ABSTRACTS

DELAYED DEVELOPMENT OF OBLITERATIVE BRONCHIOLITIS SYNDROME WITH OKT3 AFTER UNILATERAL LUNG TRANSPLANTATION *

A PLEA FOR MULTICENTER IMMUNOSUPPRESSIVE TRIALS

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There is no consensus regarding the optimal induction immunosuppression regimen after lung transplantation (LT). In addition to the potential benefit of a reduced incidence of early acute allograft rejection, cytolytic induction immunosuppression may impact on long-term allograft function. We retrospectively assessed our incidence of obliterative bronchiolitis syndrome (OBS) stages Ia and IIa in LT survivors given two different cytolytic induction immunosuppression regimens: (between March 1989 and October 1990) OKT3 (5 mg/d) x 10 to 14 days (n=11) vs (between November 1990 and April 1993) Minnesota antilymphocyte globulin (MALG) (10 to 15 mg/kg/dx5 to 7 days. Cyclosporine (CSA) (whole blood polyclonal assay=600 to 800 ng/mL), azathioprine (1 to 2 mg/kg/d), and maintenance prednisone (0.2 mg/kg/d), were similar, Surveillance spirometry was performed monthly, in accordance with accepted American Thoracic Society criteria. Fiberoptic bronchoscopy with transbronchial biopsies (TBBs) were performed for clinical indications. Surveillance TBBs were not performed during the era of this study. As defined by the ISHLT “Working Formulation for the Standardization of Nomenclature and for Clinical Staging of Chronic Dysfunction in Lung Allografts,” latencies to development of OBS stages Ia and IIa were determined by Kaplan-Meir analysis. Stepwise regression (Cox proportional hazards model) was performed for the variables: cytolytic induction regimen, episodes CMV infection, serologic CMV donor (+); recipient (-) mismatch, prior pregnancy, HLA (A,B, DR, DQ) mismatches, episodes greater than grade AI acute cellular rejection (ACR). We found that the OKT3 cohort experienced longer latencies for OBS stages Ia and IIa. Latencies to OBS stage Ia for OKT3 vs MALG were 962 ± 65 vs 354 ± 85 days (X ± SEM) respectively. Brookmeyer-Crowley 95% confidence intervals for median latencies were 744 to 1,180 vs 266 to 510 days for OKT3 vs MALG, respectively. The Cox model was significant only for the variable of the induction cytolytic immunosuppression regimen (p=0.0015). By physiologic criteria, longer course of OKT3 appeared superior to the short-course MALG protocol in delaying chronic lung allograft dysfunction. These effects may be related either to inherent differences in the antilymphocyte preparation or, alternatively, the difference in duration of treatment between groups. Surveillance TBB and treatment of detected occult ACR may serve to negate the observed differences in latencies for OBS. (CHEST 1996; 109:870-873)
COMPARATIVE STUDY OF THE CLINICAL EFFICACY OF NEDOCROMIL SODIUM AND PLACEDO*

HOW DOES CROMOLYN SODIUM COMPARE AS AN ACTIVE CONTROL TREATMENT?

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Nedocromil sodium and cromolyn sodium are the only two currently available nonsteroid anti-inflammatory agent for treatment of asthma. Clinical differences between the two agents remain under continuous investigation with reports differentiating the two on the basis of atopy of the patient and reversibility of bronchoconstriction. This study investigated the efficacy of nedocromil sodium (4 mg, qid) for treatment of mild to moderate asthma in comparison to placebo using cromolyn sodium (2 mg, qid) as an active control treatment. Patients were primarily allergic asthmatics (with at least 15% reversibility) previously maintained on a regimen of regular bronchodilator therapy. During a 2-week run-in period, the patients's slow-release theophylline therapy was removed, and the patients were randomized to treatment after deterioration of asthma control (asthma symptom summary score of 3 for 7 of the 14 days). After 8 weeks of treatment, patients were returned to as occasion requires bronchodilator therapy, as per the 2-week baseline period. The results demonstrate that patients treated with nedocromil sodium showed statistically significant improvements during the primary time period (mean weeks-3 through 8) over placebo-treated patients as evidenced by all indexes of asthma symptoms, pulmonary function measures, and decreased bronchodilator reliance (p<0.05). Patients treated with cromolyn sodium demonstrated similar improvements over placebo-treated patients. Comparisons between nedocromil sodium and cromolyn sodium showed the two agents to be comparable in this group of primarily allergic patients with reversible disease. Between-group differences were noted for 3 of the 13 variables (nighttime asthma, FEV₁, and forced expiratory flow rate between 25% and 75% of the FVC) in favor of cromolyn sodium when the data were pooled during the primary time period. The number of patients missing 1 or more days from work/school/regular actively due to asthma was significantly fewer compared with placebo, and favoring nedocromil sodium over cromolyn sodium. No differences were observed among the three treatment for adverse events. This study demonstrated that in primarily allergic patients with reversible airways disease, nedocromil sodium and cromolyn sodium are both significantly more effective than placebo for treatment of mild-to-moderate asthma.

