Ventilatory effects of aerosol gentamicin

M. B. DALLY, S. KURRLE, AND A. B. X. BRESLIN

From the Respiratory Unit, Concord Hospital, Concord, New South Wales, 2139, Australia

Dally, M. B., Kurrle, S., and Breslin, A. B. X. (1978). *Thorax*, **33**, 54–56. **Ventilatory effects of aerosol gentamicin.** Bronchial provocation tests with gentamicin solution, 40 mg/ml, and with the drug vehicle solution alone were carried out in 29 subjects aged 19 to 66 years. There were 18 subjects with bronchial asthma, four with chronic bronchitis, four with primary carcinoma of the lung, and three with no chest disease. Two millilitres of each of the two test solutions was given to each subject, in duplicate, via a nebuliser driven by a Bird Mark 8 respirator. Ventilatory function (FEV_1 and VC) was measured before and after each inhalation, and changes were expressed as percentage variations from baseline.

Seven subjects, all from the asthmatic group, developed at least one immediate FEV_1 fall of 20% or more. The reactions ranged up to 71% and occurred to both test solutions. There was a trend towards greater reactions to the vehicle. In two subjects pretreatment with salbutamol and sodium cromoglycate did not modify these reactions. In three of the seven, inhalation of 2 ml normal saline produced FEV_1 falls of 25% to 30%, but these falls were not as great as each subject's reactions to the test solutions. Skin prick tests using the gentamicin solution were negative in all subjects. These results show that substantial obstructive reactions may occur in some asthmatic subjects after inhalation of gentamicin. The reactions appear to be non-immunological in nature and may be due to an irritant effect of the drug vehicle.

The administration of antimicrobial agents by aerosol inhalation has been recommended in the treatment of certain bronchial infections caused by Gram-negative bacteria (Burns, 1973; Pines *et al.*, 1970). Immediate airways obstruction accompanying polymyxin inhalation has been reported by Dickie and de Groot (1973). This may be due to the induction of local histamine release, as polymyxin has been shown to release histamine in the skin (Halpern, 1965). The aminoglycoside, gentamicin, is sometimes used by inhalation for the treatment of bronchial infections, and episodes of immediate airways obstruction accompanying such therapy have been observed by us in a few patients. There are no reports of such reactions to this agent, and the purpose of this study was to assess the effects of gentamicin inhalation on ventilatory function in a variety of subjects.

Material and methods

Twenty-nine subjects aged 19 to 66 years were included in the study. There were 24 men and five women. Eighteen of the total had bronchial asthma, four had chronic bronchitis and chronic airways obstruction, four had primary carcinoma of the lung, and three had no chest disease. Sub-

jects were studied while in an interval state, and written informed consent was obtained before the test procedures. Antihistamines and sodium cromoglycate were discontinued 72 hours before the test procedures, and xanthine and sympathomimetic bronchodilators were discontinued 24 hours beforehand. One asthmatic subject had been receiving maintenance oral and inhaled corticosteroids and these were continued unchanged throughout the study. None of the subjects had had prior exposure to gentamicin.

All subjects underwent skin prick testing and bronchial provocation testing. Skin prick testing was performed using 23 common allergens (Bencard) and the gentamicin solution described below. Provocation testing was initially carried out with a gentamicin solution and, separately, with the same solution without the dissolved gentamicin (hereafter referred to as the 'vehicle'). The vehicle was an aqueous solution containing methylparaben, 1·8 mg/ml, propylparaben, 0·2 mg/ml, EDTA, 0·1 mg/ml, and sodium metabisulphite, 2·928 mg/ml. The gentamicin solution (Garamycin Injection, Schering Corporation, USA) contained 40 mg of gentamicin sulphate per millilitre of vehicle solution. Bronchial provocation testing was performed in each subject on

four separate occasions, twice with 2 ml of the gentamicin solution and twice with 2 ml of the vehicle solution. The order of administration of the test solutions was determined by a double-blind, randomised, balanced design. The solutions were administered from a jet nebuliser (Med-Econ 002205), stated to produce a majority of particles of size less than 5 μm. The nebuliser was driven by a Bird Mark 8 respirator using the same settings for each subject. The end-point for each inhalation was taken as the development of symptomatic airways obstruction, consumption of the test solution, or completion of 10 minutes' inhalation, whichever came first. In each subject, bronchial provocations were performed at least 5 hours apart and not more than two tests were carried out on any one day.

