LETTERS TO THE EDITOR

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 12 hours and two hours before challenge with hypertonic saline, and gave significant protection against this stimulus, displacing the geometric mean PD_{20} FEV_1 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 intersubject 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.[1] A recent study using a dose of 180 mg terfenadine administered three hours before hypertonic saline challenge showed a geometric mean increase of PD_{25} by a factor of 7·2,[3] somewhat greater than the 2·5 fold shift reported by Dr O'Hickey and colleagues. It may be supposed that after 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 workers 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.[3] 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 hypertonic saline induced bronchoconstriction reported by Dr O'Hickey and his associates.

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1 Hopp RJ, Bewtra K, Nair NM, Townley RG. Effect of terfenadine on the bronchoconstriction induced by ultrasonically nebulized distilled water. *Ann Allergy* 1988;**61**:13–6.
2 Finnerty JP, Wilmot C, Holgate ST. Inhibition of hypertonic saline-induced bronchoconstriction by terfenadine and flurbiprofen: evidence for the predominant role of histamine. *Am Rev Respir Dis* (in press).
3 Rafferty P, Holgate ST. Terfenadine (Seldane) is a potent and selective histamine H_1 receptor antagonist in asthmatic airways. *Am Rev Respir Dis* 1987;**135**:181–4.

AUTHOR'S REPLY We are pleased that 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 the four 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*,[1] who have shown that hyperosmolar nasal challenges induce the release of histamine, TAME esterases, and immunoreactive leukotrienes LTC_4, LTD_4, and LTE_4 into the nasal fluid, and that of Wilmot *et al*,[2] who have shown that pretreatment with the cyclooxygenase inhibitor flurbiprofen will attenuate hypertonic saline responsiveness in asthmatic subjects, suggesting a role for prostaglandins in the bronchoconstrictor response.

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1 Silber G, Proud D, Warner J, *et al.* In vivo release of inflammatory mediators by hyperosmolar solutions. *Am Rev Respir Dis* 1988;**137**:606–12.
2 Wilmot C, Finnerty JP, Holgate ST. Role of histamine and prostaglandins in the bronchial response to inhaled hypertonic saline [abstract]. *Thorax* 1988;**43**:865P.

Fall in peak expiratory flow during haemodialysis in patients with chronic renal failure

The occurrence of allergic manifestations[1] and hypoxaemia[2] in patients undergoing haemodialysis using a new cuprophan 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 (PEF) with dialysis induced hypoxaemia and has suggested that bronchoconstriction which occurs as a result of the poor biocompatibility of a new cuprophan dialysis membrane may be contributory.

We have studied the PEF of 12 patients undergoing haemodialysis using dialysate buffered with acetate and a new cuprophan membrane produced by two manufacturers (Terumo Clirans model TAF 08, Sede Secondaria, Rome, and Gambro Alwall, Takanawa, 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.[2] 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 cuprophan dialysis membrane and that the cause of hypoxaemia is more likely to be alveolar hypoventilation secondary to carbon dioxide washout or ventilation-perfusion disturbances produced by leucocyte sequestration in pulmonary capillaries, as previously suggested.[2]

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1 Pollack VE, Charoenpanich R, Robson M, Kant KS. Dialyser membranes: syndromes associated with first use and effects of multiple use. *Kidney Int* 1988;**33**(suppl 24):S49–52.
2 De Broe ME, Heyrman RM, De Backer WA, Verpooten GS, Vermeire PA. Pathogenesis of dialysis-induced hypoxemia: a short overview. *Kidney Int* 1988;**33**(suppl 24): S57–61.

AUTHORS' REPLY Biocompatibility is a measure of the reaction that occurs when blood is passed through an extracorporeal circuit and returned to the patient. This reaction depends on the type of dialyser 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 Dr Wu and colleagues showed that when patients were dialysed with the Terumo reconstituted cellulosic dialyser 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 dialyser with a smaller surface area. When they used a different cellulose based dialyser, 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 ultrafiltration rates. If changes in these measures 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 cuprophan dialysis membrane

Dialysis manufacturer	*Time (min) from onset of dialysis*							
	0	*15*	*30*	*45*	*60*	*120*	*180*	*End*
Terumo (TAF 08)	444 (68)	431* (60)	431* (64)	427* (62)	433 (63)	431 (59)	440 (68)	447 (55)
Gambro (ALWALL)	439 (56)	436 (55)	436 (53)	438 (52)	443 (54)	441 (54)	440 (53)	446 (52)

*p < 0·05 versus value at 0 time.