Surfactant Replacement Therapy: Benefits and Risks

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Surfactant deficiency at birth makes it difficult for the newborn to inflate its lungs. As the infant makes increasingly vigorous attempts to ventilate noncompliant lungs, delayed adsorption of lung fluid, pulmonary edema, extravasation of plasma proteins into air spaces, and lung injury occur, which cause progressive respiratory distress. Intratracheal administration of surfactant into the infant's lungs is a reasonable approach to replenish the missing surfactant.

Exogenous surfactant preparations of various types have now been evaluated in treatment of established respiratory distress syndrome (RDS) and to prevent its development. Since our initial report in 1980 (1), there have been a number of controlled studies reporting the efficacy of surfactant preparations of various types, and other trials are ongoing around the world. The prospect of surfactant therapy for premature infants is now reaching an exciting stage.

This chapter provides an overview of the available surfactant preparations for clinical use, the currently reported results, the clinical implications of such therapy on the course of RDS, and some risk versus benefit considerations.

SURFACTANT PREPARATIONS FOR CLINICAL USE

It is useful to group the available surfactant preparations into three categories. The first consists of an organic solvent extract of animal lung lavage or of minced lung saline extract with or without additives. The second is natural surfactant isolated from human amniotic fluid. Thirdly, there are artificial or synthetic surfactants (Table 1).

CLINICAL EFFICACY OF SURFACTANT PREPARATIONS

It is useful to group the reported trials of surfactant therapy into two categories: rescue trials and prophylactic trials. Rescue trials have used surfactants to treat
TABLE 1. Published randomized clinical trials of surfactants in infants with RDS

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Study</th>
<th>Surfactant</th>
<th>Dose*</th>
<th>Response</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>Halliday et al. (2)</td>
<td>DPPC/HDL</td>
<td>30 mg</td>
<td>Negligible</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Enhorning et al. (3)</td>
<td>Infasurf</td>
<td>75–100 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Kwong et al. (4)</td>
<td>CLSE</td>
<td>90 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Shapiro et al. (5)</td>
<td>CLSE</td>
<td>90 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Merritt et al. (6)</td>
<td>Human AFS</td>
<td>multiple</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Ten Centre (7)</td>
<td>ALEC</td>
<td>multiple</td>
<td>Not studied</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Kendig et al. (8)</td>
<td>CLSE</td>
<td>90 mg</td>
<td>Striking</td>
<td>Unsustained</td>
</tr>
<tr>
<td>Rescue</td>
<td>Wilkinson et al. (9)</td>
<td>ALEC</td>
<td>25 mg</td>
<td>Negligible</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Hallman et al. (10)</td>
<td>Human AFS</td>
<td>multiple</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Gitlin et al. (11)</td>
<td>Surfactant TA</td>
<td>120 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Raju et al. (12)</td>
<td>Surfactant TA</td>
<td>120 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Fujiwara et al. (13)</td>
<td>Surfactant TA</td>
<td>120 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>McCord et al. (14)</td>
<td>Curosurf</td>
<td>200 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>CEMSG (15)</td>
<td>Curosurf</td>
<td>200 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
<tr>
<td></td>
<td>Horbar et al. (16)</td>
<td>Survanta</td>
<td>120 mg</td>
<td>Striking</td>
<td>Sustained</td>
</tr>
</tbody>
</table>

*S Total lipid/kg body weight.

AFS, amniotic fluid surfactant; ALEC, artificial lung expanding compound (DPPC:phosphatidylglycerol, 7:3); CEMSG, Collaborative European Multicentre Study Group; CLSE, calf lung lavage surfactant lipid extract; Curosurf, phospholipid fraction of porcine lung extract; DPPC, dipalmitoylphosphatidylcholine; HDL, high-density lipoprotein; Infasurf, cow lung lavage surfactant lipid (additive, CaCl$_2$); Surfactant TA, a reconstituted bovine lung surfactant lipid (additives, DPPC, tripalmitin, and palmitic acid); Survanta, a modification of Surfactant TA.

Sustained effect lasts for at least 48 h after administration of surfactant.

From Fujiwara T, et al. (13).

infants with established RDS, whereas prophylactic trials have used surfactants before the infant's first breath or within minutes of delivery to modify the course of RDS in infants at high risk of RDS. Many of the therapeutic benefits of various naturally derived surfactant preparations in RDS have been described in a series of recent, randomized trials, all of which showed statistically significant improvements in respiratory function after surfactant therapy. However, the immediate physiologic responses achieved with naturally derived surfactants have not been reproduced with the currently reported synthetic surfactants (2,7,17).

