Role of histamine release in hypertonic saline induced bronchoconstriction

In a recent study Dr O'Hickey and his colleagues (August 1989;44:650-3) investigated the inhibitory effect of terfenadine on hypertonic saline induced bronchoconstriction in asthmatic subjects. Terfenadine was administered in two doses of 120 mg 4 hours and two hours before challenge with hypertonic saline, and gave significant protection against this stimulus, displacing the geometric mean PD50, PEV2, from 22 to 56 l drawn from the ultrasonic nebuliser.

The authors concluded that airway histamine release was only one of several mechanisms mediating the bronchoconstrictor response to hypertonic saline, because of the substantial inter-subject variation in the inhibitory effect of terfenadine in their study. This apparent heterogeneity may be due, among other factors, to an inadequate dose of terfenadine. Previous work, by Hopp et al, showed that when terfenadine was administered four hours before bronchial challenge with ultrasonically nebulised distilled water a drug dose of 240 mg gave better protection than that afforded by 120 mg. A recent study using a dose of 180 mg terfenadine administered three hours before hypertonic saline challenge showed a geometric mean increase of PD50, by a factor of 7.2, somewhat greater than the 2.5 fold shift reported by Dr O'Hickey and colleagues. It may be supposed that if airway mast cell degranulation a histamine concentration gradient exists, being highest close to the discharging cell, so that local histamine concentrations are higher than those encountered during inhaled histamine challenge. Thus doses of a competitive antihistamine apparently effective against inhaled histamine may be insufficient to overcome high local histamine concentrations. Moreover, although previous works have demonstrated a dose related inhibition of histamine induced bronchoconstriction, using terfenadine in doses of 60, 120, and 180 mg, the displacement of the dose-response curve varied substantially between subjects. Both the variable efficacy of terfenadine and the intrinsic variability of ultrasonic saline challenge (the repeatability of which is not quantified in this study) may account for the apparently variable contribution of histamine to the airway response induced bronchoconstriction reported by Dr O'Hickey and his associates.

The occurrence of allergic manifestations and haemodialysis patients undergoing haemodialysis using a new cuprophane membrane is well known. A study by Drs A Davenport and AJ Williams (September 1988;43:693-6) linked the fall in peak expiratory flow with PEF with dialysis induced hypoxaemia and has suggested that bronchoconstriction occurs as a result of the poor biocompatibility of a new cuprophane dialysis membrane may be contributory.

We have studied the PEF of 12 patients undergoing haemodialysis using dialysate buffered with acetate and a new cuprophane membrane produced by two manufacturers (Terumo Clark model TAF08, Sode Secondaria, Rome, and Gambro Alwall, Takana, Minato-ku, Tokyo). Patients with underlying lung or autoimmune diseases and those who were having immunosuppressive treatment were excluded. All patients were familiarised with the use of the peak flow meter before study and the best of three attempts were used for analysis. As shown in the table, a slight reduction of the PEF was observed after haemodialysis but the change was small and was not confined to the early period of dialysis, when hypoxaemia is known to occur. We therefore could not confirm the findings of Drs Davenport and Williams. Our results suggest that significant bronchoconstriction does not occur after haemodialysis with a new cuprophane dialysis membrane and that the cause of hypoxaemia is more likely to be alveolar hypventilation secondary to cardiovascular collapse with ventilation-perfusion disturbances produced by neutocyte sequestration in pulmonary capillaries, as previously suggested.

AUTHORS' REPLY Bioequivocality is a measure of the reaction that occurs when blood is passed through an extracorporeal circuit to remove waste products. The reaction depends on the type of dialser used, in terms of both the basic chemical structure and the method of manufacture of the membrane, its surface area, and the mechanics of haemodialysis; the blood and dialysate flow rates; and the chemical composition of dialysate used.

The study performed by Drs Wu and colleagues showed that when patients were dialysed with the Terumo device, a cellulosic dialser a significant reduction in PEF was observed during the first hour of dialysis. Thus they have confirmed our findings in a much smaller study using a dialysate buffered with acetate. When they used a different cellulose based dialser, however, no reduction in PEF was noted. This may reflect either a type 2 statistical error due to the small number of patients studied or differences in patient characteristics between the two dialysis treatments, such as the amount of fluid required to be removed during treatment, the blood flow, and the ultraltration rates. If changes in the treatment could be excluded then it would be logical to explain the differences observed between the two dialysis treatments as reflecting differences in membrane biocom-

Serial mean (SD) peak expiratory flow in patients undergoing haemodialysis using a new cuprophane dialysis membrane

<table>
<thead>
<tr>
<th>Dialysis manufacturer</th>
<th>Time (min) from onset of dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Terumo (TAF08)</td>
<td>444</td>
</tr>
<tr>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Gambro (ALWALL)</td>
<td>439</td>
</tr>
<tr>
<td></td>
<td>56</td>
</tr>
</tbody>
</table>

*p < 0.05 versus value at 0 time.


439 436 436 438 443 441 440 446

AUTHOR'S REPLY Dr Finnerty found our article interesting and worthy of further comment. He suggests that the variable response observed was due to an inadequate dosage of antihistamine.

We do not believe that this is so because, in three out of four of the subjects who had no protective effect from terfenadine on hypertonic saline induced bronchoconstriction, the same dosage of terfenadine induced a > 2, 13-8, and 16 fold reduction in histamine responsiveness. One subject declined further airway challenge. Thus the data indicate that the dose of terfenadine used was adequate to attenuate histamine responsiveness significantly, and further suggest a role for other mechanisms in hypertonic saline induced bronchoconstriction.

