Ketoconazole for Early Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial

The ARDS Network Authors for the ARDS Network

The acute respiratory distress syndrome (ARDS) has been recognized for more than 30 years as a severe form of acute respiratory failure. Patients with this disorder are critically ill, require mechanical ventilation in an intensive care unit (ICU), and have a high mortality, ranging from 35% to 50% in recent reports.1,2 Sepsis, severe trauma, aspiration of gastric contents, and massive blood transfusion are the most common clinical events that place patients at risk for the development of ARDS.3 Recently, the concept of ARDS has been expanded to include milder forms of the same pathophysiologic process. The entire pathophysiologic spectrum is now called acute lung injury (ALI), whereas ARDS refers to the more severe end of that spectrum.4 The degree of impairment of oxygenation of arterial blood is used to distinguish patients with ARDS from those with ALI. Despite this distinction, available data suggest the outcomes for patients with ALI are similar to outcomes of the subset of patients with ARDS.5 Supportive care is the current state-of-the-art therapy for ALI and ARDS; no specific pharmacologic therapies have yet proved efficacious.1

ALI, including ARDS, is generally considered to be a consequence of an overaggressive inflammatory response that includes inflammatory cell migration into interstitial and alveolar

Context Three clinical studies have suggested that ketoconazole, a synthetic imidazole with anti-inflammatory activity, may prevent the development of acute respiratory distress syndrome (ARDS) in critically ill patients. However, the use of ketoconazole as treatment for acute lung injury (ALI) and ARDS has not been previously studied.

Objective To test the efficacy of ketoconazole in reducing mortality and morbidity in patients with ALI or ARDS.

Design Randomized, double-blind, placebo-controlled trial conducted from March 1996 to January 1997.

Setting Twenty-four hospitals associated with 10 network centers in the United States, constituting the ARDS Network.

Patients A total of 234 patients with ALI or ARDS.

Intervention Patients were randomly assigned to receive ketoconazole, 400 mg/d (n = 117), or placebo (n = 117), initiated within 36 hours of fulfilling study entry criteria and given enterally for up to 21 days.

Main Outcome Measures Primary outcome measures were the proportion of patients alive with unassisted breathing at hospital discharge and the number of days of unassisted breathing (ventilator-free days) during 28 days of follow-up. Secondary outcome measures included the proportion of patients achieving unassisted breathing for 48 hours or more, the number of organ failure–free days, and changes in plasma interleukin 6 (IL-6) and urinary thromboxane A2 metabolites (thromboxane B2 [TXB2] and 11-dehydro-TXB2).

Results In-hospital mortality (SE) was 34.1% (4.3%) for the placebo group and 35.2% (4.3%) for the ketoconazole group (P = .85). The median number of ventilator-free days within 28 days of randomization was 9 in the placebo group and 10 in the ketoconazole group (P = .89). There were no statistically significant differences in the number of organ failure–free days, pulmonary physiology, or adverse events between treatment groups. The median serum ketoconazole level was 1.25 µg/mL and serum levels greater than 0.5 µg/mL were detected in 96% of patients assayed. Plasma IL-6, urinary TXB2, and 11-dehydro-TXB2 levels were unaffected by ketoconazole.

Conclusions In these patients with ALI or ARDS, ketoconazole was safe and bioavailable but did not reduce mortality or duration of mechanical ventilation or improve lung function. These data do not support the use of ketoconazole for the early treatment of ALI or ARDS.


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spaces, with subsequent activation and release of injurious proteases and reactive oxygen species. Pulmonary hypertension is thought to be due to activation and release of vasoactive mediators, including arachidonic acid metabolites, accompanied by diffuse pulmonary microvascular thrombosis. While the neutrophil is a major effector cell for lung injury, the alveolar macrophage probably plays a central role in the host inflammatory response that underlies ALI as a major producer of vasoactive substances, neutrophil chemoattractants, and procoagulant substances.

Ketoconazole is a synthetic antifungal imidazole that also has anti-inflammatory activities. Ketoconazole inhibits thromboxane synthase, an enzyme in the synthetic pathway of thromboxane A2 (TXA2) that acts as a potent pulmonary vasoconstrictor and aggregator of platelets and neutrophils. Ketoconazole also inhibits 5-lipoxygenase, the enzyme necessary to generate leukotrienes, and decreases leukotriene B4 (LTB4) production, 1 of the primary neutrophil chemoattractants implicated in ARDS. Cyclooxygenase is unaffected by ketoconazole. Ketoconazole also inhibits endotoxin-stimulated alveolar macrophage production of procoagulant activity. Thus ketoconazole can modulate inflammatory pathways known to be involved in ALI and ARDS.

Three clinical studies have suggested that ketoconazole may be effective in preventing the development of ARDS in high-risk critically ill patients. One of those studies even found ketoconazole to be significantly associated with a reduction in mortality. However, the use of ketoconazole as treatment for early ALI or ARDS has not been previously studied. Therefore, the primary objective of this randomized trial was to assess the effect of ketoconazole on mortality and morbidity in patients with early ALI or ARDS. There were 2 primary efficacy variables: the proportion of patients alive with unassisted breathing at hospital discharge and the number of days of unassisted breathing (ventilator-free days) at day 28 after randomization. This efficacy measure is thought to influence cost and morbidity attributable to differences in recovery time from respiratory failure.

