

LESSONS FROM A SYMPOSIUM ON RESPIRATORY MEDICINE HELD IN THE COLLEGE ON 1-2 DECEMBER 1994*

G. Hulks, Respiratory Medicine Unit, Western General Hospital, Edinburgh

Asthma

Among those concerned with respiratory medicine, there is a vigorous debate respecting the side effect profile of the drugs which form the mainstay of asthma treatment. Epidemiological studies related the epidemic of asthma deaths in New Zealand during the late 1970s to sales of one particular β -agonist, Fonoterol, which was then widely used. Clinical studies have suggested that this was probably not a class effect but due to Fonoterol having twice the potency of other β -agonists and therefore more likely to produce systemic effects. Recently, a large Canadian study showed that the greater the amount of β -agonist taken, the greater was the chance of an asthma death or a near-death episode. This generated further debate but the study may simply have reflected a correlation between β -agonist use and disease severity. Despite these criticisms, there remains some evidence that regular, as opposed to 'as required' usage of β -agonists results in poorer control of asthma symptoms and that airway reactivity increases immediately after discontinuing treatment with β -agonists. These effects are probably not relevant to the vast majority of patients but as β -agonists are so widely used they may be important for a small number of them.

This concern has been extended to the new long acting inhaled β -agonists (e.g. salmeterol, formoterol) but, thus far, any fear has not been substantiated. These agents are effective bronchodilators without evidence of tolerance and with few side effects. Improved symptom control has been obtained in patients given low-dose inhaled corticosteroids and a long acting inhaled β -agonist compared with those whose treatment has been changed from low to high-dose corticosteroids. If confirmed, this might require revision of the current guidelines for treatment.

Inhaled corticosteroids have been available for 20 years and form the backbone of preventative treatment on the basis of their anti-inflammatory effect. In adults, it is unlikely that doses $\leq 1500 \mu\text{g}$ pose any clinically significant risk to the hypothalamic-pituitary-adrenal axis, glucose and lipid metabolism or to cataract formation, although possible effects on bone metabolism are still to be elucidated. Local side-effects remain a significant problem for a number of people, although many can be helped with large volume spacers or dry powder devices which are replacing the CFC-laden propellants of metered dose aerosols.

Primary prevention should form the major thrust of asthma therapy during the next decade as no major therapeutic advances appear imminent. The majority of asthma care is rightly centred around general practice but there remains an unacceptably high threshold for reviewing medication and, by inference, symptom control. A quarter of the nurses running asthma clinics have had no evaluated training in the provision of care. Those patients who require hospital referral merit further education and personalised, written information, a process

*A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 25, p 181.

which has been shown to improve compliance and readmission rates. These interventions take time and may seem daunting in a busy out-patient clinic but by employing trained nursing staff, an imaginative use of educational material and simple consultation protocols they can be achieved. It is important to target at-risk groups and to reach those who may have only a fleeting liaison with hospital care, e.g. the casual attender at an accident and emergency department.

Sleep apnoea

The definition of sleep apnoea has been refined over the last two decades and now comprises a whole range of sleep related disorders which cause upper airway obstruction and symptomatic sleep disturbance. The marked snoring and sleepiness which characterises this disorder has long been the subject of social ridicule and may still receive a less than sympathetic response from medical personnel. This detracts from the real health problems including potentially lethal lapses of concentration and sleepiness, together with increased cardiovascular morbidity, the latter probably resulting from the great surges in blood pressure produced during arousal from sleep.

The incidence of sleep apnoea rises with age and body weight, and cranio-facial abnormalities can be an important additive factor. Exactly how many people are affected is uncertain but with the widening of the diagnostic net, it is likely that most previous studies (which reported figures ranging from $<0.5\%$ - 3%) underestimated the problem.

There are now well validated questionnaires which give a reliable indication of those who are abnormally sleepy. A history of multiple witnessed apnoeas or sleep related choking is also valuable. Unless there is an obvious obstructive lesion for most patients in whom surgical correction of snoring is contemplated it should be recalled that palatal surgery is very rarely effective for sleep apnoea and often renders it untreatable by conventional methods. Those in whom there is very low or very high index of suspicion can often be effectively diagnosed with a limited sleep study comprising oximetry, EMG and monitoring of respiratory effort which, with increasing technological sophistication, may be performed at home. When another diagnosis is entertained or when a limited study has failed to give a clear answer (as is likely in a third), full polysomnography in a sleep laboratory becomes essential.

