Effects of Intravenous Amphotericin B Infusion on Hemodynamics and Airway Mechanics in Awake Sheep*

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To gain a better understanding of the adverse pulmonary response to amphotericin B administration reported in humans, we examined the effects of this agent in the chronically instrumented awake sheep. We measured pulmonary artery and left atrial pressures (Ppa and Pla), lung lymph flow (Qlymph), dynamic lung compliance (Cdyn), resistance to airflow across the lung (Rt), lymph thromboxane B2 (TxB2), lymph 6-keto-PGF1α, peripheral leukocyte counts, and arterial blood gases. After at least one hour of stable baseline (BL) observation, amphotericin B (Fungizone, Squibb, 1 mg/kg) was infused intravenously over 1 h. Measurements were continued for 3 h after the start of infusion. Amphotericin caused an immediate decrease in Cdyn nadir at 55 percent of BL and an increase in Ppa from 21 ± 1 mm Hg at BL to 44 ± 4 at 30 minutes. Rt increased to 5.5-fold over BL by 30 minutes into infusion, and lung lymph TxB2 concentrations were increased tenfold compared with BL at the end of the 1-h infusion (p < 0.05).

In this same time interval, there were increases in Qlymph (1.5 ml/15 min at BL to 4.9 ± 0.8), but 6-keto-PGF1α concentrations did not reach maximum until 2 h after the start of infusion. There was a decrease in peripheral leukocyte count and PaO2 (80 ± 3 mm Hg at BL to 69 ± 4 at 1 h) that returned to BL over the remaining 2 h. The temporal relationship of the TxB2 peak with these pathophysiologic changes and previous data describing the effects of thromboxane in the sheep lung suggest that a component of these alterations is due to thromboxane release. We conclude that several pulmonary system abnormalities occur following amphotericin infusion in sheep and that these findings provide a better physiologic basis for explaining the human pulmonary response to amphotericin.

(Chest 1991; 99:457-62)

| Qlymph = lung lymph flow; Rt = resistance to airflow across the lung; Cdyn = dynamic lung compliance; Ppa = pulmonary artery pressure; Pla = left atrial pressure; EDTA = edetic acid; LP = lymph to plasma protein concentration ratio; CLP = lymph protein clearance; Pao2 = airway opening pressure; Pleural pressure; Ptp = transpulmonary pressure; SC = specific conductance; TxB2 = thromboxane B2; 6-keto-PGF1α = 6-keto-prostaglandin F1α; EIA = enzyme immunosorbent assay; Bo = tracer bound in absence of prostaglandin |

Since its clinical introduction in the late 1950s, amphotericin B remains the drug of choice in treating most systemic fungal infections. Despite its efficacy, adverse effects associated with amphotericin administration are common and include fever, headache, anorexia, nausea, vomiting, chills, myalgia, and nephrotoxicity with reversible reductions in renal blood flow, glomerular filtration rate, and concentrating ability. Pulmonary complications during amphotericin therapy, while uncommon, were first reported when amphotericin was administered concurrently with leukocyte transfusions in neutropenic patients and presented as hemoptysis, acute dyspnea, and hypoxia, and new infiltrates on chest roentgenograms that have been severe enough to be characterized as the adult respiratory distress syndrome. Recently, amphotericin infusion is reported to be associated with acute pulmonary deterioration during the infusion period without concurrent leukocyte transfusions.

The purpose of this study is to describe the pulmonary physiologic response of amphotericin infusion through measurement of the changes observed in hemodynamics, peripheral leukocyte counts, lung mechanics, and lung lymph following intravenous administration of amphotericin to awake sheep.

METHODS

Experimental Preparation

During a single anesthesia, sheep were instrumented for measurement of pulmonary vascular pressures and lung mechanics as previously described. Briefly, through a left thoracotomy, Silastic catheters were placed directly in the left atrium and proximal pulmonary artery. In addition, through a right thoracotomy, the efferent vessel of the caudal mediastinal lymph node was cannulated with a Silastic catheter, which was brought out through the right side of the chest. Through a second right thoracotomy, contaminating

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abdominal and systemic lymphatics were disrupted by ligating the caudal aspect of the lymph node at the level of the inferior pulmonary ligament, and by bilaterally interrupting diaphragmatic lymph vessels. Silastic pleural envelopes were placed in the pleural space via one of the right thoracotomies. Through a neck incision, catheters were placed into the right carotid artery and right external jugular vein. A tracheostomy was performed either during the same anesthesia or at a second operation. Tracheostomy tubes (No. 10 Shiley) were inserted only during experiments.

