

## Correspondence

### $\beta_2$ -Agonists and death from asthma

To the Editor:

Inhaled  $\beta_2$ -agonists have a well established role as first-line bronchodilator therapy in patients with asthma. They have been used extensively over the past 20 to 30 years.

Investigators from New Zealand<sup>1</sup> reported that the use of a selective  $\beta_2$ -agonist, fenoterol, was associated with an increased risk of death from asthma. Several methodologic aspects were difficult to analyze, and there was generalized controversy. The Saskatchewan study<sup>2</sup> concluded that an increased risk of death or near death from asthma was associated with the regular use of inhaled  $\beta_2$ -agonists, especially fenoterol.

Because fenoterol is widely prescribed in Brazil as a bronchodilator during acute attacks, mainly in solution for nebulization, the total sales of  $\beta_2$ -agonists (fenoterol and salbutamol) in the state of São Paulo were analyzed in relation to the death rates from asthma, from 1980 to 1991.

During this period, the sales of metered-dose inhalers (for administration of fenoterol and salbutamol) had increased fourfold, and the sales of fenoterol and salbutamol nebulizer solutions had increased 17-fold and fourfold, respectively.  $\beta$ -Agonist inhalation therapy is still being used regularly. However, since the publication of the National Heart, Lung, and Blood Institute asthma guidelines, there is a tendency to use it only as rescue therapy. In the same period, the mortality rate for all ages decreased (2.11 in 1980 and 1.09 in 1991), mainly determined by a decrease in the age range of 0

to 4 years (3.54 in 1980 and 1.10 in 1991). These data are more relevant to our considerations, because in this age range (0 to 4 years), the vast majority of children are treated for bronchospasm with a nebulized solution of a  $\beta_2$ -agonist. In the age range of 5 to 34 years, the mortality trend is quite stable.

Inhaled corticosteroid therapy is well recognized as an important antiinflammatory therapy and is common in São Paulo. However, because of its high cost, the consumption is less than desirable and probably cannot explain the decrease in the mortality rate.

On the basis of all the data shown in Fig. 1, we conclude that there is no support for a causal link between fenoterol and salbutamol use by inhalation and death from asthma in São Paulo, Brazil.

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### REFERENCES

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2. Spitzer WO, Suissa S, Ernst P, et al. The use of beta agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.

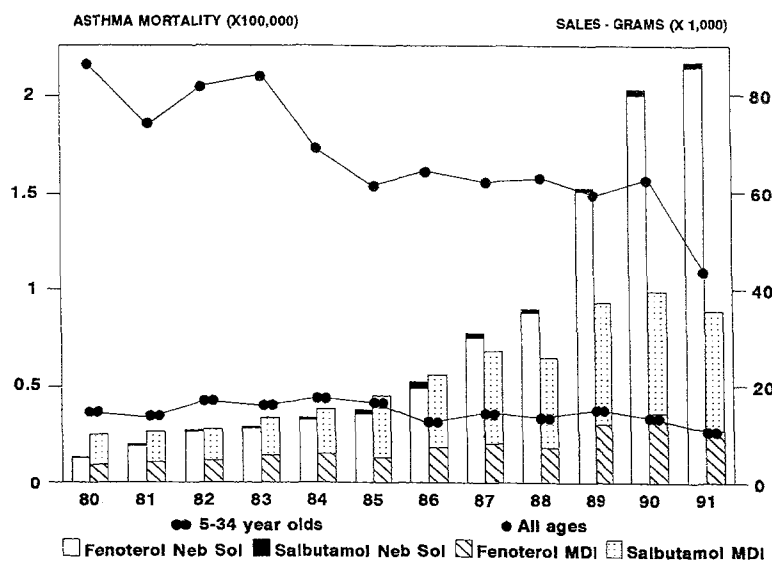


FIG. 1. Fenoterol and salbutamol nebulizer solution (0.5%) and metered-dose inhaler sales and asthma mortality trends in São Paulo, Brazil. MDI, Metered-dose inhaler.

The following abstracts were presented at the AAAI's 1994 Annual Meeting, March 4-9 in Anaheim, California. We apologize to the authors for not having included them in the January supplement of the JOURNAL. Information as to session type, day, and date of presentation is included in this correction.

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**QUANTIFICATION AND PHENOTYPE OF CUTANEOUS MAST CELLS (MC) IN CHRONIC IDIOPATHIC URTICARIA (CIU).**

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Increased levels of skin histamine have been demonstrated in patients with CIU. To determine if increased numbers of MC account for elevated skin histamine, MC have been quantified in lesional (n = 11) and non lesional (n = 9) skin from patients with CIU, and site matched healthy control skin (n = 10). MC were identified using a sensitive, double labelling immunohistochemical technique employing specific monoclonal antibodies to MC tryptase and chymase, and quantified under light microscopy with a Zeiss videoplan apparatus 0-186µm, and 186-366µm from the dermo-epidermal junction. No significant differences were observed in MC numbers between lesional, non lesional and control skin in either upper or lower dermis (Student's unpaired 't' test):

|           | <u>lesional</u> | <u>non lesional</u> | <u>control</u>  |
|-----------|-----------------|---------------------|-----------------|
| 0-186µm   | 9249<br>(3060)  | 9059<br>(3289)      | 10736<br>(2701) |
| 186-366µm | 6080<br>(2006)  | 6614<br>(2047)      | 6783<br>(1263)  |

Figures denote mean number of MC/mm<sup>3</sup>, with SD shown in parentheses. Greater than 99% of MC in all tissue sections examined were of MC<sub>c</sub> phenotype.

