advent of randomized controlled trials to prove the efficacy of treatment. The US Food and Drug Administration (FDA) allowed them to be “grandfathered in” as the standard treatment of DVT and PE in the early 1960s when proof of efficacy became required for FDA approval. Low-molecular-weight heparins have been granted approval as indications for the treatment of DVT by virtue of randomized controlled trials showing equivalence with heparin in trials that do not include “un-anticoagulated” control subjects.

For the articles and FDA correspondence detailing the case for withdrawing the indications for therapy with anticoagulants (ie, heparin, low-molecular-weight heparins, and vitamin K antagonists) in the prophylaxis and treatment of venous thromboembolism, please see my Web site (http://hometown.aol.com/~dkcundiff/home.htm).

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Adenosine Deaminase Levels in Nontuberculous Lymphocytic Pleural Effusions

To the Editor:

We would like to support the points raised in the otherwise excellent article in CHEST by Lee et al (August 2001) with a larger series of patients. Those authors stated that adenosine deaminase (ADA) levels in patients with nontuberculous lymphocytic effusions seldom exceeded the diagnostic cutoff for tuberculosis pleurisy. Thus, only two patients with lymphomas and one with a complicated parapneumonic effusion (2.8%) among 106 patients with lymphocytic effusions had ADA levels of > 40 U/L. This percentage remained practically unmodified (3.6%) if only exudates (n = 82) were considered.

We reviewed the medical records of 293 patients whose pleural fluid data showed a level of > 50% of lymphocytes, after convincingly excluding their tuberculous origin. The study was conducted at a 480-bed teaching hospital in Lleida, Spain, during the last 7 years. The clinical diagnoses of the patients were defined by known predetermined criteria. Specifically, transudates and exudates were defined by the criteria of Light et al, and the categorization of pleural fluid as malignant relied on either a positive result of cytology or biopsy specimen testing or a known cancer without an alternative explanation for the effusion. The final diagnoses of pleural effusions were as follows: malignancy (139 patients); transudates (86 patients); parapneumonic (2 patients); pericardial disease (19 patients); abdominal surgical procedures (10 patients); pulmonary embolism (6 patients); trauma (5 patients); Dressler syndrome (4 patients); connective tissue diseases (3 patients); and postcoronary artery bypass surgery (1 patient). The primary tumors in the malignant group included the following: lung (54 patients); breast (31 patients); lymphoma (13 patients); ovary (12 patients); and miscellaneous (29 patients). In our hospital, ADA activity is determined by Giusti’s colorimetric method, with 40 U/L serving as the cutoff for the identification of tuberculous effusions. Eight patients (2.7%) in our population surpassed this cutoff as follows: non-Hodgkin lymphomas, three patients (ADA levels, 67.5, 46, and 45.9 U/L); acute lymphoid leukemia, one patient (ADA level, 346 U/L); colorectal cancer, one patient (ADA level, 47.1 U/L); small cell lung cancer, one patient (ADA level, 45.9 U/L); and uncomplicated parapneumonic effusions, two patients (ADA levels, 58.9 and 40.5 U/L). If we excluded transudates, the percentage of false-positive elevations was raised insignificantly (3.9%).

In conclusion, our findings are nearly identical to those reported by Lee et al, namely that false-positive elevation is rare...
(ie, < 4%) when the criterion of ADA levels is applied to lymphocytic exudates only. Due to its high sensitivity and specificity, measurement of the pleural fluid ADA level is an excellent test both for ruling out and ruling in a suspected diagnosis of tuberculous effusion, at least in areas with a high prevalence of tuberculosis.3,4

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To the Editor:

Evidence suggests the relationship between the perceptibility of dyspnea and the hypoxic ventilatory response:1,2 Doxapram, a potent ventilatory stimulant, is known to affect primarily the hypoxic ventilatory response by acting on peripheral chemoreceptors.3 Although the ventilatory effect of doxapram has been investigated,4,5 the effect of doxapram on the sensation of dyspnea has not been investigated. Therefore, we investigated the effect of doxapram on the perception of dyspnea during inspiratory resistive loading.

Hypoxic ventilatory response and perception of dyspnea during inspiratory resistive load (20.0 cm H2O/L/s and 30.9 cm H2O/L/s) was measured using the rebreathing circuit with a Validyne pressure transducer (Validyne Engineering; Northridge, CA) as previously described1 in seven healthy male volunteers (age range, 26 to 46 years) who did not know the purpose of the study.1 All subjects were previously measured without doxapram administration. The experiment was performed in a single-blind fashion; however, in each case, doxapram was administered after saline solution placebo in order to avoid the residual effects of the drug. Measurements of dyspnea and the hypoxic response were started after a 15-min placebo infusion via a forearm vein at the rate of 10 mL/h and after the ventilation rate became stable. Following the completion of the measurements with placebo treatment, the infusion was stopped for 1 h as a resting period, and then doxapram diluted in saline solution was infused in the same manner as placebo at the rate of 2.0 mg/kg/h. The measurements were started 15 min after the doxapram infusion because 15 min is required to stabilize the serum doxapram concentration.5

All subjects completed the experiments without any side effects. Ventilatory parameters such as minute ventilation (Ve), frequency, tidal volume, mouth pressure 0.1 s after the start of inspiration against occluded airway (P0.1), peak inspiratory mouth pressure, and arterial oxygen saturation (SpO2) during stable ventilation were not significantly different between placebo and doxapram infusion. The end-tidal tension of carbon dioxide was significantly lower during doxapram infusion than placebo infusion. The hypoxic ventilatory responses expressed in the Ve slope (ΔVe/ΔSpO2) and the P0.1 slope (ΔP0.1/ΔSpO2) were significantly increased during doxapram infusion (p < 0.05 for both by paired t test; Fig 1). The Borg scores of individual subjects during breathing with resistances of 20.0 cm H2O/L/s and 30.9 cm H2O/L/s also significantly increased during doxapram infusion (p < 0.01 and p < 0.05, respectively, by paired t test).

These results showed that doxapram administration augments the dyspnea sensation as well as the hypoxic ventilatory response. Although we could not clarify the mechanisms by which doxapram augments the perception of dyspnea with resistive load, our finding provides some clinical implications. Since doxapram is occasionally used for the treatment of patients with respiratory failure, one should be aware that this drug possibly increases dyspnea. However, it has been reported that the blunted perception of dyspnea as well as lowered hypoxic chemosensitivity play a role in some pathologic conditions such as death from asthma and respiratory failure in Parkinson disease.1,2 Because doxapram can improve both dyspnea sensation and hypoxic chemosensitivity, it is of interest to investigate the effect of a drug like doxapram on these patients.

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Doxapram and Perception of Dyspnea

To the Editor:

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