Experimental Protocol

After surgical preparation, the sheep were allowed to recover for at least five days. On the day of experimentation, sheep were observed for 1 h of stable baseline measurements. Amphotericin B (Fungizone, E. R. Squibb and Sons, Princeton, NJ) was reconstituted with 10 ml of sterile water and 40 mg (approximately 1 mg/kg) was added to 180 ml of 5 percent dextrose and water. The amphotericin was protected from light and administered to the sheep through the right external jugular vein with a Harvard pump (Harvard Apparatus Co., Dover, CA) over 1 h with physiologic measurements made during the infusion and for the ensuing 2 h. Six sheep had serial measurements of lung lymph flow (Qlymph) and airway mechanics measurements, including resistance to airflow across the lung (Rl), dynamic lung compliance (Cdyn), and functional residual capacity (FRC). An additional seven sheep had serial measurements of systemic blood pressure (Psa), pulmonary artery pressure (Ppa), left atrial pressure (Pia).

Blood and Lymph Measurements

Pulmonary artery pressure, Pia, and Psa were monitored continuously using physiologic pressure transducers, series 1290-C (Hewlett-Packard Co., Palo Alto, CA), in conjunction with amplifiers (Validyne Engineering Corp., Northridge, CA) and a model 2800 eight-channel pen recorder (Goeld Inc, Instruments Div. Cleveland, OH). Lymph was collected over edetic acid (EDTA) and indomethacin in plastic collection tubes with the volume recorded every 15 minutes and each 30-minute sample pooled for analysis. Protein analysis was performed on lymph and plasma using the modified biuret method and an automated analysis system (AutoAnalyzer, Technicon Instruments Corp., Tarrytown, NY). Lymph protein concentration was divided by plasma protein concentration to obtain the lymph to plasma protein concentration ratio (L/P). Lymph protein clearance (Clv) was calculated by multiplying Qlymph \times L/P. Heparinized samples of arterial blood were drawn anaerobically into a plastic syringe from either the carotid artery catheter or the left atrial catheter at baseline, 15 minutes, after beginning the amphotericin infusion, and every 30 minutes thereafter. The samples were stored in ice for subsequent measurement of arterial pH and partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2) with an automated blood gas analyzer (model 158, Corning, Medfield, MA). Arterial to alveolar oxygen tension difference (PA-aO2) was calculated by using the alveolar gas equation, and by assuming a respiratory exchange ratio of 0.8. Blood for total white blood cell count (WBC) was drawn every 30 minutes in conjunction with the blood gas sample as noted above. The samples were collected on EDTA, diluted (Couler Diluter, model WRD2), and analyzed (Couler Counter, model ZBI, Hialeah, FL). Peripheral blood smears were made from each blood sample, stained, and counted under a microscope for the percentage of polymorphonuclear leukocytes and lymphocytes.

Lung Mechanics Measurements

Sheep were studied awake, standing in a specially constructed whole-body pressure-compensated integrated-flow plethysmograph. The plethysmograph is constructed of 1-cm-thick clear Plexiglas and has a volume of 285 L. The sheep's tracheostomy tube was connected to an external valve, which was used to briefly obstruct the airway during determinations of FRC via flexible noncollapsible tubing. This permitted the animal to move without interfering with measurements. A loosely fitting sling was placed under the sheep to prevent it from lying down while in the plethysmograph and such that it was not restrictive with regard to pulmonary mechanics measurements. A constant bias flow was used to reduce the effective dead-space of the tubing. Tidal volume (V) was measured by pressure compensating the integrated signal from the plethysmographic pressure transducer. Flow (V) was obtained by electrically differentiating the volume signal. Airway opening pressure (Pao) was measured using a multiple side hole catheter positioned 0.5 cm past the end of the tracheostomy tube and into the tracheal lumen. Pleural pressure (Ppl) was measured using the balloon previously placed in the pleural space. Transpulmonary pressure (Pt) was the pressure difference between Ppl and Pao. All pressure signals were processed using Validyne Engineering Corp equipment (Validyne Engineering, Northridge, CA). The signals from pressure transducers, catheters, and Silastic envelopes were tuned at 6 Hz to eliminate phasic distortion.