Forced expiratory volume in one second (FEV_1) and vital capacity (VC) were measured with a dry wedge spirometer (Vitalograph), and the better of two attempts on each occasion was recorded. Before each provocation test spirometry was measured at five-minute intervals for 15 minutes, and the readings were averaged to provide baseline values. Before any subsequent provocation tests could proceed, each subject's FEV_1 baseline on that day was required to be within ±20% of the values recorded on previous test days. After administration of a test solution, spirometry was measured at 0, 3, 6, 10, 15, 20, 30, 45, and 60 minutes. If a fall in FEV_1 of 20% or more of baseline occurred in any of the four bronchial provocation tests, a further separate provocation test was performed using 2 ml normal saline to assess non-specific bronchial reactivity.

The effects of pretreatment with salbutamol and sodium cromoglycate (SCG) were assessed. Two further provocation tests with gentamicin solution were performed in each of two subjects who had developed FEV_1 falls of greater than 20% in response to the original test solutions. Salbutamol metered aerosol, 200 μg, and SCG, 20 mg, were used separately as pretreatment, and each was given 30 minutes before administration of gentamicin.

Results

SKIN PRICK TESTS
Multiple immediate positive reactions to common allergens were seen in all the asthmatic subjects, in two of those with chronic bronchitis, in one with carcinoma, and in two with no chest disease. There were no skin reactions to the gentamicin solution.

BRONCHIAL PROVOCATION TESTS
Seven subjects, all from the asthmatic group, developed immediate falls in FEV_1 of 20% or more on at least one occasion after bronchial provocation. The falls ranged from 20% to 71%, as shown in the Table. Reactions occurred to both solutions, and there was a trend towards greater reactions to the vehicle. In response to the saline inhalation, three of the seven developed FEV_1 falls of 27%, 28%, and 29%. Five of the seven, including the subject receiving maintenance corticosteroids, had airways obstruction before testing, compared with only four of the remaining 11 asthmatics. The patterns of the FEV_1 falls in the seven were similar, and Fig. 1 provides an example. Pretreatment with inhaled salbutamol and SCG did not prevent FEV_1 falls, and the reactions were similar to those seen without pretreatment (Figs 2 and 3). Salbutamol, 200 μg, given during an obstructive reaction did, however, accelerate the return of FEV_1 to baseline (Fig. 3).

Discussion

The results of this study show that substantial obstructive reactions can occur in some asthmatic subjects after inhalation of aerosol gentamicin. Asthmatics who had airways obstruction before bronchial provocation were more prone to react. All the reactive asthmatics were atopic, so that any contribution by atopy to the reactions is undetermined. The failure to prevent reactions with sodium cromoglycate, the negative skin tests to the gentamicin solution, and the lack of previous contact with the drug suggest that the reac-

Table *FEV₁ falls according to material inhaled*

	Gentamicin		Vehicle		
Subject	First occasion	Second occasion	First occasion	Second occasion	Saline
9	1·44–1·40 (3)	1·56–1·25 (20)	1·43–1·05 (30)	1·75–0·70 (60)	1·90–1·70 (11)
14	2·54–2·75 (0)	2·41–2·05 (15)	2·44–1·90 (21)	2·60–2·25 (14)	2·39–2·20 (8)
15	2·40–1·45 (42)	2·14–1·05 (51)	2·54–0·85 (67)	2·89–0·85 (71)	2·55–1·80 (29)
21	3·56–3·00 (16)	3·50–3·00 (14)	3·50–2·90 (17)	3·56–2·40 (33)	3·53–3·20 (7)
23	1·43–0·70 (51)	1·70–1·30 (24)	1·28–0·60 (53)	1·40–0·50 (64)	1·48–1·20 (19)
24	1·95–1·10 (44)	2·50–1·60 (36)	2·74–1·80 (34)	2·73–1·28 (53)	2·63–1·90 (28)
29	2·80–2·50 (11)	2·50–1·20 (52)	2·60–2·50 (4)	2·60–1·80 (27)	2·63–1·90 (27)

