Bronchodiolar Therapy: Comparison of Acute Response to Three Methods of Administration*

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Nine men with stable COPD were studied to evaluate any difference in the acute response to aerosol isoproterenol administered by IPPB or by two simpler constant flow nebulizer devices. The responses to isoproterenol of flow rates, airway resistance and diffusion were measured over four consecutive test days. After a control day a different device was used on each subsequent day in a random pattern. All patients showed a beneficial response to bronchodilator in flow rates and airway resistance. No patient had a significant change in diffusion. We concluded that IPPB was no more effective than simpler, and less expensive, constant flow devices in delivering bronchodilator to stable, ambulatory COPD patients.

The administration of aerosol bronchodilator medication has become a widely used method of treatment for obstructive airways disease. The response of the airways to aerosol isoproterenol and other bronchodilator medication has been well documented.1 Various nebulizer devices for producing an aerosol suspension have been designed and the necessity for the use of a nebulizer which produces a particle of one to five micron size has been established.2

The airflow for the nebulizer can be provided by a simple rubber hand bulb, a hand nebulizer unit with Freon propellant, a simple constant flow device without pressure regulation, or an intermittent positive pressure breathing device (IPPB). IPPB is used widely in hospitals and often in the home. Its use at home has been questioned on the grounds that it is more costly than simpler devices and produces a particle of one to five micron size has been established. The work of Cohen and Hale,4 demonstrated no difference in ambulatory patients in response to isoproterenol when administered by IPPB or a Freon propelled aerosol dispenser. Goldberg and Cherniack5 confirmed this for IPPB compared to a hand bulb aerosol dispenser. This is in contrast to the definite advantages of IPPB in acute respiratory insufficiency or in patients who are too weak to utilize any of the hand actuated devices accurately.

The present study was designed to evaluate differences in physiologic response to bronchodilator when given by IPPB, or by two different hand actuated constant flow nebulizer devices. These latter devices were the Hand-E-Vent, and a Devilbiss nebulizer with an air compressor.

Materials and Methods

Nine adult men with a previously well established diagnosis of chronic obstructive airways disease (COPD) were entered into the study. The average age was 54.8 and ranged between 48 and 67 years. The patients met the following criteria: They had a clinical history of at least two years of cough productive of sputum and exertional dyspnea. Physical examination revealed diminished breath sounds throughout the chest. There was physiologic evidence consistent with airway obstruction on the basis of decreased flow rates (MEF25-75) and the maximal mid-flow rate (MMF25-75 percent).

On the basis of the criteria of history, physical examination, and pulmonary function studies, a clinical and laboratory decision was made that chronic obstructive pulmonary disease was present and that heart failure, if present, was secondary to pulmonary disease and not the prime cause of symptoms. Finally, the patient had recovered from any acute episode which may have initiated hospitalization and he was considered a candidate for long-term aerosol bronchodilator therapy. All patients met the criteria for COPD of the American Thoracic Society.6 All patients were stable clinical-
ly at the time of study. They were all outpatients living at home and, if disabled, were not in a debilitated state. Clinical characteristics are given in Table 1.

The study period consisted of four consecutive days of pulmonary function testing during which the studies were performed on an hourly basis. Patients were studied by means of spirometry on a 13.5 liter Collins spirometer. Forced expiratory volume (FEV), forced expiratory volume in one second (FEV1.0), maximum mid flow (MMF25-75percent), and maximal expiratory flow rate (MEFR500-1200) were determined. Normal values for the subjects were based on characteristics means of 27 subjects. Patients were studied by spirometry at the time of study. They were all outpatients living at home and, if disabled, were not in a debilitated state. Clinical characteristics are given in Table 1.

The body airway resistance (Raw) and the volume of thoracic gas (Vtg) were calculated by using the formula Vtg = Raw(VxR). The body plethysmograph was utilized to determine the airway resistance (Raw) and the volume of thoracic gas (Vtg) in the patients. Specific resistance was derived by multiplying the Vtg by the Raw (V x R). Carbon monoxide diffusing capacity (DLco) was determined by the steady state end-tidal sampling method.