(CHEST 1996; 109:945-52)
PARTIAL VS FULL $\beta$-RECEPTOR AGONISM*
A CLINICAL STUDY OF INHALED ALBUTEROL AND FENOTEROL

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Study objective: To compare the maximal extrapulmonary effects of the $\beta$-agonists albuterol and fenoterol in eight healthy volunteers.

Subjects and methods: In this double-blind study, we have examined the maximum cardiac effects (electromechanical systole [QS2I] - a measure of inotropy, heart rate, BP) and metabolic effects (plasma K+ and cyclic adenosine monophosphate [cAMP]) of repeated inhalation of albuterol and fenoterol. In eight healthy volunteers, 400 µg of each drug was administered every 10 min until QS2I and plasma K+ had reached a plateau (+0.1 mmol/L for K+, and ±10 ms QS2I). The maximum response (Emax) and the dose of albuterol required to produce 50% of the maximum response to fenoterol (ED50F) were calculated.

Results: The Emax for fenoterol was significantly greater than albuterol for plasma K+ (-1.4 vs -1.03 mmol/L; p<0.002), QS2I (-71.8 vs 57.5 ms; p=0.047), and cAMP (33.8 vs 18.1 nmol/L; p<0.002). The dose required to produce the ED50F was significantly greater for albuterol than for fenoterol with potency ratios of 1.75, 1.61, and 2.26 for plasma K+, QS2I, and cAMP, respectively. There were no significant differences between fenoterol and albuterol with respect to heart rate (Emax, 44.9 vs 32.5 beats/min; p=0.19; potency ratio, 1.98; p=0.052).

Conclusions: These findings suggest that albuterol behaves as a partial agonist at $\beta$-receptors when compared with fenoterol, and that when inhaled in doses currently recommended for severe asthma, albuterol will result in lesser maximum cardiac and metabolic effects than fenoterol. These findings are consistent with the hypothesis that the property of full receptor agonism may contribute to the increased risk of death associated with fenoterol.

(CHEST 1996; 109:957-62)
TRENDS IN COMPLIANCE WITH BRONCHODILATOR INHALER USE BETWEEN FOLLOW-UP VISITS IN A CLINICAL TRIAL*

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Study Objective: To assess objectively measured, long-term trends in compliance with physician-prescribed metered-dose inhaler (MDI) use during a clinical trial.

Design: A prospective study.

Setting: The Lung Health Study, a 5-year clinical trial to determine the effect of special intervention with an intensive smoking cessation program and bronchodilator therapy in cigarette smokers 35 to 60 years of age with minimal to moderate airflow limitation due to COPD.

Participants: Two hundred thirty-one participants who were issued an MDI with an attached Nebulizer Chronolog (NC) (Forefront Technologies Inc; Lakewood, Colo) which electronically records the date and time of each MDI actuation. One hundred two participants were not informed of the recording capabilities of the attached NC, while 129 participants were aware of the NC's monitoring function.

Intervention: Following an initial 12-week period of counseling, participants returned to the clinic every 4 months.

Measurements and results: Analysis of the data from the NC collected over a period of 2 years indicates that compliance with the prescribed medication regimen was best immediately following each follow-up visit and gradually declined during the interval between follow-up visits. The level of compliance after each visit was lower for each successive follow-up. These trends could not be observed from self-report or weighing the medication canisters at follow-up visits. The participants who were informed of the NC's function and who were provided with detailed feedback about their inhaler use generally showed better compliance.

