysis

Statistical analysis for paired comparisons was performed using the signed rank test, except for differences on an ordinal scale: in such cases the sign test was used. The Kruskal-Wallis test was used to determine possible statistically significant differences between the three groups. Probability values of ≤0.05 were considered to be significant.

Results

Daytime laboratory measurements

The effects of CMA, ACET, placebo and oxygen therapy on daytime blood gas values are shown in table 2. Daytime hypoxaemia improved to the same extent with ACET (1.9 kPa) and O_2 therapy (2.5 kPa); whereas, CMA increased Pa_{O_2} just slightly (0.6 kPa), a result not significantly different from placebo (0.4 kPa). Mean Pa_{CO_2} decreased significantly during CMA and ACET therapy 0.7 and 0.5 kPa, respectively. During supplemental oxygen, Pa_{CO_2} increased by 0.6 kPa.

The patient compliance in taking the capsules was good, since in all male patients who received CMA, mean testosterone levels decreased significantly, mean (SD) 35 (20) $nmol \cdot l^{-1}$ before CMA, to 15 (15) $nmol \cdot l^{-1}$ during CMA. With ACET the base excess shifted to metabolic acidosis in all patients, mean (SD) decrease in base excess 6.7 (3.3) $mmol \cdot l^{-1}$ ($p<0.05$).

After one week of ACET administration mean serum creatinine levels increased from 92 to 94 $\mu mol \cdot l^{-1}$, mean potassium levels decreased from 3.7 to 3.4 $mmol \cdot l^{-1}$, and chloride levels increased from 98 to 100 $mmol \cdot l^{-1}$ (all changes $p<0.05$).

Ventilation

The patients had low hypercapnic and hypoxic ventilatory responses as compared to normals, whereas the breathing frequency was rather high (table 3) [16].

Table 2. – Effects of CMA, ACET and O_2 on daytime blood gas values

	CMA (n-18)		ACET (n=17)		Placebo (n=18)		During (n=53)	
	Before	After	Before	After	Before	After	Room Air	O_2
Pa_{O_2} kPa	7.2 (1.1)	7.8 (1.4)*	7.5 (1.1)	9.4 (1.4)*#+	7.6 (0.8)	8.0 (0.9)*	7.4 (1.0)	9.9 (1.1)*+
pH	7.42 (0.03)	7.43 (0.03)	7.42 (0.03)	7.35 (0.04)*#+	7.41 (0.04)	7.40 (0.04)	7.42 (0.03)	7.40 (0.04)*†
Pa_{CO_2} kPa	6.5 (1.3)	5.8 (1.2)*+	6.4 (1.3)	5.9 (1.3)*+	6.3 (0.8)	6.6 (1.0)*	6.4 (1.2)	7.0 (1.3)*†+
BE $mmol \cdot l^{-1}$	+6.2 (5.3)	+4.2 (5.4)*+	+6.6 (4.6)	-0.1 (4.8)*#+	+4.8 (2.0)	+5.1 (2.4)	+5.8 (4.2)	+6.7 (4.5)*†+

Data are presented as mean and SD in parenthesis. n = number of patients in each group. *: $p<0.05$, comparison with data before therapy; #: $p<0.05$, comparison ACET to CMA; †: $p<0.05$, comparison O_2 to ACET; +: $p<0.05$, comparison to placebo; BE: base excess. For further abbreviations see legend to table 1.

Table 3. – Effects of CMA and ACET on ventilation

	CMA (n=18)		ACET (n=17)		Placebo (n=18)	
	Before	After	Before	After	Before	After
HCVR $l \cdot min \cdot kPa$	2.3 (1.5)	3.3 (2.0)*#	2.7 (2.4)	3.7 (2.9)#	2.2 (1.2)	2.0 (1.4)
HVR $l \cdot min^{-1} \cdot \%$	0.20 (0.20)	0.20 (0.20)	0.22 (0.16)	0.34 (0.19)*	0.19 (0.10)	0.24 (0.10)*
$\dot{V}_E$ $l \cdot min^{-1}$	9.6 (2.7)	11.8 (3.3)*#	10.5 (2.7)	10.5 (2.5)	9.4 (2.1)	9.5 (1.7)
V_T l	0.55 (0.2)	0.60 (0.2)	0.61 (0.2)	0.66 (0.2)	0.56 (0.2)	0.57 (0.2)
f breaths$\cdot min^{-1}$	19 (5)	21 (5)*#	19 (5)	18 (5)	18 (4)	18 (4)

Data are presented as mean and SD in parenthesis. *: $p<0.05$, comparison with room air data; #: $p<0.05$, comparison to placebo. $\dot{V}_E$: minute ventilation; V_T: tidal volume; f: breathing frequency. For further abbreviations see legend to table 1.

