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## THE BRONCHODILATOR EFFECT OF A NEW ADRENERGIC AEROSOL —SALMEFAMOL—

By

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Since *Barger & Dale* (1) described the chemical structure and sympathomimetic action of adrenaline-like amines, adrenaline and adrenergic drugs have been extensively used for the treatment of asthma. Adrenaline itself is active only when it is given parenterally or by inhalation, whereas the more recently introduced synthetic agents are more stable and can be given by inhalation or in tablet form.

In recent years inhalation therapy has become more practical as a result of technical advances in the administration of dry fine particulate aerosols, which are stored under pressure in small cartridges and delivered in metered doses. The short term bronchodilator effect of Isoprenaline with its undesirable cardio-vascular effects is well documented, as is the longer sustained bronchodilator effect of Orciprenaline and Salbutamol (1, 4, 5). The purpose of this presentation is twofold: (1) to present data concerning the efficacy of a new preparation termed Salmefamol\*, and (2) to compare the effect of this drug with other adrenergic agents already in use.

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\* Developed by Glaxo Laboratories Ltd.

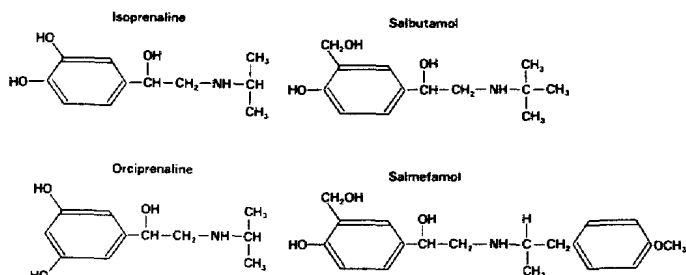


Fig. 1.

The formulae of Isoprenaline, Orciprenaline, Salbutamol and Salmefamol.

### Chemistry

Salmefamol is chemically related to Isoprenaline and Orciprenaline but more closely to Salbutamol. The structural formulae of these four compounds are shown in Fig. 1. The substitution of the meta-OH of Isoprenaline by a primary alcohol prevents inactivation by catechol-O-methyl transferase. The substitution of the N-isopropyl group of Isoprenaline makes inactivation by N-dealkylation unlikely.

### PATIENTS AND METHODS

Ten asthmatic individuals were chosen for investigation. From previous studies, all these patients were known to have a fairly consistent response to aerosol adrenaline or adrenergic drugs by inhalation. Objective physiological measures were made on the patients before and at regular intervals after the inhalation of Salmefamol over a period of four hours. After this time an inhalation of adrenaline hydrochloride 1/1000 was administered by means of a Collison inhaler and the final measurement was recorded ten minutes later. The Salmefamol was delivered as a metered aerosol from canisters designed to deliver 50  $\mu$ g per puff. The response of patients to 100  $\mu$ g Salmefamol and at a later date to 200  $\mu$ g Salmefamol was recorded.

Similar investigations were also carried out to assess the effect of inert inhalant (placebo), Orciprenaline, and Salbutamol on the ten patients.

The physiological measure used for this investigation was the Indirect Maximum Breathing Capacity expressed in litres per minute (I.M.B.C. as described by Kennedy (3). Special records were kept of any untoward symptoms and also the pulse rate, blood pressure, the achilles reflex time, and samples of

the patient's signature throughout the period of observation to detect evidence of tremor.

## RESULTS

The overall picture of the response of the ten patients to the different drugs under trial was obtained by plotting the average IMBC values as a percentage change of the pre-treatment values. Fig. 2 shows the changes following the administration of both 100  $\mu\text{g}$  and 200  $\mu\text{g}$  Salmefamol. After 100  $\mu\text{g}$  there is a good early response reaching a peak at some thirty minutes and this is well maintained throughout the rest of the period of observation, i.e. up to 240 minutes or four hours. There is a further response following the administration of wet aerosol adrenaline at 240 minutes. From this and other

