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Levomepromazine (Nozinan) reduces nonspecific bronchial hyperreactivity in asthmatics

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Levomepromazine (Nozinan) reduces nonspecific bronchial hyperreactivity in asthmatics. P. Faurschou, F. Madsen, H. Pals, A. Rosetzsky.
ABSTRACT: Ten patients with bronchial asthma were challenged with histamine before and after receiving saline and active drug (levomepromazine or antazoline) (a total of six challenges). The antihistaminic effect of levomepromazine (25 mg) was found to be comparable to that of antazoline (100 mg), evaluated from skin prick tests. Prechallenge forced expiratory volume in one second (FEV_1) was found to be larger after levomepromazine than after antazoline ($p<0.05$), indicating a direct bronchodilating effect. This increased threshold airway calibre may have influenced the results of challenge, but change in provocative concentration producing 20% fall (PC_{20}) was not statistically significantly correlated to change in FEV_1. Levomepromazine increased PC_{20} 2-doubling concentration compared to antazoline ($p<0.05$). Variation was observed in two minutes' ventilation during tidal volume breathing challenge. However, there was no statistically significant variation in two minutes' ventilation during challenge after receiving levomepromazine or antazoline. It was concluded that levomepromazine possesses a bronchodilating capacity and reduces bronchial hyperreactivity.
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Nonspecific bronchial hyperreactivity is a part of the asthmatic syndrome [1, 2]. Several drugs, effective in the treatment of bronchial asthma, have also been shown to reduce response to bronchial challenge [3]. In particular the inhaled β_2-adrenergic agonists, ipratropium and, to a lesser degree, methylxanthines have shown an acute effect on both bronchial asthma and nonspecific bronchial hyperreactivity.

Thus, the bronchial challenge is a useful experimental model of bronchial asthma. Drugs which reduce nonspecific bronchial hyperreactivity may be of potential value in the treatment of bronchial asthma.

We have used the analgesic and sedative effect of levomepromazine in almost 900 patients with acute myocardial infarction [4]. Some of these patients had reduced ventilatory capacity due to asthmatic attacks or congestive heart failure. In these patients we have observed improved ventilatory capacity, lower respiratory frequency, and an increase in tidal volume after administration of levomepromazine in doses from 25–400 mg.

Since these clinically observed effects may be of potential value in the treatment of chronic obstructive pulmonary disease, this study was designed to test the effect of levomepromazine on nonspecific bronchial hyperreactivity in patients with bronchial asthma.

Methods

Ten stable asthmatics were included after informed consent had been obtained. The study was approved by the local Ethical Committee. Anthropometric data are given in table 1. The patients had to be hyperreactive, provocative concentration causing 20% fall (PC_{20}) histamine <4 mg·ml^{-1} (see challenge protocol) and forced expiratory volume in one second (FEV_1) before the challenge had to be above 50% of the predicted value [5]. No patient had neuromuscular disorders, and all patients had normal chest roentgenograms.

Design

Since levomepromazine has an antihistaminic effect, the study was designed with placebo and antihistamine control. The study was patient- and observer-blind, and patients were randomized to receive the alternative treatments on two different days (fig. 1).

One technician performed the skin prick test and another the bronchial challenge. They were not informed about the treatment and were not aware that saline (placebo) was always given as the first injection. This was known by the physician giving the injections (fig. 1). Levomepromazine and antazoline (Antistin) were given in a double-blind manner. Antazoline was chosen as the control drug because of its antihistaminic and sedative effect. Each patient had completed the study within one week.

Skin sensitivity

Skin prick tests were performed with unbuffered histamine dihydrochloride, 1 mg·ml^{-1} and 10 mg·ml^{-1}, and

0.1 mg intracutaneously (ic). Wheal reactions were measured after 15 min, marked with a pencil and transferred to paper by means of tape. Digital planimetry was used to measure the area reported in cm^2. Geometric mean area and coefficient of variation (1 $mg \cdot ml^{-1}$ 0.10 cm^2, 54%), (10 $mg \cdot ml^{-1}$ 0.28 cm^2, 37%), (0.1 mg ic 6.57 cm^2, 8%).

