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 hyperresponsiveness 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.7 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 breakthrough wheezing. These principles have been used in Finland since 1994 with remarkable success in treating asthma.7 The new BTS guidelines would do well to follow their example.

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References

Authors’ reply

We would like to thank Dr Strube for his interest in our recent paper7 and his stimulat- ing 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 in- flammation, airway structural change (remodelling), lung function, and bronchial hyperreactivity to methacholine in patients with mild to moderate symptomatic asthma.

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This included a longitudinal limb characteris- ting the temporal effects of inhaled cortico- steroid (ICS) treatment using a high proof of concept dosage (750 µg fluticasone propionate twice daily). The physiology, airway inflammation, and remodelling in asthma were found to be interrelated and improved by ICS, but the changes were not temporally concordant, with prolonged treatment necessary for maximal benefit in remodelling and bronchial hyperresponsiveness (BHR). We felt that the results support early and long term intervention with ICS, even in relatively mild asthmatics. This is a view shared by some and, arguably, provides a complement- tary pathophysiological and mechanistic con- text to recent clinic studies such as the OPTIMA trial.8 This year long study found that ICS treatment, even in mild asthmatics who had not previously been treated with corticosteroids, was associated with a signifi- cant effect on clinical exacerbations.

In his letter Dr Strube states that “without anti-inflammatory treatment, symptoms result- ing from bronchial hyperresponsiveness are never controlled and optimal lung function is never attained”. Our interpretation of the current BTS guidelines is that guidelines not only provide for—but also, indeed, indicate—regular ICS medication in such cir- cumstances, with no prescriptive requirement to work linearly through the stages. This is because the outcome of the escalating stepwise management is to attain control of symptoms and lung function: “theimport- ance of gaining control of asthma is re-emphasised…by starting treatment at a level likely to achieve this”.7 It also seemed appropriate to consult the pre-publication draft of the 2002 update of the guidelines which have been available at the BTS website for comment.4 These state at step 2: “the threshold for introduction of inhaled steroids has never been firmly established” and that “patients with lower inhaler requirements (short acting β2 agonist less than 2–3 times a day) may benefit”. Hence, the latest available guidelines further emphasise the importance of anti-inflammatory treatment with scope for early intervention based on clinical judg- ement. It would appear to us that Dr Strube’s valid concerns about the potential of under- treatment in some asthmatics, also apparent in studies such as OPTIMA, is also articulated in the BTS guidelines, but expressed slightly differently.

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 parameters in determining appropriate treatment only by reference to symptoms and lung function, as in current international and draft BTS guide- lines, or even against indices of inflammation, may be oversimplistic, with prolonged treat- ment 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 resourced and is not currently practicable.7

We also realise that the demanding and detailed preparation of the BTS asthma guidelines has followed a due process reliant on the available evidence base with “levels of evidence” leading to “grades of recommen- dation” 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 multidiscipli- nary 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.

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References
4 http://www.brit-thoracic.org.uk/guidelines.html
Chronic respiratory failure

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

We recently saw two patients also with central hypventilation 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, was referred to our outpatient clinic with polyyglobulia. Arterial blood gas analysis revealed marked hypoaxemia (Pao, 4.8 kPa) and hypercapnia (PaCO2 6.9 kPa). An intensive search for the cause showed no abnormality on cardiac lung function indicating only marginal chronic obstructive pulmonary disease (FEV1/VC 68%) but his hypoxic ventilatory response was markedly decreased and his hypercapnic ventilatory response was absent.

The patient was treated with acetazolamide, acetazolamide and oxygen on awake gas exchange in patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1994;7:850–5.

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 that 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-smoking adults (five men, 13 women) 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) levels of exhaled NO were significantly increased from baseline values 0.5 hour after caffeine consumption (median 19.9 (5.4–21.8) ppb, 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=0.007).

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 hyposomnia 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 Ptolemaic royal family 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 figure 1. Ptolemy I (case 1) was morbidly obese. Athenaeos 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 Philopater (case 3), 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 hypventilation disorders.

References


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 VII Euergetes (case 4) also developed extreme obesity and used to fall asleep during social and political events. Athenaeos 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—"Physkon" (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 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 the familial aggregation of obstructive sleep apnea. 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**


3. Strabo. XVII. 1.5.