No bronchodilator medication was given for at least eight hours prior to testing. The first day of testing was a control day with hourly testing as noted from 9 AM to 1 PM. Second, third, and fourth days were experimental days. Baseline studies were done at 8:20 AM followed by 10 minutes of administration of 0.5 ml isoproterenol diluted with 1.5 ml saline via either a Bird Mark VII IPPB device, a Hand-E-Vent device or a Devilbiss nebulizer No. 40 with a compressor-nebulizer system. When using the flow devices each patient actuated his own nebulizer. The tests were then repeated hourly from 9 AM to 1 PM as on the control day. The sequence of daily use of each of the devices by the patients was randomized. The patient’s subjective symptoms at the outset were recorded and the subjective response to bronchodilator medication. This subjective response to each method of bronchodilator administration was then compared for the various patients.

**RESULTS**

The data was first analyzed for the effectiveness of the bronchodilator therapy on FEV1.0, MEFR, DLco, and specific resistance (VxR) by the method of analysis of variance. The average of the 9 and 10 AM measurement (10 and 70 minutes after bronchodilator) minus the 8:20 measurement (control of initial daily value) was used. The three factors considered were: 1) the individual patients, 2) the order of different days and 3) the device to administer the bronchodilator. The group was inhomogeneous in terms of patient to patient response to bronchodilator assessed by FEV1.0, but the response was significant. p<0.001. On the other hand VxR more uniformly documented improve-

**Table 1—Clinical Characteristics of Patients in Bronchodilator Study**

<table>
<thead>
<tr>
<th>Duration of dyspnea, yr</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>2</td>
</tr>
<tr>
<td>4-9</td>
<td>2</td>
</tr>
<tr>
<td>&gt;9</td>
<td>5</td>
</tr>
<tr>
<td>Cough and sputum</td>
<td>9</td>
</tr>
<tr>
<td>Wheezing</td>
<td>7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 2—Mean Improvement in Patients Using Different Bronchodilators**

<table>
<thead>
<tr>
<th>Method</th>
<th>FEV1.0</th>
<th>MEFR</th>
<th>VxR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devilbiss</td>
<td>0.276</td>
<td>0.657</td>
<td>-11.13</td>
</tr>
<tr>
<td>Bird</td>
<td>0.258</td>
<td>0.571</td>
<td>-12.83</td>
</tr>
<tr>
<td>Hand-E-Vent</td>
<td>0.343</td>
<td>0.884</td>
<td>-12.00</td>
</tr>
</tbody>
</table>

man (F ratio = 7.250 p<0.001) with a decrease in specific resistance over a range from -3.45 to -21.75. The measured FEV1.0 increased over a range of 0.062 liters up to 1.247 liters.

When the order of different days was considered there was a low F ratio with no statistical significance. The three methods of bronchodilator administration were homogeneous regardless of the order of day applied with a low F ratio (statistically insignificant) for FEV1.0, MEFR, VxR, and DLco. When the mean change for all patients was considered for the individual devices, no significant differences could be found (Table 2).

In the subsequent analysis the measurement on the control days was discarded. Only the differences between the before and after treatments as classified by the sequence of the days, and the aerosol devices on various patients were analyzed by the multiple lathe squares method. The results on all

**Figure 1.** The time course of specific resistance (VxR) in patient B1, who demonstrated a good response to bronchodilator. All three methods of treatment are demonstrated, and includes the control day. (C=Control; B=Bird; D=Devilbiss; H=Hand-E-Vent.)
four measurements $FEV_{1.0}$, $MEFR$, $VxR$, and $DLco$, showed that there was no significant difference among either the three devices for delivering the medication or the days on which any one device was used. In fact, despite the huge variations among different patients (significant in all cases except $DLco$), the average improvement after the medication is remarkably close for each of the three devices (Table 2).