The hypercapnic ventilatory response and minute ventilation significantly increased during CMA therapy. After ACET administration, both the hypercapnic and the hypoxic ventilatory responses were augmented. In addition to the increase in hypercapnic ventilatory response, a considerable shift to the left was seen (fig. 1).

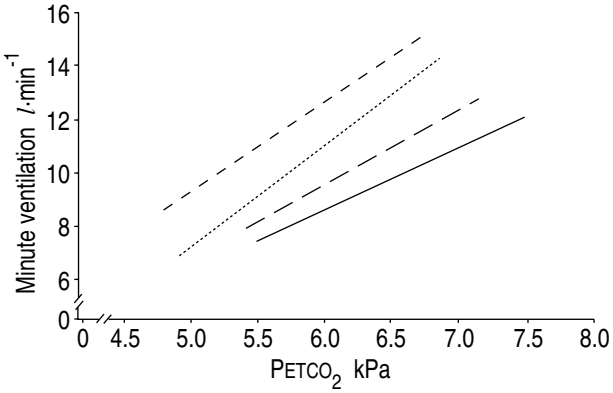

Fig. 1. – Hypercapnic ventilatory responses before and after CMA and ACET. ———: after CMA; ·····: after ACET; — —: before ACET; ———: before CMA. P_{ETCO_2}: end-tidal carbon dioxide tension; CMA: chlormadinone; ACET; acetazolamide.

All CMA patients and 16 of the 18 ACET patients (89%) were able to decrease their Pa_{CO_2} by at least 0.7 kPa during voluntary hyperventilation.

Subjective parameters

Beneficial effects. In the CMA group, 7 of the 18 patients said they benefited from this therapy. Seven of the 16 patients who had received ACET reported a favourable reaction. In the placebo group, 8 of the 18 patients claimed to feel better.

Side-effects. Three patients reported side-effects during CMA therapy (vertigo, palpitations and stomach cramps). In the ACET group, two patients complained of paraesthesia in the fingertips, one of vertigo and one of nausea. Three of the 18 patients in the placebo group complained of vertigo, nausea and increased dyspnoea.

Subjective sleep quality. The results of the St Mary's Hospital Sleep Questionnaire are shown in table 4. CMA and O_2 had no beneficial effect, whereas ACET therapy partly improved the subjective quality of sleep, since most patients reported sleeping better and longer during the treatment night.

Table 4. – Results of the SMH sleep questionnaire during CMA, ACET, placebo and oxygen compared to room air

	During CMA (n=18)			During ACET (n=16)			During placebo (n=18)			During O_2 (n=53)		
	Better	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better	Worse	Same
Depth of sleep (Q5[#])	2	5	11	10*	3	3	1	7	10	25	15	13
Awakenings (Q6)	6	7	5	9	6	1	8	7	3	26	15	12
Hours asleep (Q7)	7	9	2	12*	3	1	5	11	2	33	18	2
Value of sleep (Q9)	5	8	5	10*	2	4	4	5	9	27	15	11
Alertness in the morning (Q10)	6	4	8	5	5	6	6	3	9	22	11	20
Early awake (Q11)	3	5	10	7	3	6	0	4	14	13	5	35
Difficulty in falling asleep (Q12)	4	4	10	9[†]	2	5	2	8	8	23	14	16

Values are number of patients. *: $p<0.05$, comparison with room air night; [†]: $0.05 < p < 0.01$ comparison with room air night; [#]: number of question in SMH questionnaire. SMH: St Mary's Hospital. For further abbreviations see legend to table 1.

