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Association of oral almitrine and medroxyprogesterone acetate: effect on arterial blood gases in chronic obstructive pulmonary disease

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Almitrine (A) and medroxyprogesterone acetate (MA) given separately improve arterial blood gases in some patients with chronic obstructive pulmonary disease (COPD); the aim of this study was to assess the effect of the two drugs given together.

Forty-eight patients with irreversible COPD and hypoxaemia were prospectively enrolled into a 14-day run-in period and received single-blind oral treatment with double placebo. Patients whose PaO_2 remained stable (less than 10% change; $n=29$, 25 males, mean age 65·6 years) were included in a 14-day active treatment period and randomly assigned to three groups. They received double-blind oral treatment with: A (50 mg bid, group A, $n=10$); MA (20 mg tid, group MA, $n=9$); A (50 mg bid) and MA (20 mg tid, group A+MA, $n=10$).

Anthropometric and spirometric measurements were similar in the three groups and so were the arterial blood gas values at the beginning and the end of the run-in period. At the end of the active treatment period, blood gas changes (mean ± SE) were significantly different between groups ($P<0{\cdot}05$, Kruskal–Wallis test), with improvement in both hypoxaemia and hypercapnia in group A+MA only: $\Delta PaO_2 = 7{\cdot}4 \pm 1{\cdot}9$ mmHg, $\Delta PaCO_2 = -5{\cdot}1 \pm 1{\cdot}7$ mmHg ($P<0{\cdot}05$, Wilcoxon test).

In short-term treatment, the association of A and MA is more efficient than either drug alone at improving arterial blood gases in COPD patients.

Key words: almitrine; medroxyprogesterone acetate; blood gases; hypercapnia; hypoxaemia.

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Introduction

Blood gas impairment is a consequence of advanced chronic obstructive pulmonary disease (COPD). The therapies used for severe hypoxaemia (long-term oxygen therapy) and hypercapnia (mechanical ventilation) are both costly and cumbersome. An oral drug that is able to improve arterial blood gases would therefore be a valuable alternative.

Almitrine (A) and medroxyprogesterone acetate (MA) are two drugs that have been able to improve blood gases in COPD patients. They have been studied in large series (1–3) and in small groups of selected COPD patients (4–6), respectively; however, they have never been tested in association.

Are the effects of A and MA on blood gases potentiated, or at least cumulated, when the two drugs are administered in association? We tested this hypothesis in a double-blind randomized study of three parallel groups of COPD patients suffering from stable blood gas impairment.

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Methods

COPD was defined according to the criteria of American Thoracic Society (7). In order to be considered for this prospective study, patients had to meet the following criteria: forced expiratory volume in 1 sec (FEV_1)/forced vital capacity (FVC): less than 0·65; less than 20% increase in FEV_1 with an inhaled β-adrenergic bronchodilator; measured PaO_2 less than mean normal value for age minus 2 SD (8); stable clinical state as estimated by the attending physician at an outpatient routine follow-up visit at least 1 month after any hospitalization. Other respiratory diseases were excluded. Ineligibility criteria were treatment with A during the month preceding entry and contraindications to A or MA treatment (hepatic failure, severe peripheral neuropathy, severe systemic hypertension, ischemic heart disease, thromboembolism, pregnancy, breast-feeding). Measurements included: FEV_1 and FVC (water-sealed spirometer; Warren E.Collins, Braintree, MA U.S.A.);

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arterial blood gases at rest, in the seated position while breathing room air for at least 30 min (ILmeter 1304; Instrument Laboratory, Paris, France); dyspnoea assessed with a 10-cm visual analogue scale.

Forty-eight patients (42 males, mean age 67·0 years) gave informed consent. They were given single-blind oral treatment with double placebo (A-placebo and MA-placebo) for a 14-day run-in period, at the end of which arterial blood gases were re-measured. Only patients whose hypoxaemia had remained stable (PaO_2 change at the end of the run-in period less than 10% of initial value) could be included. These patients were randomly assigned to three groups, entered into a 14-day active treatment period, and given double-blind oral treatment with: A-verum (50 mg bid) and MA-placebo (group A); A-placebo and MA-verum (20 mg tid; group MA); A-verum (50 mg bid) and MA-verum (20 mg tid; group A+MA). All other treatments, including long-term domiciliary oxygenotherapy, remained unchanged during both the run-in and active treatment periods, otherwise the patient would have been excluded. Arterial blood gases and dyspnoea were measured during visits at the beginning and the end of the run-in period, and at the middle and end of the active treatment period. Compliance with treatment was checked by counting pills at each visit.