Mechanical ventilator usage and initial ventilator settings vary from one study to another, but our protocol (13,18) includes initial ventilator settings of 20–30 breaths/min, positive inspiratory pressures of 20–30 cm H$_2$O, positive end-expiratory pressures of 4 cm H$_2$O, and inspiratory duration of 1.0, which are optimal for most RDS patients weighing less than 1,750 g. After treatment FiO$_2$ is reduced, followed by reductions in peak pressures and ventilator rates. The FiO$_2$ can usually be reduced to less than 0.3 to 0.4 by 1 hour when treated within 30 min of birth and by 3 hours when treated at 6 hours of age, and an accelerated course of weaning from a mechanical ventilation can be accomplished. Figure 1 illustrates improvements in oxygenation and ventilatory requirement of RDS patients weighing 750–1249 g following treatment with surfactant TA.
In most trials surfactant preparations have been evaluated in comparison with conventionally ventilated infants from 23 to 30 weeks' gestation. However, most study designs have not required that premature infants treated with surfactant have evidence of surfactant deficiency. Surfactant deficiency was documented in only five (6,9,10,13,18) of the 16 clinical trials reported to date either through a biochemical measure of lung maturity (i.e., lecithin-to-sphingomyelin ratio) in amniotic fluid (6,9,10), or by biophysical analysis of surfactant (stable microbubble rating (19) in gastric aspirates obtained at birth (13,18). Patient selection is a key factor because of the higher frequency of mature lung function among infants (40-60%) of <30 weeks' gestation. A prophylactic strategy is a reasonable approach only when the infant has surfactant deficiency. Unfortunately, it is not always known which infants have surfactant deficiency. Perhaps definite lung immaturity justifies prophylactic surfactant strategy.

Studies with human amniotic fluid surfactant have shown a nonsustained response in 41% of infants with established RDS and in 71% of infants treated prophylactically. In both of these studies (6,10) infants needed multiple doses of surfactant to sustain the therapeutic response. In contrast to the prophylactic trial by Enhorning et al. (3), a recent similar trial using a single dose of CLSE (calf lung lavage extract) showed that the effects diminished between 24 and 48 h after surfactant administration (8).

By and large, study groups in different clinical trials reported to date have not been comparable, and the question as to optimal timing of surfactant therapy remains unanswered. The reason for the variation in response and for the nonresponse in

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**FIG. 1.** Sequential values of arterial/alveolar oxygen tension ratio (a/APO$_2$) (A) and mean airway pressure (MAP) (B) of RDS patients weighing 750-1,249 g following surfactant treatment. ○—○, Surfactant TA ($n = 23$); •—•, air placebo ($n = 19$). Age at treatment: surfactant, 5.5 h; placebo, 4.8 h. Mean ± SE. *$p <0.05$, **$p <0.01$, ***$p <0.001$ (Wilcoxon rank sum test, two-tailed). Reprinted with permission from ref. 13.
some infants has not been clarified. Besides demographic variation, many factors may account for such variation in response, including a multitude of routine practices, approach to the management of patent ductus arteriosus, severity of RDS, differences in conventional ventilatory techniques, variations in the dose of surfactant, or variability in biophysical and physiologic activity among the different surfactant preparations.

The important issue regarding the correlation between the in vitro surface properties and in vivo surface properties has been extensively studied by Notter (20). A major concern about naturally derived surfactants (amniotic fluid surfactant, CLSE, or porcine surfactant) has been related to quality control. Natural surfactant obtained by lung lavage contains various forms of phospholipid micelles with different surface active properties (21) and different metabolic characteristics (22). Recent studies from our laboratory (23) demonstrated striking differences between Surfactant TA and other naturally derived or synthetic surfactants with respect to the minimal quantity required to display the acceptable in vitro surface active properties, the capability of forming stable microbubbles (diameter <15 mm), and microstructures. These studies suggest that treatment with preparations rich in the less surface-active components relative to the active components would require a larger dose to have an equivalent clinical response to that seen with surfactant rich in the more surface-active components.

Another important factor recently recognized is the variability in sensitivity of surfactants to alveolar protein inhibitors. Surfactant TA is quite resistant to alveolar protein inhibitors as compared with other surfactants (24). It is unclear whether infants having a more favorable response to surfactant release less inhibitor, have lower effluent protein concentrations, or both. In vitro studies suggest that a higher dose of surfactant can overcome the inhibitory effects of plasma components on surfactant (25).

