Withdrawal of Treatment in the ISOLDE Study

To the Editor:

I read with interest the recent article by Calverley et al (October 2003),¹ who address the use of withdrawal from treatment as an outcome in the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study. They conclude that losing patients with rapidly deteriorating health status and lung function from follow-up may reduce the power of a study to achieve its primary end point. While I am in complete agreement with this notion from a statistical perspective, I would like to comment on the clinical implications of their findings. Approximately 58.5% and 41.5% of the fluticasone-treated patients completed and withdrew from the study, respectively. These numbers suggest that a substantial number of patients with COPD do not appear to benefit from inhaled corticosteroid therapy. While one could argue that a much larger sample size than that studied in the ISOLDE study would be needed to see a significant effect on the rate of decline in lung function with inhaled corticosteroids, such a study may not be helpful in guiding clinicians to identify those patients who might benefit from inhaled corticosteroids, particularly since the majority of primary care physicians do not utilize spirometry in the management of COPD.² Increasing the statistical power of a study such as the ISOLDE study would do little to influence the proportion of patients who ultimately withdraw prematurely, thereby making it difficult to apply any positive statistical findings to the general COPD population. While there is little doubt that inhaled corticosteroids have an important role in the management of COPD, there remains a significant gap between what has been learned from pivotal trials such as the ISOLDE study and how such data may be applied in a real-world setting.

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REFERENCES


PET Scanning in Thymic Neuroendocrine Tumors

To the Editor:

We read with interest the recent report by Tiffet and colleagues (July 2003)¹ of their series of 12 cases of thymic neuroendocrine tumor. They note that although octreotide scintography has been reported as useful in detecting thymic neuroendocrine tumors,²,3 scanning for somatostatin receptors was not of help in their series. In addition, only one patient in the series of Tiffet and colleagues¹ was noted to be meta-iodobenzylguanidine (MIBG) positive. The accurate localization of the primary tumor site and possible metastases is crucial for optimum treatment of these tumors. We have recently treated two patients with this rare disease, both of whom presented with Cushing syndrome caused by ectopic adrenocorticotropic hormone secretion. In both cases, we found that positron emission tomography (PET) scanning with fluorine-18 fluorodeoxyglucose was useful either to localize the tumor or identify metastases.

In our first case (patient 1), the tumor, a typical carcinoïd (well-differentiated neuroendocrine carcinoma), was not localized with CT and an octreotide scan result was negative. How-
ever, the tumor did show up as a focal “hot spot” on subsequent PET scanning (Fig 1). A gated MRI of the hot spot gave further, accurate localization. PET scanning therefore localized the tumor when other modalities had failed. In the second case (patient 2), an atypical carcinoid (moderately differentiated neuroendocrine tumor), the tumor was localized with a CT scan of the chest but subsequent PET scan revealed an unsuspected metastasis in the lumbar spine (Fig 2). The lumbar metastasis required orthopedic fixation before the surgery to remove the mediastinal tumor. Octreotide scanning was not performed in patient 2, but MIBG scanning revealed the same distribution of metastases as the PET scan, and the patient received radioactive (I131) MIBG treatment.

As far as we are aware, PET scanning has not previously been described as a useful investigative tool for neuroendocrine tumors of the thymus. However, on the basis of our limited experience with this condition, we would suggest that in addition to CT, MRI, octreotide, and MIBG scanning, PET may be a valuable tool. Where available, it could be used and evaluated further in patients presenting with thymic neuroendocrine tumors. The sensitivity and specificity of PET compared to octreotide and MIBG scanning is unknown and requires further investigation.

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Blood and Starch in Cardiac Surgery*

To the Editor:

The recent article by Avorn et al (October 2003) purports to show an association between the use of hydroxyethyl starch (HES) and excessive postoperative bleeding after coronary artery bypass surgery (CABG). This article resurrects the unresolved controversy regarding the use of HES in cardiac surgery and the emerging concern of clinically significant bleeding. Several prospective randomized trials, observational studies, and meta-analyses have investigated the suspected association between HES use and bleeding after CABG.

Most randomized studies on HES and bleeding have failed to show any clinically significant bleeding differences. The published retrospective studies showing an increased incidence of blood loss have received the most press but are inherently limited due to study design. Cope et al retrospectively reviewed the use of hetastarch infusion based on perioperative exposure to HES and transfusion requirements during the first 24 h postoperatively. The selection bias of this study favored those with hemodynamic compromise or those with greater severity of illness. The meta-analysis by Wilkes et al shows that the difference in pooled mean blood loss in the albumin group was 350 mL compared with 789 mL in the HES group, a difference of 439 mL only.

We believe that the article by Avorn et al fails to show an association between HES and postoperative bleeding, as cited in the majority of related studies. The title leads the reader to believe that hetastarch increases the risk of bleeding, but the authors did not report any single measure of bleeding. They did not account for the number of bleeding episodes nor did they use quantifiable measures, ie, chest tube drainage volume. Some of the study design limitations were that no clear definitions of nonsurgical bleeding or proper criteria for correction of microvascular bleeding were used. Measurement of hematocrit from the drainage fluid and collection of blood samples for baseline