Archives of Disease in Childhood, 1970, **45**, 766.

Evaluation of the Effects of Isoprenaline and Salbutamol Aerosols on Airways Obstruction and Pulse Rates of Children with Asthma*

G. HAMBLETON and E. A. SHINEBOURNE

From the Department of Paediatrics, St. Thomas's Hospital, London.

Hambleton, G. and Shinebourne, E. (1970). *Archives of Disease in Childhood*, **45**, 766. **Evaluation of the effects of isoprenaline and salbutamol aerosols on the airways obstruction and pulse rates of children with asthma.** Investigation of $FEV_{1\cdot0}$ and pulse rates in 10 asthmatic children who were given inhalations of isoprenaline, salbutamol, and placebo separately showed that both drugs had a similar effect on airways obstruction. Salbutamol has a longer duration of action. Neither drug caused a tachycardia at the dosage used.

Administration of bronchodilators is an established treatment for airways obstruction in children with asthma. Drugs which may be given in this way include isoprenaline, atropine, adrenaline, and orciprenaline. Other than atropine all have sympathomimetic actions and cause β-adrenergic cardiac effects. Salbutamol is a new sympathomimetic agent which has been claimed to have a specific β-adrenergic bronchodilator action and minimal cardiac effects as judged by experiments on cats, dogs, guinea-pigs, and isolated tissues (Hartley *et al.*, 1968; Cullum *et al.*, 1969). These effects have been studied in adults (Kelman, Palmer, and Cross, 1969; Kennedy and Simpson, 1969; Choo-Kang, Simpson, and Grant, 1969; Riding, Chatterjee, and Dinda, 1969; Palmer and Diament, 1969; Warrell *et al.*, 1970). The present study was designed to ascertain in children with asthma (i) whether salbutamol given as aerosol inhalation is an effective bronchodilator; (ii) whether it differs from isoprenaline in effectiveness or duration of action; (iii) whether it differs from isoprenaline in its effect on pulse rate.

The aerosol canisters and dosages used were essentially the same as those generally available, and the respiratory function apparatus used is also commercially available for clinical use.

Received 8 June 1970.

* This paper was originally read at a meeting of the Paediatric Research Society,

† Present address: University of California Medical Center, Cardiovascular Research Institute, School of Medicine San Francisco, California 94122, U.S.A.

Subjects and Methods

Ten children who attended out-patients regularly were selected; their ages ranged from 5 to 13 years. There were 6 girls and 4 boys, all of whom were considered on clinical grounds to be severe or moderately severe asthmatics. They attended on six separate occasions receiving a single inhalation each visit, taking placebo, salbutamol, and isoprenaline on two occasions each. They had no treatment for 24 hours before the experiments were carried out. The trial was double-blind, and the order in which the children received the various drugs was randomly decided. The aerosol canisters were lettered, the results were analysed, and the canisters decoded after the trial was completed.

Respiratory function tests. Measurements were made of forced expiratory volume in 1 second ($FEV_{1\cdot0}$) and the forced vital capacity (FVC) using an Air-Shields Pulmonary Function Recorder. The children rested for 15 minutes and then the three resting values were taken at 15-minute intervals; the aerosol was then given and further measurements made at 5, 10, 60, and 120 minutes. On each occasion 3 values of FVC and $FEV_{1\cdot0}$ were taken.

Each child received a single inhalation from the canister, the doses being as follows: salbutamol 100 μg., and isoprenaline 100 μg.

The placebo contained Arcton 11 and Arcton 12 with a small amount of oleic acid as a surfactant. The children were seated during the investigation and appeared able to co-operate easily.

The mean was obtained of three resting values and all subsequent measurements compared with this mean. For each timed measurement the best of three readings of $FEV_{1\cdot0}$ was taken.

From all children 60 mean resting values of $FEV_{1\cdot0}$, FVC, and $FEV_{1\cdot0}$/FVC ratio were obtained. For comparison of effects on airways obstruction only those occasions when the resting $FEV_{1\cdot0}$/FVC ratios were abnormal are included in the statistical analysis. There were 22 such occasions, the ratios ranging from 34·0% to 67·9%. There were only two ratios over 65%—one of 67·9% and the other of 66·7%. These have been included together with those which were below 65%, the conventional lower limit of normal. Of the 22 abnormal ratios the number of occasions on which the various drugs were subsequently given were:—isoprenaline 9, salbutamol 7, and placebo 6.