Most of the trials reported to date have shown that although there is a statistically significant benefit of surfactant treatment in decreasing the severity of RDS when compared with controls, the majority of the infants still suffer from the disease. In prospective randomized (13,18) and nonrandomized (26) trials, we have shown that the majority of surfactant recipients require minimal ventilatory support equivalent to that of most ventilated preterm infants without parenchymal lung disease. Optimal response seen in this group of infants may typify the response in "pure" RDS, in which surfactant deficiency is the primary factor. On the other hand, suboptimal response (ventilatory index >0.03 or FiO₂ >0.3 and MAP >6 cm H₂O) seen in some of the surfactant recipients are related to several factors: (a) some degree of early lung injury due to surfactant deficiency occurring before surfactant therapy (27); (b) increased alveolar capillary permeability and secondary surfactant inactivation by proteins leaking into the alveolar space (28); (c) some degree of structural immaturity; or (d) pathophysiologic conditions of RDS other than surfactant deficiency (26,29). Recent clinical and experimental evidence suggests that some of these factors affecting the response to surfactant can be eliminated by treating at birth (3), sooner after birth (30), increasing dosage (18), and/or using a multiple-dose strategy (31).
Clinical trials comparing the prophylactic or very early versus rescue strategies are in progress.

**EFFECT OF SURFACTANT THERAPY ON COMPLICATIONS OF RDS**

The surfactant therapy eliminates the surfactant deficiency component of the complex pathophysiology of RDS (26). Since surfactant therapy reduces the severity of RDS and restores sufficient lung function to permit a reduction in ventilatory support (lower $\text{FiO}_2$ and lower mean airway pressures), one might predict that surfactant therapy will reduce the major morbidity factors of RDS such as air leaks, bronchopulmonary dysplasia (BPD), and intracranial hemorrhage (ICH). The controlled clinical trials of both prophylactic and rescue types reported the substantial reduction in the frequency of the major complications of RDS. These trials are not equivalent, yet they are sufficiently similar for us to have summed the complications across studies as shown below.

**Prophylactic Trials**

To date, 104 infants have been treated prophylactically in three controlled trials with naturally derived surfactants, which have shown a significant impact on the complications of RDS and prematurity (Fig. 2). Estimates derived from 95% confidence intervals (CI) are that pneumothorax decreases by between 7% and 28% ($p = 0.003$), and pulmonary interstitial emphysema (PIE) decreases by between 18% and 40% ($p < 0.001$). There was no statistically significant reduction in the frequency of ICH and BPD. The 95% CI for the overall increase in survival in the group treated prophylactically was between 2% and 31% ($p = 0.009$). Of the prophylactic trials, those of Enhorning et al. (3) and Merritt et al. (6) showed a substantial reduction in mortality. In recent prophylactic trials (17) using a saline suspension of the DPPC/PG mixture, the beneficial effect on gas exchange was found to begin 18 h after multiple-dose treatments, associated with a substantial reduction in ICH and morbidity.

**Rescue Trials**

In the rescue trials, 262 infants have been treated (Fig. 3). The incidence of pneumothorax or PIE was also significantly reduced.

In contrast to prophylactic trials, the frequency of ICH decreased significantly from 47% to 37%, with a 95% CI of between 1% and 18% ($p = 0.043$). In the two Japanese rescue trials (13,18) reporting a significant decrease of ICH, the study designs have required the absence of ultrasonographic evidence of ≥ grade 2 ICH at randomization, and the timing of occurrence of hemorrhage during the study period was determined in a prospective fashion using scheduled cranial ultrasonographic
FIG. 2. Effects of "prevention" surfactant therapy on complications of RDS. The complications were summed (see text) across the studies reported by Enhorning et al. (3), Merritt et al. (6), and Kendig et al. (8) who used naturally derived surfactant preparations. PNTX, pneumothorax; PIE, pulmonary interstitial emphysema; PDA, patent ductus arteriosus; ICH, intracranial hemorrhage; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. Probability of less than 0.05 by Fisher exact test (two-tailed) was considered significant; 95% confidence intervals for difference in incidence.

scans. Since any ICH may occur very early, i.e., within a few hours of birth (32,33) some infants with such early hemorrhage might have been enrolled in trials in which no beneficial effect of surfactant on hemorrhage was found. Unless ultrasonographic scans were performed on all infants at delivery, none of the prophylactic studies can provide documentation of prestudy ICH status at birth.

The reduction in the frequency of BPD was marginally significant \( (p = 0.056) \), and between 3% and 22% \( (p = 0.008) \) more infants survived. Of these trials, that of Raju et al. (12), using a single 120 mg/kg dose of Surfactant TA, observed a reduction in mortality from 54% for the control group to 18% for the treated infants. The collaborative European multicenter study group (15), using a single 200 mg/kg dose of Curosurf, also observed a reduction in mortality from 51% to 31% when treated infants were compared with controls. In both of these studies, the death rate in control infants was much higher than the 17–26% observed in other studies. Different patient selection criteria may have contributed to the differences in outcome among the studies.