(CHEST 1996; 109-963-68)

ANOVA=analysis of variance JHU=Johns Hopkins University; MDI=metered-dose inhaler; NC=Nebulizer Chronolog; SI=special intervention; UC=usual care; UCLA=University of California, Los Angeles
INHALATION OF SINGLE VS MULTIPLE METERED-DOSE BRONCHODILATOR ACTUATIONS FROM RESERVOIR DEVICES*

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Differences in inhalation technique with reservoir or spacer devices may affect metered-dose inhaler (MDI) dose availability to a patient.

Purpose: This study examined the effect of single vs multiple actuations of an MDI into reservoir devices on dose delivery of albuterol, with three clinically available reservoir brands.

Methods: An in vitro lung model simulated inspiration from the MDI reservoir system. Albuterol (Proventil; Schering) was delivered by MDI, with the Monaghan Aerocamper, the Diemolding Healthcare Division (DHD) aerosol cloud enhancer (ACE), and the Schering InspirEase, using standardized volumes and inspiratory flows of 30 L min⁻¹. The MDI was actuated into each brand of reservoir 1.2, or 3, times in rapid succession, followed by a single inhalation. Aerosol dose at the reservoir mouthpiece was captured on a cotton filter, dissolved in ethanol, and measured with a spectrophotometer at 278 nm.

Results: For all three brands of reservoir, less accumulated dose of drug is delivered with multiple actuations than with multiple single actuations each followed by inhalation. The total dose in milligrams increased significantly with two multiple actuations compared with one actuation in the Aerocamper and ACE (p<0.01), but not in the InspirEase ((p>0.05). The Aerocamper, ACE, and InspirEase delivered a mean total dose (SD) of 0.0264 mg (0.012), 0.0271 mg (0.007), and 0.0136 mg (0.006), respectively, with one actuation compared to 0.0243 mg (0.006), 0.0226 mg (0.006), and 0.0109 mg (0.005), respectively, with two multiple actuations, for losses of 8.0%, 16.6%, and 19.9% in dose per actuation for each brand. A further decline in delivery per actuation to 0.0164 mg (0.001), 0.0184 mg (0.004), and 0.009 mg (0.005) for the 3 brands, respectively, was found with 3 multiple actuations before inhalation. This was a loss of 37.9%, 32.1%, and 28.7% of the dose per single actuation to each brand. There was no significant difference between the Aerocamper and the ACE in dose availability with 1,2 or 3 actuations, but both of these brands provided significantly more drug than the InspirEase.

Conclusion: Maximal aerosol bronchodilator from an MDI reservoir was given by single actuations for any of the brands tested (p>0.05). Although total dose increased with multiple actuations, a decline in efficiency was seen with two and three multiple actuations, compared to single actuation. The dose delivered per actuations decreased for the Aerocamper, ACE and InspirEase from 0.0264 mg (0.012), 0.0271 mg (0.007), and 0.0136 mg (0.006) with one actuation, to 0.0243 mg (0.006), 0.0226 mg (0.006), and 0.0109 mg (0.005), respectively, with two multiple actuations, for losses of 8.0%, 16.6%, and 19.9% in dose per actuation for each brand. Two rapid actuations followed by a breath will give a significant accumulation of dose with some loss when compared to two single actuations each followed by inhalation. Three multiple actuations led to a loss of approximately one third of the drug dose obtainable with three single actuations each followed by inhalation, for all three brands.

(CHEST 1996; 109:969-74)

ANOVA=analysis of variance; MDI=metered-dose inhaler;
MSLI=multistage liquid impinger.
EVALUATION OF PULMONARY LESIONS WITH FDG-PET*
COMPARISON OF FINDINGS IN PATIENTS WITH AND WITHOUT A HISTORY OF PRIOR MALIGNANCY

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Study Objective: The purpose of this study was to evaluate the accuracy of positron emission tomography (PET) using F-18-fluorodeoxyglucose (FDG) in differentiating benign from malignant pulmonary lesions both in patients with and without a history of prior malignancy.

Design: Forty-eight consecutive patients with pulmonary lesions suspicious for malignancy underwent FDG-PET scanning. Group 1 included 27 patients without and group 2 included 21 patients with a history of malignancy. Pathologic proof of diagnosis was obtained for 32 patients and 16 patients were followed up clinically and radiographically for at least 6 months. The standard uptake ratio (SUR) and the lesion to background (L/B) ratio were determined in 45 patients.