Before each measurement of lung mechanics, the sheep's lungs were inflated to a Pao of 40 cm H2O using the bias flow and an occluded airway. Simultaneous VV and V/Pt were then recorded during spontaneous respiration on a dual-beam storage oscilloscope (Tektronix, Inc, Beaverton, OR) and photographed for calculation of Cdyn and Rl. Dynamic compliance was calculated as V divided by Ptp at points of zero flow and expressed in liters per centimeter water (L/cm H2O) at body temperature pressure saturated (BTPS). Resistance to airflow across the lung was calculated by the method of Von Neergard and Wirz19 by dividing Ptp by V at midtidal volume and was expressed as cm H2O/L/s at BTPS. Functional residual capacity was measured by using Boyle's law and the method of DuBois et al.18 The airway was manually obstructed at end expiration allowing the sheep to continue to make respiratory efforts against the obstruction for one to three breaths. A graph of the change in plethysmographic volume against the change in FRC was traced on the oscilloscope and photographed for calculation of FRC. Specific conductance (gCl) was calculated by dividing the reciprocal of Rl (conductance) with FRC and expressed as seconds per centimeter H2O at BTPS.

Measurement of Thromboxane and Prostaglandin Metabolites

Thromboxane B2 (TXB2) and 6-keto-prostaglandin F1α (6-keto-PGF1α) were measured in lung lymph specimens collected during baseline, 15 minutes after amphotericin infusion, and every 30 minutes thereafter using an enzyme immunoassorbent assay (EIA).20 The samples were dissolved in the EIA assay buffer (pH 7.4) (0.1 mol/L potassium phosphate buffer with 0.01 percent NaN3, 0.4 mol/L NaCl, 1 mmol/L EDTA, and 0.1 percent bovine serum albumin) and analyzed as described by Pradelles et al.21 Briefly, 50 μL of each sample or buffer was placed in one well of a 96-well microtiter plate that was previously coated with mouse monoclonal IgG antibody (2 μg/well) (Pel-Freez Biologicals, Rogers, AR). Enzyme tracer (50 μL), consisting of 6-keto-PGF1α or TXB2 covalently coupled to purified acetycholinesterase from the electric eel, was added. Finally, 50 μL of a specific rabbit 6-keto-PGF1α or TXB2 antiserum was added. The plates were incubated for 16 to 24 hours at 4°C, washed with 10(2)-M phosphate buffer, at a pH of 7.4, containing 0.05 percent Tween-20 using an automatic washer (Flow Laboratories, McLean, VA). The plates were automatically filled with 200 μL/well of the following medium: 2 μg/mL acetylthiocholine iodide and 2.15 μg/mL of 5-5' -dithiobis'-2'-nitrobenzoic acid in 10(2)-M phosphate buffer. The production of a yellow colored product was measured at 414 nm by an automatic plate reader (Titer Tek Multiskan MC, Flow Laboratories). Each sample was assayed in duplicate at two different dilutions. Standards were assayed on each plate at concentrations of 6-keto-PGF1α and TXB2, ranging from 3 to 500 pg/ml and 7.0 to 1000 pg/ml, respectively. Nonspecific binding
Figure 1. Effect of amphotericin B (40 mg, intravenous) on pulmonary artery pressure and left atrial pressure in the awake sheep. Data are expressed as mean ± SEM and the p value indicates comparisons of experimental values to baseline values.

Statistics

The effects of amphotericin administration over time were compared with baseline using analysis of variance and Student's t test where differences were demonstrated. Because baseline lung lymph thromboxane levels were not normally distributed, we used a nonparametric test and analyzed these data using the Wilcoxon signed rank test. Data are expressed as the mean±SEM and differences were considered to be significant at the p<0.05 level.

