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Response to Rimiterol and Salbutamol Aerosols Administered by Intermittent Positive-pressure Ventilation

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Summary

The bronchodilator and cardiac effects produced by aerosols of 0.5% salbutamol and 0.5% and 1% rimiterol administered for three minutes in 40% oxygen by intermittent positive-pressure ventilation (I.P.P.V.) were compared in 15 asthmatic patients. Salbutamol and both the concentrations of rimiterol were equipotent in peak bronchodilator effect, but salbutamol had a significantly longer duration of bronchodilator action. There was significantly less increase in heart rate after rimiterol than after salbutamol. Aerosols of 0.5% rimiterol, 0.5% salbutamol, and saline were administered by I.P.P.V. to 10 normal volunteers. There was no difference between the mean heart rates after 0.5% rimiterol and saline but a highly significant increase in mean heart rate was observed after 0.5% salbutamol. It was concluded that 0.5% rimiterol was an effective short-acting bronchodilator drug with little or no cardiac beta₁-adrenergic activity when administered for three minutes by I.P.P.V. in 40% oxygen.

Introduction

Rimiterol—erythro-(3, 4 dihydroxyphenyl (2-piperidyl) methanol hydrobromide—is a member of a new series of sympathomimetic amines, the aryl-2-piperidyl carbinols (Sankey and Whiting, 1972), in which the side chain is cyclized around the alpha-carbon atom to form a piperidyl ring. In-vitro and in-vivo animal studies have shown rimiterol to have a preferential bronchodilator action with less cardiovascular activity than isoprenaline (Laity, 1971; Carney et al., 1971; Bowman and Rodger, 1972; Gailer et al., 1971). Studies

in volunteers and patients with asthma have shown rimiterol and isoprenaline equipotent weight-for-weight as bronchodilators (Turner and Griffin, 1971; Shenfield and Paterson, 1973), but rimiterol has been reported to have less chronotropic action on the heart than isoprenaline, Svedmyr et al., 1972; Griffin et al., 1973) and salbutamol (Phillips et al., 1972).

This investigation was planned to compare the bronchodilator properties and cardiac stimulant effects of rimiterol and salbutamol when administered by intermittent positive-pressure ventilation (I.P.P.V.) using the technique described by Choo-Kang et al. (1970). Since these workers concluded that a 0.5% solution of salbutamol delivered by I.P.P.V. for three minutes provided "maximum bronchodilatation without important tachycardia" the same concentration of salbutamol was used in this study for comparison with rimiterol in 0.5% and 1% solutions.

Patients and Methods

The plan of the trial was similar to that described by Choo-Kang et al. (1970). Fifteen patients received for periods of three minutes on consecutive days aerosols of 0.5% rimiterol, 1% rimiterol, and 0.5% salbutamol and 40% oxygen delivered during each inspiratory cycle by I.P.P.V. from a Bennett ventilator. Patients received one of the treatments on each of three consecutive days. The sequence of drug administration was determined by a latin square experimental design. The identity of the drug and its concentration were unknown to the patient and medical observers. The highest of three readings of forced expiratory volume in one second (FEV₁) from a Gaensler spirometer was recorded at 10 minutes, five minutes, and one minute before treatment and at 5, 15, 30, 60, 120, 180, and 240 minutes after treatment. The heart rate was read from a Hewlett-Packard cardiac monitor immediately before drug administration, at 5-minute intervals for 60 minutes afterwards, and thereafter at hourly intervals for the next three hours. The electrocardiograph was observed for arrhythmias during and for one hour after drug administration.

Ten normal volunteers were also studied in a subsidiary investigation and each received on consecutive days 0.5% rimiterol, 0.5% salbutamol, and saline. The sequence of drug administration was randomized and procedures and measure-

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ments for this investigation were as in the main trial except that the medical observers knew the nature of the nebulized solutions.