Table 5. – Effects of CMA, ACET and oxygen on nocturnal parameters

	CMA (n=18)		ACET (n=17)		Placebo (n=18)		During (n=53)	
	Before	During	Before	During	Before	During	Room Air	O_2
Mean Sa_{O_2} %	82 (11)	84 (12)*	85 (11)	89 (6)*[+#]	86 (4)	87 (3)	85 (10)	92 (3)*[+†]
SD of mean Sa_{O_2}	3.6 (2)	3.6 (2)	3.4 (2)	3.1 (1)	3.1 (1)	3.5 (1)	3.4 (2)	2.6 (1)*[†]
Lowest Sa_{O_2} %	71 (15)	72 (16)	70 (22)	77 (12)*[+]	75 (6)	74 (7)	72 (15)	85 (7)*[+†]
Fall in Pa_{O_2} kPa	2.3 (1)	2.5 (1)	2.7 (1)	3.1 (1)	2.5 (1)	2.7 (1)	2.5 (1)	2.9 (1)
No. 4% dips	17 (9)	17 (9)	19 (16)	15 (12)*	16 (5)	18 (8)	17 (11)	10 (9)*[+†]
Baseline P_{ETCO_2} awake kPa	5.0 (0.7)	4.5 (1.0)*[+]	5.2 (0.7)	4.7 (0.7)*[+]	5.4 (1.2)	5.4 (1.0)	5.2 (0.9)	5.5 (0.9)*[†]
Baseline P_{ETCO_2} asleep kPa	5.2 (1.0)	4.7 (1.1)*	5.3 (0.9)	5.0 (0.7)*	5.7 (1.3)	5.5 (1.2)	5.4 (1.0)	5.7 (1.1)*[†]
Highest P_{ETCO_2} asleep kPa	6.6 (1.4)	6.0 (1.7)*[+]	6.7 (1.1)	6.1 (0.9)*[+]	6.9 (1.3)	7.0 (1.9)	6.7 (1.3)	7.2 (1.4)*[†]
Desaturation time min	41 (55)	39 (61)	62 (89)	31 (34)	41 (39)	43 (37)	47 (63)	10 (27)*[+†]

Data are presented as mean and SD in parenthesis. *: $p<0.05$, comparison with data before treatment; [+]: $p<0.05$, comparison with placebo; [#]: $p<0.05$, comparison ACET to CMA; [†]: $p<0.05$, comparison O_2 to ACET. Fall in Pa_{O_2} calculated from the fall in Sa_{O_2} with Hill equation. P_{ETCO_2}: end-tidal carbon dioxide tension. For further abbreviations see legend to table 1.

Nocturnal parameters

Mean nocturnal oxygen saturation improved substantially during ACET (5%) and oxygen (7%) therapy (table 5). During CMA treatment, the mean Sa_{O_2} at night only increased slightly (2%). No significant difference in the fall in nocturnal Pa_{O_2}, as calculated from changes in Sa_{O_2} (Hill equation), was observed during any of the therapies. Both CMA and ACET decreased the baseline P_{ETCO_2} values during sleep to the same extent mean change (0.5 kPa), whereas oxygen increased the P_{ETCO_2} (0.3 kPa). The rise in P_{ETCO_2} throughout the night did not significantly change during any of the treatments, compared to the room air night.

Eleven percent (SD 19) of the desaturating episodes during the room air night were associated with apnoeas. Only 4 of the 53 patients experienced more than five apnoeas per hour of sleep. During the oxygen night 21 (SD 38)% (NS) more of the desaturations were accompanied by apnoeas. During CMA and ACET administration, a significant decrease in apnoeas was shown from 14 to 3% (CMA), and from 11 to 0% (ACET). In the placebo group the percentage of desaturations caused by apnoeas remained unchanged (9%).

Discussion

This investigation of the effects of CMA, ACET and O_2 on awake and asleep blood gas values in 53 hypoxaemic COPD patient was randomized, double-blind and placebo-controlled; hence suggestibility was minimized, changes could be made for any possible placebo effect, and cross-over effects could not obscure results. Supplemental oxygen was delivered from a nasal cannula, causing inspired oxygen concentration to be variable. Noctural P_{ETCO_2} measurement was used as an indicator of increased or decreased hypoventilation. Obviously, quantitative changes in P_{ETCO_2} were not considered to be representative of those of arterial or alveolar carbon dioxide tension (P_{CO_2}).

In this study we found that CMA and ACET therapy decreased day and night-time P_{CO_2} levels to a similar degree, whereas supplemental oxygen caused increased CO_2 retention during the day and night. Awake and asleep oxygenation improved most with oxygen therapy, although ACET also achieved a substantial improvement. CMA had virtually no effect on Sa_{O_2}. These findings are comparable with those of other studies [5, 7], although some investigators have shown a more favourable effect of progesterone on nocturnal oxygenation in a few selected COPD patients [3, 4, 6].

No significant change was observed in the fall of the Pa_{O_2} or in the rise of the P_{ETCO_2} throughout the night with any of the three therapies. This suggests that the improvement of the nocturnal Sa_{O_2} observed during the three therapies, as well as the decrease in P_{ETCO_2} during CMA and ACET and the increase during oxygen supplementation were mostly due to different initial daytime blood gas values. In other works, nocturnal hypoventilation still occurred. This is consistent with the hypothesis that the major cause of hypoventilation during rapid eye movement (REM) sleep is the reduction in activity of the inspiratory muscles and that diminished chemical ventilatory responses, which may be influenced by respiratory stimulants, only play a minor role [1, 17].