Setting: Vanderbilt University Medical Center.

Results: In group 1, the average SUR and L/B ratio for malignant lesions (n=14) were 8.9±4.9 and 20.6±14.2, respectively. For benign lesions (n=12), the average SUR was 3.3±3.2 and L/B ratio was 5.2±5.5. In group 2, the average SUR and L/B ratio for malignant lesions were not significantly different from group 1. Using either a SUR greater than 2.5 or L/B ratio greater than 5 as an cutoff level to differentiate benign and malignant lesions, the sensitivity and negative predictive value in both groups were 100%. There were five false-positive studies in group 1 and one in group 2, including tuberculosis (n=2), a granulomatosus lesion (n=1), an inflammatory lesion (n=1), a schwannoma (n=1); and a fibrous mesothelioma (n=1). The overall accuracy was 88%, 81% in group 1, and 95% in group 2.

Conclusion: FDG-PET can identify malignant pulmonary lesions both in patients without and with a history a prior malignancy with a high sensitivity and negative predictive value for lesions greater than 1 cm (100% in this study). High FDG uptake by some inflammatory processes and benign tumors may cause false-positive results. Semiquantitative evaluation using SUR or L/B ratio provides similar accuracy.

(CHEST 1996; 109;982-88)
A CLINICOPATHOLOGIC STUDY OF RESECTED CASES OF ADENOSQUAMOUS CARCINOMA OF THE LUNG*

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Adenosquamous carcinoma of the lung is an uncommon form of the lung cancer. Owing to the infrequent occurrence of this disease, no series reported to date (and to our knowledge) has been of adequate size for definitive statistical analysis. In this study, survival curves and background factor affecting prognosis in those with resected adenosquamous carcinoma of the lung were reviewed. In the period from 1973 to 1994, a total of 1,284 patients with primary lung cancer, including 44 cases (3.4%) of adenosquamous carcinoma, were surgically treated in our department. The cumulative 5-year postoperative survival rate, for all cases of adenosquamous carcinoma of the lung, was 18.5%. When the survival rates were compared by histologic type, the outcomes of patients with adenosquamous carcinoma were statistically worse than for patients with squamous cell carcinoma and adenocarcinoma, owing to the highly aggressive pathologic stage of adenosquamous carcinoma. The background factors most closely associated with the survival rate in those with adenosquamous carcinoma, using Cox’s proportional hazard model, were gender and the degree of nodal involvement. Five-year survival was obtained in seven patients as follows: T1NOMO in one patient, T2NOMO in three, T2NIMO in two, and T3NOMO in one. Of these seven patients, all had received complete resections, and five were NO cases. Although our series is small, this study suggests that adenosquamous carcinoma of the lung is an aggressive tumor that grows rapidly.

*(CHEST 1996; 909-989-94)*
THE EFFECTS OF NEUROMUSCULAR PARALYSIS ON SYSTEMIC AND SPLANCHNIC OXYGEN UTILIZATION IN MECHANICALLY VENTILATED PATIENTS*

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Objective: To evaluate the effect of neuromuscular paralysis and splanchnic oxygen utilization in patients in respiratory failure during controlled mechanical ventilation.

Setting: A university-affiliated teaching hospital.

Intervention: Mechanically ventilated patients, who were undergoing hemodynamic monitoring and who had a gastric intramucosal pH (pHi) of
less than 7.35, were studied. Prior to paralysis, the patients were sedated with lorazepam and morphine to standard end points, and the cardiac output and oxygenation were optimized. The patients were then paralyzed with doxacurium and the ventilator rate adjusted to keep the 
PaCO$_2$ at baseline value. The hemodynamic and oxygenation profile and pH$_i$ were determined prior to paralysis and repeated 2 to 2.5 h later.