These data suggest that increased skin histamine in CIU is not due to increased numbers of MC, and may alternatively reflect either an increase in histamine content/MC, an increased activation state of MC, or recruitment of basophils into skin in patients with CIU.

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**INCREASED EXPRESSION OF MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1) IN ASTHMATIC AIRWAYS.**

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Bronchial asthma is a chronic inflammatory condition characterised by an increased cellular infiltrate, such as macrophages, into the bronchial wall. Chemotaxis may have an important role in the presence of these cellular infiltrate. Therefore the expression of MCP-1 protein was assessed, *in vivo*, by immunohistochemistry on frozen bronchial biopsies from 12 asthmatic and 12 normal subjects. Both a monoclonal (F9) and a polyclonal antibody were employed to detect MCP-1, while the mouse myeloma protein (MOPC21) was used as a negative control. Hue-saturation-intensity colour image analysis was used to quantify the staining. Strong positive reactions for MCP-1 were seen in the asthmatic bronchial epithelium, subepithelial macrophages, blood vessels and bronchial smooth muscle. With the monoclonal antibody, asthmatic airway epithelium and subepithelium stained significantly more than those of the normal subjects (p<0.0001, p<0.002 respectively). The polyclonal anti-MCP-1 antibody also gave strong reactions in the asthmatic epithelium and subepithelium, with much weaker reactions in the normal (p<0.0001 for the epithelium staining). These increased levels of MCP-1 in the asthmatic airways suggest that it may play a role in macrophage recruitment and activation and thereby contribute to inflammatory pathology of bronchial asthma.

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**URINARY  $LTE_4$  LEVELS IN ASPIRIN SENSITIVE ASTHMA BEFORE AND AFTER ASPIRIN DESENSITISATION**

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Asthmatic patients with aspirin sensitivity (ASA) can be desensitised to aspirin by the administration of incremental doses of aspirin. There is accumulating evidence for the central role of leukotriene release in ASA, but the mechanisms of desensitisation are unknown. There are at least two possibilities. These include downregulation of leukotriene production following aspirin ingestion following desensitisation or reduction in airway sensitivity to leukotrienes (Am Rev Respir Dis 1991; 144:957-58). To test the hypothesis that there may be a reduction in leukotriene release we have studied 4 patients (2 males) with ASA. They were aged 41 (2.8) yrs (mean SEM) with baseline  $FEV_1$  of 87 (4.6)% predicted and a mean threshold aspirin dose of 50 (16.8)mg. Urinary  $LTE_4$  was measured before and after ingestion of threshold dose of aspirin and then at regular intervals during desensitisation up to 600 mg aspirin. Prior to desensitisation to maximum fall in  $FEV_1$  following threshold aspirin dose was 19.5(2.8)% and this was accompanied by a change from a baseline value of 174(45)pg/mg creatinine  $LTE_4$  to a maximum value of 1858(713) pg/mg to creatinine  $LTE_4$ . After desensitisation and following 600 mg aspirin there was a mean maximum fall in  $FEV_1$  of only 5.6(3.2)% and this was accompanied by a change in urinary  $LTE_4$  levels from a baseline of 520(310) pg/mg to 2054(861) pg/mg creatinine  $LTE_4$ . We conclude that there is still substantial leukotriene release in ASA following aspirin desensitisation, although there is no change in lung function after aspirin ingestion. We suggest that decreased target organ sensitivity to the bronchospastic effects of  $LTE_4$  is largely responsible for the efficacy of aspirin desensitisation.

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**TRANSCRIPTIONAL REGULATION OF IL-5 GENE EXPRESSION IN HUMAN T-CELLS**

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The cytokines IL-3, IL-5 and GM-CSF can cause eosinophil differentiation, however IL-5 is the only specific eosinophil differentiating factor. Whilst the function of IL-5 is extensively investigated the available data for the regulation of its expression is very limited. The IL-5 gene is on chromosome 5q31 in close proximity with IL-3, GM-CSF, M-CSF and IL-9 which suggests that there may be a common mechanism of their regulation.

Using DNase I footprinting and band retardation assays we have studied the transcription factors involved in the activation of IL-5 gene expression. We have found several *cis* acting elements in the promoter of the IL-5 gene:

- 1) A 15 nucleotide sequence **A T T A T T C A T T T C C T C**. It is fully conserved between mouse and human IL-5 and differs by only one nucleotide (underlined T) from GM-CSF. Although this sequence is not found in other genes it binds transcription factors found in many different cells.
- 2) A A G A T T C T T C, which is present with low homology in the promoters of many lymphokine genes was also found to be occupied by a DNA-binding protein(s).
- 3) G A G G A A, which binds transcription factors of the ets family, different to the ets-1/ets-2 factors found in activated T-cells. This sequence is not present in the GM-CSF promoter.
- 4) We have also discovered a new cytokine specific element which binds several different tissue specific nuclear proteins. It has related sequences in the promoters of GM-CSF and IL-4 genes, but not in the INF- $\alpha$  gene. These elements may have implications in the T-cell differentiation in the context of T-helper subsets.

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