The calculated alveolar-arterial oxygen gradient diminished significantly during ACET therapy from 5.4 (SD 1.0) kPa to 4.1 (SD 1.2) kPa. During CMA therapy, the alveolar-arterial oxygen gradient remained unchanged (from 5.6 to 5.9 kPa). Therefore, part of the rise in Pa_{O_2} during ACET therapy can probably be attributed to improved ventilation-perfusion ratios.

On CMA, minute ventilation increased in association with an augmentation of the hypercapnic ventilatory response, whereas the hypoxic ventilatory response remained unchanged. In this study, the hypoxic ventilatory response during therapy was measured at "hypocapnic post-drug" level. In some other studies, hypoxic ventilatory response was measured at relatively high pretreatment P_{ETCO_2} levels. In these studies, an increased hypoxic ventilatory response after progesterone treatment was observed [6]. It has been suggested that progesterone stimulates ventilation through the central nervous system [6]. The fact that, in the current study, CMA affected the hypercapnic ventilatory response without effect on the hypoxic ventilatory response supported this theory. Medroxyprogesterone can be expected to have similar effects [18].

We found that hypercapnic and hypoxic ventilatory responses were augmented by ACET. This suggests that it had an effect both on peripheral and central receptors. From the literature, the exact mechanism of this action of ACET is not yet clear [8, 19].

SKATRUD *et al*. [4] who studied the effects of medroxyprogesterone and ACET, divided their patients into "correctors" and "noncorrectors" by using the criterion of a decrease of more or less than 0.67 kPa in daytime Pa_{CO_2} during treatment. They suggested that the noncorrectors in their study had more severe obstructive airway disease (lower FEV_1 values) and more hyperinflation (higher functional residual capacity (FRC) values), and were not able to lower their Pa_{CO_2} on voluntary hyperventilation. Furthermore, patients who increased tidal volume rather than respiratory rate would react more favourably to respiratory stimulants. In the current study, no significant difference in characteristics was found between correctors and noncorrectors to CMA or ACET. Furthermore, neither in the CMA group nor in the ACET group could a significant correlation be established between the response of Pa_{CO_2} and either the severity of the obstruction (FEV_1 % predicted), the degree of hyperinflation (FRC and residual volume (RV) % predicted), any other patient characteristic tested, or the concomitant response of ventilation parameters. Apparently, the response in our patients to the respiratory stimulating drugs used was not dependent on their ventilatory limitation. Indeed, all CMA patients and 89% of ACET patients were able to decrease their Pa_{CO_2} by at least 0.7 kPa by means of voluntary hyperinflation. Hence, we could not confirm any of the possible predictors of responses to ventilatory stimulants that were suggested by SKATRUD *et al* [4]. Neither could we find any other predicting characteristic.

In COPD patients fewer nocturnal desaturations are associated with apnoeas during CMA and ACET therapy compared to breathing room air alone. These results are in agreement with findings in patients with the sleep apnoea syndrome [20, 21]. Hypoxaemic COPD patients with mild sleep apnoea <5 apnoeas·h^{-1} may then benefit from CMA or ACET therapy. Oxygen in these patients may lead to prolonged apnoeas and therefore severe CO_2 retention and acidosis [22]. CMA and ACET may correct Pa_{CO_2} and diminish the occurrence of apnoeas.

The subjective daytime benefit of both CMA and ACET was probably a placebo effect, since in all three groups the same percentage of patients felt better when taking any of the capsules. The improvement of sleep quality during ACET therapy may have contributed to the daytime benefit. This increased sleep quality may be due to the sedative effect of ACET and not to direct effects on ventilation. The side-effects could be partly explained by a placebo effect, although paraesthesia and nausea are probably "true" side-effects of ACET [4, 20].

In the placebo group, a slight increase in awake Pa_{O_2} was observed. This probably represents random fluctuation in a group of patients undergoing intensive study. The slight increase in hypoxic ventilatory response in the placebo group could be explained by the increased Pa_{CO_2} [23].

We conclude that in our group of severe COPD patients the effects of ACET treatment on gas exchange are more favourable than those of CMA. Oxygen therapy improves oxygenation slightly more than ACET, but aggravates CO_2 retention.

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