METHODS

ARDS Network

The National Heart, Lung, and Blood Institute organized and funded the ARDS Network, a consortium of 10 clinical centers and a clinical coordinating center in the United States, to design and conduct multicenter clinical trials of novel therapies for ALI and ARDS. Each clinical center is composed of 1 or more university medical centers and affiliated hospitals. This report describes data from the Ketoconazole and Respiratory Management in ALI and ARDS (KARMA) Trial, the first study conducted by this network. This study had a 2 x 2 factorial design comparing 400 mg/d of ketoconazole with placebo and a ventilatory strategy comparing a tidal volume of 6 ml/kg with 12 ml/kg. This report describes the results from the ketoconazole vs placebo arm of the study. The ventilator management arm of the study will be reported separately.

Study Patients

Patients were enrolled from 24 hospitals at the 10 centers constituting the ARDS Network. Patients were eligible for the study if they were in an ICU, required positive pressure ventilation via endotracheal or tracheostomy tube, and had acute onset of significantly impaired oxygenation with a PaO2-to-FIO2 ratio less than or equal to 300 (adjusted for barometric pressure), bilateral infiltrates consistent with pulmonary edema on a frontal chest radiograph, and no clinical evidence of left atrial hypertension or, if a pulmonary artery catheter was in place, a pulmonary artery occlusion pressure less than or equal to 18 mm Hg. Patients had to be enrolled within 36 hours of developing these criteria. The study was approved by the institutional review board at each hospital. Consent was obtained from all patients or their surrogates before enrollment.

Exclusion criteria were age younger than 18 years, participation in other interventional trials within the previous 30 days, pregnancy, increased intracranial pressure, neurologic conditions that could impair weaning from ventilatory support, sickle cell disease, severe chronic respiratory disease, morbid obesity, burns covering at least 30% of total body surface area, malignancy or other irreversible condition for which 6-month mortality was estimated to be at least 50%, or a history of bone marrow or lung transplantation. Patients were also excluded if the clinicians caring for them were not agreeable to using volume-cycled assist/control ventilation for at least 12 hours or were not committed to providing aggressive life support at the time of enrollment. Finally, patients were excluded if they received any imidazole within 7 days or terfenadine, astemizole, or cisapride within the preceding 3 days; had an allergy to imidazoles or their derivatives; had severe chronic liver disease (defined as a Child-Pugh score of ≥10); or had evidence of acute viral, ischemic, or toxic hepatitis with moderate or severe acute hepatocellular or cholestatic injury, defined as an aspartate aminotransferase or alanine aminotransferase level of 500 U/L or more or an alkaline phosphatase level of at least 240 U/L.

A primary risk factor for ALI or ARDS was assigned by the investigators at the time of randomization. Study subjects were later classified by primary risk factor as having direct lung injury (eg, pneumonia, aspiration of gastric contents) or indirect lung injury (eg, sepsis, multiple trauma, pancreatitis). The groups were treated equally with regard to mechanical ventilation based on simultaneous enrollment in the ventilator strategy arm of the study. Mechanical ventilation was performed in strict accordance with the study protocol. Weaning from ventilatory support was also done according to the protocol and commenced when patients...
met all of the following criteria: at least 12 hours since initial protocol ventilator change; FiO2 of 0.40 or less; positive end-expiratory pressure and FiO2 values less than or equal to those from the previous day; not receiving neuromuscular blockade; inspiratory efforts exhibited by the patient; and systolic blood pressure of at least 90 mm Hg without vasopressor support. Once qualified, patients were weaned from ventilatory support with a pressure support protocol.

**Study Drug Administration**

After informed consent was obtained, the data coordinating center provided assignment using a computer-generated randomized, stratified by tidal volume assignment, to either 400 mg/d of ketoconazole or placebo. The local research pharmacist was unblinded to the treatment assignment and prepared the study drug for administration while the patients, investigators, study coordinators, and all clinical personnel remained blinded to the randomization.

Ketoconazole and placebo were dissolved in 60 mL of Coke Classic (The Coca-Cola Company, Atlanta, Ga) at room temperature.18 The liquid was gently stirred for 5 minutes or until the tablet was completely dissolved. Disolved placebo and ketoconazole had identical appearances. The study drug was administered enterally via gastric, duodenal, or jejunal tubes within 4 hours of randomization. Each dose was flushed through the enteral tube with 20 mL of normal saline; the tube was clamped for 1 hour following drug administration. Subsequent doses were administered once daily for 21 days or until the patient achieved 48 hours of unassisted breathing. Unassisted breathing was defined as either extubation with or without supplemental oxygen, T-tube breathing, tracheostomy mask breathing, or continuous positive airway pressure less than or equal to 5 cm H2O without pressure support or intermittent mechanical ventilator assistance. Study drug was discontinued if possible drug-induced hepatic injury developed as defined by an aspartate aminotransferase or alanine aminotransferase level of at least 500 U/L, or a rise in aspartate aminotransferase or alanine aminotransferase level greater than 8 times baseline, or an alkaline phosphatase level of at least 240 U/L that was 3 times greater than the baseline value.

