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;49:562–6). 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, 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 sensitive 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.1

Our study on the effects of inhaled beclamethasone dipropionate on bone metabolism and density2 is referenced by Kerstjens et al as one of several previous studies on the subject which were short term and under-controlled. 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.

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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 this influence therapeutic decisions in patients with asthma?

(1) Determining the number of fractures asks for extraordinarily 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.

(2) Withholding inhaled steroids from patients with mild and moderately severe disease leads to new fractures at a rate of 1-2%. An unknown number of patients will eventually receive maintenance dosing of oral steroids; the amount can be reduced or abolished by inhaled corticosteroids. 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 main 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 take into account 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.

Bone turnover and inhaled corticosteroids

Patients treated previously with oral corticosteroids had a reduction in bone mineral density at the spine and hip.2 The question then arises whether corticosteroids are the cause of the reduced bone density, or whether the reduced bone density is a marker of the severity of the disease. If the latter is true, then this information is worth noting, but it is of limited clinical relevance. It is not clear from the studies of other authors that the effects of oral corticosteroids are the same as those of inhaled corticosteroids.

In a recent report,2 we have shown that systemic steroids do not induce bone loss, but they do lead to a greater skeletal response to trauma than do inhaled corticosteroids. This finding is consistent with other reports.4,5

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 particularly with their concern regarding the cost factor and possible morbidity and mortality of pleurodesis with thoracoscopic talc poudrage. They mentioned the 5% mortality and considerable morbidity in the patients studied by Ohri et al. However, this series included terminally ill patients. As pointed out by Sahni, pleurodesis is best reserved for those patients expected to live for several months. With this in mind, we have found the mortality after thoracoscopic talc poudrage to be zero and morbidity limited to occasional cellulitis of the chest tube site and short lived fever.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 stay is considerably shorter than most reports with traction catheter, and the fact that we need to do the procedure only once – even with low pH effusions – suggests that thoracoscopic talc poudrage should cost considerably less than pleurodesis with tetracycline or bleomycin.

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

Malignant pleural effusion

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Does talc poudrage influence hospital stay?

We believe there is no clear evidence of a detrimental effect of inhaled corticosteroids on bone metabolism and density, or of any effect of inhaled corticosteroids on patients with asthma.

We wish to respond to the recent comments by Packe and Douglas.2 We agree that in our study the patients were not randomised, but we strongly believe that the study represents the clinical situation. In fact, many patients with severe asthma receive high dose inhaled corticosteroids for three years or more. Our study showed that this treatment was accompanied by a reduction in bone mineral density at the spine and hip, possibly the result of the steroid treatment, or of the disease itself.

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AUTHORS’ REPLY We thank Professor Aelony for his information regarding thoracoscopic talc poudrage and pleurodesis in the man...
management of malignant pleural effusion. Thoracicoscopic inspection of the pleural space provides optimal conditions for effective pleurodesis by facilitating a dry pleural cavity and may be more important, with regard to success, than the choice of sclerosant. Nevertheless his experience with talc is most interesting, and we agree that further data in the form of a prospective randomised trial are required to clarify management which remains largely a matter of personal experience and reflects local expertise.

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Corynebacterium parvum for malignant pleural effusions

I have read the article by Dr AG Villanueva et al (January 1994;49:23–5) on tetracycline pleurodesis for malignant pleural effusions. Tube thoracostomy drainage before instillation of tetracycline is necessary to achieve successful pleurodesis, and the authors found that short term drainage was as effective as long term drainage. Since insertion of a drainage tube is uncomfortable, the use of a sclerosing agent which can be injected into the pleural cavity without an intercostal tube is preferable. Corynebacterium parvum (CBP), unlike other sclerosing agents, has this feature. In fact, in the study by Leahy et al treatment with CBP was as effective as tetracycline injected via an intercostal tube.

I wish to report results on 28 consecutive patients treated with intrapleural CBP (Corynebacterium parvum, Wellcome Foundation, London, UK) without tube drainage. Four patients were not evaluable as they died within one month. A complete response (total resolution of pleural effusion after a maximum of three injections of CBP) was seen in 22 of the remaining 24 patients. The side effects were fever (in 50% of patients) usually lasting 2–4 days, and mild or moderate chest pain (32% of patients), both of which were effectively controlled with paracetamol or non-steroidal anti-inflammatory drugs.