Treatment for sleep apnoea is successful in most cases and comprises the use of a small, portable, nasal continuous positive airway pressure (CPAP) machine which prevents the upper airway collapsing and thus normalises sleep patterns with a dramatic reduction in morbidity and mortality. The newest generation of such machines may be used in both computer aided diagnosis and treatment of sleep apnoea.

Chronic lung disease

Previous attempts to classify smoking-related airflow limitation into chronic bronchitis and emphysema are now considered unhelpful given the mixture of clinical, epidemiological and pathological definitions which characterise them. The term *chronic obstructive pulmonary disease* (COPD) is to be preferred as it is airway obstruction which is responsible for morbidity and mortality and which is correlated with prognosis. Bronchial biopsies in COPD show an increase in inflammatory cells similar to, but less numerous than, that seen in asthma and it is possible that these diseases should be considered as forming a single continuum.

Responses to standard bronchodilator tests in COPD are fraught with problems however and an improvement in both walking distances and perception of dyspnoea has been shown which bears no relation to changes in the standard measure of airflow obstruction, FEV₁. Of those who do show reversibility by standard criteria about two-thirds respond to a β -agonist and not to corticosteroid whilst the remainder respond to both but show a larger effect with anti-inflammatory medication; the latter group has also been identified as having a higher mortality. Two large European studies are underway to address the vexed problem of corticosteroids in COPD and preliminary results should be available towards the end of this year.

Currently defined as 'right ventricular enlargement resulting from structural lung disease', cor pulmonale is instead used by many when peripheral oedema complicates COPD. Right ventricular hypertrophy occurs in less than 50% of patients with COPD, but fluid retention is seen in up to 70% with an FEV₁ < 0.6 litres. It is true that survival can be related to pulmonary artery pressure but it can similarly be correlated with blood gases, FEV₁ and other parameters. There is much evidence to suggest that there is little wrong with right ventricular function in COPD and that pulmonary hypertension is probably no more than an index of disease severity. What then is responsible for oedema formation in so-called cor pulmonale? The renin-angiotensin system is markedly activated in cor pulmonale, more so than in left ventricular failure, and a number of parameters of renal function are related to PaCO₂, such that fluid retention is thought to be a renal rather than cardiac phenomenon. The important conclusion of this *volte face* is that interventions which affect cardiac function or produce pulmonary vasodilatation are unlikely to confer a significant survival benefit in pulmonary hypertension secondary to COPD. A more logical therapeutic approach is to correct hypoxaemia or to investigate the long term effects of more specific therapies aimed at improving salt, water and hormonal balance.

Long term oxygen therapy has been shown to improve survival in severely hypoxic COPD and is now recommended to those patients who can comply with its use for at least 15 hours daily. Nasal intermittent positive pressure ventilation (NIPPV) also has proven of benefit but it is unlikely that those who are truly intolerant of long term oxygen therapy would be any more tolerant of NIPPV and it is unlikely to achieve widespread use. NIPPV has proved much more successful in other groups with nocturnal hypoventilation including chest wall deformities, neuromuscular diseases and also cystic fibrosis where it has been used as a bridge to transplantation. A number of simple domiciliary ventilators are now available costing £3-4,000 and pulmonary physicians are becoming increasingly familiar with their use.

Non-surgical management of lung cancer

Lung cancer accounts for one-third of all cancer related deaths in the UK and although mortality is falling in men it remains static in women, possibly reflecting the more recent growth of the smoking habit among them.