Pulse rates. These were measured by palpation of the radial artery for 30 seconds immediately before the respiratory function tests.

Results

Airways obstruction. Table I shows mean resting values of $FEV_{1\cdot0}$/FVC ratio and there is no significant difference between the three groups (Student 't' test).

TABLE I

Resting $FEV_{1\cdot0}$/FVC Ratios† of Groups of Children Included in Analysis of Drug Effects on $FEV_{1\cdot0}$

Mean Resting $FEV_{1\cdot0}$/FVC Ratio (± 1 SD)	Drug Subsequently Given
58·5±10·2	Isoprenaline (n = 9)
55·5±9·5	Placebo (n = 6)
57·0±9·5	Salbutamol (n = 7)

†Selected as being less than 68·0%.

Table II shows the mean percentage changes in $FEV_{1\cdot0}$ compared with resting values and placebo. Placebo had no significant effect. Isoprenaline significantly improved $FEV_{1\cdot0}$ at 5 and 10 minutes, but was no different from placebo at 60 and 120 minutes. Salbutamol significantly improved $FEV_{1\cdot0}$ at all times.

Table III compares the differences between salbutamol and isoprenaline. Isoprenaline and salbutamol were equally effective at 5 and 10 minutes; salbutamol was significantly better than isoprenaline at 60 and 120 minutes.

TABLE III

Significance of Differences Between Salbutamol and Isoprenaline, in Effect on $FEV_{1\cdot0}$

Percentage Improvement in Mean Resting $FEV_{1\cdot0}$ ± 1 SD			
Time (min.)	Isoprenaline (n = 9)	Salbutamol (n = 7)	P
5	24·0±15·8	25·7±11·8	N.S.
10	29·4±16·6	31·3±15·2	N.S.
60	11·8±16·6	32·1±10·8	<0·02
120	3·1±19·5	29·4±12·2	<0·01

Pulse rates. All pulse rates of all children are reported.

Table IV shows mean changes from resting rates. Neither isoprenaline nor salbutamol caused any significant change, and tachycardia was not observed. With the placebo, pulse rates tended to fall and analysis shows this to be statistically significant at 10, 60, and 120 minutes ($p<0\cdot05$ each time) though the mean value of the fall was only 4·5 beats per minute.

Discussion

The results show that aerosol administration of 100 μg. salbutamol produced a useful improvement in reversible airways obstruction which was of the same order as isoprenaline 100 μg., whereas placebo had no significant effect. The duration of action of salbutamol was longer than that of isoprenaline, evidence of the effect being apparent at 2 hours, with little indication of decline. This is probably explained by the fact that salbutamol is absorbed from the gastro-intestinal tract (Warrell *et al.*, 1970) in contrast to isoprenaline. Any portion of the

TABLE II

Mean Percentage Changes ±1 SD from Mean Resting $FEV_{1\cdot0}$

Drug	5 min.	10 min.	60 min.	120 min.
Isoprenaline (n = 9)	24·0±15·8 ($p<0\cdot01$)†	29·4±16·6 ($p<0\cdot001$)	11·8±16·6 (N.S.)	3·1±19·5 (N.S.)
Placebo (n = 6)	−2·9±8·8 (N.S.)	4·8±20·4 (N.S.)	−3·2±11·7 (N.S.)	−12·5±14·0 (N.S.)
Salbutamol (n = 7)	25·7±11·8 ($p<0\cdot01$)	31·3±15·2 ($p<0\cdot01$)	32·1±10·8 ($p<0\cdot001$)	29·4±12·2 ($p<0\cdot001$)

† p values calculated from Student 't' test.