**Biochemical Measurements**

Serum samples were obtained on study day 3 for the measurement of ketoconazole levels. Ketoconazole was assayed by a modification of the bioassay method of Bodet et al.19 Blood and urine specimens were collected at baseline (study day 0, prior to initial study drug dose) and on study day 3. Blood was drawn into EDTA-anticoagulated tubes, centrifuged, and frozen at −70°C. Urine was similarly centrifuged and frozen. Interleukin 6 (IL-6) was measured in 2 laboratories by immunoassay. Thromboxane B2 (TXB2), a metabolite of TXA2, was measured in the urine using an enzyme immunoassay kit. For the measurement of 11-dehydro-TXB2, 1 mL of urine was spiked with 1.0 ng of a tetradecuterated analog of 11-dehydro-TXB2 and extracted on a liquid chromatography column. The sample was then exposed to a 1% solution of hydrogen chloride for 2 hours, purified by thin-layer chromatography with a mobile phase of ethyl acetate and acetic acid (48:1). The purified compounds were then converted to their pentafluorobenzyl esters and purified by thin-layer chromatography, with a mobile phase consisting of ethyl acetate and heptane (3:1). The trimethylsilyl ether was formed and quantification was achieved. Mass over charge (m/z) 511 and m/z 515 were monitored for endogenous 11-dehydro-TXB2, and the tetradecuterated internal standard, respectively. Urinary TXB2 and 11-dehydro-TXB2 values were divided by urinary creatinine to account for differences in renal function.

**Statistical Methods**

The study was analyzed on an intention-to-treat basis. The primary efficacy variables were the proportion of patients alive with unassisted breathing at hospital discharge and the number of days alive with unassisted breathing (ventilator-free days) through day 28, assuming a patient survived for at least 48 consecutive hours after initiating unassisted breathing. Secondary efficacy variables assessed during the 28 days from randomization included: (1) the proportion of patients who achieved unassisted breathing for 48 hours or more, (2) the number of organ failure–free days, (3) the number of days meeting “commence weaning” criteria, (4) the proportion of patients withdrawn because of possible liver toxicity, and (5) the occurrence of barotrauma.

Patients were considered to have survived if they were discharged from the hospital alive with unassisted breathing. Patients who were still receiving assisted ventilation or in a hospital were considered censored observations at 180 days (the last day of follow-up). The Kaplan-Meier estimate and its SE at the last death time before 180 days was used as the 180-day mortality estimate.

Analyses of mortality and ventilator-free days were performed for the subgroups with ARDS at baseline, sepsis-induced ALI or ARDS, trauma-induced ALI or ARDS, and direct vs indirect lung injury. These subgroup analyses were prospectively defined, although the study was not specifically powered to detect differences within subgroups.

Days without organ failure were defined separately for each form of failure. Each patient was evaluated for cardiovascular failure (systolic blood pressure ≤90 mm Hg or required vasopressor support); central nervous system failure (Glasgow coma score ≤12); coagulation failure (platelet count ≤ 80 × 10^9/L, [80 × 10^9/L]); hepatic failure (bilirubin ≥ 2 mg/dL [34.2 µmol/L]); and renal failure (serum creatinine ≥ 2 mg/dL [176.8 µmol/L]). The total number of days in organ failure was calculated and subtracted from 28 or survival time, whichever was less, to obtain the value for organ failure–free days.
An analysis of variance was used to compare the change of TXB2, 11-dehydro-TXB2, and IL-6 levels with ketoconazole from baseline to day 3. The covariates were baseline level and ventilator strategy.

A Mantel-Haenszel test was used to compare the frequency of qualitative patient characteristics and adverse events between ketoconazole and placebo, adjusting for the respiratory management group. For quantitative characteristics, a 2-way analysis of variance was used to test for a treatment effect in the presence of covariates that were thought to be prognostic (APACHE III score, sepsis, and trauma were defined a priori20 or were unbalanced between treatments. A Poisson regression was used to test for a difference in the frequency of mild, moderate, severe, and life-threatening adverse events for each organ system using the World Health Organization classification. All statistical tests were performed using statistical analysis software.

**Data and Safety Monitoring**
The trial design required periodic review of the data by the data and safety monitoring board after enrollment of 200, 400, 600, and 800 patients. The progress of the ventilator study was considered separately from that of the ketoconazole study, and it was possible that 1 could be discontinued while the other continued to accrue patients. As a superiority trial, the ketoconazole study was designed to have 80% power of finding a significant difference at a 2-sided \( P = .05 \) significance level if the true mortality difference between the treatment groups was 10%. O’Brien-Fleming boundaries were developed to stop the trial early if superiority of 1 treatment was found.21 The study was also designed to stop early if the observed improvement in mortality was less than 3% in favor of ketoconazole.

**RESULTS**
The study began on March 18, 1996, and all treatment with ketoconazole and placebo was stopped on January 13, 1997, by the data and safety monitoring board because of lack of efficacy. The ventilator management trial was continued.

