

LETTERS TO THE EDITOR

Bone turnover and inhaled corticosteroids

We wish to take issue with several statements made by Kerstjens *et al* in their recent paper (July 1994;49:652-6). We believe that their conclusion that there is no clear evidence of a detrimental effect of inhaled corticosteroids on bone metabolism is unsubstantiated by the results of their study. They were able to demonstrate a significant fall in osteocalcin levels after four weeks of inhaled corticosteroid treatment, which implies a reduction in bone formation. This fall was no longer evident after two years of treatment. A less benign interpretation of these results is that reduced bone formation occurred at the start of treatment,¹ resulting in a fall in bone density. At a later stage bone metabolism may have returned to its previous equilibrium; any bone loss may not have been rectified by a later increase in bone formation. Unfortunately it is impossible to put the authors' results into a clinical context because they importantly failed to measure bone density.

A confounding factor in the interpretation of the effects of inhaled corticosteroids is the effect of courses of systemic corticosteroids. Some patients in study II of their paper must have received systemic corticosteroids yet we are given no information about this. It would be important to know whether the control and treated groups received equivalent doses of systemic corticosteroids over the 2.5 year study period.

The authors question the validity of osteocalcin measurements and suggest that measurement of serum levels of propeptide of type I collagen (PICP) may be a more valid marker of bone formation than osteocalcin (which was measured in our study). Nevertheless there is contrary evidence indicating that PICP may be a less sensitive marker of bone formation than osteocalcin.²

Our study on the effects of inhaled beclomethasone dipropionate on bone metabolism and density³ is referenced by Kerstjens *et al* as one of several previous studies on the subject which were short term and uncontrolled. In fact, our study did include a well matched control group of patients with asthma who had not previously received corticosteroids. Furthermore, the median duration of treatment among the asthmatic subjects in our study who were receiving high dose inhaled corticosteroids was three years.

G E PACKE
J G DOUGLAS
Department of Thoracic Medicine,
Aberdeen Royal Infirmary,
Forresterhill,
Aberdeen AB9 2ZD, UK

- 1 Reid DM. Corticosteroid-induced osteoporosis. In: Smith R, ed. *Osteoporosis*. London: Royal College of Physicians of London, 1990:99-117.
- 2 Ebeling PR, Peterson JM, Riggs BL. Role of type I pro-collagen propeptide assays in metabolic bone diseases. *Bone Miner* 1992;17(Suppl 1):206.
- 3 Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic steroids. *Thorax* 1992;47:414-7.

AUTHORS' REPLY We believe there are three relevant questions at stake with respect to inhaled corticosteroids and bone turnover. (1) Do they cause fractures? (2) Do they cause excess fractures? (3) If so, how does that influence therapeutic decisions in patients with asthma?

(1) Determining the number of fractures asks for extremely long trials of 20 years or more. Proxies are therefore often employed in studies and subsequently cited. We particularly addressed the value attached to short term changes in blood parameters of bone formation. Since the human body has a remarkable capacity for correcting acute imbalances in many systems, we made the point that long term changes in bone turnover, and especially increases in fractures, should not be deduced from short term (often four weeks or less) changes in blood parameters such as osteocalcin. Additionally, we agree with Drs Packe and Douglas that measurement of bone density as a proxy of future fractures is perhaps the best - though still imperfect - parameter available at this moment. A randomised three year study is currently ongoing: in the EUROSCOP trial of inhaled corticosteroids versus regular treatment without inhaled corticosteroids (in patients with COPD) bone densitometry is followed up, at least in some centres.¹

(2) Withholding inhaled steroids from patients with mild and moderately severe disease leads to more courses of oral steroids.^{2,3} An unknown number of patients will eventually receive maintenance dosing of oral steroids; the amount can be reduced or abolished by inhaled corticosteroids.⁴ Any definitive study on the effect of inhaled corticosteroids on any marker of bone turnover should therefore be prospective, randomised, and should compare patients with the same severity of disease. In our opinion the study by Dr Packe and colleagues was relatively uncontrolled; the retrospectively defined comparison group with "steroid naive" and hence very mild asthmatics does not represent a relevant control group. Their study was certainly non-randomised. Although we agree with Dr Packe that we should have mentioned the number of prednisolone courses administered in our study (36 one week courses in the 70 patients on inhaled corticosteroids and 74 courses in the 85 patients not on inhaled corticosteroids), the important point is that our study represented the clinical situation; if *by design and at random* inhaled corticosteroids are not administered, the proper comparison of effects on bone turnover can be made with the patients not having received inhaled corticosteroids.

