

The Journal of
ALLERGY
and
CLINICAL IMMUNOLOGY

VOLUME 52

NUMBER 6

The effects of isoproterenol Mistometer, with recommended use

Stanley Sherbell, M.D., and Harold A. Lyons, M.D. Brooklyn, N. Y.

Isoproterenol as an effective bronchodilator drug has achieved widespread clinical use. In recent years there have been reports of deleterious side effects of this drug with regard to changes in arterial blood gases, cardiovascular effects, and possible unexpected mortality. However, prior reports have not considered the effects of this drug when the dosage and mode of administration are the same as in the clinical situation. This study indicates that the administration of isoproterenol in a standard commercially available device by the method advised for clinical use does result in effective bronchodilation with a mean maximal increase in FEV₁ of 43 per cent and of FVC of 32 per cent as compared to baseline values. Electrocardiographic changes and arrhythmias were not observed. Nor did clinically significant changes in heart rate or blood pressure occur. No statistically significant changes were observed in pH, arterial carbon dioxide tension (PaCO₂), or arterial oxygen tension (PaO₂) during the study. However, analysis of the data with regard to each individual subject did demonstrate a decrease in PaO₂ of possible clinical significance in one of the 10 subjects. This study would suggest that the effects of isoproterenol Mistometer with recommended use provide bronchodilator action without significant subjective or objective negative side effects in the patient with acute asthma.

The use of isoproterenol by aerosol has proved to be an effective bronchodilator drug in the symptomatic patient with bronchial asthma. Symptoms of airway obstruction and objective parameters of ventilatory function can be shown to improve following the administration of aerosolized isoproterenol.^{1, 2} Numerous reports have been published on the effects of this drug on the cardiovascular system and arterial blood gases of the asthmatic patient. However, there is a

From Pulmonary Disease Division, Department of Medicine, State University of New York, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N. Y. 11203.

Supported in part by United States Public Health Service training grant No. HE 11932-03 and Winthrop Laboratories.

Received for publication Aug. 10, 1972.

Reprint requests to: Dr. Harold A. Lyons, State University of New York, 450 Clarkson Ave., Brooklyn, N. Y. 11203.

lack of agreement by all authors on the magnitude, duration, and clinical significance of these side effects.

A decrease in PaO_2 has been reported by several observers³⁻¹² following isoproterenol inhalation in some patients with bronchial asthma. There was, however, a marked variability in the dosage of drug administered, method of administration, and time intervals of observations in these studies. Cardiovascular responses of heart rate and blood pressure have been evaluated by some observers, but again there is a lack of uniformity in the methods employed and the results obtained.^{1, 9, 12, 13}

In the opinion of some authors the production of significant hypoxemia and an increased mortality have been associated with the administration of aerosolized isoproterenol.^{14, 15} The *American Medical Association Drug Evaluations Manual* states: "Palpitation, tachycardia, cardiac arrhythmias and hypotension occur frequently. Excessive inhalation causes refractory bronchial obstruction cardiac enlargement and myocarditis. Rarely sudden death has occurred."¹⁶ Since isoproterenol has a beta adrenergic activity, it might well be expected that excessive or injudicious use of this drug could lead to major side effects. However, because of the apparent clinical value of this drug as a bronchodilator in the acute asthmatic patient, it was thought necessary to evaluate the effects of aerosolized isoproterenol on the asthmatic patient when the drug is administered exactly as advised by the brochure accompanying the drug. It is anticipated that the results obtained by this approach will reflect the changes actually occurring in the clinical situation.

MATERIALS AND METHODS

Subjects

Ten patients with well-documented episodic bronchial asthma by accepted criteria¹⁷ were studied during an acute exacerbation requiring visiting the emergency room or hospitalization at the Kings County Hospital Center. None of the patients had taken any medication for at least three hours prior to the study. All subjects had an initial PaO_2 of less than 85 mm. Hg (range, 64 mm. Hg-84 mm. Hg, mean, 75 mm. Hg). The normal PaO_2 in our laboratory for the age group under consideration is greater than 90 mm. Hg. Two of the patients had an initial PaCO_2 of 41 mm. Hg and 43 mm. Hg, respectively, with the remainder having PaCO_2 of 40 mm. Hg or less (range, 31 mm. Hg-40 mm. Hg, mean, 38 mm. Hg). initial $\text{FEV}_1/\text{FVC} \times 100$ values were all less than 66 per cent (range, 32.2 per cent to 66 per cent, mean, 49 per cent). The patients' ages ranged from 19 through 52 years of age and included 6 men and 4 women.