The 15 patients included in the main study consisted of 11 men and four women aged 24 to 71 years (mean 48 years). All had chronic asthma. Two were receiving treatment with daily prednisolone, four with daily prednisolone and beclomethasone by inhalation, four with beclomethasone alone, and five were taking only bronchodilator drugs. The mean daily dose of prednisolone for the six patients taking this drug was 11 mg (range 4–20 mg). The eight patients treated with beclomethasone by inhalation were all receiving 400 µg/day. No alterations in the dose of prednisolone or beclomethasone were made for at least five days before the first test day or during the trial, and each patient was instructed not to take any bronchodilator drugs on the mornings of the three test days.

All patients on admission to the study had an FEV₁ of at least 25% below the highest figure recorded in the previous 12 months. If the pretreatment FEV₁ recordings on any of the three days of the investigation differed by more than 10% the patient was not included in the trial to ensure that the pretreatment FEV₁ values were relatively constant for each patient. The mean pretreatment FEV₁ was 1.29 l. (range 0.62–2.85 l). The ten normal volunteers consisted of five men and five women aged 21 to 30 years (mean 23.5 years). None was taking any treatment during the trial period. The mean pretreatment FEV₁ was 4.08 l.

Results

FEV₁

In all 15 patients the FEV₁ rose quickly in the first 15 minutes after administration of each of the three aerosols. After rimiterol the FEV₁ rose steeply in the first hour and then declined rapidly. After salbutamol the FEV₁ rose steeply in the first hour, remained high or even increased slightly during the next hour, and gradually declined in the third and fourth hours (fig. 1).

Statistical analyses showed no significant difference between and FEV₁ levels for the three drugs immediately before drug administration or at five and 15 minutes after. From 30 minutes until 240 minutes, however, the FEV₁ measurements after salbutamol were significantly higher than those after either dose of rimiterol ($P < 0.01$).

FIG. 1—Effect of 0.5% salbutamol and 1% and 0.5% rimiterol on mean FEV₁ in 15 asthmatic patients.

As an indication of “total effect” the area under the FEV₁ curve and above the pretreatment value was calculated for each patient. In every patient salbutamol produced the largest “total effect.” On average the area under the FEV₁ curve and

above the pretreatment baseline for 0.5% salbutamol was more than twice that for either concentration of rimiterol. There was virtually no difference in “total effect” on FEV₁ between 1% and 0.5% rimiterol. In the subsidiary investigation of ten normal volunteers there was no significant change in FEV₁ after 0.5% salbutamol, 0.5% rimiterol, and saline.

HEART RATE

In the 15 asthmatic patients the heart rate fluctuated considerably but there was a clear tendency for 0.5% salbutamol to produce a higher peak effect and a more prolonged increase in heart rate than either concentration of rimiterol (fig. 2). From 15 until 180 minutes after drug administration the differences between salbutamol and 1% rimiterol were statistically significant at the 5% level, as were the differences at all times after five minutes between the mean heart rates after salbutamol and 0.5% rimiterol. The mean heart rate after 1% rimiterol was higher than that after 0.5% rimiterol from five to 60 minutes with the exception of the mean values at 20 minutes, but these differences were not significant except at the five-minute point.

FIG. 2—Effect of 0.5% salbutamol and 1% and 0.5% rimiterol on mean heart rate in 15 asthmatic patients.

FIG. 3—Effect of 0.5% salbutamol and 0.5% rimiterol and saline on mean heart rate in 10 normal subjects.

As an indication of “total effect” the area under the heart rate curve above the pretreatment level was calculated for each patient. There was no difference between 1% and 0.5% rimiterol, but 0.5% salbutamol had a significantly greater

"total effect" than both rimiterol concentrations. ($P < 0.01$). In the subsidiary investigation of 10 control subjects salbutamol produced the highest peak heart rate and the most sustained increase above the pretreatment level (fig. 3). From five until 180 minutes the difference between the mean heart rate after 0.5% salbutamol and 0.5% rimiterol was significant at the 1% level, and from 180 to 240 minutes it was significant at the 5% level.