A total of 234 patients were enrolled in the study: 117 were randomized to ketoconazole and 117 to placebo (FIGURE 1). The number of patients enrolled at each center ranged from 10 to 38. The ventilation strategies were evenly balanced between groups. Baseline variables did not differ by treatment group with regard to primary cause of lung injury, severity of lung injury, severity of illness, age, sex, arterial blood gas values, or positive end-expiratory pressure (TABLE 1). ARDS (\( \text{PaO}_2/\text{FiO}_2 \leq 200 \)) was present at the time of study entry in the majority of enrolled subjects; only 13% (\( n = 31 \)) had a \( \text{PaO}_2/\text{FiO}_2 \) ratio greater than 200 and up to 300 at the time of randomization. Follow-up was complete for all 234 patients.

**Mortality and Ventilator-Free Days**
The in-hospital mortality (SE) was not different: 34.1% (4.3%) for placebo and 35.2% (4.3%) for ketoconazole (\( P = .85 \)). A proportional hazards regression model was created using terms for treatment, APACHE III score, sepsis, trauma, and neuromuscular blocker use. The APACHE III score was significantly predictive, but there was no drug effect in a model that corrected for this measure of severity of illness. There was no significant center effect; thus, we did not adjust the main analysis for center. Kaplan-Meier survival plots for the treatment groups were virtually identical (FIGURE 2).

The median number of ventilator-free days was not different between the ketoconazole group (10 days) and the placebo group (9 days) (\( P = .89 \)). The patients without ventilator-free days died or, rarely, were still receiving assisted ventilation at 28 days. The same proportion of patients in each arm achieved unassisted ventilation within 28 days (59%) (FIGURE 3). The time to when patients first met “commence weaning” criteria was also the same in each group, with a median of 3 days.

Analyses of mortality and ventilator-free days were performed for the subgroups with ARDS at baseline, sepsis-induced ALI or ARDS, trauma-induced ALI or ARDS, and direct vs indirect lung injury. No differences were detected between treatment groups for these selected subgroups. In addition, there was no significant interaction, positive or negative, with the ventilator arm of the study.16

**Physiologic Responses and Organ Failure**
We examined changes in pulmonary physiology for the first 4 days after randomization. There were no significant differences between study groups for lung injury score, \( \text{PaO}_2/\text{FiO}_2 \) ratio, static total respiratory system compliance, or positive end-expiratory pressure (TABLE 2).
Organ failure–free days describe the number of days that a surviving patient is free of any organ failure during the 28-day window and are a measure of morbidity in survivors. The median number of organ failure–free days was not significantly different between treatment groups (Table 3). There were no significant differences between study groups in the proportions of patients who received vasopressors (51% for placebo vs 54% for ketoconazole), nor was there a difference in the number of days of vasopressor use.

**Biochemistry**

The lower limit of detectable ketoconazole in our bioassay was 0.5 µg/mL. Ketoconazole levels greater than 0.5 µg/mL were detected in 96% of patients assayed in the ketoconazole group. The median serum level was 1.25 µg/mL with the highest level being 9.5 µg/mL. The mean was not estimable because of the relatively high detection limit in our assay (0.5 µg/mL).

Baseline and day 3 urinary TXB$_2$ levels were assayed in 173 subjects and 11-dehydro-TXB$_2$ levels were assayed in 40 subjects. Values were divided by urinary creatinine to adjust for renal function. There were no significant differences between study groups for either of the thromboxane metabolites. Mean (SD) baseline levels of urinary TXB$_2$ were 6.9 (6.8) ng/mg of creatinine for placebo (n=88) and 6.2 (5.3) ng/mg of creatinine for ketoconazole (n=85). At day 3, the levels were 7.5 (11.3) ng/mg of creatinine for placebo and 7.4 (8.4) ng/mg of creatinine for ketoconazole. Mean (SD) baseline levels of urinary 11-dehydro-TXB$_2$ were 4.14 (4.23) ng/mg of creatinine for placebo (n=20) and 7.18 (12.9) ng/mg of creatinine for ketoconazole (n=20). At day 3, the levels were 4.84 (5.57) ng/mg of creatinine for placebo and 12.8 (26.9) ng/mg of creatinine for ketoconazole. The change from baseline to day 3 for ketoconazole was not statistically different than the change for placebo (P=.08).

Ketoconazole did not alter plasma IL-6 levels measured in 2 laboratories using distinct immunoassay methods.

**Safety**

Barotrauma (pneumothorax, subcutaneous emphysema, or pneumomediatinum) and the use of chest tubes was not significantly different between the 2 groups (19% for placebo vs 24% for ketoconazole; P=.38). There were no significant differences in the proportions of patients with a worsening radiographic score, receiving neuromuscular blockade, or receiving sedatives.