Small cell cancer remains the most chemosensitive with up to 50% of patients with limited disease now expected to obtain a 'complete' response, although median survival remains disappointingly poor at about 15 months. Current ideas for improving this dismal state of affairs include intensification of therapy, either by more frequent or bigger doses of chemotherapy and/or concurrent radio-

therapy with the option of hyper-fractionation. Despite the myelosupportive agents now available, initial results of more intensive drug therapy have not been encouraging. The newer applications of radiotherapy appear to confer some advantage, particularly on the younger patient. Non-small cell tumours comprise about 85% of all bronchial cancers and for these surgery offers the best chance of cure. Recent meta-analysis of the results of cisplatin-containing combination chemotherapy has suggested a significant survival benefit for chemotherapy over best supportive care even when quality of life measures are included.

Advances in radiological imaging and intervention

Computerised axial tomography (CT scanning) has been a major advance in thoracic imaging although its indications and limitations are still being explored. There are some data to suggest that CT scanning may be as sensitive to bronchoscopy in demonstrating endobronchial tumours although most practising chest physicians would be unwilling to relinquish the opportunity of a direct view and their interventional skills are necessary for histological confirmation. High resolution CT has a more certain place in the diagnosis of bronchiectasis in which it has >95% sensitivity and specificity compared to bronchography, these figures being even better when haemoptysis is the presenting feature. It is difficult to conclude which procedure now represents the 'gold standard' and indeed this question will never be answered as the appropriate contrast material is no longer manufactured.

Diseases of the bronchioles remain difficult to demonstrate radiologically, and even clinically, until relatively advanced. However, high resolution CT scans performed in expiration show different tissue densities in areas of bronchiolitis thought to result from localised air trapping from hypoxic vasoconstriction. This procedure demonstrates abnormalities in other intriguing scenarios such as the contralateral lung in Macleod's syndrome and the post RSV (i.e. supposedly normal) lung in children and it has been suggested that previously occult bronchiolitis may pre-date the formation of bronchiectasis in some cases.

Various forms of intra-thoracic vascular embolisation, and recanalisation techniques for superior vena caval obstruction (SCVO), are now well established. Massive haemoptysis carries a mortality rate in excess of 80% with conservative treatment and over 20% with aggressive surgical intervention. Bronchial artery embolisation carries a primary technical success rate of up to 90% in experienced hands, but up to half will re-bleed in the long term either because of non-bronchial systemic arterial supply, disease progression or recanalisation of previously embolised arteries. 80% of pulmonary arteriovenous malformations are secondary to hereditary haemorrhagic telangiectasiae and can account for a marked right to left shunt. The favoured technique in these cases uses coils to embolise any lesion >3 mm and, although this may involve a hundred or more coils in severe cases, perseverance can effect a considerable reduction in shunt.

SVCO relapses in up to 20% of cases after chemo- or radiotherapy and may be treated by thrombolysis with insertion of a stent to maintain patency. If primary patency cannot be re-established by pharmacological means it is now possible to core out and macerate *in situ* thrombus.

Pneumothorax

Primary pneumothorax has an incidence of ~12/100,000 and most general physicians would be comfortable with their management of all but the most

difficult cases. Nevertheless, recent guide-lines based on a national survey amongst thoracic physicians should provide a powerful incentive to change. Formal inter-costal tube drainage is probably not necessary in up to 80% of cases—either observation or simple needle aspiration will suffice as management. It is not possible to determine in advance those cases which will resolve by aspiration alone although the average volume aspirated in successful procedures was ~1.6 litres. It is therefore suggested that aspiration should be abandoned if significant re-expansion has not been achieved after 2 litres air has been withdrawn.

Thoracoscopic surgery

Thoracoscopic surgery may now be employed in the biopsy of intra-pulmonary lesions, assessment of malignant disease, the definitive treatment of pneumothorax and the resection of any lobe or even an entire lung. In uncomplicated cases it employs a simple 3-port technique with chest drains inserted through the ports at the end of the procedure. Operative blood loss and hospital stay are all significantly less with the thoracoscopic approach and post-thoracotomy syndrome is completely abolished. These advantages more than compensate for the slightly longer primary procedure when compared to the open approach. Two caveats must be remembered when assessing what seems such a major surgical advance however; the operator must always be able to convert to an open technique and therefore needs to be fully trained in 'conventional' thoracic surgery, and the *internal* physiological insult from thoracoscopic resection remains unchanged despite the less aggressive approach. Those patients with insufficient pulmonary reserve to tolerate loss of lung tissue by open resection will therefore be similarly unable to tolerate thoracoscopic resection, although the marked improvement in post-operative morbidity will benefit all others.