Results: Eight patients were studied; their mean age was 63±8 years and acute physiology and chronic health evaluation II score was 22±4. The mean fraction of inspired oxygen, positive end-expiratory pressure, and venous admixture ratio prior to the study was 0.7±0.14, 11.8±2.4 cm H$_2$O and 26±9%, respectively. Prior to paralysis, the mean set assist controlled ventilation rate was 15±2 breaths/min and the patient rate was 23±5 breaths/min. With neuromuscular paralysis, the cardiac index fell from 4.6±2.2 to 4.3±2.4 L/min/m$^2$ (p=0.1), the oxygen delivery fell from 537±129 to 471±95 mL/min/m$^2$ (p=0.03), and the oxygen consumption and extraction ratio fell from 200±77 to 149±35 mL/min/m$^2$ (p=0.03) and 36±5 to 31±10, respectively (p=0.2). The pH$_i$ increased from 7.21±0.16 to 7.29±0.1 (p=0.02).

Conclusion: In critically ill patients in respiratory failure, neuromuscular paralysis decreases whole body oxygen consumption and increases pH$_i$. Presumably, by eliminating the work of breathing, there is a redistribution of blood flow from the respiratory muscle to the splanchnic and other nonvital vascular beds.

*(CHEST 1996; 109:1038-42)*

| AC=assist controlled ventilation; CO=cardiac output; PCWP=pulmonary artery wedge pressure; pH$_i$=gastric intramucosal pH |
CONTINUOUS FIBEROPTIC ARTERIAL AND VENOUS BLOOD GAS MONITORING IN HEMORRHAGIC SHOCK*

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Study objective: To compare the performance of continuous fiberoptic blood gas monitoring with standard, intermittent blood gas sampling in the measurement of arterial and central venous blood gases during marked hemodynamic changes.

Design: Prospective, consecutive, enrollment, experimental study.

Setting: Research laboratory at a university medical center.

Participants: Seven anesthetized, mechanically ventilated pigs.

Interventions: Severe shock was induced by hemorrhage in pigs monitored by a pulmonary artery catheter, an arterial line, and two fiberoptic blood gas sensors: one intra-arterial, and the other inserted into the superior vena cava via right internal jugular vein cutdown. Fiberoptic blood gas monitor measurements were compared with standard intermittent blood gas sampling.

Measurements and results: A total of 184 blood gas samples were compared in seven animals at baseline, during shock, and after resuscitation. The baseline mean (±1 SD) cardiac output decreased from 4.0±0.9 to 1.2±0.6 L/min during shock and returned to baseline after retransfusion (3.9±1.3 L/min). The comparison of continuous fiberoptic blood gas monitoring with intermittent blood gas sampling showed a bias ± precision of
0.035±0.047 for arterial pH, 0.021±0.031 for central venous pH, -4.09±2.96 mm Hg (-0.55±0.39 kPa) for arterial PCO₂, 3.67±2.44 mm Hg (-0.49±0.33 kPa) for central venous PCO₂, 5.79±9.64 mm Hg (-0.77±1.29 kPa) for arterial PO₂, and -7.85±8.32 mm Hg (-1.05±1.14 kPa) for central venous PO₂.

Conclusions: Continuous fiberoptic blood gas monitoring agrees closely with standard intermittent blood gas sampling during severe hemodynamic shifts and has a comparable accuracy for both arterial and venous blood gas measurements. Changes in venous PCO₂ have recently been shown to correlate with changes in global tissue perfusion (eg, changes in cardiac output). Such data, available immediately via continuous venous blood gas monitoring, may be useful for monitoring shock and the response to resuscitation.

(CHEST 1996; 109:1049-55)
The past 15 years have seen a rise in mortality and morbidity resulting from asthma, despite a concurrent rise in general knowledge about the disease. The step-care strategy recognized these changes in its approach to asthma management; however, this approach should be used only with attempts to control environment allergens. Step-care therapy requires that patients be categorized by the severity of illness. Step-one therapy is used for mild, infrequent symptoms and involves treatment based primarily on inhaled bronchodilators. Step-two therapy is instituted in all asthmatics except the mildest cases; it involves treatment by inhaled corticosteroids, cromolyn, or nedocromol. Step-three treatment targets cases of severe asthma through the use of oral corticosteroids. In all phases of treatment, however, it should be remembered that patient education is of critical importance. Education improves patient compliance and is critical to the successful treatment of asthma.

(AHR=airway hyperresponsiveness; EIB=exercise-induced bronchoconstriction; MDI=metered-dose inhaler; PEF=peak expiratory flow)