(3) Finally, doctors and patients should be aware of adverse effects of any medication taken, but the final therapeutic decision will always have to be one of balancing the beneficial with the adverse effects, all relative to the severity of the disease. Based on clinical impressions after 22 years of use, it seems reasonable to expect at best a relatively small excess probability of fractures with inhaled corticosteroids. The largest adverse effect of inhaled corticosteroids in moderate, and certainly in severe, asthmatics might well be to withhold them.

H A M KERSTJENS
D S POSTMA
Department of Pulmonary Medicine,
University Hospital Groningen,
Oosterlingel 59 9713 EZ Groningen,
The Netherlands

- 1 Pauwels RA, Lofdahl CG, Pride NB, Postma DS, Laitinen LA, Ohlsson SV. European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): hypothesis and design. *Eur Respir J* 1992;5:1254-61.
- 2 Haahntela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, *et al*. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
- 3 Kerstjens HAM, Brand PLP, Hughes MD, Robinson NJ, Postma DS, Sluiter HJ, *et al*. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy in obstructive airways disease. *N Engl J Med* 1992;327:1413-9.
- 4 Lacronique J, Renon D, Georges D, Henry-Amar M, Marsac J. High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. *Eur Respir J* 1991;4:807-12.

Malignant pleural effusion

The editorial by Drs Reid and Rudd (August 1993;48:779-80) is a succinct up to date contribution. Many of the questions they raise about the efficacy of various sclerosing agents will require further data as they indicated. I would like to take issue primarily with their concern regarding the cost factor and possible morbidity and mortality of pleurodesis with thorascopic talc poudrage. They mentioned the 5% mortality and considerable morbidity in the patients studied by Ohri *et al*.¹ However, this series included terminally ill patients. As pointed out by Sahn,² pleurodesis is best reserved for those patients expected to live for several months. With this approach we have found the mortality after thorascopic talc poudrage to be zero and morbidity limited to occasional cellulitis of the chest tube site and short lived fever.^{3,4}

As for cost, USP talc is sold locally for US\$4.95 a pound, a life time supply for many hospitals. We sterilised enough talc for our entire region (comprising a 2.5 million catchment area) in a single sitting.⁵ If we use the operating room this adds some cost, but our average four day hospital stay⁷ is considerably shorter than most reports with tetracycline, and the fact that we need to do the procedure only *once* - even with low pH effusions⁶ - suggests that thorascopic talc poudrage should cost considerably less than pleurodesis with tetracycline or bleomycin.

I expect that a serious look at thorascopic talc poudrage would show it to be both effective and as cost effective in the UK as it is elsewhere.

YOSSEF AELONY
Harbor-UCLA (Pulmonary),
25825 South Vermont Avenue,
Harbor City,
California 90710-3599,
USA

- 1 Ohri SK, Oswal SK, Townsend ER, Fountain SW. Early and late outcome after diagnostic thoracoscopy and talc pleurodesis. *Ann Thorac Surg* 1992;52:1038-41.
- 2 Sahn SA. Malignant pleural effusions. *Clin Chest Med* 1985;6:122.
- 3 Aelony Y, King R, Boutin C. Thorascopic talc poudrage pleurodesis for chronic recurrent pleural effusion. *Ann Intern Med* 1991;115:778-82.
- 4 Boutin C, Vaillat JR, Aelony Y. *Practical thoracoscopy*. Berlin: Springer-Verlag, 1991.
- 5 Aelony Y. Talc sterilization for thorascopic talc poudrage. *Am J Respir Rev Crit Care Med* 1994;149:A512.
- 6 Aelony Y. Pleurodesis pH and thorascopic talc poudrage. *Chest* 1993;104/5:1318-9.

AUTHORS' REPLY We thank Professor Aelony for his information regarding thorascopic talc poudrage and pleurodesis in the man-