Twenty percent of all patients developed liver enzyme level elevations meeting the criteria for possible drug-induced hepatic injury. A cholestatic pattern was present in 14% (placebo, 11% vs ketoconazole, 16%) and a hepatocellular injury pattern developed in 6% of all patients (placebo, 6% vs ketoconazole, 5%). However, there was no difference between placebo and ketoconazole groups in the incidence of liver enzyme level elevations, regardless of pattern (P=.53). Because of potential drug interactions, we examined the frequency of patients’ astemizole, terfenadine, or cisapride use. Seven patients received cisapride during the study, while no patients received the other 2 drugs. No cardiac arrhythmias were reported for any of these 7 patients, nor was there a difference in the incidence of arrhythmias between the 2 groups (placebo, 7% vs ketoconazole, 9%; P=.61).

We examined the frequency of spontaneously reported adverse events by body system class. There was a trend toward more reports of cardiovascular

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### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=117)</th>
<th>Ketoconazole (n=117)</th>
<th>Total (N=234)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/FIO$_2$ &gt;200 and ≤300</td>
<td>15 (13)</td>
<td>16 (14)</td>
<td>31</td>
<td>.79</td>
</tr>
<tr>
<td>PaO$_2$/FIO$_2$ ≤200 (ARDS)</td>
<td>90 (78)</td>
<td>90 (83)</td>
<td>183</td>
<td>.61</td>
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<tr>
<td>PaO$_2$/FIO$_2$ &gt;300†</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>6</td>
<td>.41</td>
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<tr>
<td>PaO$_2$/FIO$_2$ = NA‡</td>
<td>5 (4)</td>
<td>9 (8)</td>
<td>14</td>
<td>.41</td>
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**Lung injury category, %**

<table>
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<tr>
<th>Category</th>
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<th>Ketoconazole</th>
<th>Total</th>
<th>P Value</th>
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</thead>
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<tr>
<td>Direct injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (15)</td>
<td>15 (15)</td>
<td>16 (15)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>15 (15)</td>
<td>15 (15)</td>
<td>30 (25)</td>
<td>.99</td>
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</table>

**Indirect injury**

<table>
<thead>
<tr>
<th>Category</th>
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<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Sepsis§</td>
<td>31 (28)</td>
<td>32 (28)</td>
<td>31 (28)</td>
<td>.99</td>
</tr>
<tr>
<td>Trauma‡</td>
<td>9 (8)</td>
<td>10 (8)</td>
<td>10 (8)</td>
<td>.99</td>
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<tr>
<td>Multiple transfusions</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>.99</td>
</tr>
<tr>
<td>Not classified</td>
<td>26 (23)</td>
<td>25 (23)</td>
<td>25 (23)</td>
<td>.99</td>
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</table>

**Baseline variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=117)</th>
<th>Ketoconazole (n=117)</th>
<th>Total (n=234)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52 (18)</td>
<td>55 (19)</td>
<td>53 (19)</td>
<td>.23</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>62 (55)</td>
<td>58 (51)</td>
<td>60 (55)</td>
<td>.57</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>81.0 (2.5)</td>
<td>81.6 (2.1)</td>
<td>81.3 (2.1)</td>
<td>.83</td>
</tr>
<tr>
<td>PaO$_2$/FIO$_2$</td>
<td>150 (7)</td>
<td>139 (6)</td>
<td>145 (5)</td>
<td>.24</td>
</tr>
<tr>
<td>Paco$_2$</td>
<td>36 (1)</td>
<td>31 (1)</td>
<td>36 (1)</td>
<td>.97</td>
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<tr>
<td>pH</td>
<td>7.40 (0.01)</td>
<td>7.40 (0.01)</td>
<td>7.40 (0.01)</td>
<td>.76</td>
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<tr>
<td>PEEP</td>
<td>8.3 (0.3)</td>
<td>8.4 (0.4)</td>
<td>8.4 (0.4)</td>
<td>.72</td>
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<tr>
<td>Systolic blood pressure</td>
<td>117 (2)</td>
<td>115 (2)</td>
<td>116 (1)</td>
<td>.42</td>
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</table>

**Baseline CXR, %¶**

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>Placebo (n=112)</th>
<th>Ketoconazole (n=111)</th>
<th>Total (n=223)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>1 quadrant</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>.60</td>
</tr>
<tr>
<td>2 quadrants</td>
<td>8 (8)</td>
<td>5 (5)</td>
<td>13 (11)</td>
<td>.60</td>
</tr>
<tr>
<td>3 quadrants</td>
<td>15 (14)</td>
<td>14 (14)</td>
<td>29 (25)</td>
<td>.60</td>
</tr>
<tr>
<td>4 quadrants</td>
<td>76 (68)</td>
<td>81 (68)</td>
<td>157 (134)</td>
<td>.68</td>
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</table>

**Baseline vasopressors, %**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Ketoconazole</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 (42)</td>
<td>49 (45)</td>
<td>47 (44)</td>
<td>.68</td>
</tr>
</tbody>
</table>