Procedures

An indwelling 18 gauge Courand needle was placed in a brachial artery approximately 30 minutes before any measurements were made, with the patient maintained in a seated position. Control baseline preisoproterenol determinations were then made, including a 12 lead electrocardiogram, brachial artery blood pressure recordings, determinations of FVC, FEV_{10} , and measurement of PaO_2 and arterial pH.

Following the determination and recording of all control baseline preisoproterenol data, the patient was instructed in the use of standard isoproterenol aerosol inhalant precisely as directed in the brochure accompanying the drug.* Holding the aerosol device in an inverted

*Mistometer, Winthrop Labs., New York, N. Y.

position, a single deep inhalation was followed by 5 seconds of breathholding. The delivered measured dose at the mouthpiece of this aerosol is approximately 125 mcg. of isoproterenol. A second inhalation was carried out one minute later, followed by similar breathholding. This was now considered zero time for the postisoproterenol inhalation study.

Cardiovascular studies

The heart rate and arterial pressure were recorded continuously and measured at baseline, 2 minutes, 4 minutes, 8 minutes, 12 minutes, 20 minutes, and 32 minutes after zero time. The FVC, FEV₁, PaO₂, PaCO₂, and arterial pH were determined at baseline, 5 minutes, 10 minutes, 15 minutes, and 30 minutes after zero time.

A full 12 lead electrocardiogram was taken at baseline and at 32 minutes after zero time. One lead (Lead II) was monitored and continuously recorded through out the study on the electronics for Medicine DR-8 recorder. Brachial artery pressure was monitored by a Satham No. P23BB strain gauge connected to an indwelling 18 gauge Courmand needle and recorded continuously on the Electronics for Medicine Recorder.

Ventilatory tests

Measurements of air flow at the mouth were made with a noseclip and mouthpiece in place through a heated Fleisch pneumotachygraph connected to a Satham P-97 transducer and recorded on the Electronics for Medicine recorder. Electrical integration converted the flow signal to volume and was simultaneously recorded. Calibrations were made before and after each recording. The FEV₁ and FVC were determined from these recordings.

Blood gases

The PaO₂, PaCO₂, and arterial pH were determined in duplicate at baseline, 5 minutes, 10 minutes, 15 minutes, and 30 minutes after zero time on blood collected in glass syringes with the dead space filled with heparin. All blood samples were collected prior to the testing of ventilation at the appropriate time periods. Determinations were not accepted unless the duplicate PaO₂ were within ± 0.5 mm. Hg. The duplicate PaCO₂ were within ± 1 mm. Hg and the duplicate pH were within ± 0.005 units. Blood gases were analyzed on an Instrumentation Laboratory 113-02 analyzer using standard electrodes that were calibrated daily with gases previously analyzed by Scholander microgas analyzer technique. This calibration was further checked using tonometered blood twice weekly.

Subjective responses

The patients were questioned during and following the study as to whether they experienced any untoward side effects, including headache, tremor, dizziness, weakness, flushing of the skin, sweating, or precordial pain.

RESULTS

The changes observed in heart rate and systolic and diastolic blood pressures were not of clinical significance. Two of the patients (6 and 7) exhibited increase of > 10 mm. Hg of both systolic and diastolic arterial pressures (range 16 mm. Hg systolic-11 mm. Hg diastolic). The remainder of the patients demonstrated lesser degrees of change in these parameters. Maximal change in heart rate did not exceed 10 beats per minute other than for Patient 2 who evidenced a maximal decrease of 38 beats per minute.

Review of the continuous electrocardiographic recordings, as well as the full 12 lead electrocardiogram records before and following the study, revealed no evidence of tachyarrhythmia, ectopic beats, or myocardial alterations.

