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Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study

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Long-term treatment of chronic obstructive lung disease by Nifedipine: an 18-month haemodynamic study. A.Y. Saadjian, F.F. Philip-Joet, R. Vestri, A.G. Arnaud.

ABSTRACT: This long-term controlled study was undertaken to assess the haemodynamic effects of chronic administration of Nifedipine (N). Twenty patients suffering from pulmonary hypertension secondary to chronic obstructive lung disease were divided into two groups. One group (treatment group) was instructed to take 30 mg of N daily and the other (control group) did not take N. Haemodynamic measurements were recorded before and after an 18-month observation period. For patients in the treatment group, Nifedipine was stopped 24 h prior to the second investigation. Acute response to a single dose of Nifedipine (10 mg sublingually) was also evaluated in all patients during the first and second investigations in order to estimate a possible tachyphylaxis. No significant modification in heart rate, mean pulmonary pressure, mean arterial pressure or blood gases was observed. Conversely, a 10% decrease in cardiac output ($p<0.05$) occurred in the control group. Pulmonary vascular response to acute administration of Nifedipine was the same in both groups before and after the observation period. These results suggest that while long-term administration of Nifedipine to patients with chronic obstructive lung disease does not improve pulmonary pressure, it may prevent a decrease in cardiac output. No tachyphylaxis was noted.

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Encouraged by the benefits of long-term oxygen therapy, several investigators [1–3] have suggested that administration of vasodilators in chronic obstructive lung disease (COLD) might improve pulmonary circulation by reversing pulmonary arteriolar constriction which exacerbates pulmonary hypertension. Vasoconstriction is ultimately mediated by the intracellular action of calcium, and thus calcium blockers should theoretically constitute a specific and effective agent for the treatment of secondary hypoxic pulmonary hypertension. Indeed several acute studies have indicated that Nifedipine (N) has beneficial haemodynamic effects in clinically stable patients [1, 4]. N improves oxygen transport to peripheral tissues by increasing cardiac output [1, 3, 4]. On the other hand, arterial desaturation is observed due to transpulmonary shunting of blood through poorly ventilated alveoli [5].

Despite promising results from short-term trials in patients with hypoxic pulmonary hypertension [4, 6–8], few extended studies have been devoted to the long-term benefits of calcium blockers [8–10]. The present controlled study was undertaken to evaluate the haemodynamic effects of N therapy over an average period of 18 months in patients with pulmonary hypertension secondary to COLD and to assess acute response to a single dose of N before and after chronic administration.

Patients and methods

Patient population

This study included twenty patients with pulmonary hypertension secondary to COLD (mean pulmonary artery pressure >20 mmHg) and functional tests showing evidence of serious respiratory impairment (forced expiratory volume in one second (FEV_1) between 20 and 40% of predicted as per C.E.C.A. tables). All had dyspnoea and fatigue after minimal or moderate exertion but were in a clinically stable condition and free of bronchopulmonary infection, acute respiratory distress or right ventricular failure for at least two months prior to entry into the study. None was being treated with vasodilators, long-acting theophylline, $ß_2$-agonists, almitrine, diuretics or digitalis. All were in sinus rhythm with no clinical, electrocardiographic, X-ray, or echocardiographic evidence of left ventricular dysfunction.

The patients were randomly distributed into a control group (C) and a treatment group (N). As shown in table 1, these two groups were identical with regard to clinical, functional, and haemodynamic data. Five patients in each group were undergoing long-term oxygen therapy for more than 14 h per day and this treatment was

maintained during the study but was discontinued 4 h before each haemodynamic investigation.

Table 1. – Anthropometric, clinical and spirographic data

Parameters	Control patients	Nifedipine patients	
n	10	10	
Sex	male	male	
Age yrs	60.5±2.3	63.5±2.3	NS
Weight kg	63.5±3.0	68.7±3.1	NS
Height cm	168±2.5	170±27	NS
Observation period months	18.3±1.8	18.6±1.8	NS
TLC % *	116±2.2	124±2.8	NS
FEV_1 % *	29±1.4	32±2	NS
FVC % *	44.4±2.6	46±2.2	NS
RV/TLC %*	140±1.5	138±1.5	NS
pHa	7.38±0.001	7.38±0.0001	NS
Pao_2 mmHg	63.7±3.6	63.3±2.7	NS
$Paco_2$ mmHg	46.2±1.4	44.8±1.5	NS
MPAP mmHg	29.3±2.8	31.7±2.3	NS

TLC: total lung capacity; RV: residual volume; FVC: forced vital capacity, FEV_1: forced expiratory volume in one second; MPAP: mean pulmonary artery pressure. * (%) of predicted values (C.E.C.A. Tables).