*FIO$_2$ indicates fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; PEEP, positive end-expiratory pressure; and CXR, chest x-ray film.
†PaO$_2$/FIO$_2$ for these 6 patients averaged 134 (range, 61-263) at the time they met entry criteria but increased to more than 300 during the interval between meeting entry criteria and enrollment.
‡Not available.
§Details of the trauma, such as multiple fractures or pulmonary contusion, were not captured.
¶Number of quadrants with pulmonary infiltrates.
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adverse events in the ketoconazole group ($P = .07$). There were 5 reports of circulatory failure in patients taking ketoconazole (4 lethal), 3 cases of hypotension (1 lethal), and 1 case of hypertension. Three of these reports were from the same patient, and none were reported by investigators to be either unexpected in the course of ARDS or associated with the intervention. There were 2 reports of circulatory failure in patients given placebo (1 lethal and 1 severe), neither of which was considered by investigators to be either unexpected in the course of ARDS or associated with the intervention. There were 2 reports of circulatory failure in patients given placebo (1 lethal and 1 severe), neither of which was considered by investigators to be either unexpected in the course of ARDS or associated with the intervention.

There was no significant difference in survival between groups ($P = .85$).

**Table 2.** Changes in Pulmonary Physiology During the First 4 Study Days*

<table>
<thead>
<tr>
<th>Variable, by Study Day</th>
<th>Mean (SD) Values</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Lung injury score†</td>
<td>1</td>
<td>2.25 (0.09)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.38 (0.09)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2.51 (0.11)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.55 (0.13)</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>1</td>
<td>166 (8)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>167 (7)</td>
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<tr>
<td></td>
<td>3</td>
<td>165 (7)</td>
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<tr>
<td></td>
<td>4</td>
<td>165 (8)</td>
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<tr>
<td>Lung compliance‡</td>
<td>1</td>
<td>33 (13)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>31 (11)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>32 (15)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>31 (15)</td>
</tr>
</tbody>
</table>

*Fi$_O_2$ indicates fraction of inspired oxygen.
†Lung injury score calculated as reported by Murray et al.\textsuperscript{22}
‡Lung compliance indicates total respiratory system compliance (tidal volume/static airway pressure − Set positive end-expiratory pressure; mL/cm H$_2$O.

**Table 3.** Median Number of Organ Failure–Free Days Through Day 28

<table>
<thead>
<tr>
<th>System</th>
<th>Placebo</th>
<th>Ketoconazole</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>23</td>
<td>22</td>
<td>.52</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>10</td>
<td>14</td>
<td>.56</td>
</tr>
<tr>
<td>Coagulation</td>
<td>25</td>
<td>25</td>
<td>.62</td>
</tr>
<tr>
<td>Hepatic</td>
<td>24</td>
<td>22</td>
<td>.92</td>
</tr>
<tr>
<td>Renal</td>
<td>27</td>
<td>26</td>
<td>.25</td>
</tr>
</tbody>
</table>

**COMMENT**

The strengths of this study are its relatively large size and its multicenter composition, leading to a heterogeneous population of patients with ALI or ARDS. In addition, baseline clinical characteristics were well balanced between the 2 groups, and drug absorption in an acidic beverage led to good bioavailability in critically ill patients. Unfortunately, ketoconazole did not improve mortality, time free from mechanical ventilation, or lung function.

Ketoconazole can modify the inflammatory response of macrophages in a manner that might be expected to improve the course of ALI and ARDS.\textsuperscript{11} Two small, single-center randomized trials of high-risk patients demonstrated that ketoconazole prophylaxis leads to less frequent development of ARDS and improved survival.\textsuperscript{13,14} After our study was under way, a third study was published supporting these observational findings.\textsuperscript{15} If efficacy could be established in ALI and ARDS, ketoconazole would be an attractive treatment option because of its low cost and toxicity.

The 2 previous clinical trials studied the effects of ketoconazole in critically ill patients at risk for ARDS.\textsuperscript{13,14} Slotman et al\textsuperscript{12} used 200 mg/d of ketoconazole, administered enterally, in 71 high-risk surgical patients and found ARDS developed in 31% of the placebo group, compared with 6% of the ketoconazole-treated group ($P < .01$). A reduction in median ICU length of stay was also observed but was not significantly altered. Yu and Tomasa\textsuperscript{14} began with a 200-mg/d dose of ketoconazole, also administered enterally, but the dose was doubled after the first 5 patients were treated because of low serum concentrations of the drug. The patients ($n = 54$) in that study were surgical patients with sepsis. The fre-
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quency of ARDS development in the placebo group was 64% compared with 15% in the ketoconazole-treated group \((P = .002)\). A reduction in mortality from 39% to 15% \((P = .05)\) was also observed, although significant reductions in ventilator and ICU days were not achieved. The third, more recent study compared the use of a ketoconazole practice guideline for ARDS prophylaxis in 1 hospital ICU with no guideline in another hospital’s ICU. The guideline called for 200 mg of ketoconazole via nasogastric tube for 21 days or until ICU discharge in patients at risk for ARDS. Forty patients were studied, 20 in each ICU. Implementation of the guideline was associated with a significantly lower rate of ARDS. Serum drug concentrations were not measured.