TABLE IV

Pulse Rates per Minute, Means of All Children ±1SD

Drug	Resting n = 60	5 min. n = 20	10 min. n = 20	60 min. n = 20	120 min. n = 20
Placebo	94·63±10·27	90·9±11·58	91·0±9·85	91·9±7·78	91·2±7·96
Isoprenaline	95·50±10·27	95·0±7·94	93·8±10·18	91·6±9·59	94·1±11·02
Salbutamol	97·43±9·45	97·0±7·99	95·1±8·31	92·1±8·28	94·1±8·28

salbutamol which is not inhaled will usually be swallowed and thus still be capable of exerting an effect. In addition, salbutamol is relatively resistant to metabolic breakdown or inactivation, significant quantities being excreted unchanged in the urine after inhalation (Kennedy and Simpson, 1969). The prolonged action of salbutamol has been shown in adults, where effects up to 5 hours have been observed (Riding *et al.*, 1969; Choo-Kang *et al.*, 1969).

No tachycardia was observed with either salbutamol or isoprenaline at this dosage, even at 5 minutes. Studies in adults have shown the effect on pulse to be evident at this time for isoprenaline (Choo-Kang *et al.*, 1969; Kelman *et al.*, 1969). It is probable that in the children reported here insufficient quantities of either drug had been given to cause tachycardia. There is no evidence in man that bronchodilatation occurs with lower circulating levels of isoprenaline than are required to produce tachycardia, and the marked bronchodilatation found in our patients is presumptive evidence of adequate drug absorption. However, the response to isoprenaline is known to be extremely variable and what appears a more likely explanation is that, in children, especially during attacks of bronchospasm, the heart rate is so labile that the naturally occurring variations in rate are as great as those occurring after a sympathomimetic agent. It is thus reasonable to conclude that in children at doses of 100 μg. isoprenaline and salbutamol do not cause tachycardia, but nevertheless produce clinically useful improvement in airways obstruction.

Our conclusions are that salbutamol is to be preferred to isoprenaline because of its longer duration of action. In asthmatic children when isoprenaline and salbutamol were administered in the standard aerosol dosage, no tachycardia was demonstrated.

We wish to thank Drs. B. D. R. Wilson and D. G. Cottom for permission to investigate their patients. The Pulmonary Function Recorder was kindly loaned by Messrs. Air-Shields, Inc.; the pressurized aerosols were prepared by Messrs. Allen and Hanburys, Ltd., Miss Angela Brinton gave assistance which is much appreciated. Professor W. I. Cranston gave advice.

REFERENCES

Choo-Kang, Y. F. J., Simpson, W. T., and Grant, I. W. B. (1969). Controlled comparison of the bronchodilator effects of three B-adrenergic stimulant drugs administered by inhalation to patients with asthama. *British Medical Journal*, **2**, 287.

Cullum, Valerie, A., Farmer, J. B., Jack, D., Levy, G. P. (1969). Salbutamol: a new, selective β-adrenoceptive receptor stimulant. *British Journal of Pharmacology*, **35**, 141.

Hartley, D., Jack, D., Lunts, L. H. C., and Ritchie, A. C. (1968). New class of selective stimulants of β-adrenergic receptors. *Nature* (London), **219**, 861.

Kelman, G. R., Palmer, K. N. V., and Cross, M. R. (1969). Cardiovascular effects of AH.3365 (Salbutamol). *Nature* (London), **221**, 1251.

Kennedy, M. C. S. and Simpson, W. T. (1969). Human pharmacological and clinical studies on Salbutamol: a specific β-adrenergic bronchodilator. *British Journal of Diseases of the Chest*, **63**, 165.

Palmer, K. N. V. and Diament, M. L. (1969). Effect of Salbutamol on spirometry and blood-gas tensions in bronchial asthma. *British Medical Journal.*, **1**, 31.

Riding, W. D., Chatterjee, S. S., and Dinda, P. (1969). Clinical trial of a new β-adrenergic stimulant in asthma. *British Journal of Clinical Practice*, **23**, 217.

Warrell, D. A., Roberson, D. G., Newton Howes, J., Conolly, M. E., Paterson, J. W., Beilin, L. J., and Dollery, C. T. (1970). Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. *British Medical Journal*, **1**, 65.

Correspondence to Dr. G. Hambleton, St. Thomas' Hospital, London S.E.1.