RESULTS

Amphotericin elicited an increase in the mean Pa from 21±1 cm H2O at baseline to a peak of 44±4 cm H2O 30 minutes after beginning the amphotericin infusion and remained significantly elevated at the end of observation (p<0.05). Left atrial pressure also increased from 1±1 cm H2O at baseline to a peak of 5±1 cm H2O at 45 minutes into the infusion (p<0.05) and returned to baseline 45 minutes after the completion of the amphotericin infusion (Fig 1). Systemic arterial pressure was not significantly effected by amphotericin (p>0.05).

Lung lymph flow increased markedly in response to amphotericin from a baseline value of 1.5±0.2 ml/15 min to a maximum of 4.9±0.8 ml/15 min 15 minutes after completing the infusion (p<0.05). Lymph to plasma protein ratio fell from 0.68±0.04 at baseline to 0.50±0.02 30 minutes after the completion of the infusion (p<0.05) (Fig 2). Plasma protein did not change significantly, so the change in L/P was due to a fall in the lymph protein concentration. When the data are expressed as CLP, there is an increase from 0.99±0.11 ml/15 min at baseline to 2.2±0.5 ml/15 min at the end of the amphotericin infusion (p<0.05). By the end of the experiment, Qlymph, L/P, and CLP had returned to baseline levels.

Airway mechanics measurements of Cdyn, FRC, RL, and sGl expressed as percentage of baseline were altered by amphotericin infusion. Dynamic compliance began decreasing 15 minutes after beginning the amphotericin infusion and by 45 minutes had fallen to 55 percent of baseline (p<0.05). Functional residual capacity also decreased significantly to 80 percent of baseline 45 minutes into the amphotericin infusion (p<0.05). Resistance to airflow across the lung increased 15 minutes after starting amphotericin infusion reaching a maximum of 550 percent of baseline values by 45 minutes (p<0.05). Specific conductance decreased to 36 percent of baseline at the end of the amphotericin infusion (p<0.05). By 2 h after completion of the infusion, airway mechanics measurements were not significantly different from baseline (Fig 3).

Room air alveolar to arterial oxygen tension difference increased from a baseline value of 25±3 mm Hg to 40±3 mm Hg at the end of the amphotericin infusion and was mainly due to a decrease in PaO2 from 80±3 mm Hg at baseline to 69±4 mm Hg (p<0.05) (Table 1). These abnormalities persisted throughout the infusion but returned to baseline soon after its cessation. The PaCO2 and pH were not significantly affected by amphotericin infusion (p>0.05).
DYNAMIC LUNG COMPLIANCE [% BASELINE]

RESISTANCE TO AIRFLOW ACROSS THE LUNG [% BASELINE]

SPECIFIC CONDUCTANCE [% BASELINE]

Figure 3. Effect of amphotericin B (40 mg, intravenous) on dynamic lung compliance, resistance to airflow across the lung, and specific conductance. Data are normalized by expressing values as percent of baseline values and are expressed as mean ± SEM; p values refer to experimental values compared with baseline values.

The peripheral WBC count fell with amphotericin infusion, decreasing from a baseline of 7,125 ± 632 cells/cu mm to 4,504 ± 525 cells/cu mm at the end of amphotericin (p < 0.05) (Fig 4). Counts then increased slowly and were not significantly different from baseline by hour 3. Differential WBC counts performed on peripheral blood smears revealed a trend toward a decrease in the percentage of polymorphonuclear leukocytes from 63 percent to 49 percent and a corresponding increase in the percentage of lymphocytes (p = 0.08) by the end of amphotericin administration that reversed toward the end of the observation period.

Amphotericin produced an increase in lung lymph TxB₂ levels to greater than ten times baseline at the end of the 1-h amphotericin infusion (0.37 ± 0.05 ng/ml to 4.3 ± 1.5, p < 0.05) (Fig 5). There was also a trend toward an increase in the 6-keto-PGF₁α levels from baseline. In contradistinction to the TxB₂ peak at 1 h, there was no change in 6-keto-PGF₁α at one hour. Instead, peak 6-keto-PGF₁α increases came 2 h after the start of the amphotericin infusion (0.27 ± 0.08 ng/ml compared with 0.11 ± 0.03 at baseline, p = 0.09).