All nine patients responded to isoproterenol with at least a 10 percent improvement in specific resistance ($VxR$). Figure 1 depicts the response of specific resistance ($VxR$) in a very responsive patient ($Bi$) for all three devices and the control day. The similarity of results from the Bird, Devilbiss, and Hand-E-Vent is noticeable. Six patients had a 25 percent or better response with all three devices, one with only the Devilbiss and the Bird, one with the Hand-E-Vent and Devilbiss only, and one patient failed to achieve a 25 percent response with any of the three devices. The least responsive patient is illustrated in Figure 2 where the time course of specific resistance ($VxR$) is noted for all three devices and the control day. The responses of each patient in general were greater on days when they started with a higher $VxR$. A response in all patients was noted in both the airway resistance and the $Vtg$ at FRC. This contrasts with the findings of Goldberg and Cherniack\textsuperscript{5} who claimed no significant change in airway resistance unless weighted for $Vtg$ by specific conductance. Our findings are consistent with those of Payne, Chester and Hsi.\textsuperscript{1} The response of other pulmonary function variables was generally similar to that of the $VxR$, but in several patients the response was of lesser magnitude. The duration of response was variable from patient to patient and device to
device, but in most cases lasted from only one to two hours. However, some patients sustained a better than 10 percent response for four to five hours. When the same patient is restudied on a subsequent date with the same bronchodilator, we have observed that the airway responsiveness may vary.1

The pattern of response of the specific resistance for each patient and for the control day is represented in Figure 3. The FEV$_{1.0}$ individual responses is presented in Figure 4. The illustrations show clearly that there was no superiority of one device over any other. They also demonstrate that there was some variation of the initial control values on any given day over the values on the control day. But in most cases, this variation did not approximate the magnitude of changes secondary to isoproterenol. Despite the lack of difference between devices the subjective responses of the patients showed a clear preference for the Bird device. Four patients reported their best response with the Bird device. Another two patients stated their best response was equally with the Bird and the Devilbiss. Two patients believed that the Hand-E-Vent and the Bird were equally effective for producing the best response. One patient stated the Hand-E-Vent response was his best. Despite these subjective feelings there was no confirmation by objective data of a superior response to the Bird. On certain days the patients felt much more congested than on others, and had by far their best response on such days. Yet, they did not rate that as the best day unless they received the Bird.

**Discussion**

This study confirms the impression of others that the method of delivery of bronchodilator makes little immediate difference in stable patients who are able to handle the various devices correctly.3,5,12-15 On the basis of our study, we cannot comment whether these devices differ in efficacy over a prolonged period of use. The work of Cohen and Hale4 and others13,15-17 have indicated that it is the bronchodilator which benefits patients with obstructive airways disease and not the enhanced ventilation produced by IPPB. Feinmann18 has studied the comparison of a hand actuated nebulizer with a constant flow nebulizer and found the hand nebulizer in that particular study slightly better as regards response to bronchodilator effect. The ability of IPPB to enhance ventilation and lower arterial CO$_2$ in patients with severe obstructive disease in times of respiratory failure has been well documented.19 The advantages of IPPB are less apparent in patients such as those in this study who are clinically stable and existing at a level of compensation which allows them to be out of the hospital, up and about in a house, or even actively employed.

Parsons20 has demonstrated no significant redistribution of ventilation to perfusion in normal lungs with IPPB or even with constant positive pressure

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**FIGURE 4.** The response of FEV$_{1.0}$ in all nine patients during a five hour period of observation.

(Hand-E-Vent---; Devilbiss---; Bird---; Control---.)
breathing. Studies of COPD patients by Cohen have demonstrated that the increased ventilation when using IPPB alone is not always apparent and he emphasized that the concurrent use of isoproterenol significantly improved ventilation.

Emmanuel et al, comparing IPPB and voluntary hyperventilation in patients with relatively stable COPD failed to demonstrate significant differences between the two methods of ventilation. These studies support the impression that the major benefit in ambulatory COPD patients is from the bronchodilator and that IPPB provides no added benefit.

The IPPB device demonstrates its most effective use in patients in respiratory failure who require respiratory assistance. In other patients who may not be as ill, but who are too weak to manage the hand actuated devices adequately, IPPB is also beneficial.