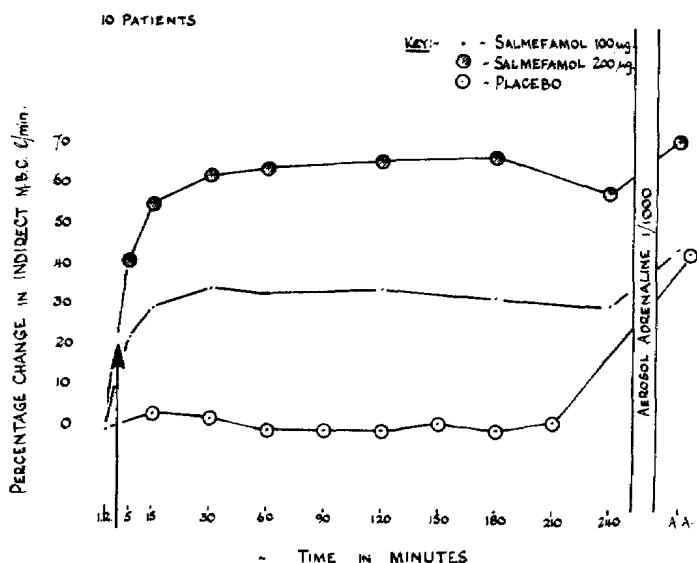


Fig. 2.

The mean time response curves following the inhalation of 100  $\mu\text{g}$  Salmefamol, 200  $\mu\text{g}$  Salmefamol, and placebo—10 patients.

observations it was clear that the response to 100  $\mu\text{g}$  Salmefamol was not the maximal response of these patients.

Consequently, further trials were carried out using 200  $\mu\text{g}$  and the response to this dosage was nearly double that of the smaller dosage. On the higher dosage the peak occurs at 180 minutes and the response is still maintained at 240 minutes and there is very little difference between the peak response and the response which occurs following the further inhalation of wet aerosol adrenaline.

Neither the 100  $\mu\text{g}$  nor the 200  $\mu\text{g}$  of Salmefamol was associated with any side-effects. There was no evidence of tachycardia, no blood pressure change and no evidence of tremor.

In Fig. 3 the mean time response curves of ten patients following 200  $\mu\text{g}$  of Salmefamol, 200  $\mu\text{g}$  Salbutamol, and

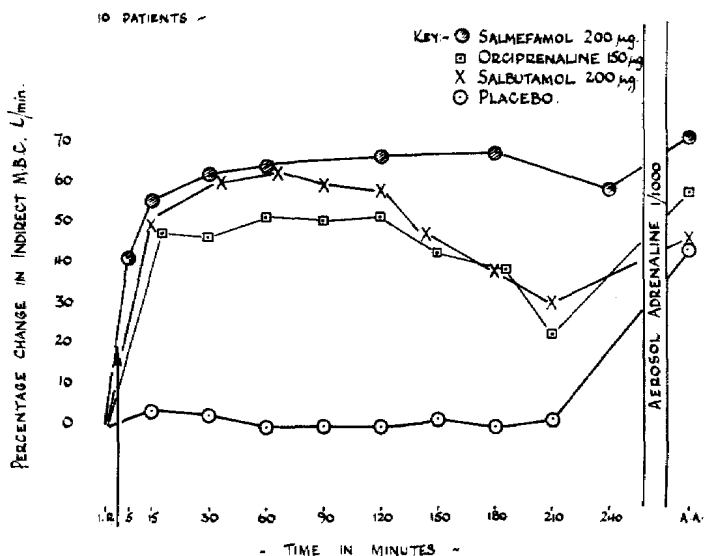


Fig. 3.

The time response curves following the inhalation of 200  $\mu\text{g}$  Salmefamol, 150  $\mu\text{g}$  Orciprenaline, 200  $\mu\text{g}$  Salbutamol, and placebo—10 patients.

150  $\mu$ g Orciprenaline is given. The response over the first sixty minutes after the inhalation of these three aerosols is similar. Salmefamol is marginally better than Salbutamol, which is better than Orciprenaline. By 150 minutes, however, the effect of both Orciprenaline and Salbutamol is beginning to wane and continues to wane until the end of the period of observation at 210 minutes. On the other hand, the effect of Salmefamol is fully sustained up to 180 minutes and shows only a slight deterioration at 240 minutes.

### CONCLUSIONS

In conclusion, one can say that this new adrenergic agent Salmefamol is a potent bronchodilator. The chemistry and pharmacological effects of this drug are similar to Salbutamol. Both drugs given by aerosol at a dose level of 200  $\mu$ g result in near-maximal bronchodilation, i.e. the maximal bronchodilation that can be achieved by adrenergic therapy. However, the response from Salmefamol is better maintained and there is still near-maximal response some four hours after the inhalation. 200  $\mu$ g Salmefamol is not associated with any side-effects, there is no tachycardia, no change in the blood pressure and no evidence of tremor. From these observations it appears that Salmefamol, like Salbutamol, is a beta-adrenergic stimulant which appears to be selective for  $B_2$  receptors.

### REFERENCES

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