Statistical analysis was done with tests for non-parametric data: Kruskal-Wallis (three groups), Wilcoxon (paired data) and rank Spearman (correlation) tests, as appropriate (9). A two-tailed P-value less than 0·05 was considered significant.

Approval by the hospital ethics committee was given to the study.

Results

At the end of the run-in period visit, PaO_2 changes superior to 10% of initial value were observed in 15 patients (PaO_2 improved in nine, worsened in six), and four patients could not be included for other reasons (two for non-compliance with placebo, two for non-presentation at the visit).

The twenty-nine included patients (25 males; mean age 65·6. years) completed the active treatment period: group A, $n=10$; group MA, $n=9$; group A+MA, $n=10$. Anthropometric and spirometric measurements were similar in the three groups, and so were the dyspnoea scores and the blood gas values at the beginning and the end of the run-in period (Table 1). Mild hypercapnia was present in addition to hypoxaemia. No patient had suffered from an exacerbation nor had received A during the preceding 3 months. Seven patients were receiving long-term domiciliary oxygenotherapy (two in group A, two in group MA, three in group A+MA).

At the end of the active treatment period, blood gas changes (ΔPaO_2 and $\Delta PaCO_2$; mean $\pm$ SE) were statistically different between the three groups ($P<0·05$, Kruskal–Wallis test, Fig. 1), with improvement in both hypoxaemia and hypercapnia in group A+MA only: $\Delta PaO_2 = 7·4 \pm 1·9$ mmHg, $\Delta PaCO_2 = -5·1 \pm 1·7$ mmHg ($P<0·05$, Wilcoxon test). In this group, nine of 10 patients improved more than 5 mmHg in PaO_2. Blood gases did not change in group A: $\Delta PaO_2 = 2·0 \pm 0·3$ mmHg, $\Delta PaCO_2 = 1·3 \pm 1·2$ mmHg; only hypercapnia improved in group MA but the change was not statistically significant: $\Delta PaO_2 = 2·9 \pm 1·1$ mmHg, $\Delta PaCO_2 = -4·0 \pm 2·2$ mmHg. In group A+MA, there was no correlation (Spearman test) between PaO_2 and $PaCO_2$ changes. At mid-time, improvement in hypoxaemia and hypercapnia was already present in group A+MA: $\Delta PaCO_2 = 5·8 \pm 2·1$ mmHg, $\Delta PaCO_2 = -3·1 \pm 1·3$ mmHg, whereas the blood gases had not changed in groups A and MA.

Dyspnoea scores did not change significantly in any of the three groups. No side-effects were reported and all patients remained in clinically stable condition throughout the study.

Discussion

Potentiation or addition of the effects of A and MA could be expected because the drugs have different mechanisms of action. MA stimulates overall ventilation with a subsequent increase in alveolar ventilation (4). Oral A, at the doses we used, redistributes bloodflow within the lungs without changing ventilation (10). The lack of relationship we found between individual PaO_2 and $PaCO_2$ changes fits the idea of different mechanisms of action. The fact that the blood gas changes after the two-drug association were larger than those induced by either drug alone supports our initial hypothesis.

PaO_2 did not improve with A alone, in group A. In larger studies PaO_2 was usually assessed after a 3-month treatment period (1–3). Too short duration of treatment is, however, an unlikely explanation for our negative finding: bloodflow redistribution occurred within hours after oral intake of A (10) and increases in PaO_2 have been observed after 2 weeks of treatment (11–13). In the light of these later studies and because we wished to avoid possible changes in our patients' clinical condition with subsequent PaO_2 fluctuations, we elected to treat our patients for 2 weeks. As we included only patients whose PaO_2 did not change over the run-in period and because their clinical condition remained stable for the entire study, one can assume that the blood gas changes we observed at the end of the active treatment period were due to the drugs.