Despite the reduction of airway resistance in our study, there is no evidence that the $\Delta_{E0}$ is improved by any of the devices nor by the bronchodilator. This infers that the subjective improvement depends upon a lower resistance to airflow and not upon an increase of gas transport across the lung.

It is of interest that eight of the nine patients reported as good or better response to the Bird than to any other modality of therapy. Possibly some other physiologic test might have indicated an objective basis for this preference. However, in our study, we could document no objective reason for this preference. This would assume a subjective preference for the more elaborate and complicated machinery. The same preference is certainly noticeable among physicians and other personnel involved in inhalation therapy and may well explain the strong preference given the IPPB devices in hospitals and in home therapy. Our findings in this study and the findings of others indicate that the more expensive IPPB device should be reserved for hospital use and those patients incapable of actuating the simpler flow devices because of weakness or any other reason. In our hospital we provide a simple constant flow device for outpatient use when indicated. We try to keep home use of the positive pressure devices to a minimum.

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REFERENCES

New Wrinkle

Columbus found natives smoking tobacco in Y-shaped pipes, one fork of the pipe inserted into each nostril. Cigarettes were first made in Spain in the middle of the 17th century. Some three hundred years later, Ipren et al reported that they observed prevalence of facial wrinkles in female smokers (J Soc Cosmet Chem 16:305, 1965). Confirmatory findings and augmented pertinent information were recorded by Danieli (New Engl J Med 280:1, 1969; Ann Int Med 75:873, 1971). He noted striking association between cigarette smoking and facial wrinkling in BOTH sexes soon after the age of 30 years. The depth, length and number of wrinkles were proportionate to the duration and intensity of smoking, often associated with yellow-gray pallor and absence of flesh-pink coloration of the cheeks. "Wrinkles exhibited by cigarette smokers sometimes differed from those of non-smokers. In the crow's-foot area smokers' wrinkles were narrow, deep, sharply contoured in contrast to the broad-based, more widely open, round-edged wrinkles of non-smokers. These differences were most evident in women. Prominent perioral wrinkles were prevalent among both male and female habitual cigarette smokers." The skin is the largest organ of the body. It constitutes 15 percent of the body weight. The dermis consists of elastic fibrous proteins, elastine and collagen. The latter is synthesized within the cells of the connective tissue and discharged into the intercellular space. Also, the dermis contains small blood vessels, fat cells, loose connective tissues and nerves. Aging of the skin results in wrinkles because of loss of elasticity, reduction in its moisture, in underlying fat and because of retrogressive changes in supportive subcutaneous layers and muscles. As to factors responsible for wrinkles of the skin of cigarette smokers, the following may be considered: 1. Hypoxia of the skin, 2. Impaired utilization of ascorbic acid. Hypoxia of the skin is brought about by vasoconstriction in the skin and by hydrogen cyanide present in cigarette smoke. The term nicotine derives from the name of Jean Nicot, French Ambassador to Portugal, who in 1560 extolled the curative powers of tobacco. During smoking, 22 percent of the nicotine content of cigarettes enters the mouth and about 90 percent of the inhaled nicotine is absorbed. It causes a release of sympathomimetic amines, norepinephrine and epinephrine from various sites, including blood vessel walls and the skin. The resulting peripheral vasoconstriction causes a drop in skin temperature which may be as much as 15°F. Cigarette smoke contains about 3.2 percent CO. Its inhalation is followed by formation of carboxyhemoglobin. The latter may reach levels which reduce the transportation of O2 and its dissociation at tissue level. Hydrogen cyanide, one of the 1,200 components of cigarette smoke, is highly toxic to respiratory enzymes of tissues cells. Smoking interferes with the utilization of ascorbic acid. Deficiency in ascorbic acid hinders formation of collagen significantly. The consequent impairment of extracellular ground substance of the skin might be instrumental in the appearance of smokers' wrinkles. Perhaps it is not boundless optimism to hope that, among laudable serviceable means, repeated emphatic references to this "new wrinkle" may accelerate—by its appeal to human vanity—the success of antismoking endeavors.

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