The study reported here was designed as an early treatment in contrast to the studies that were reported as prevention trials. However, many patients in the Yu and Tomasa study already had what would now be considered ALI or ARDS by current American-European Consensus Conference definitions. Many of the patients had PaO\(_2\)/FiO\(_2\) ratios less than 300 and some had ratios less than 200, suggesting that several patients may have had early ALI at the time of enrollment (M. Yu, MD, oral communication, February 1996). For those with ALI or ARDS at the time of enrollment, ketoconazole still appeared efficacious in their study. The mortality in the treatment group with a PaO\(_2\)/FiO\(_2\) ratio less than 300 was 19% compared with 63% in the comparable placebo group (M. Yu, MD, oral communication, February 1996). Therefore, the timing of the drug delivery (prior to ARDS vs early in the course of ARDS) does not appear to explain fully the differences in study results.

Patients enrolled in the studies by Slotman et al. and Yu and Tomasa were predominantly surgical patients with trauma and/or sepsis, and ours were a mixture of medical and surgical patients. Therefore, we performed a subgroup analysis of patients with ALI complicating trauma or sepsis and found that these subgroups did not derive a survival benefit from ketoconazole. Inferences need to be made cautiously, because our study was not powered for these subgroup analyses. However, we do not believe that patient selection alone can explain the contrasting results between this trial and prior studies.

We used the same dosage of ketoconazole used by Yu and Tomasa. In that study, ketoconazole concentrations of 0.202 (0.341) µg/mL were achieved in patients who did not develop ARDS, compared with levels of 0.146 (0.127) µg/mL in those patients who subsequently developed ARDS. Therapeutic concentrations for fungal treatment are reported to be between 0.1 and 10 µg/mL. We delivered ketoconazole via the gastrointestinal tract as in both previous studies, but we first dissolved the ketoconazole in Coke Classic, which has a pH of 2.5. Dissolving the drug in acidic beverages circumvents problems of dissolution and, thus, absorption in patients with high gastric pH such as those treated with histamine-2 blockers or antacids. Once dissolved, ketoconazole is well absorbed from the gut independent of pH. The use of an acidic beverage to deliver ketoconazole probably explains why we achieved ketoconazole blood levels nearly 10 times higher (median value = 1.25 µg/mL) than those reported by Yu and Tomasa.

As an assessment of the bioactivity of ketoconazole at the drug levels achieved in this population, we measured urinary TXB\(_2\) and 11-dehydro-TXB\(_2\), the major urinary metabolites of TXA\(_2\), to estimate the effect of ketoconazole on thromboxane synthase activity. Plasma TXB\(_2\) levels were lower in ketoconazole-treated patients compared with placebo in 1 study, and another study demonstrated a decrease in plasma of TXB\(_2\) after treatment with ketoconazole compared with no change with placebo. However, use of plasma TXB\(_2\) to assess in vivo production of TXA\(_2\) is problematic, because variable ex vivo platelet activation during blood drawing can radically alter results.

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It is possible that the lack of effect of ketoconazole on clinical outcomes relates to the lack of a clinically significant effect on pulmonary and systemic inflammation. While the dosage chosen for this study was reasonable given previous clinical data, the dose-response curve of ketoconazole in ALI is unknown. It is conceivable that lower blood levels of ketoconazole, such as those seen in Yu and Tomasa’s study, have more of an anti-inflammatory effect than the higher levels achieved in this study. Biphasic dose-response effects have been observed when manipulating arachidonic acid metabolism as well as in the treatment of severe sepsis.

Although 21% of patients receiving ketoconazole developed abnormalities in liver enzymes with a hepatocellular or cholestatic liver injury pattern sufficient to suggest drug-induced hepatitis, this number was not significantly different from the placebo group (17%), and no serious adverse effects related to liver failure were reported. Thus, we believe most of these abnormalities were due to coexistent illness rather than to ketoconazole.

This large, multicenter trial did not confirm promising initial reports from 3 smaller studies. Given the heterogeneous population studied, we believe our findings are generalizable to the majority of patients with ALI. The dosage and timing of the ketoconazole administration and patient selection do not appear to explain these disappointing results. Higher blood levels of ketoconazole were achieved than in previ-
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References

The Alzheimer's Association convened an advisory board to examine the current state of EOL care in ADRD and to draft recommendations for improvement of care for persons with terminal dementia. The panel defined high-quality EOL care for persons with terminal dementia as characterized by appropriate interventions, good EOL care, and ongoing processes of educated decision making established early in the diagnosis; and integrated, coordinated provision of care. The opposite—poor quality of care—is characterized by inappropriate interventions, poor symptom management, and inappropriate use of services. The panel formulated 8 recommendations organized into 4 categories (Table).

**Comment.** End-of-life care for persons dying with dementia requires specialized knowledge and service arrangements, education for professional and lay caregivers, and continuing education and improvement. Because persons dying with ADRD are vulnerable and depend on others to meet their needs, the US health care system must attend to these unique needs and develop policies to promote compassionate high-quality care.

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**Acknowledgment:** Names of the members of the advisory board, expert panel, and steering committee are available from the authors on request.