Hand grip strength

Hand grip strength was measured with a vigorimeter (Gebraader Martin, Tuttlingen, BRD) which measures the hand grip strength [6]. This test was used, since levomepromazine has a sedative effect and valid determination of FEV_1 demands a maximum forced expiratory manoeuvre. Thus, the hand grip strength is a measurement of neuromuscular performance. Hand grip strength was tested three times with an interval of 5 s. The largest value was reported as the result. Hand grip strength 1.19 $kPa \cdot cm^{-2}$, coefficient of variation 9%.

Bronchial challenge

Before each challenge a standardized interview took place to ensure that patients had abstained from: smoking (4 h), inhaled β_2-adrenergic agonists (8 h), oral β_2-adrenergic agonists (12 h), methylxanthine (48 h), ipratropium (12 h), and antihistamines (4 wks). Steroids were continued unchanged. No patient had had respiratory tract infections within 3 wks.

Table 1. – Anthropometry, FEV_1, immunoglobulin E (IgE), skin prick test, eosinophils and smoking habits

Patient	Age	Sex	Height	FEV_1	Duration of asthma	IgE $KU \cdot l^{-1}$	Skin prick test ≥10 HEP and/or RAST ≥ class 2	Eosinophils in blood per μl	Cigarettes per day
n	yrs		cm	% pred	yrs	(0–120)			
1	20	F	166	54	18	100	+	25	20
2	41	F	160	68	6	69	+	6	20
3	45	M	175	68	3	140	-	244	2
4	27	M	185	34	3	461	-	538	15
5	39	M	181	76	36	59	+	169	0
6	24	F	178	94	1	69	-	910	0
7	52	F	167	101	6	173	-	656	0
8	44	F	165	78	6	53	-	940	3–4
9	23	M	174	71	1.5	29	+	1040	0
10	37	F	170	97	7	95	+	250	10

FEV_1: forced expiratory volume in one second; RAST: radio-allergosorbent test.

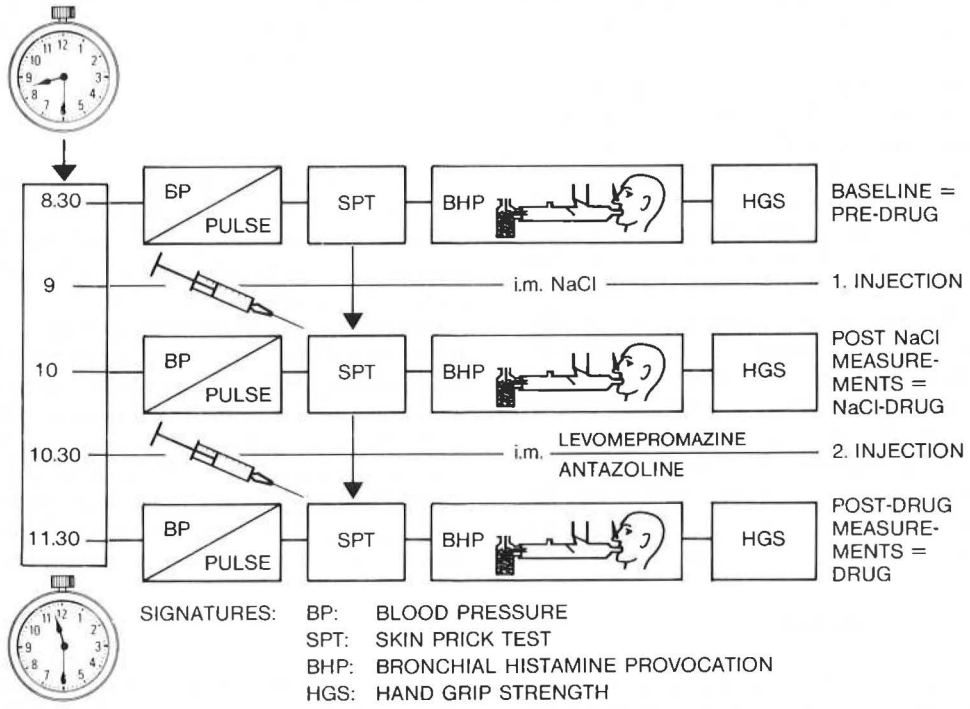

Fig. 1. – Study protocol. Time schedule for the patients.