These data confirm that instillation of CBP without intercostal tube drainage is an effective, simple, and well tolerated method of controlling malignant pleural effusions. Our patients had a longer survival time (mean 7–7 months) than that reported by Villanueva et al, and three are still alive with survival times of 11.3, 9.9, and 5.1 months. Our results are also superior to those of patients treated with talc (1–9 months in patients with low pleural fluid glucose levels and low pH and 5–7 months in patients with high glucose and high pH levels), and to those treated with mustard (3–9 months). This fact is emphasised by other authors14,15 and suggests that CBP may be acting, not only as a sclerosant, but also as an immunostimulant.

Unfortunately, CBP has been discontinued by the Wellcome Foundation. So, there is injectable tetracycline in Italy injectable tetracycline, doxycycline, minocycline, and rolitetracycline are not available. The treatment of malignant pleural effusions therefore currently requires more expensive agents or more invasive methods.

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BOOK NOTICE


Most British chest physicians also practise general medicine, and all will have passed the MRCP. At one time Hunter's Diseases of Occupations was essential reading for those taking the examination, not least because Donald Hunter was a notoriously idiosyncratic examiner. The original classic textbook in its later editions lost much of its value except as an historical reference, but this 8th edition has been completely rewritten, breaking at last with the original format but honouring the original purpose "to review with emphasis on its clinical aspects the problem of disease in relation to occupation". This task inevitably requires a team of contributors, and the authors have selected the strong one. They have also achieved a reasonable uniformity of style and structure which makes the book easy to read and clinically informative.

The first five chapters contain information on preventive legislation, compensation, and medical report writing that is not readily available elsewhere. The rest of the book consists of descriptions of occupational diseases as seen nowadays, properly emphasising the common problems of musculoskeletal, psychological, skin, and hearing diseases that are of interest to other specialists. The chapters on occupational lung disorders are concise, clearly written and accurate, but necessarily lack the detail to be found in more specialised textbooks. The short chapter on indoor air pollution is one that many who are confused by the various "sick building" syndromes will find particularly helpful.

This is a much better book than the 7th edition, and deserves to be in all hospital and medical school libraries. All doctors training in general medicine should read it and will find it opens its eyes to previously unappreciated causes of disease and possibilities for prevention. And with the growing interest in environmental causes of disease, who knows – it could even once again become essential reading for passing the MRCP! – AS

NOTICES

Scadding-Morrison Davies Joint Fellowship in Respiratory Medicine 1995

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respiratory medicine. Medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade, may apply. Applicants should submit a curriculum vitae together with a detailed account of the duration and nature of the work, the centres to be visited, confirming that these have agreed to provide the facilities required, and giving the sum of money needed for travel and subsistence. A sum of up to £12,000 can be awarded to the successful applicant, or the sum may be divided to support two or more applications. Applications should be sent by 31 January 1995 to Dr D A Campbell, Secretary to the Scadding-Morrison Davies Fellowship, Llandough Hospital, Penarth, South Glamorgan CF64 1XX.

Lung and Asthma Information Agency

The Lung and Asthma Information Agency aims to bring together, interpret, and disseminate information about lung disease in order to increase awareness and understanding of the burden of lung disease and of its prevention and care. It is jointly supported by the National Asthma Campaign, the British Lung Foundation, and the British Thoracic Society. Since its launch at the BTS Summer Meeting in July 1992 it has concentrated on three areas: the production of factsheets, developing a comprehensive respiratory database, and providing an information service to the sponsors. So far, it has produced factsheets on asthma mortality in the elderly, pneumoconiosis, and sarcoidosis. It has also published five factsheets on respiratory illness in children, seasonal variations in asthma, air pollution, and asthma prevalence. From 1995 further factsheets will be distributed with Thorax, the first on "Trends in hospital admissions for asthma" appearing with this issue. Multiple copies of factsheets, back copies of earlier factsheets, and further information about the Agency may be obtained from: Elizabeth Hardgrove, Lung and Asthma Information Agency, Dept of Public Health Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE. Tel: 0181 725 5489.
Malignant pleural effusion.

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