LETTERS TO THE EDITOR

Revision of BTS guidelines for treatment of asthma

The paper by Ward et al confirms the findings of Laitinen et al showing that airways inflammation is even in patients with mild asthma. This emphasises the importance of using anti-inflammatory drugs (steroids) as soon as the diagnosis of asthma has been confirmed, even in patients thought to have only “mild asthma”. Without anti-inflammatory treatment, symptoms resulting from bronchial hyperreactiveness are never controlled and optimal lung function is never attained. Over time, structural changes (remodelling) occur leading to a progressive decline in lung function and the risk of fixed obstruction (chronic obstructive pulmonary disease).

The present widespread dependence on bronchodilators in the UK may contribute to the fact that we have one of the highest respiratory death rates in Europe. The use of bronchodilators alone as in step 1 of the BTS guidelines should be discouraged, and treatment started at step 2 with regular inhaled corticosteroids to control symptoms and maximise peak flow rate. Bronchodilators should be used only as necessary for break-through wheezing. These principles have been used in Finland since 1994 with remarkable success in treating asthma. The new BTS guidelines would do well to follow their example.

George Strube
33 Goffs Park Road, Crawley, West Sussex RH11 9AX, UK
Gstrube@blii.net

References

Authors’ reply

We would like to thank Dr Strube for his interest in our recent paper1 and his stimulating letter which is topical given that the new BTS guidelines on asthma management are currently in preparation.

Our study was an attempt to investigate the interrelationships between airway inflammation, airway structural change (remodelling), lung function, and bronchial hyperreactivity to methacholine in patients with mild to moderate symptomatic asthma.

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The editors will decide as before whether to also publish it in a future paper issue.

Our paper is supportive of a further point, adding to work from others, which we feel is potentially substantive, of possible importance to future guideline considerations, and perhaps relates to some of Dr Strube’s concerns. The potential paradigm shift is that determining appropriate treatment only by reference to symptoms and lung function, as in current international and draft BTS guidelines, or even against indices of inflammation, may be oversimplistic, with prolonged treatment necessary to benefit airway remodelling reflected by improvement in BHR. It should be recognised that this remains a hypothesis and, pragmatically, it is of interest that the inclusion of BHR as an asthma management tool in the UK is not resource and is not currently practicable.2–7

We also realise that the demanding and detailed preparation of the BTS asthma guidelines has followed a due process warranted on the available evidence base with “levels of evidence” leading to “grades of recommendation” and, in turn, to “recommended best practice”. If appropriate pathophysiological research relevant to the clinical questions does not exist, it cannot be included. We feel that longitudinal data that seek to integrate information on airway inflammation, airway remodelling, lung function, and bronchial hyperreactivity and the effects of treatment are required. Such work, though demanding, is possible and would require multidisciplinary cooperation, dialogue, and appropriate support.

Chris Ward is a European Respiratory Society long term research fellow. The work was also supported by Australian NHMRC and a grant in aid from Glaxo Smith Kline.

C Ward
Lung Biology and Transplant Group, University of Newcastle upon Tyne and The Freeman Hospital, Newcastle upon Tyne, UK
chris.ward@ncl.ac.uk

D Reid, E H Walters
Clinical Sciences, University of Tasmania, Australia

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4 http://www.brit-thoracic.org.uk/guide/guidelines.htm
Chronic respiratory failure

The recent case report by Smyth and Riley describes an extremely uncommon chronic respiratory failure due to hypoventilation secondary to brainstem stroke, and documents a new treatment option with medroxyprogesterone acetate.

We recently saw two patients also with central hypoventilation resulting in chronic type II respiratory failure and treated both with, among other things, medroxyprogesterone acetate (30 mg twice daily) with good results. The first patient, a 69 year old man with a medical history of glomus caroticum resection due to malignancy with postoperative radiotherapy, presented to our outpatient clinic with polyglobulia. Arterial blood gas analysis revealed marked hypoxaemia (Pao, 4.8 kPa) and hypercapnia (Paco, 6.9 kPa). An intensive search for the cause showed no abnormality (acetazolamide lung function indicated only marginal chronic obstructive pulmonary disease (FEV/FVC 68%) but his hypoxic ventilatory response was markedly decreased and his hypercapnic ventilatory response was absent. The patient was treated with acetazolamide, theophylline, and medroxyprogesterone acetate and his blood gas tensions improved within days to normal values (Pao, 10.3 kPa, Paco, 5.1 kPa). The second patient, a 38 year old woman, was known from birth to have a hypothalamic pituitary gland deficiency with (stable) adiopositas (quetedet index 53). She had comorbid obesity, general malaise, and episodic hypoventilation. She was supposed to have been treated with acetazolamide and medroxyprogesterone acetate normalised her arterial blood gas tensions within days. Furthermore, she now follows an intense weight reduction programme and has lost more than 10 kg in weeks.

Acetazolamide has been shown to augment both the hypoxic and hypercapnic ventilatory response and to decrease Pao levels significantly in patients with chronic obstructive pulmonary disease (COPD). The mechanism of the effect is possibly due to a direct effect on the peripheral chemoreceptors (carotid bodies) as well as an effect on cerebral blood flow regulation.