A standard tidal volume breathing inhalation challenge was used [1, 7]. The aerosol was generated by a Wright nebulizer filled with 2 ml of solution and driven by compressed air at 1.2 bar and at an air flow of 13 $l \cdot min^{-1}$. Pressure was monitored continuously on a manometer calibrated against a mercury column. Under these conditions the output is 148 $\mu g \cdot min^{-1}$ (SD 7 $\mu g \cdot min^{-1}$). The output was determined by calibration of the actual set-up. The complete nebulizer including valve box was weighed on a Mettler balance and output reported as the mean and standard deviation of ten determinations. Under these conditions the count aerodynamic diameter of 95% of the dry particles varied between 0.5 μm and 1.8 μm. The aerosol was led through a unidirectional valve (Astra-Meditek). Since the inspiratory flow during inhalation of the aerosol was higher than the air flow through the nebulizer, accessory air was led through the system *via* an air vent. Ventilation was determined by measurement of expired air. Exhalations were performed through a dry gasometer (Vedras, type 2E, Copenhagen, Denmark) calibrated against a wet Tissot spirometer before and after the study. Reproducibility of 2 minutes' ventilation measurements during spontaneous tidal breathing (without aerosol inhalation) has previously been found to be high [8]. Reproducibility, expressed as the residual standard deviation for replicated measurements, was 2.07 $l \cdot 2$ min^{-1}. Mean ventilation 19.1 *l*, coefficient of variation 26%.

Inhalations were performed for 2 min with intervals of 5 min. Following isotonic saline, unbuffered histamine chloride (HC) was inhaled in doubling concentrations from 0.03 to 64 $mg \cdot ml^{-1}$. The challenge was continued until a histamine chloride dose inducing at least 20% decrease in post-saline FEV_1 was reached (threshold dose). FEV_1 was measured 30 and 90 s after termination of the inhalation. Thereafter, the provocative concentration of histamine chloride (PC_{20} FEV_1) resulting in a 20% decrease in FEV_1 was determined by linear interpolation between the last two points on the log dose response curve. FEV_1 and forced vital capacity (FVC) were measured on a calibrated dry wedge spirometer (Vitalograph Ltd, Buckingham, England). At least two technically correct forced expiratory manoeuvres with a variation of less than 5% were obtained, and the highest value was used for further calculations. Values are reported at ambient temperature, atmospheric pressure and saturated with water vapour (ATPS).

Blood pressure and pulse

The mean values and coefficient of variation were: systolic blood pressure 116 mmHg, 9%; diastolic blood pressure 76 mmHg, 13%; pulse 78·min^{-1}, 10%.

Statistics

Logarithmic transformation of results was carried out, since results varied over several orders of magnitude. Means were calculated together with the 95% confidence interval for the mean. When means were compared, the mean difference was reported together with the 95% confidence interval for the mean difference [9]. Changes in bronchial responsiveness are usually reported in unit two-fold concentration differences, and the effect of a drug on PC_{20} is, therefore, most easily interpreted if expressed in two-fold concentration differences, since PC_{20} expressed in $mg \cdot ml^{-1}$ varies over several orders of magnitude. One-way analysis of variance (ANOVA) was used to compare several means. Reproducibility is reported as coefficient of variation. Interdependence was examined by means of linear regression.