Study procedure

After giving informed consent, each patient underwent right heart catheterization with a 7 F flow-directed balloon-tipped thermodilution catheter (Roche-Kontron) via an antecubital or femoral vein. Systemic arterial pressure measurements and arterial blood sampling were performed through a 4 F cannula in a radial or femoral artery. Intravascular pressures were measured relative to atmospheric pressure with reference to a zero level located on the mid-axillary line. Pressures were measured during apnoea at the end of expiration. Cardiac output (CO) was determined by the thermodilution technique using an automatic device (Roche-Kontron) and expressed as the mean of four consecutive determinations varying less than 10%.

Arterial oxygen tension (Pao_2), arterial carbon dioxide tension ($Paco_2$), and pH were determined with a Radiometer BMS 3 MK2 blood gas analyser and arterial oxygen saturation (Sao_2) with a Radiometer OS M2 device. Haemoglobin levels (Hb) were measured with a Technicon M 6000.

Derived haemodynamic variables were calculated as follows: cardiac index (CI) ($l \cdot min^{-1} \cdot m^2$)=CO/body surface area; pulmonary arteriolar resistance (PAR) ($dynes \cdot s \cdot cm^{-5}$)=mean pulmonary artery pressure (MPAP) - pulmonary artery wedge pressure (PWP) x 80/CO; total pulmonary resistance (TPR) ($dynes \cdot s \cdot cm^{-5}$)= MPAP x 80/CO; total systemic resistance (TSR) ($dynes \cdot s \cdot cm^{-5}$)=mean arterial pressure (MAP) x 80 /CO; right ventricular stroke work index (RVSWI) ($g \cdot systole \cdot m^2$)=MPAP-RVEDP·SI·0.0136·1.055 where RVEDP stands for right ventricular end-diastolic pressure and SI for stroke index ($ml \cdot systole \cdot m^2$). RVEDP is measured at the nadir following the a-wave of the right ventricular pressure curve and SI is obtained by dividing CI by heart rate(HR); oxygen delivery (To_2) ($ml \cdot min^{-1} \cdot m^2$)=CI·$Cao_2$/10 where Cao_2 is arterial oxygen content ($ml \cdot l^{-1}$ of blood)=(13.4·Sao_2·Hb)+(0.031·Pao_2) and Hb is expressed in $g \cdot l^{-1}$.

Study design

All twenty patients underwent two catheterizations: one at the beginning of the study and the other an average of eighteen months later. These investigations were performed under strictly identical conditions by the same operator using the same equipment and techniques. Each included the measurement of haemodynamic data and an acute pharmacological test. Control data were recorded 30 min after catheterization and then 10 mg of N were administered sublingually. In the following hours readings and samples were taken every 20 min and the peak effect was considered to coincide with the maximum increase in CO.

During the eighteen months following the initial study, the patients in the treatment group were instructed to take 10 mg of N orally every 8 h, *i.e.* 30 mg per day. At the end of the observation period, a 24 h withdrawal period was allowed before recatheterization. The mean plasma elimination half-life of N is 3 h. The purpose of this withdrawal was to assess the haemodynamic parameters during the second study independently of the influence of the last intake.

Between the two catheterizations, all patients were regularly followed at the out-patient clinic every 3 months (clinical examination, ECG, blood gas). Compliance was checked by counting the empty blister sheets returned by the patients.

Statistical analysis

All values are expressed as means±SEM. Statistical comparisons of haemodynamic data measured before and after long-term N treatment were performed by two way analysis of variance and the t-test for paired samples. Comparisons between the two groups were carried out using the t-test for unpaired values [11].

Results

All the patients completed the study. The only significant side effect of N was mild ankle oedema observed in one patient. After 18 months of N treatment, no statistically significant difference could be detected with regard to heart rate, mean right atrial pressure, MPAP, RVEDP, PAR, TPR, RVSWI, MAP, TSR, Pao_2, Sao_2, $Paco_2$, or To_2. Although a small decrease in Pao_2 was measured in both groups after 18 months, no significant difference was observed between the two groups or within a single group. No major desaturation was observed.

The only significant difference was that the decrease in CO noted in the control group was not observed in

the treatment group. At the end of the observation period, CI was on average 10% lower in the control group ($p<0.05$) than in the treatment group. In treated patients CO remained constant (table 2). Although TPR and TSR were appreciably higher in the control group after 18 months, this difference did not reach the level of statistical significance.