Table I indicates the mean, standard deviation, and p values of the FEV₁ and

TABLE I. Mean, standard deviation, and p values for FEV₁ and FVC at baseline and indicated time intervals

	Baseline	5 minutes	10 minutes	15 minutes	30 minutes
<i>FEV₁ (L.)</i>					
Mean	1.12	1.48	1.46	1.47	1.35
Standard deviation	0.39	0.40	0.46	0.45	0.49
p value		< 0.001	< 0.001	< 0.01	< 0.05
<i>FVC (L.)</i>					
Mean	2.08	2.53	2.56	2.43	2.58
Standard deviation	0.51	0.63	0.72	0.68	0.74
p value		< 0.01	< 0.01	< 0.01	< 0.001

TABLE II. Mean, standard deviation, and p value (mm. Hg) of PaO₂ at baseline and indicated intervals after isoproterenol inhalation

	Baseline	5 minutes	10 minutes	15 minutes	30 minutes
Mean	75.0	74.0	76.0	76.0	77.0
Standard deviation	6.9	6.7	8.7	8.1	8.1
p value		> 0.3	> 0.3	> 0.5	> 0.1

TABLE III. Summary of changes in PaO₂ with regard to magnitude, direction, and duration

Patient	Age	Sex	Decrease PaO ₂ (mm. Hg)	PaO ₂ (mm. Hg)	Time of maximum change (min.)	Remarks
1	46	M	83-73	10	15	Increased to 76 mm. at 30 min.
2	52	M	68-65	3	15	Increased to 67 mm. at 30 min.

Patient	Age	Sex	Increase PaO ₂ (mm. Hg)	PaO ₂ (mm. Hg)	Time of maximum change (min.)	Remarks
3	29	F	82-89	7	15	Decreased to 85 mm. at 30 min.
4	28	M	64-66	2	15	Remained increased at 30 min.
5	23	F	84-90	6	15	Remained increased at 30 min.
6	24	F	70-78	8	30	Remained increased at 30 min.
7	19	M	72-74	2	10	Decreased to 70 mm. at 30 min.
8	25	M	77-81	4	5	Decreased to 78 mm. at 30 min.
9	26	M	79-82	3	10	Remained increased at 30 min.
10	38	F	71-80	9	30	Increased to 75 mm. at 15 min.

the FVC at baseline pre-isoproterenol and at 5 minutes, 10 minutes, 15 minutes, and 30 minutes after isoproterenol inhalations. The p values of FEV₁ ranged < 0.001- < 0.005 and the p values of FVC ranged < 0.001- < 0.01. The p values obtained for the changes in both FEV₁ and FVC are of clear statistical significance.

Fig. 1 charts the change in FEV₁ and FVC for the individual patients. The FEV₁-FEV₁ baseline/FEV₁ baseline × 100 is indicated in the upper portion of the figure. The maximal individual increases of this parameter ranged 7 per cent to 83 per cent, mean, 43 per cent. The lower portion of Fig. 1 indicates the FVC-FVC baseline/FVC baseline × 100 for each of the patients, and the maximal values ranged 12 per cent to 88 per cent, mean, 32 per cent.

Analysis of the results of changes observed in PaO₂, PaCO₂, and pH following the isoproterenol inhalations was without statistical significance. Arterial pH and PaCO₂ values are not listed.