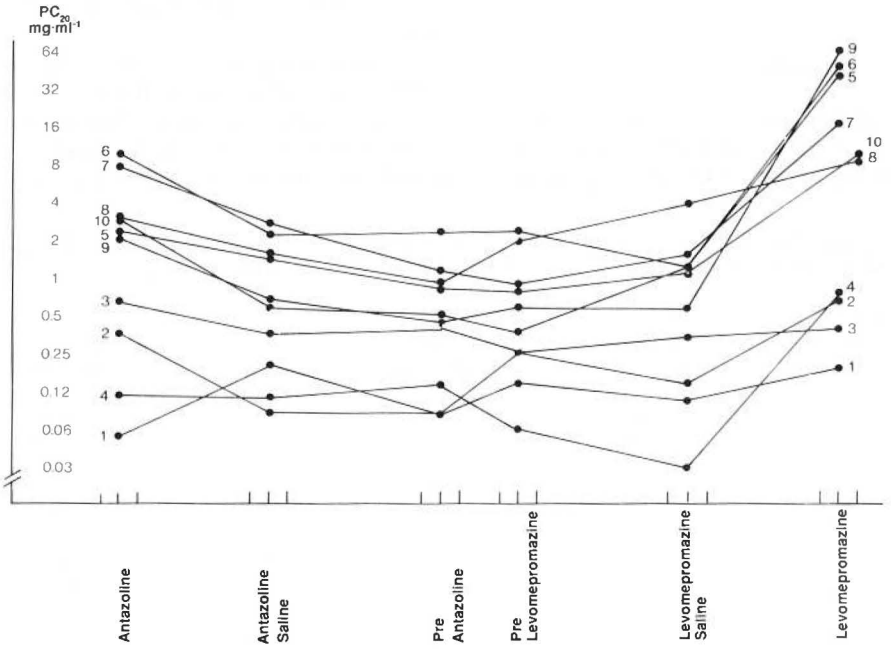

Fig. 2. – PC_{20} $mg \cdot ml^{-1}$ individual patient responses. PC_{20} determined before and after saline and after either levomepromazine or antazoline.

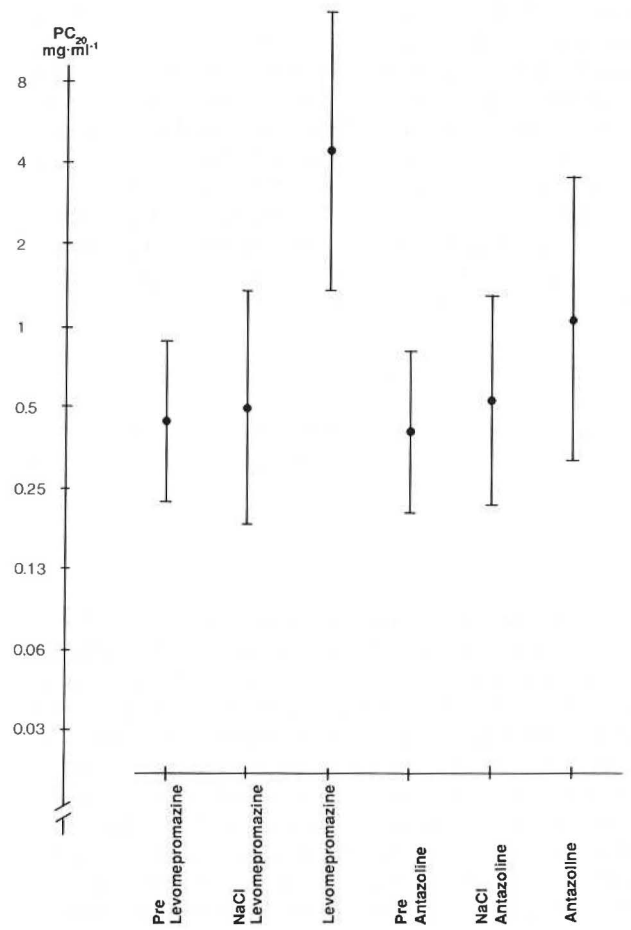

Fig. 3. – PC_{20}, mean and 95% confidence interval for the six challenges determined before and after saline and after either levomepromazine or antazoline.

Results

Most patients showed a larger increase in PC_{20} after levomepromazine treatment than after antazoline treatment (fig. 2). The patients were moderately hyperreactive before treatment, with PC_{20} values about 0.25–1 mg (fig. 3). In figure 4 the mean differences between groups are reported with 95% confidence interval for the mean difference. When comparing the PC_{20} values before medication and after saline, it is seen that the PC_{20} determinations were highly reproducible. The 95% confidence interval for the mean difference was below 1-doubling (1-doubling=1 ln2) concentration difference.