The same response to acute administration of N was observed in both groups at the beginning and end of the study. CI increased in all patients ($p<0.001$). In the control group, the average increase was 679±111 $ml \cdot min^{-1} \cdot m^2$ (23%) for the first study and 808±130 (22%) for the second. In the N group, it was 665±120 (24%) and 656±103 (24%), respectively. MPAP decreased ($p<0.05$): in the control group, the average decrease measured in the first and second investigations was 2.5±0.9 mmHg (8%) and 3.7±1.3 (12%), respectively, whilst in the N group it was 2.0±0.8 (6%) and 2.2±0.8 (7%). These responses suggest the absence of tachyphylaxis (table 3). Comparisons of the subgroups

Table 2. – Measurements before and after an 18-month observation period in the control and treatment group

Parameters	Control patients			Nifedipine patients		
	Initial study	18 month study		Initial study	18 month study	
HR beats·min^{-1}	88±4	81±3	NS	81±4	83±4	NS
RAP mmHg	9±1	9±1	NS	10±1	10±1	NS
MPAP mmHg	29±2.6	30±3.6	NS	32±2.5	31±1.8	NS
PWP mmHg	13±2	13±2	NS	14±1	13±1	NS
CI·*l*·min^{-1}·m^2	3±0.1	2.7±0.1	p<0.05	2.7±0.1	2.7±0.1	NS
PAR dynes·cm^{-5}·s^{-1}	284±31	312±63	NS	297±28	320±36	NS
TPR dynes·cm^{-5}·s^{-1}	472±42	561±41	NS	546±44	547±47	NS
RVSWI gm m·syst·m^2	8.3±1.6	7.9±1.4	NS	8.2±0.8	9±1.3	NS
PaO_2 mmHg	63.7±3	61±3	NS	63.3±2	58.6±2	NS
$PaCO_2$ mmHg	46.7±1.9	40.9±1.9	NS	45.9±2.2	45±2	NS
SaO_2 %	85.9±2.2	85.5±2.4	NS	89.5±1.3	86.5±2.4	NS
TO_2 ml·min^{-1}·m^2	523±36	444±29	NS	465±31	411±25	NS

HR: heart rate; RAP: right atrial pressure; MPAP: mean pulmonary artery pressure; PWP: pulmonary capillary wedge pressure; CI: cardiac index; PAR: pulmonary arteriolar resistances; TPR: total pulmonary resistances; MAP: mean arterial pressure; TSR: total systemic resistances; RVSWI: right ventricular stroke work index; PaO_2: arterial oxygen tension; TO_2: oxygen delivery.

Table 3. – Response to acute administration of 10 mg of Nifedipine sublingually

Parameters		Control patients			Nifedipine patients		
		Basal	Peak effect	*Difference*	Basal	Peak effect	*Difference*
MPAP	T0	29±2.6	27±1.8	p<0.05	32±2.5	30±2.1	P<0.05
mmHg	T18	30±3.6	26±3	p<0.05	31±1.8	28±2	p<0.05
	Difference	NS	NS		NS	NS	
CI	T0	3.0±0.14	3.67±0.11	p<0.001	2.70±0.15	3.37±0.16	p<0.001
l·min^{-1}·m^2	T18	2.7±0.11	3.50±0.18	p<0.001	2.70±0.14	3.36±0.54	p<0.001
	Difference	p<005	NS		NS	NS	
TPR	T0	472±42	369±27	p<0.001	546±44	435±24	p<0.001
dynes·cm^{-5}·s^{-1}	T18	561±41	386±69	p<0.001	547±47	443±38	p<0.001
	Difference	NS	NS		NS	NS	
MAP	T0	98±3.3	83±2.6	p<0.005	88±2.9	75.1±2.9	p<0.005
mmHg	T18	99±9.1	80±5	p<0.005	89±5.5	72.3±4	p<0.005
	Difference	NS	NS		NS	NS	
TSR	T0	1395±83	1056±32	p<0.005	1371±111	1029±52	p<0.005
dynes·cm^{-5}·s^{-1}	T18	1400±88	1064±71	p<0.005	1363±35	1031±53	p<0.005
	Difference	NS	NS		NS	NS	

T0 and T18 are the values recorded during the first and second catheterizations respectively.

of patients treated or not treated by long-term oxygen therapy did not show any difference.