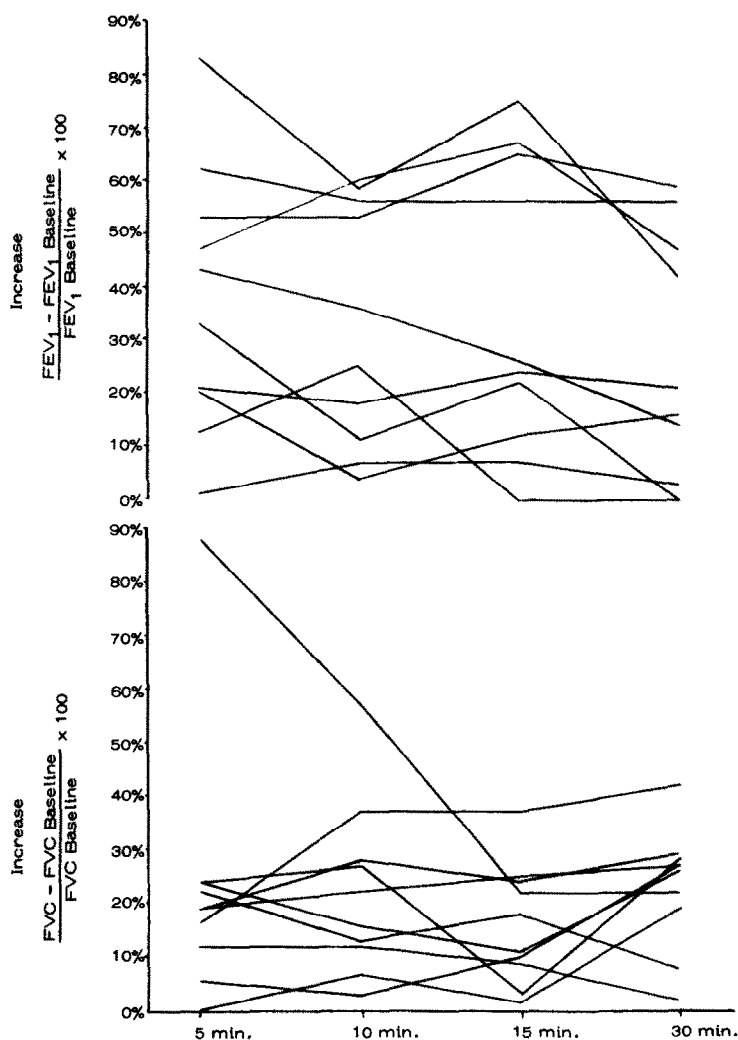


FIG. 1. Increases in FEV_1 and FVC after isoproterenol inhalation at indicated time intervals.

Table II indicates the mean, standard deviation, and p values for the patients at baseline and post-isoproterenol periods with respect to PaO_2 . A summary of the changes in PaO_2 observed in the individual patients is tabulated in Table III. The maximal increase noted in 8 patients in PaO_2 ranged 2 mm. Hg- 9 mm. Hg, mean, 5 mm. Hg. The maximal decreases noted in 2 patients in PaO_2 were 3 mm. Hg and 10 mm. Hg, respectively.

None of the patients experienced side effects of headache, tremor, dizziness, weakness, sweating, flushing, or precordial pain during the study.

DISCUSSION

The administration of isoproterenol by aerosol inhalation is certainly one of the most frequently utilized treatments in patients with acute bronchial asthma. It is generally accepted that this form of therapy is effective both in reducing

symptoms of bronchospasm and in improving objective studies of airway obstruction such as the FEV₁. A number of authors have commented on the changes in blood gases, observed following isoproterenol inhalation in the patient with bronchial asthma.³⁻¹⁰ Most of these studies have stressed the observed decrease in PaO₂ despite improvement in symptoms and frequent objective improvement of bronchial obstruction. Although this apparent paradoxical fall in PaO₂ has been stressed in the literature, most of these reports have documented a variability in blood gas changes with either no change or an increase in PaO₂ in many of the patients studied.³⁻¹⁰ It is difficult to compare these reports because of the lack of homogeneity in the patient populations, the dosage and mode of drug administration, and the time periods of observation of the studies. An attempt to correlate changes in pulmonary function tests and blood gas changes was made by Palmer and Diamant.¹⁸ Improvement in FVC was observed to be associated with an increase in PaO₂ after isoproterenol inhalation. There was, however, no correlation of increased PaO₂ with improvement in FEV₁ unless the FVC also increased. However, Crosbie and his associates¹⁹ demonstrated a correlation between an increase in FEV₁ and increase of PaO₂ following isoproterenol inhalation with a decrease in PaO₂ in patients in whom an increase in FEV₁ did not occur. However, changes in FVC were not reported by these authors. Review of our data with regard to relating changes in FEV₁ or FVC with the observed changes in PaO₂ failed to reveal any such clear correlations. The indicated changes in FEV₁ and FVC values are in agreement with clinical bronchodilator activity previously reported following isoproterenol inhalation.^{1, 2}

Cardiovascular side effects after the inhalation of isoproterenol have been reported.^{1, 9, 12, 13} Isoproterenol has beta-1 adrenergic activity with inotropic and chronotropic properties resulting in tachycardia and potential arrhythmia and systemic blood pressure changes.^{20, 21} However, in the present study no clinically significant changes were observed in pulse rate or arterial blood pressures. No arrhythmias, changes in electrocardiogram pattern, or subjective symptoms of palpitation or precordial pain were recorded.

The present study indicates that the use of aerosolized isoproterenol by the exact method advised for clinical use did not result in adverse cardiac or other side effects in 10 patients during an acute asthmatic attack. Clinically significant bronchodilator activity was observed in all of the patients. Changes in arterial blood gases were not statistically significant for the group. However, considerations of individual patients with regard to PaO₂ indicated a decrease of 10 mm Hg in one patient, which could have clinical significance in a patient with a low initial PaO₂. The drug was administered in a commercially available aerosol unit rather than via multiple nebulizer techniques of varying dosages as in other studies. Observation of potentially deleterious side effects may be expected when a pharmacologically active drug is used without careful control of dosage, method, and frequency of administration of the drug.