This hypothesis is supported both by the work of Silber et al, who have shown that hyperosmolar nasal challenge induces the release of histamine, TAME esterases, and immunoreactive leukotrienes LTC4, LTD4, and LTE4, into the nasal fluid, and that of Wilmott et al, who have shown that pretreatment with the cyclooxygenase inhibitor subirupfen was associated with histamine bronchoconstriction in asthmatic subjects, suggesting a role for prostaglandins in the bronchoconstrictor response.

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patibility. The temporal relation in the fall in PEF and arterial oxygen tension during haemodialysis, confirmed by Dr Wu and his colleagues, supports our initial contention that changes in PEF may be due to the activation of inflammatory mediators consequent on the activation of complement, neutrophils, monocytes, and platelets after the blood-dialyser interaction, resulting in an increase in pulmonary arteriolar tone and ventilation-perfusion mismatch and a reduction in tissue oxygen delivery. This is supported by data obtained during the use of cuprophan dialysers, when the expected fall in PEF and arterial oxygen tension and increase in platelet activation were much less than when the dialysers was used the first time.

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We were interested to read the article by Dr AR Webb and others (August 1989;44:674-5) showing patients’ preference for lignocaine gel over lignocaine aerosol for topical nasal anaesthesia preceding fibroptic bronchoscopy. Seven years ago we reported the same preference for lignocaine gel by patients and normal subjects. Nasal anaesthesia was equally effective with these two different methods, but the use of the aerosol was often associated with considerable nasal discomfort, an unpleasant taste, and epiphora, which did not occur with the gel. The additional advantage of the lubricating effect of the gel in passing the bronchoscope noted by Dr Webb and colleagues was also reported in our study. Furthermore, in our study plasma lignocaine concentrations were lower after the same dose of lignocaine gel by comparison with the aerosol, suggesting that the gel might also be safer in terms of lignocaine toxicity.

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We strongly support the conclusion of Dr AR Webb and others (August 1989;44:674-5) that lignocaine gel is preferable to lignocaine spray as a topical nasal anaesthetic for fibroptic bronchoscopy. We suspect that any physician who has applied both agents to his own nostrils would agree with this suggestion as the spray preparation tends to cause an unpleasant stinging sensation when it comes in contact with the nasal mucosa. We have used lignocaine gel for many hundreds of bronchoscopic procedures with few complaints of discomfort from patients.

The technique which the authors used to apply the gel to the nose does, however, seem somewhat laborious. Although the revised technique described in the discussion section of the paper is more convenient than that used in the trial, we can recommend an alternative technique for gel application which we have found to be both convenient and effective.

We use a 12.5 cm hollow plastic applicator (Everett, Kwll) to draw up 10 ml of lignocaine gel from its tube into a syringe. The same applicator is then used to inject the gel into each nostril. The 4 mm diameter applicator can easily be advanced to any desired depth within the nasal cavity, whereas the conical applicator on the tube of lignocaine will barely enter the anterior nares. We ask the patient to sniff, while occluding the opposite nostril, as the gel is applied, and we find that some of the gel is drawn into the pharynx, where it seems to provide useful preliminary topical anaesthesia before the introduction of the bronchoscope.

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Disturbance in respiratory mechanics in infants with bronchiolitis

I have read the report by Dr J Seidenberg and others (August 1989;44:660-7) on lung function in infants with bronchiolitis with considerable interest given our own studies in this field. Whereas their results relating to forced and passive expiratory flow are certain in line with what we expect in this obstructive lung disease, it appears that they, like us, are in fact finding surprisingly low values for thoracic gas volume (TGV). It is true that in the acute phase their average TGV was 130% of predicted and in the chronic phase 126%, but the scatter was wide (see their SEM values) and several infants must have had values in or below their normal range. In our study in the chronic phase we noted many infants with TGV values below our normal range, which is somewhat higher than the range used by Dr Seidenberg and his colleagues.

The differences in normal range I suspect that the two studies contain an appreciable number of bronchiolitic infants with surprisingly low TGV values. They do not really come to grips with the torturous problem of whether or not TGV measurements are reliable in bronchiolitis. How, for example, do they know that all their values are both the high and the low values in the acute and chronic phases are not underestimated? I was delighted to see their results, which seem to confirm our own anxieties and suggest that our results were not simply an artefact. I should most interested in their further thoughts on this issue.

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Adverse effect of additional weight on exercise capacity in patients with chronic obstructive airways disease

The conclusions of Dr C R Swinburn and others (September 1989;44:716-20) can be derived from common sense and an elementary knowledge of physics.

Acceleration or deceleration of a mass requires a force. If the mass is increased, a greater force is needed for the same acceleration. Alternatively, if the force is unchanged, less acceleration is produced (force = mass x acceleration). In man the force is produced by muscle contraction, which allows the energy is proportional to the force produced. When one walks at a steady pace, the legs alternately accelerate and decelerate but the body does not. Therefore, the wearing of lead aprons will not substantially increase energy requirements, unless they are worn on the legs, not the thorax. Clearly, in step testing the whole body accelerates and decelerates in a vertical plane against gravity. So the wearing of lead aprons will make a difference to energy expenditure and hence oxygen consumption during this form of exercise.
Fall in peak expiratory flow during haemodialysis in patients with chronic renal failure.

P Wu, I K Cheng and W K Lam

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