No statistically significant difference between groups existed regarding PC_{20}, when no active medication was given (the 95% confidence interval includes ln1=0). When levomepromazine is compared to saline (NaCl), an increase in PC_{20} of more than 2-doubling concentration differences is seen ($p<0.05$, fig. 4). When antazoline is compared to saline, a significant difference is seen ($p<0.05$, fig. 4), but the mean difference is significantly lower than for the difference between NaCl and levomepromazine ($p<0.05$, fig. 4).

The mean difference in PC_{20} between levomepromazine and antazoline is above 2-doubling concentration differences with a 95% confidence interval for the mean difference being 1.5–2.5-doubling concentration differences. This shows that 25 mg of levomepromazine is about twice as effective as 100 mg of antazoline for reduction of nonspecific bronchial hyperreactivity.

Prechallenge FEV_1 was found to be higher after levomepromazine than after antazoline (table 2) ($p<0.05$).

Skin histamine sensitivity (10 HEP skin prick test and 0.1 $mg \cdot d^{-1}$ ic were significantly reduced by both antazoline and levomepromazine ($p<0.05$), but no difference was seen between levomepromazine and antazoline concerning skin sensitivity (table 2).

Hand grip strength, blood pressure (BP), pulse and ventilation were not effected by saline or active drugs.

PC_{20} was found to be independent of both ventilation and prechallenge FEV_1. No linear relationship between change in FEV_1 and change in ln PC_{20} was observed ($r^2=0.29$, $p>0.1$), although approaching statistical significance.

One-way analysis of variance and linear regression showed no significant difference in mean ventilation between treatment groups, when all patients were analysed. ANOVA of individual patients ventilation showed significant difference in ventilation between the six

Table 2. – Skin reactivity (geometric mean and GSD), FEV_1 (mean and SD); $\dot{V}E$ (mean and SD) and PC_{20} (geometric mean and GSD) before and after saline, levomepromazine and antazoline administered intramuscularly

	Pre Levome-promazine	NaCl Levome-promazine	Levome-promazine	Pre Antazoline	NaCl Antazoline	Antazoline
Skin test	6.57	6.30	3.25	6.41	5.89	3.75
0.1 $mg \cdot cm^2$ ic	1.48	1.58	2.08	1.73	1.94	1.61
FEV_1 *l*	2.41	2.45	2.80	2.44	2.44	2.55
	0.60	0.65	0.70	0.62	0.64	0.72
$\dot{V}E$	20.1	21.1	18.8	20.6	19.2	21.0
$l \cdot 2\ min^{-1}$	8.2	7.4	7.4	8.6	6.9	7.8
PC_{20}	0.45	0.50	4.69	0.40	0.53	1.04
$mg \cdot ml^{-1}$	3.15	4.56	8.80	3.10	3.74	5.76

FEV_1: forced expiratory volume in one second; $\dot{V}E$: minute ventilation; PC_{20}: provocative concentration producing 20% fall.

challenges performed in each patient. More than one minute ventilation ($\dot{V}E$) was determined in the individual patient after each drug, and, therefore, the mean $\dot{V}E$ is reported in table 2.

possible. In one patient (No. 9), however, histamine dose had to be increased to 64 $mg \cdot ml^{-1}$ after levomepromazine, before significant bronchoconstriction was induced.