It has been shown that medroxyprogesterone acetate also acts on the peripheral chemoreceptors (directly) as well as on the central chemoreceptors (indirectly) and progestosterone receptors in the hypothalamic in cats. This was also found in hypercapnic COPD patients, indicating that medroxyprogesterone acetate acts centrally on the respiratory centres. This support the hypothesis of medroxyprogesterone acetate in central hypoventilation. Furthermore, the combined treatment of acetazolamide and medroxyprogesterone acetate increases ventilation and improves arterial blood gas values—that is, it decreases Pao to normocapnic values and increases Paco, to almost normocapnic values in hypercapnic and hypoxic patients with COPD. In conclusion, we agree with Smyth and Riley that medroxyprogesterone acetate can be used in patients with central hypoventilation disorders.

References


Caffeine and exhaled nitric oxide

We read with interest the paper by Bruce et al which reported a significant decrease in exhaled nitric oxide (NO) levels 1 hour after caffeine consumption. However, we do not believe this study has fully clarified the relationship between caffeine consumption and exhaled NO levels.

When ascertaining the normal ranges for offline exhaled NO measurements we observed that some individuals had raised exhaled NO levels after caffeine consumption. To further clarify this effect, exhaled NO (parts per billion (ppb)) levels were measured at baseline and 0.5 and 1 hour after drinking a hot cup of coffee in 18 healthy non-asthmatic adults (five men) aged 17–56 years. Exhaled NO was measured by chemiluminescence (NOA 280, Sievers Instruments Inc, Boulder, CO, USA) using an offline technique in which subjects performed a slow vital capacity manoeuvre into a mylar balloon against a resistance of 5 cm H2O which corresponded to a flow rate of 50 ml/s. In order to minimise NO contamination from the upper airways and dead space, the first portion of the exhalation was not collected. Median (interquartile range) values of exhaled NO were significantly increased from baseline values 0.5 hour after caffeine consumption (median (interquartile range)) ppb: (4.1–2.5) (4.2–8.5) ppb, difference between medians 2.9 ppb (95% CI 1.4 to 12.4), p=0.007). There was no significant difference between baseline levels and the levels 1 hour after caffeine consumption (4.7 (2.6–6) ppb, p=0.081).

We conclude that levels of exhaled NO are significantly increased compared with baseline values 0.5 hour after caffeine consumption and have returned to baseline levels by 1 hour. The mechanism for this remains unclear. These results may need to be taken into consideration alongside the results of the previously mentioned study when designing studies and interpreting exhaled NO levels in adults.

References


Morbid obesity and hypersomnolence in several members of an ancient royal family

Recent studies have described an inherited basis for the sleep apnoea syndrome, as suggested by reports of families with multiple affected members. We present evidence indicating that several members of the Ptolemys, the royal family that ruled Egypt from 305 to 30 BC, suffered from obesity and sleep disordered breathing. Most of the information was reported by the Greek philosopher and historian Athenaeus (170–230 BC). The family’s pedigree with all affected members (shaded) is shown in fig 1. Magas I (case 1) was morbidly obese. Athenaeus reported that Magas “was weighted down with monstrous masses of flesh in his last days; in fact he choked himself to death.” Ptolemy II (case 2) and his sister Arsinoe III were extremely obese. Ptolemy II was not an energetic man and he disliked physical exertion. Although he lived to the age of 62, he was troubled by ill health throughout most of his life. Ptolemy IV the Philosopher (case 3),
Ptolemy VIII Evergetes II (case 6) was described as licentious even by the standards of his contemporaries. Calvin Wells reported that he was obese and he languished in habitual lethargy, perhaps because of chronic illness. Ptolemy V Epiphanes (case 4) also developed extreme obesity and used to fall asleep during social and political events. Athenaecos wrote: "One day, Aristomenes, his Prime Minister and chief advisor, had the effrontery to nudge the king awake when he dozed off during a diplomatic reception". Ptolemy VI Philometor (case 5) was portrayed by historian Polybios as "good and kind" and "apt to be lethargic and inert". Justinus added that he was extremely obese and sluggish. Ptolemy VIII Evergetes II (case 6) was morbidly obese. Apart from naming him Evergetes (benefactor), Alexandrians labelled him Kakergetes (malefactor) and—because of his obesity and large belly—"Physcon" (large bubble). Ptolemy VIII’s belly was so large that its circumference was wider than two arms extended. In order to cover his belly he wore a long tunic that extended down to his ankles with sleeves up to his wrists. Because of his obesity he was unable to walk, apart from an occasion when he went to meet the Roman Consul Skipion, the African. In a poem entitled “Ptolemy VIII Evergetes II or Kakergetes” the Greek poet Constantine Cavafy wrote: "Most obese, slothful Ptolemy Physkon, and due to gluttony somnolent observed: wise poet your verses are somewhat exaggerated...... And from obesity heavy as a stone, and from veracity somnolent the unalloyed Macedonian could scarcely keep his eyes open.”

Ptolemy X Alexander I (case 7) was so grossly obese that he had a man on either side to help him walk. He was idle, drunken, and extravagant in his lifestyle. From these descriptions it is clear that obesity was present in all of them and, in at least four of the seven kings, there were reports of daytime somnolence. This dynasty was probably the first reported family with sleep disordered breathing that had a familial predisposition.

**References**