Ventilation–perfusion mismatch was certainly present in the lungs of our patients. If neither the ventilation of alveoli with severely obstructed airways nor the distribution of bloodflow changed, overventilation of lung areas with permeable airways would help fighting hypercapnia but not hypoxaemia, due to the peculiar shape of the SaO_2–PaO_2 dissociation curve. MA-induced increase in alveolar ventilation was thus expected to improve $PaCO_2$, with little or no change in PaO_2, as we observed in two group M. With the two-drug association, it can be speculated that A improved the perfusion of lung areas the ventilation of which was simultaneously increased by MA; as a result, both hypoxaemia and hypercapnia improved. In group A, the bloodflow redistribution may not have reduced the ventilation–perfusion mismatch sufficiently for PaO_2 to

TABLE 1. Patients' characteristics in the three groups A, MA and A+MA. Anthropometric and spirometric measurements; blood gas values and dyspnoea scores at the beginning (T1) and the end (T2) of the run-in period are shown. Data are expressed as mean ± SE.

		Group A ($n=10$)	Group MA ($n=9$)	Group A+MA ($n=10$)	P*
Age (years)		62·8 ± 7·0	68·1 ± 9·7	66·1 ± 7·6	NS
Body mass index		22·1 ± 4·4	23·2 ± 3·6	22·2 ± 4·2	NS
FEV_1/FVC		0·47 ± 0·11	0·47 ± 0·10	0·49 ± 0·11	NS
FEV_1 (% predicted)		33·6 ± 15·6	33·0 ± 14·6	34·9 ± 15·7	NS
PaO_2 (mmHg)	T1	60·3 ± 7·1	62·6 ± 7·7	56·3 ± 10·9	NS
	T2	60·7 ± 7·6	61·1 ± 7·6	56·1 ± 11·9	NS
$PaCO_2$ (mmHg)	T1	46·9 ± 5·6	45·6 ± 5·2	45·1 ± 8·1	NS
	T2	44·7 ± 4·6	45·0 ± 4·8	45·4 ± 9·4	NS
Dyspnoea score	T1	4·6 ± 2·9	4·8 ± 2·1	5·0 ± 1·5	NS
	T2	5·3 ± 2·5	4·7 ± 2·9	5·3 ± 1·7	NS

*Kruskal–Wallis test.
NS: difference not significant.

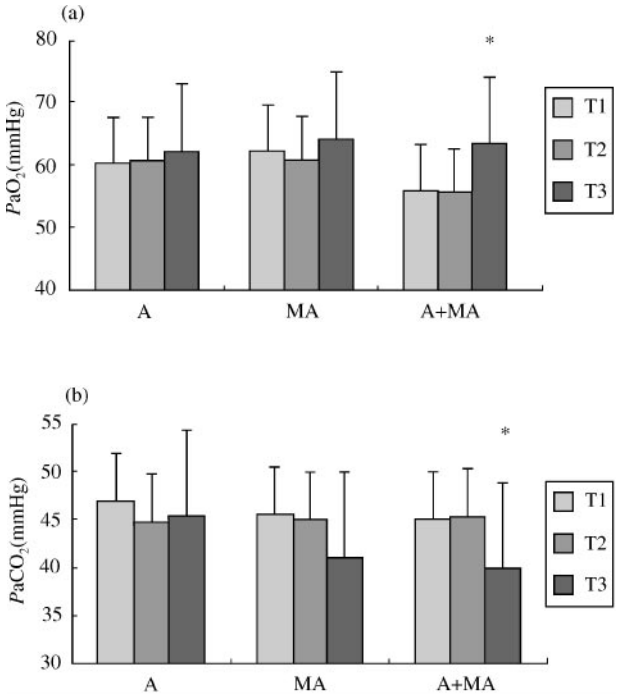

FIG. 1. Blood gas changes at the start (T1), the end (T2) of the run-in period and after active treatment period (T3) in groups A, MA and A+MA. Data are expressed as mean, ± SE. (a) PaO_2 measurement, (b) $PaCo_2$ measurement. *Difference between groups was significant ($P<0·05$, Kruskal–Wallis test), with improvement in both hypoxaemia and hypercapnia in-group A+MA only ($P<0·05$, Wilcoxon test).

improve. Previous studies showed that PaO_2 did not improve in about one-third of patients (1–3).

Since the association of A and MA caused improvement in both hypoxaemia and hypercapnia that may be clinically relevant without noticeable side-effects, we believe it deserves further evaluation in patients with more severe chronic respiratory failure. We should mention possible adverse effects of this drug, e.g. risk of neuropathy with A or pulmonary hypertension. Long-term studies assessing quality of life and mortality are also needed before the two-drug association can be recommended for clinical use. Acute worsening of hypoxaemia and hypercapnia as a consequence of COPD exacerbation is another clinical situation where a trial of A plus MA association can be considered.

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