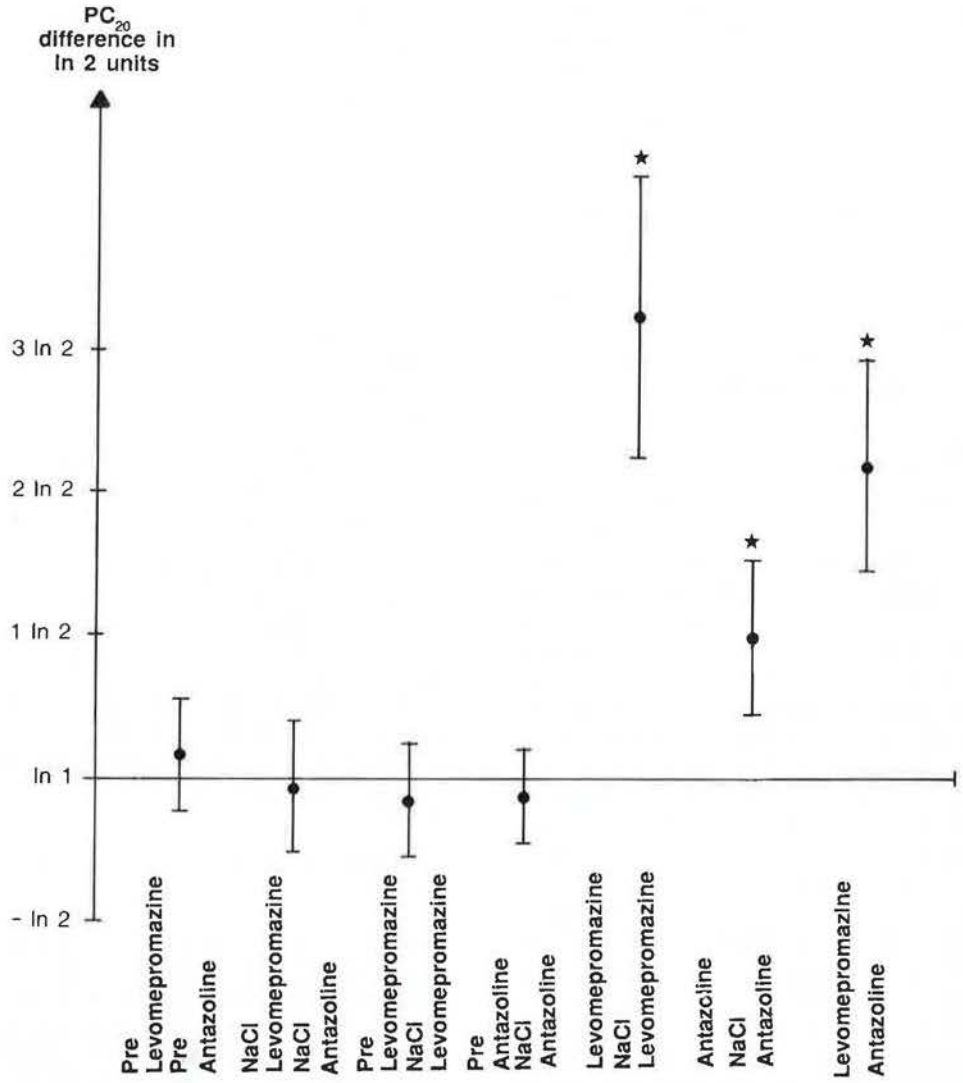

Fig. 4. – Mean differences between treatments with 95% confidence interval (no difference=ln 1=0). There was no difference in baseline PC_{20} and PC_{20} determined after injection of placebo (saline). Furthermore, it is seen that placebo did not change PC_{20}, since the 95% confidence interval between prechallenge PC_{20} and PC_{20} after saline includes ln 1=0. Both levomepromazine and antazoline increase PC_{20}, 3 ln 2 and 1 ln 2, respectively (ln 2=1 two-fold concentration difference). The effect of levomepromazine compared to the effect of antazoline (levomepromazine-antazoline) was 2 ln 2, which corresponds to a protective effect of levomepromazine approximately 4 times that of antazoline.

Discussion

Levomepromazine (25 mg) was followed by a larger increase in PC_{20} and prechallenge FEV_1 than antazoline (100 mg) ($p<0.05$). An inhibitory effect of levomepromazine on histamine- induced bronchoconstriction was expected, from uncontrolled clinical observations, but an effect of levomepromazine on ventilatory capacity and ventilation during challenge was not expected [10]. The patients in this study were moderately hyperreactive (figs 2 and 3) making changes of PC_{20} in both directions

The study was antihistamine-controlled, because levomepromazine has an antihistaminic effect [11]. Levomepromazine also possesses anticholinergic effects and, therefore, it would have been preferable if the study had been both antihistamine- and anticholinergic-controlled.

