There is now clear evidence that misuse of corticosteroid metered-dose inhalers is associated with decreased asthma control, and previous studies have reported a decreased bronchodilator response in patients not using the pressurized metered-dose inhaler correctly. Incorrect use of inhalation devices has been reported frequently in the past; in the literature search reported by Cochrane et al., the frequency of efficient inhalation technique ranged from 46 to 59%. These findings support our view that the most important recommendation to clinicians about the prescription of an inhaler is the confirmation by observation that the device can be used efficiently. The conclusions of the meta-analyses reported by Dolovich et al. do not emphasize the importance of checking inhaler technique in all patients prior to the prescription of any inhalation device for the first time, and the need to check technique regularly thereafter especially if there is poor symptom control.

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To the Editor:

Teaching patients correct inhaler technique and reinforcing this technique with each subsequent office visit are indeed key steps to the successful implementation of aerosol therapy, as aptly stated by Drs. Barnes and Crompton. In 1982, Crompton identified the difficulties patients had when using their metered-dose inhalers; and this article, along with eight others, were discussed in the introduction to our meta-analysis. In addition, the take-home message from the meta-analysis was that for patients unable to master the required inhalation technique for a specific delivery device, other choices for inhalers delivering equivalent drug doses and providing the same clinical efficacy were often available. The importance of correct inhaler technique to successful therapy was stressed throughout the body of the text, with the points made in the Abstract re-emphasized in the concluding paragraphs, in which we restated that competence in the use of an inhaler needed to be confirmed by the physician or health-care worker when choosing an aerosol delivery device for their patient.

The selection criteria for studies included in the meta-analysis were randomized controlled trials (RCTs) in which responses to the same drug were tested using different delivery devices, thus eliminating the influence of device/drug combinations. In the descriptions of the methods and subject inclusion criteria for the many studies we reviewed, patient ability to use the various devices was one of the variables frequently mentioned. One can only assume that an inability to use a device correctly excluded a subject from a trial, but also that correct inhaler technique was taught prior to study entry. The studies selected for analysis included trials in which devices were tested under conditions of actual clinical use (type 1 studies) or in a laboratory setting with well-trained subjects (type 2 studies). In the former, inhaler technique may have been reinforced on clinic visits but not monitored otherwise. Barnes and Crompton have stated that the use of correct inhaler technique in all studies analyzed resulted in our not discerning differences in efficacy between devices, and this may be true. However, the purpose of the meta-analysis was to test whether device performance influenced response, independent of drug, and with patients able to use the devices correctly. β2-Agonists were the test drugs for the majority of the RCTs, with doses sufficient to achieve the plateau of the dose-response curve. Only four studies of corticosteroids met the selection criteria for inclusion in the analysis; these RCTs compared metered-dose inhaler plus spacer to dry powder inhaler use in well-controlled adult asthmatics and showed no differences in response using either delivery device. It is possible that these results were only a consequence of patients using the correct inhaler technique. We do agree that poor inhaler technique is a contributing factor to loss of asthma control and would welcome RCTs comparing delivery devices in this population. We fully agree with Drs. Barnes and Crompton that a patient’s ability to use an aerosol delivery device correctly is an exceedingly important aspect when choosing an inhaler, and thank them for underscoring this point in their review of the guidelines.

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Mometasone and Beclomethasone Comparison Article Observations

To the Editor:

Chrousos et al. (July 2005) cited an article by this letter’s coauthor stating that “… as dry powder inhaler delivery of ICS
results in higher lung deposition than delivery via CFC and HFA propellants... " The referenced article by LeSouef, "The Meaning of Lung Deposition," does not in any way state or imply that dry powder inhalers (DPIs) have greater lung deposition than propellant-driven inhalers. In fact, the article cited shows that lung deposition is unique to each device and drug combination. Furthermore, data from the LeSouef article is presented that shows that the specific hydrofluoroalkane (HFA)-metered-dose inhaler (MDI) tested with and without add-on spacers demonstrated much higher lung deposition than the DPI assessed (ie, 60% HFA-MDI vs 40% for the DPI). In addition, the tested chlorofluorocarbon (CFC) MDI also showed higher lung deposition values than the DPI (ie, 45% for the CFC-MDI vs 40% for the DPI). The high HFA-beclomethasone dipropionate (BDP) MDI (QVAR; 3M Pharmaceuticals; St. Paul, MN) lung deposition values have been reproduced and published many times.²,³ To the best of our knowledge, no DPI has ever been demonstrated to achieve >40% lung deposition, and indeed most marketed DPIs show values much <30%.

We have also taken note of the claims³ of the association of mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve compared with the mometasone DPI with a significantly lesser decrease in serum cortisol concentration area under the curve. However, cortisol suppression is associated with less than 10% to 20% reduction of total cortisol suppression. This is in part because no efficacy data was presented in this population. Thus, even if there was a clinically significant lack of a drop in cortisol with the mometasone DPI, the dose actually delivered to the patients was not shown to be efficacious in this study, whereas that dose of HFA-BDP has previously been shown to be efficacious.⁵ The assertions espoused by Chrousos et al.¹ that DPIs demonstrate higher lung deposition than MDIs as well as the clinical significance of the lack of cortisol suppression, are therefore somewhat questionable.