Since the number of patients studied is limited, we would not rule out the possibility that individual responsiveness to isoproterenol might produce a varied response in a larger series of patients. In addition, we cannot predict the effects of this drug in a patient with a complex problem such as asthma complicated

by pneumonia or the presence of concomitant independent cardiac pathology. The patients in this study were carefully chosen to represent uncomplicated acute episodic bronchial asthma, and the results obtained are suggested to be an indication of the alterations to be expected in the clinical use of isoproterenol in the asthmatic patient. The need to be cautious in comparing studies is stressed when the patient populations, methods, and materials are not uniform.

REFERENCES

- 1 Mushin, G. J.: Time factor in the measurement of response to bronchodilators, *Thorax* **22**: 538, 1967.
- 2 Altounyan, R. E. C.: Variation of drug action on airway obstruction in man, *Thorax*, **19**: 406, 1964.
- 3 Knudson, R. J., and Constantine, H. P.: An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subject, *J. Appl. Physiol.* **22**: 402, 1967.
- 4 Gazioglu, K., Kaltreider, N. L., and Hyde, R. W.: Effect of isoproterenol on gas exchange during air and oxygen breathing in patients with chronic pulmonary diseases, *Am. Rev. Resp. Dis.* **104**: 188, 1971.
- 5 Waddell, J. A., Emerson, P. A., and Gunstone, R. F.: Hypoxia in bronchial asthma, *Br. Med. J.* **2**: 402, 1967.
- 6 Palmer, K. N. V., and Diamant, M. C.: Effect of aerosol isoprenaline on blood gas tensions in severe bronchial asthma, *Lancet* **2**: 1232, 1967.
- 7 Tai, E., Read, J.: Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma, *Thorax* **22**: 543, 1967.
- 8 Field, G. V.: The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma, *Clin. Sci.* **32**: 279, 1967.
- 9 Palmer, K. M. V., Legge, J. S., Hamilton, W. F. D., and Diamant, M. L.: Comparison of effect of salbutamol and isoprenaline on spirometry and blood gas tensions in bronchial asthma, *Br. Med. J.* **2**: 23, 1970.
- 10 Ingram, R. H., Jr., Krumpe, P. E., Duffell, M., and Maniscalco, B.: Ventilation-perfusion changes after aerosolized isoproterenol in asthma, *Am. Rev. Resp. Dis.* **101**: 364, 1970.
- 11 Palmer, K. N. V., and Diamant, M. L.: Spirometry and blood gas tensions in bronchial asthma and chronic bronchitis, *Lancet* **2**: 383, 1967.
- 12 Pierson, R. N., Jr., and Grieco, M. H.: Isoproterenol aerosol in normal and asthmatic subjects, *Am. Rev. Resp. Dis.* **100**: 533, 1969.
- 13 Warrell, D. A., Robertson, D. G., Howes, J. M., Connolly, M. E., Paterson, J. W., Beilin, L. J., and Dollery, C. T.: Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma, *Br. Med., J.* **1**: 65, 1970.
- 14 Caplin, I., and Haymes, J. T.: Complications of aerosol therapy in asthma, *Ann. Allergy.*, **27**: 65, 1969.
- 15 Eisenstadt, W. S., and Nicholas, S. S.: The adverse effect of adrenergic aerosols in bronchial asthma, *Ann. Allergy*, **27**: 283, 1969.
- 16 A. M. A. Drug evaluations manual, p. 341, 1971.
- 17 American Thoracic Society: Chronic bronchitis, asthma and pulmonary emphysema. A statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases, *Am. Rev. Resp. Dis.*, pp. 85, 762, 1962.
- 18 Palmer, K. N. V., and Diamant, M. L.: Bronchodilators, blood-gas tensions, and spirometry, *Lancet*, **1**: 1972, 1968.
- 19 Crosbie, W. A., Kidner, P. H., Miller, J. N., and Pride, N. B.: Studies on the pulmonary physiological effect of sympathomimetic Amines in bronchial asthma, *J. Asthma Res* **8**: 99, 1971.
- 20 Ferrer, M. I., Enson, Y., Kileoyne, M. M., and Harvey, R. M.: Effects of Isoproterenol on the pulmonary circulation in patients with chronic obstructive lung disease. *Circulation*, **43**: 528, 1971.
- 21 Krasnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B., and Gorlin, R.: Isoproterenol and cardiovascular performance, *Am. J. Med.* **37**: 514, 1964.