Discussion

Pulmonary hypertension develops very slowly and progressively during the course of COLD [12, 13]. In most patients, a reduction in CO at rest or during exercise also occurs [7, 12, 14]. Because this progression is so slow, therapy must be evaluated in long-term controlled studies. For example, it was only quite recently that the benefit of long-term oxygen therapy was confirmed and the guidelines for its use defined [15–18].

In theory, calcium channel antagonism is a logical approach to the treatment of pulmonary hypertension secondary to COLD. Short-term studies have shown these drugs to have both beneficial and detrimental effects. These effects include a large increase (about 25%) in CO, a slight decrease in pulmonary artery pressure, small but significant arterial desaturation secondary to an impairment of the ventilation perfusion ratio [5, 9], a slight but significant increase in mixed venous oxygen tension and saturation and an increase in oxygen transport. The improvement in oxygen transport is the result of increased CO which is thus the chief effect of acutely administered N [1].

Our study suggests that chronic administration of N can prevent the spontaneous decrease of CO since this parameter was on average 10% higher in the treatment group after the 18-month observation period. Although this difference is small, it is nevertheless statistically significant. In this regard, it is important to point out that the second measurements were performed after a 24-h withdrawal from N, *i.e.* more than four times the half-life of N. This was carried out in order to determine whether chronic administration of N had changed the course of pulmonary pressure and other haemodynamic parameters independently of the influence of the last intake. This design also allowed comparison between the control and treatment groups at the beginning and at the end of study under the same conditions, *i.e* basal state and after a single intake to check for possible tachyphylaxis.

The large increase in CO observed in the initial investigation after acute sublingual administration was also observed in the second investigation. Thus it is reasonable to speculate that chronic administration of N maintains higher CO levels. In a 3–5 month study of a new calcium antagonist, felodipine, BRATEL *et al.* [9] showed a statistically significant increase in stroke volume (+13%) associated with a border-line reduction of PAR at rest and during exercise. Maintaining cardiac output could be important since it plays a central role in oxygen transport and is a main determinant in ventricular function [6, 19, 20]. It is noteworthy that CO has been repeatedly proposed as a main prognostic factor [17, 19, 21]. Nevertheless no modification in survival has yet been demonstrated with a Nifedipine-based therapy [10].

With regard to side effects, acute administration studies performed on selected patients in stable condition have shown that right ventricular function improves and that N has no deleterious effects on right heart haemodynamics [1, 3, 4, 22]. Our study which was performed on the same type of patients revealed no adverse effects of N on cardiac function after one and a half years of treatment, since right and left ventricular filling pressures (RAP, PWP) were unchanged and CI did not decrease as in the control group.

Under our study conditions and at the dose used, N failed to decrease pulmonary hypertension or to affect systemic circulation. However, it did appear to maintain CO. This action was not associated with any significant impairment of arterial oxygen tension.

The study of acute reactivity to N before and after long-term administration showed no tachyphylaxis. The response of pulmonary and systemic arterial beds remains constant and intact. Larger multicentre studies will be required to confirm our results and evaluate the long-term effects of associating oxygen therapy with vasodilator therapy.

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RÉSUMÉ: Cette étude contrôlée à long terme a été entreprise pour déterminer les effets hémodynamiques de l'administration chronique de nifedipine. Vingt sujets souffrant d'hypertension pulmonaire secondaire à une bronchopneumopathie chronique obstructive, ont été divisés en deux groupes. Le groupe traitement a pris 30 mg de nifedipine par jour, et le groupe contrôle n'a pas pris de nifedipine. Les mesures hémodynamiques ont été enregistrées avant et après une période d'observation de 18 mois. La nifedipine a été interrompue chez les patients du groupe traité 24 h. avant la deuxième investigation. Une réponse aiguë à une dose unique de nifedipine (10 mg par voie sublinguale) a été étudiée chez tous les patients pendant la première et la deuxième investigation, pour estimer une éventuelle tachyphylaxie. Aucune modification du rythme cardiaque, de la pression pulmonaire moyenne, de la pression artérielle moyenne, ou des gaz du sang, n'a été observée. Par contre, on a noté un abaissement de 10% du débit cardiaque ($p<0.05$) dans le groupe contrôle. La réponse vasculaire pulmonaire à l'administration aiguë de nifedipine s'est avérée égale dans les deux groupes, avant et après la période d'observation. Ces résultats suggèrent que, l'administration au long cours de nifedipine à des patients atteints de bronchopneumopathie chronique obstructive n'améliore pas la pression pulmonaire, mais qu'elle peut prévenir une diminution du débit cardiaque. On n'a noté aucune tachyphylaxie.