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To the Editor:

We thank Drs. Leach and LeSouef for their interest in our article,¹ and we welcome the opportunity to comment on their observations. The issue of pulmonary drug deposition with various inhaled formulations is complex and influenced by many factors, as outlined by Dr. Le Souef in the article² we cited. Chlorofluorocarbon (CFC) metered-dose inhalers (MDIs) are associated with low lung drug deposition (<10% to 20%).²,³ Reduction of static charge within the spacer with a detergent can increase markedly the lung deposition via an MDI device.⁴ Hydrofluoroalkane (HFA)-beclomethasone dipropionate (BDP)-MDI devices achieve lung deposition rates of 37 to 56% in patients with asthma; younger individuals have lung deposition rates at the lower end of this range.³,⁵ Dry powder inhalers (DPIs) are associated with pulmonary deposition rates of up to 40%, or intermediate between results with CFC and HFA MDI devices.² Despite different lung distribution rates, there is, however, no appreciable impact on the efficacies of inhaled corticosteroids delivered by DPI or MDI.⁷ Furthermore, the delivery of a greater fraction of the actuator dose to the lung vs the oropharynx does not necessarily translate into lower systemic bioavailability. At one half the daily inhaled dose of BDP, HFA-MDI treatment was associated with a virtually identical mean percentage decrease from baseline in 24-h area under the curve serum cortisol as compared with CFC-MDI delivery. This occurred despite far less BDP being delivered to the oropharynx after HFA-MDI treatment. Despite presumably greater lung and lower oropharyngeal deposition of HFA-BDP, the corresponding hypothalamic-pituitary-adrenal (HPA)-axis suppression was significantly greater than with mometasone furoate (MF)-DPI. MF is a more potent steroid than BDP but has a low systemic bioavailability after inhaled dosing of approximately 1%.⁸ We would suggest that it is the high systemic bioavailability of BDP and its active metabolite⁹ irrespective of MDI delivery method—that determines its effects on the HPA axis.

Drs. Leach and LeSouef suggest that the results obtained in our study are not clinically significant, in part because no efficacy data were presented in parallel. The efficacy of MF-DPI at the dose used in our study (400 μg one puff qd) in the treatment of persistent asthma is well documented in peer-reviewed literature.¹⁰,¹¹ Our study was designed to examine the effects on the HPA axis of 14 days of treatment with MD-DPI, HFA-BDP, and CFC-BDP. Thus, our main end points were 24-h area under the curve serum cortisol and timed urinary-free cortisol collections, as these are appropriate tests for detecting HPA-axis impairment.¹² From a purely endocrine perspective, it is important to be aware that a decrease of nearly one fourth in mean daily serum cortisol secretion can occur due to treatment with BDP, irrespective of HFA or CFC-MDI delivery. Given that MF-DPI, 400 μg one puff qd, is effective in the treatment of asthma, we believe
that the finding of significantly lower HPA-axis suppression as compared with HFA-BDP and CFC-BDP is useful information when assessing the therapeutic profiles of inhaled corticosteroids for use in the clinical setting.

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Noninvasive Ventilation and Dyspnea in Palliative Medicine

To the Editor:

We read with great interest the position paper of the American College of Chest Physicians about palliative and end-of-life care for patients with cardiopulmonary disease.1 We agree that it was about time for the “respiratory world” to write an official document on this hot topic. Having said that, we are concerned that little emphasis was paid to the important problem of dyspnea and particularly on its treatment. Pain is one of the major fears of human beings, and every effort should be made to relieve this symptom. In the position paper,1 it is stated for example that “the factors most commonly associated with a request for physician-assisted suicide are patients’ fear of losing control of mental faculties and experiencing severe pain”. Pain is a classic symptom for example of patients with end-stage cancer. We are, however, pulmonologists dealing not only with cancer patients but also with the patients with end-stage COPD, in whom the “pain of the respiratory system” (ie, dyspnea) is the predominant symptom. In the position paper,1 it was mentioned that the therapeutic options for dyspnea are oxygen, opioids, anxiolytics, and not-better-specified nonpharmaceutical intervention, basing this statement on an article2 published 4 years ago. In these last years, several studies were, however, published on the use of noninvasive ventilation (NIV) in patients with do-not-intubate order, with end-stage disease and severe dyspnea and/or respiratory distress. In the two more recent studies,3,4 it was demonstrated that about half of the patients survived the episode of respiratory distress and were discharged from the hospital. Indeed, in a pilot investigation5 it was showed that in a large portion of patients with end-stage solid cancer admitted to a palliative care unit for acute respiratory distress, NIV was able to significantly reduce dyspnea after only 1 h of ventilation. A randomized international trial is in progress in 10 palliative care units in order to evaluate the effect of oxygen therapy alone or in combination with NIV, the main outcomes being the reduction in dyspnea and in the use of opioids. Again we congratulate the authors of the position statement for their efforts, but we also wish that the chest physicians will consider in future the possibility of using NIV in the palliative treatment of dyspnea as a peculiar and unique tool of the respiratory world.

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