Discussion

In the main study the improvement in ventilatory function achieved by both solutions of rimiterol and by 0.5% salbutamol was the same though the duration of FEV₁ improvement was much more prolonged with salbutamol. This significantly shorter duration of bronchodilator activity in the case of rimiterol was expected because this drug is rapidly inactivated by catechol-O-methyl transferase whereas salbutamol is not. There was no significant difference between the maximum mean increase in FEV₁ after 0.5% and 1% rimiterol, and the mean duration of the bronchodilator effect of each concentration was virtually identical. For that reason the 0.5% rimiterol solution was chosen for the subsidiary heart rate studies in normal volunteers since the 1% rimiterol solution seemed to have no clinical advantages. Similarly, we propose to discuss and compare the properties of 0.5% rimiterol and 0.5% salbutamol since this concentration of salbutamol delivered by I.P.P.V. has been recommended for the treatment of patients with status asthmaticus (*British Medical Journal*, 1972; Stark, 1972).

The significantly greater increase in heart rate after salbutamol was more prolonged than that after rimiterol, persisting for more than four hours. In contrast, the mild tachycardia after 0.5% rimiterol subsided within 25 minutes, and there was then a slight fall to below the pretreatment level suggesting the initial recordings were not truly basal measurements. Since heart rate is easily influenced by many physical and psychological stimuli it is indeed doubtful whether basal measurements can ever be made in this type of trial; all the patients are aware that they are to be given a new drug and it is thus virtually impossible to prevent some degree of apprehension. The fall in heart rate to below pretreatment level could have been due to an unknown cardiac decelerator effect of rimiterol, and the subsidiary trial in healthy volunteers was designed to test this hypothesis. In these subjects a reduction in mean heart rate below pretreatment level of only four beats per minute was observed after both rimiterol and saline and a cardiac decelerator action of rimiterol can, therefore, be excluded. The increase in mean heart rate in the normal subjects after 0.5% rimiterol was no greater than that recorded after placebo, but there was a highly significant increase in mean heart rate after 0.5% salbutamol and most subjects complained of palpitations and tremor. Larger quantities of drugs administered by I.P.P.V. may be absorbed from normal lungs and this could explain why a more marked degree of tachycardia was produced by salbutamol in normal subjects than in

asthmatics. It could not account, however, for the significantly greater increase in heart rate which was observed after salbutamol than after rimiterol in normal subjects. Since all the asthmatic patients had been receiving regular treatment with salbutamol before the trial development of some degree of tolerance to this drug may be the explanation of the greater degree of tachycardia observed in the normal group. Whatever the explanation, the heart rate responses of the normal volunteers to 0.5% salbutamol and 0.5% rimiterol indicated that rimiterol weight-for-weight has considerably less beta₁-adrenoreceptor stimulant activity than salbutamol.

Choo-Kang *et al.* (1970) decided that 0.5% salbutamol was the optimum concentration for administration by I.P.P.V., but their data indicate that 0.25% salbutamol had only slightly less bronchodilator activity than the 0.5% solution and that the tachycardia induced by the weaker solution was minimal. We therefore propose in a later study to compare the bronchodilator and cardiac stimulant effects of 0.25% salbutamol with those of 0.5% rimiterol. This investigation will also include a comparison of the effects of two doses of the short-acting rimiterol (the second given two hours after the first) with those of a single dose of the long-acting salbutamol.

The results of the preliminary investigations of rimiterol published here indicate that it is an effective short-acting bronchodilator with little or no beta₁-adrenoreceptor stimulant activity when given in a 0.5% solution in 40% oxygen by I.P.P.V. for three minutes. If these findings are confirmed it may well become the bronchodilator drug of choice for use by I.P.P.V. in the treatment of status asthmaticus because in this clinical condition short duration of action is not necessarily a disadvantage but paucity of beta₁-stimulant properties is highly desirable.

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