**CORRECTIONS**

Incorrect Unit of Measure and Numbers: In the Original Contribution entitled “Cognitive-Behavioral Therapy, Imipramine, or Their Combination for Panic Disorder” published in the May 17, 2000, issue of the JOURNAL (2000;283:2529-2536), the units of measure for imipramine and desipramine should be ng/mL instead of mg/dL on page 2532 and ng/mL instead of mg/mL on page 2535. On page 2530 under “Study Design,” patients randomized to CBTplacebo should number 56 per block of 24, not 25. In the “Treatment Conditions” section on page 2531, near the end of the third paragraph, “. . . the dosage [of imipramine] could be increased up to 300 mg/d by week 5” should read “week 7.”

Author Omitted: In the Caring for the Critically Ill Patient article entitled “Ketoconazole for Early Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome” published in the April 19, 2000, issue of the JOURNAL (2000;283:1999-2002), an author was inadvertently omitted from the ARDS Network listing on page 2002. Brian Christman, MD, should have been listed with the Vanderbilt University group and identified as an author.
future CONSORT group discussions to receive feedback from other CONSORT group members. We disagree with Drs Djulbegovic and Clarke, however, that the CONSORT statement should explicitly address ethics. We wrote, “Some items not considered essential may well be highly desirable and should still be included in an RCT report even though they are not included in CONSORT. Such items include approval of an institutional ethical review board. . . .” Thus, its omission does not indicate that it is unimportant. Quite the contrary, the self-evident importance of such oversight leads to widespread institutional and journal review. Moreover, international organizations, such as the World Medical Association, and national organizations, such as the Office for Human Research Protections in the United States, provide thorough guidance. The CONSORT statement cannot add much to those extensive efforts.

Djulbegovic and Clarke state that “a randomized trial can adhere to all of the CONSORT statement’s recommendations and still be biased if the investigators have selected an inferior comparator intervention for their control group.” As a point of clarification, they use the term “biased” in an unusual and potentially inappropriate context. Bias usually refers to issues of internal validity. In that context, a trial could be methodologically sound thereby producing an unbiased comparison between an intervention group and a placebo/no therapy control group, but that control group could still be ethically inappropriate, or vice versa.

Unless we receive clear indications to the contrary from the CONSORT group, we will leave specific ethical issues to the layers of ethical review groups that embody expertise in that area. We have never suggested that the CONSORT statement is all encompassing. It facilitates critical appraisal and interpretation of RCTs by providing guidance to authors on how to improve the reporting of their trials. We intend to keep the items addressed to a reasonable number. Nevertheless, the CONSORT statement is an evolving document. We appreciate Djulbegovic and Clarke leading us to reevaluate this topic and encourage such recommendations for improving the quality of reports of parallel-group randomized trials. We have never suggested that the CONSORT statement is all encompassing. It facilitates critical appraisal and interpretation of RCTs by providing guidance to authors on how to improve the reporting of their trials. We intend to keep the items addressed to a reasonable number. Nevertheless, the CONSORT statement is an evolving document. We appreciate Djulbegovic and Clarke leading us to reevaluate this topic and encourage such suggestions. Within the constraints of brevity, we will continually appraise potential additions to the statement.

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RESEARCH LETTER

Pain Associated With Injection Using Frozen vs Room-Temperature Needles

To the Editor: Although typical cooling agents such as ice packs and ethyl chloride sprays are often used to achieve local anesthesia, the effect of lowering the temperature of piercing agents has not been studied.

Methods. I studied 77 patients who were receiving bilateral injections of botulinum toxin (12.5 units per injection) symptomatically into the right and left facial corrugator muscles using a 30-gauge needle. Each patient received 1 of the injections with a room-temperature needle and the other with a needle that had been frozen overnight at −7°C. An assistant placed the needles on the syringes, and both patients and physicians were blinded to the condition. The needles were randomized as to the order in which they were used. Patients immediately reported the severity of their pain using a pain scale of 0 to 10. Results were analyzed using the paired t test.

Results. The frozen needles were less painful in 59 (76.6%) patients, more painful in 14 patients (18.2%), and there was no reported difference in 4 patients (5.2%). Mean (SD) pain score for the frozen needles was 1.7 (1.34) vs 2.9 (1.86) for the room-temperature needles (P < .001). Use of frozen needles resulted in statistically significant less pain (mean difference, 1.2; SD, 1.7; P < .001). Eighty-three percent of the injections using frozen needles resulted in a pain score of 1 or 2, compared with 58% using room-temperature needles.

Conclusion. Using prefrozen needles is simple and inexpensive, and appears to reduce the pain of injection for many patients. The reduction in pain is similar to that reported for the use of buffered vs unbuffered local anesthetics. It is unclear why some patients felt more pain with frozen needles. No adverse effects were noted. Since the gauge of the needle used in this study is similar to that used by patients with diabetes, these findings may lead to a simple method for reducing the discomfort of those who require frequent injections.

Keith Denkler, MD
Department of Surgery
University of California–San Francisco


Correction


On page 2000, in the footnote to Table 2, the lung injury score was calculated as reported by Arons et al (not Murray et al). The correct reference 22 should be: Arons M, Wheeler AP, Hudson LD, et al. Developing an improved lung injury score. Am J Respir Crit Care Med. 1997;155:A584.