The first value is the baseline reading and the second value is the lowest reading obtained after provocation. The percentage falls are in parentheses.
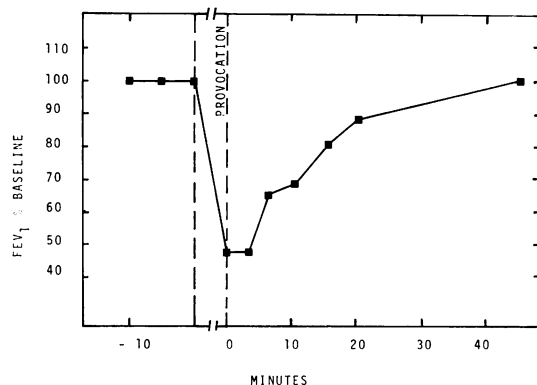
Fig. 1   *Subject 29. Reaction in response to inhalation of 2 ml gentamicin solution over eight minutes.*
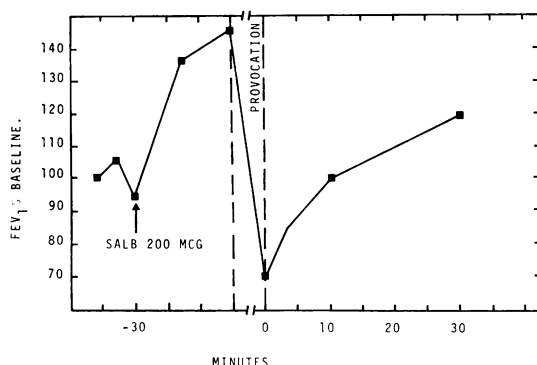

Fig. 2   *Subject 23. Reaction, after pretreatment with 200 µg salbutamol, in response to inhalation of gentamicin solution for three minutes.*
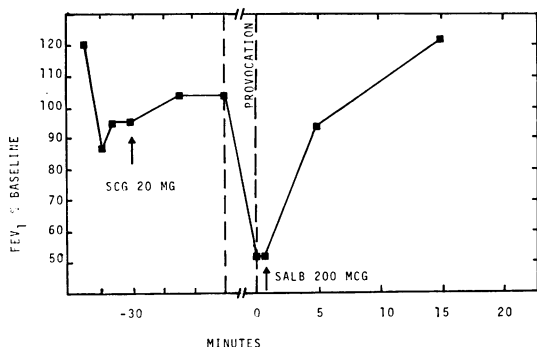

Fig. 3   *Subject 15. Reaction, after pretreatment with 20 mg SCG in response to inhalation of gentamicin solution for two minutes. Reaction terminated with 200 µg salbutamol.*

tions are not due to immunological mechanisms. The negative skin prick tests also indicate that this gentamicin solution does not induce histamine release, at least in the skin. Although there were no significant reactions in the chronic bronchitic subjects, the numbers are too small to allow conclusions to be reached. It is possible that reactions may occur in chronic bronchitic subjects who have significant variability in airways obstruction. The failure of salbutamol pretreatment to prevent reactions partially or completely appears inconsistent with that drug's ability to hasten resolution of a reaction once it has occurred. The explanation for these observations cannot be given from the data obtained in this study.

The pattern of the results suggests that the vehicle, and not gentamicin itself, is the cause of the reactions. Of the four vehicle constituents, the antioxidant sodium metabisulphite seems most likely to produce irritation of airways. If the mechanism of airways obstruction is bronchial irritation, there are differences from that produced by saline in this study. It is possible that the additional effect of the drug is related to the production of a local inflammatory response causing either local mediator release or stimulation of vagal afferents. Further study of the effect of pretreatment with atropine would be of interest.

References

Burns, M. W. (1973). Significance of *Pseudomonas aeruginosa* in sputum. *British Medical Journal*, **3,** 382.

Dickie, K. J., and de Groot, W. J. (1973). Ventilatory effects of aerosolized kanamycin and polymyxin. *Chest*, **63,** 694–697.

Halpern, G. M. (1965). A propos des propriétés histamino-liberatrices de la colistine. *Revue Française d'Allergie*, **5,** 233–240.

Pines, A., Raafat, H., Siddiqui, G. M., and Greenfield, J. S. B. (1970). Treatment of severe pseudomonas infections of the bronchi. *British Medical Journal*, **1,** 663–665.

Requests for reprints to: Dr. A. B. X. Breslin, Respiratory Unit, Concord Hospital, Concord, NSW 2139, Australia.