Cystic fibrosis: screening and gene therapy

To enable genetic counselling for cystic fibrosis (CF) at the earliest appropriate stage, it would be necessary to screen all young adults through primary care. Such an approach has been attempted and demonstrated a 60–70% take up following a personal invitation but a very poor response to a standard written invitation. The resource implications for this sort of approach are large and not practicable. Most studies have therefore concentrated on the ante-natal population with the partner screened only if the mother is found to be a carrier. If both parties are heterozygous pre-natal diagnosis is offered and almost three-quarters of affected cases can be detected. Several studies have shown at least 70% take up by this approach which, theoretically, could reduce the CF population by 50%.

Gene therapy offers hope to CF sufferers in the foreseeable future. A number of problems relating to the appropriate DNA, vector systems and stability of integration have been overcome and there are large on-going studies in both the UK using a liposome vector and the USA, largely using an adenovirus vector. Initial results show a variable and somewhat unpredictable insertion of DNA in the target organ but there is good reason to expect this will improve and that some form of gene therapy for CF will be available by the end of the decade.

LESSONS FROM A SYMPOSIUM ON HYPERTENSION HELD IN THE COLLEGE ON 8 FEBRUARY 1995*

B. R. Walker, Department of Medicine, Western General Hospital, Edinburgh

WHO SHOULD BE GIVEN ANTI-HYPERTENSIVE DRUGS?

Systemic blood pressure (BP) is a continuously distributed variable in the population with an approximately normal distribution. The incidence of cardiovascular disease rises with increasing BP across a wide range including those values which we conventionally think of as within normal limits. For example, the risk of stroke in someone with a diastolic BP of 85 mmHg is higher than that in one whose diastolic BP is 80 mmHg. Any definition of hypertension is therefore arbitrary; it is a trait rather than a disease, a quantitative rather than a qualitative difference between individuals. In a research programme, it is easy to divide and compare subjects who are hypertensive or normotensive. However, in clinical practice the threshold of BP above which an individual should be treated with drugs and the action required for those whose BP oscillates around that threshold, remain contentious.

During the last 30 years, a series of intervention studies have consistently demonstrated the benefits of anti-hypertensive therapy (with thiazide diuretics and/or β -blockers) in reducing the incidence of stroke. These benefits accrue even in groups with diastolic BP as low as 90 mmHg (MRC Mild Hypertension Trial, 1985), and importantly also in elderly patients with diastolic BP < 90 mmHg but systolic BP \geq 160 mmHg (Systolic Hypertension in the Elderly Programme, 1992). However, because the benefits are in a fixed proportion (30–40%) of the incidence, they are greatest in those whose absolute risk of stroke is greatest. Thus, extrapolating from the above trials one would have to treat 566 young but 286 elderly patients with bendrofluazide for one year to prevent one stroke. It is clear that treatment should be limited to those likely to gain most.

Increasing age is not the only factor associated with a higher risk of cardiovascular disease at any given BP. The risk is magnified by the presence of other factors (smoking, diabetes mellitus, male sex, hypercholesterolaemia, obesity, positive family history and previous evidence of atheromatous disease). For example, the presence of non-insulin dependent diabetes approximately doubles the risk. The management of hypertension is now moving towards a clearer stratification of the risks of cardiovascular disease for the individual patient which should facilitate recognition of the level of BP at which treatment should begin. This strategy is reflected in the most recent guidelines of the British Hypertension Society (*Br Med J*, 1993; 306: 983–7). The principal recommendation is that all patients below the age of 80 years who have sustained BP of \geq 160 mmHg systolic or \geq 100 mmHg diastolic should receive anti-hypertensive drugs. In addition the large cohort of the population with a diastolic BP between 90–99 mmHg should receive drugs if any of the above cardiovascular risk factors is present, or if they have evidence of damage to the heart, retinae or kidneys, or if they are older than 60 years.

*A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 25 p. 354.