**Discussion**

The mechanism of inhibition of fungal growth by amphotericin is complex and incompletely understood. Several of the hypotheses aimed at explaining amphotericin's antifungal activity may also explain the pulmonary toxicity of this agent. First, amphotericin binds to ergosterol, a sterol unique to fungal membranes, forming transmembrane channels that increase the cell's permeability to ions and small metabolites. In animal cells, an analogous event occurs when amphotericin binds with cholesterol, the principal sterol in animal cell membranes, and increases water and solute permeability. Second, amphotericin auto-oxidizes to produce lethal free radical products. Amphotericin infusion in rat lungs increases oxidized glutathione concentrations and also produces

**Table 1—Effect of Amphotericin B on the Arterial to Alveolar Oxygen Tension Difference (P(A-a)O₂), Arterial Partial Pressure of Oxygen (PaO₂), and Total White Blood Cell Count**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>P(A-a)O₂, mm Hg (N = 12)</th>
<th>PaO₂, mm Hg (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>28.4 ± 2.9</td>
<td>80.2 ± 3.2</td>
</tr>
<tr>
<td>30</td>
<td>31.7 ± 3.0</td>
<td>78.6 ± 3.2</td>
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<tr>
<td>60</td>
<td>39.9 ± 3.3†</td>
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</tr>
<tr>
<td>90</td>
<td>34.9 ± 3.0†</td>
<td>75.8 ± 3.1</td>
</tr>
<tr>
<td>120</td>
<td>33.4 ± 3.2</td>
<td>77.2 ± 3.0</td>
</tr>
<tr>
<td>150</td>
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<td>77.1 ± 3.4</td>
</tr>
<tr>
<td>180</td>
<td>33.7 ± 2.9</td>
<td>75.8 ± 3.2</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SEM.

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increases in the albumin escape index that can be attenuated with free radical scavengers.\textsuperscript{30} Finally, amphotericin stimulates humoral and cell-mediated immune systems in animals.\textsuperscript{15,31} For example, amphotericin is associated with the release of prostaglandins and leukotrienes (slow reacting substance of anaphylaxis) in cell and animal models.\textsuperscript{30,32} Since clinical pulmonary toxicity has been reported but remains poorly understood, we sought to conduct a series of experiments in the chronically instrumented sheep lung lymph fistula model to gain a better understanding of this toxicity. Our results document significant effects on hemodynamics, lung mechanics, gas exchange, and lymph flow changes in the awake sheep following amphotericin infusion. All of these alterations appear reversible, returning to baseline 2 h after infusion except for $P_{pa}$, which remained slightly elevated at the end of monitoring.

Of the parameters measured, those showing the most rapid and marked response to amphotericin were $P_{pa}$ and the airway mechanics measurements of $R_{L}$, $C_{dyn}$, and $sG_{L}$. Along with these alterations in lung mechanics, our data reveal changes in gas exchange as shown by an increase in the $P(A-a)O_{2}$ and decrease in $P_{a}O_{2}$. In association with these changes, there was a sharp rise in thromboxane production, as determined in lung lymph by measurement of its stable metabolite TxB$_{2}$. Thromboxane is a potent bronchoconstrictor and vasoconstrictor in sheep,\textsuperscript{32} suggesting that hemodynamic and airway changes observed immediately after amphotericin infusion may be related to the increased levels of TxB$_{2}$ or other arachidonic acid constrictors. Also, the subsequent improvement in lung mechanics and hemodynamics appears to be temporally related to decreases in thromboxane levels, yet prostacyclin metabolite levels increase about this same time, suggesting that the release of this or other dilator arachidonic acid products may be responsible for the improvements in pulmonary hemodynamics and lung mechanics.