The study was observer-blind concerning all effect parameters and double-blind and randomized concerning administration of active drugs. Administration of NaCl was not randomized but patient- and observer-blind. This design permits assessment of repeatability of all tests performed and detection of effects other than antihistamine effects.

Hand grip strength was measured to ensure that neuromuscular performance was not changed, making spirometry invalid as a consequence of severe sedation.

Intracutaneous test was reduced equally by antihistamine and levomepromazine indicating a comparable antihistaminic effect of the two dosages.

The bronchial challenge was a modified COCKCROFT *et al.* [1] and CHAI *et al.* [7] method. We added determination of ventilation during challenge to the standard protocol, because random variations in ventilation during challenge have been observed, together with a systematic fall in ventilation, as threshold dose is approached [8]. These variations may lead to differences in the dose delivered to the mouth after receiving levomepromazine and antazoline, thus invalidating the results.

Differences in prechallenge FEV_1 between drugs might also lead to a systematic change in PC_{20} [12]. Analyses of FEV_1 and ventilation during challenge show systematic differences between drugs. FEV_1 was higher after levomepromazine than after antazoline, and ventilation during challenge was larger after antazoline than after levomepromazine, although the correlation coefficient for these changes was not statistically significant. Low prechallenge FEV_1 may lead to a decrease in PC_{20}, although never documented [12]. The total dose of bronchoconstrictor delivered to the mouth is a major determinant of the response to challenge. In the tidal volume breathing method this dose is determined by the output of the nebulizer and the inspiratory time. Inspiratory time was not determined in this study, but ventilation was measured and showed significant variation between drugs. This weakens the conclusions concerning drug effects. On the other hand, it is of interest to detect an effect of levomepromazine on FEV_1 and of antazoline on ventilation. A mean increase in FEV_1 of approximately 300 ml may be of clinical significance. A diurnal increase in FEV_1 was not observed, and a significant difference was seen in FEV_1 between drugs ($p<0.05$). This might be due to an anticholinergic effect of levomepromazine. The increased variation in ventilation during challenge after antazoline cannot be explained.

From this study we conclude that levomepromazine 25 mg has a bronchodilating effect when compared to the saline and antazoline 100 mg, but does not change ventilation during bronchial challenge. In doses with equal effect on skin sensitivity to histamine, levomepromazine has a significantly larger effect than antazoline on PC_{20} histamine. Both levomepromazine and antazoline reduce bronchial hyperreactivity compared to saline.

It will, therefore, be of interest to investigate further the bronchodilating and protective effect on bronchial hyperreactivity of levomepromazine in asthmatics.

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La levomepromazine diminue l'hyperréactivité bronchique non spécifique chez les asthmatiques. P. Faurschou, F. Madsen, H. Pals, A. Rosetzsky.

RÉSUMÉ: Chez dix patients atteints d'asthme bronchique, l'on a réalisé un test de provocation à l'histamine, avant et après administration de solution saline et de médicament actif (levomepromazine ou antazoline). Un total de six provocations a été réalisé. L'effet antihistaminique de la levomepromazine (25 mg) s'avère comparable à celui de l'antazoline (100 mg) si on l'évalue à partir de prick-tests cutanés. Le VEMS avant provocation s'avère plus élevé après levomepromazine qu'après antazoline (<0.05), ce qui indique un effet bronchodilatateur direct. Ce calibre accru des voies aériennes au départ pourrait avoir influencé les résultats de la provocation, mais les modifications de la PC_{20} ne sont pas statistiquement en corrélation significative avec les modifications du VEMS. La levomepromazine a augmenté de 2 doublements la PC_{20}, par comparaison à l'antazoline ($p<0.05$). On a observé des variations de la ventilation de deux minutes pendant les provocations au volume courant. Toutefois, on n'a pas observé de variation significative de la ventilation de deux minutes pendant la provocation, lorsque le patient avait reçu préalablement levomepromazine ou antazoline. On conclut que la levomepromazine a non seulement une activité bronchodilatatrice, mais qu'elle réduit également l'hyperréactivité bronchique.

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