Mathé *et al.* (1968) prolonged the periods of remission in patients with acute leukaemia, using B.C.G. Burdick and Hawk looked for autoantibodies in the serum of their patient after successful treatment, but failed to show any cytotoxic activity of the serum *in vitro*. This is not surprising, since they used isologous (not autologous) melanoma cells, and, as Lewis *et al.* (1969) showed, cytotoxic antibodies directed against the surface antigens of malignant melanoma cells are specific for each individual tumour; cross-reactions do not occur with cells from other patients.

Another possibility is that the inflammation caused by the virus might allow cytotoxic autoantibodies or cytotoxic lymphocytes to come into better contact with tumour cells. Lewis *et al.* (1969) showed that most patients with localized melanoma possess cytotoxic autoantibodies. It would thus be of interest to know the immunological status of patients treated with vaccinia, and further work to test these hypotheses is being carried out by one of us (I. H.-C.) in a collaborative effort with the Chester Beatty Research Institute. It is hoped that this will be the subject of a subsequent report.

At present direct inoculation of tumour deposits offers a safe and simple method of control of locally advanced malignant melanoma, particularly when the disease is intradermally situated. The remissions so far achieved compare favourably with those seen following regional cytotoxic therapy or irradiation. With regard to the possibility of vaccination for early potentially curable disease, we consider it unwise to depart from the orthodox surgical approach on present evidence, for the following reason: local recurrence

after excision is in some instances due to failure to remove adjacent invisible satellite foci. The response to vaccination, in our experience and in most recorded instances, is strictly localized to the site of inoculation, and such satellite foci might well escape treatment, with adverse effect on the course of the disease.

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Comparison of the Effect of Alprenolol and Propranolol on Specific Airway Conductance in Asthmatic Subjects

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Summary: Alprenolol did not cause a significant fall in the mean of the specific airway conductance in nine asthmatic subjects who did show a significant fall with propranolol. Thus alprenolol is not contraindicated in asthmatic subjects, though it should be used with caution intravenously, as one subject showed a substantial fall in airway conductance at three minutes which recovered within 30 minutes. Until further studies are completed these results should not be applied to bronchitics with increased airway resistance.

Introduction

Drugs which block beta-adrenergic receptors are contraindicated in asthma. The resting endogenous beta-adrenergic activity, which may be considerable even in remission, is counteracted. This produces a rise in airway resistance (Richardson and Sterling (1969). Alprenolol (1-(2-allylphenoxy)-3-isopropylamino-2-propanol) blocks beta-adrenergic receptors but also stimulates them (Åblad, 1967; Åblad, Brogård, and Ek, 1967). This modifies its haemodynamic effects and the resting cardiac output remains unaltered after intravenous injection (Forsberg and Johnsson,

1967). The net effect of the dual action of alprenolol on bronchial calibre in asthma is probably small (Beumer, 1968). We have compared alprenolol and propranolol in a double-blind study.

Subjects and Methods

Nine subjects with mild to moderate asthma, unchanged for three months, were studied. No aerosols (including cigarette smoke) were allowed on the day of the test. Therapy was otherwise unchanged. Informed consent for these studies was obtained in every case.

A solution of 10 mg. of alprenolol in 10 ml. of water and a similar preparation of propranolol were provided in identical numbered phials. The solution was administered intravenously. Each drug was given to the subjects in a random order, unknown to the patient and the observer. The interval between experiments was from 6 to 15 days. Airway resistance (Raw) and thoracic volumes (Vtg) were measured in the body plethysmograph. Readings were made direct from the oscillograph. They were checked in most cases with a photographic record, which gave similar results. Three separate estimations were made at each time. Readings were made at 15-minute intervals for half an hour before and one hour after injection. Additional readings were taken at three minutes (the

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earliest practicable time) and 120 minutes after injection. Specific airway conductance (SGaw) was calculated from the formula:

$$SGaw = \frac{1}{R_{aw}} \times \frac{1}{V_{tg}}$$

Results were recorded as a percentage of the mean of the control SGaw.

Results

The resting SGaw confirmed the mild nature of the asthma, the range being 0.071 to 0.42 (normal SGaw is >0.11) (see Table). The changes in SGaw after injection are also given in the Table. The average fall after propranolol (18%) was significant ($P < 0.001$), while the fall after alprenolol (1.5%) was not significant. The fall in mean SGaw at each time after injection was significantly greater with propranolol than with alprenolol (t test on each pair, $P < 0.05$). The mean readings are plotted in the Chart. After injection the 95% confidence interval contains the baseline at all times with alprenolol, but is always below it with propranolol. Subjective changes with both drugs were small and no patient was distressed.

Discussion

Alprenolol has a stimulatory as well as a blocking effect on beta-adrenergic receptors. This may account for reduced bronchoconstriction, which we have shown in man. It does, however, have therapeutic effects similar to propranolol in subjects with angina and arrhythmias (Arstila, Iisalo and Kallio, 1969; Anthony, Jick, and Spodick, 1969; Ikram, 1970). Its effect on blood pressure is not yet fully evaluated.

These results suggest that alprenolol is safer than propranolol in asthmatic subjects. Nevertheless, intravenous alprenolol should be used with caution in severe asthmatics. Though the mean fall in SGaw was only 9% three minutes after the injection of alprenolol, in Subject 5 there was a fall of 33% at that time. He had completely recovered within 30 minutes. It is uncertain whether the further fall seen in Subject 7 at 30 minutes was spontaneous or due to alprenolol.

Effect on SGaw of the intravenous injection of 10 mg. of propranolol O—O and alprenolol ●—●. 95% confidence intervals are shown.

We would therefore suggest careful observations on asthmatic subjects for at least one hour after injection.

As beta-blocking drugs are often effective in the treatment of symptoms of ischaemic heart disease in the elderly, the question of their use arises more frequently in chronic bronchitis than in asthma. We do not, however, consider it safe to apply our results to subjects with chronic bronchitis, and are at present undertaking further studies with both drugs.

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Change in SGaw, Expressed as a Percentage of a Mean of the Control Reading, after Injection of Alprenolol and Propranolol

Subject:				1		2		3		4		5		6		7		8		9	
Drug:				P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.
Resting SGaw:				0.42	0.23	0.098	0.071	0.100	0.071	0.103	0.083	0.113	0.138	0.091	0.088	0.141	0.127	0.089	0.094	0.098	0.129
Time:																					
3 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
15 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
30 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
45 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
60 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
120 min.				..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

P. = Propranolol. A. = Alprenolol.