Other studies have demonstrated inflammatory mediators associated with amphotericin: McDonnell et al\textsuperscript{30} found rat tissue leukotriene $B_{4}$ and $C_{4}$ levels both rose significantly following amphotericin infusion, and Stewart et al\textsuperscript{32} demonstrated elevations of PGE$_{2}$ in human monocytes incubated with amphotericin. PGE$_{2}$ and leukotriene $C_{4}$ are known pulmonary vasoconstrictors,\textsuperscript{23,34} and the observed persistence of $P_{pa}$ elevations in our experiments may be due to the presence of these or other mediators not measured in our experiments.

Lung lymph flow and CLP increased but the L/P decreased during amphotericin infusion. Lymph flow, L/P, and CLP returned to baseline within 2 h after completing the amphotericin infusion. Previous studies employing the sheep lung lymph fistula model show that increased permeability is marked not only by a significant increase in $Q_{lymph}$ but also by a normal or increased L/P ratio.\textsuperscript{25} Increases in $Q_{lymph}$ due to increased hydrostatic forces are associated with a decreased L/P ratio. In our studies, we observed an increase in microvascular pressure (increased $P_{pa}$ and $P_{la}$) and a decrease in L/P ratio, suggesting that the increase in $Q_{lymph}$ was on a hydrostatic basis. However, under these circumstances, it is difficult to differentiate a small change in microvascular permeability secondary to amphotericin in addition to the hydrostatic effects. Studies by Berliner et al\textsuperscript{35} using electron microscopy show that amphotericin damages alveolar capillary endothelial cells of rabbits within one hour of injection, and isolated rat lungs perfused with amphotericin demonstrate extravascular escape of albumin and water.\textsuperscript{36} Therefore, a transient permeability increase contributing to the observed increase in $Q_{lymph}$ and CLP would be reasonable to expect. However, it appears that increased microvascular pressure accounts for most of the rise in $Q_{lymph}$.

Several reports implicate neutrophils as the mediators of amphotericin-induced lung damage. Studies by Wright et al\textsuperscript{37} suggest that concomitant administration of amphotericin and leukocyte transfusions in patients can produce acute respiratory deterioration. Amphotericin-induced lysis of aggregated neutrophils in the microvasculature is proposed to account for this form of lung injury, and there are studies that demonstrate amphotericin's toxicity toward human neutrophils.\textsuperscript{27,28} Studies in rabbit lungs suggest that amphotericin causes an in vivo aggregation of activated neutrophils that produces pulmonary hemorrhage;\textsuperscript{30} however, rats depleted of neutrophils do not demonstrate an attenuation of their lung injury.\textsuperscript{30} Our findings that amphotericin causes a decline in circulating
leukocyte count of about 33 percent 60 to 90 minutes after amphotericin infusion accompanied by a 20 percent decrease of polymorphonuclear leukocytes suggests that pulmonary sequestration may be occurring in our model, but since we did not perform lung biopsies or perform experiments with neutrophil-depleted sheep, we cannot speculate on the role of neutrophils and amphotericin lung injury. In any case, these major changes in leukocyte number and proportion suggest that there is a significant inflammatory component to the reaction to amphotericin.

In summary, administration of amphotericin to sheep by continuous infusion in doses similar to those given humans produces marked changes in pulmonary artery pressure, airway mechanics, and lung lymph flow. The temporal relationship of these changes to lymph thromboxane concentration suggests that these changes may be mediated by thromboxane. Other potential mediators include complement, histamine, free radicals from amphotericin auto-oxidation, tumor necrosis factor, neutrophil proteases from activated neutrophils, and other arachidonic acid products. We conclude that amphotericin causes significant pathophysiologic changes in the sheep pulmonary system and these changes may be similar to those experienced by some humans receiving this drug. Further, this study suggests that cyclooxygenase inhibition may be useful in ameliorating at least some of the pulmonary changes associated with amphotericin infusion, since products of the release and metabolism of arachidonic acid appear to play a role.

ACKNOWLEDGMENTS: The authors wish to thank Cheryl Bunn for assistance in manuscript preparation, Gayle King for conducting eicosanoid assays, Frank Biotic for surgical assistance, and Bridget Swindell, R.N., for assistance in data handling.

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