Potential Risk

Remarkably little adverse effect (or toxicity) has become apparent in the animal and clinical studies of surfactant (34).
Although most infants tolerate the intratracheal instillation of liquid surfactant, this unusual route of drug administration is not without risks for a tiny preterm infant; decrease in oxygenation, increase in PaCO₂, and some disturbance in systemic blood pressure may occur during the period of administration of surfactant (35). Care must be taken to minimize perturbations in systemic blood pressure and/or cerebral blood flow during surfactant administration. Ventilation with near 100% oxygen and use of longer inspiratory times and slightly higher peak inspiratory pressures during the period of administration of surfactant, along with continuous monitoring of tc-PO₂, PaCO₂, and systemic blood pressure, appear helpful (26). Our protocol includes continuous monitoring of systemic blood pressure during the period of administration of surfactant (Fig. 4) and during the subsequent course, in the light of recent work showing that infants at highest risk for ICH can be identified before the onset of hemorrhage by the presence of fluctuations in arterial blood pressure and/or cerebral blood flow velocity (36).

There has been some concern about bovine surfactant because of the presence of a small amount of cow proteolipid apoproteins (1%, SP-B,C), which are the functionally important constituents of exogenous surfactant (37). However, attempts to immunize goats with Surfactant TA by a vigorous hyperimmunization technique that was repeated for 6 months were unsuccessful. We have been unable to detect any antibodies against this protein in more than 600 sera from the 204 patients treated with Surfactant TA (38). Others (39) also were unable to detect antibodies against the proteolipid proteins in 1,202 sera from the 359 patients who were treated with Surfactant TA.
FIG. 4. Continuous tracings of heart rate (beats/min), systemic blood pressures (mm Hg), transcutaneous PO\textsubscript{2} (mm Hg), and transcutaneous PCO\textsubscript{2} (mm Hg) before, during, and after administration of Surfactant TA in an infant with severe RDS (birth weight 860 g, age 6 h), reproduced from the recordings on a Hewlett-Packard monitor (78834A). Pre-S bagging indicates manual bagging when the infant was disconnected from ventilator to have inserted a F-4 feeding tube attached to the syringe containing surfactant through the endotracheal tube. Note that there are no significant changes in heart rate, systolic and diastolic blood pressures, and transcutaneous PCO\textsubscript{2} levels during the period of intratracheal instillation of surfactant and subsequent course.

Liechty et al. (40) recently found no differences in the concentrations of plasma atrial natriuretic factor between RDS patients given Salvanta and those given placebo.

Follow-up of Surfactant-Treated Infants

Several studies on follow-up of surfactant-treated infants are in progress around the world. Dunn et al. (41) found no differences between the infants given a bovine-based surfactant and control infants with respect to allergic symptoms, respiratory problems, or neurodevelopmental outcome. Vaucher et al. (42) demonstrated improved neurodevelopmental performance among infants treated with human surfactant and speculated that decrease in the frequency of BPD should ultimately lead to improved long-term outcome.
SUMMARY

This overview analysis of the current clinical trials of various surfactant preparations suggests that use of these preparations to both prevent and treat RDS should be effective in decreasing major morbidity factors of RDS and mortality. The benefits of such therapy greatly exceed the putative hazards.

The beneficial effects of surfactant therapy have been shown to last for at least 72 h in several studies, but these effects were not consistently seen in other studies. Clinical experience with surfactant treatment, and a little future projection, suggest that the impact on bronchopulmonary dysplasia, intracranial hemorrhage, and mortality should eventually be greater. Using our therapeutic regimen with a single dose Surfactant TA, we have had increased survivors without BPD and/or ICH.

Although we still see some infants with mild BPD, requiring little, or less than 30%, supplemental oxygen, the prevalence of such chronic lung disease in tiny infants treated with surfactant does not differ from that of intubated infants without lung disease, of comparable gestational age and birth weight.

Surfactant therapy unmasks the relative contributions of other mechanisms to the overall spectrum of RDS which include a hemodynamically significant PDA, persistent fetal circulation (clear lung with hypoperfusion), cardiogenic shock, transient myocardial dysfunction with or without tricuspid regurgitation associated with severe perinatal asphyxia, etc. In assessing the effectiveness of surfactant treatment we should consider possible effects of these underlying abnormalities that may complicate the interpretation of the response. Serial-echo and color Doppler echocardiographic examinations are useful in identifying these underlying abnormalities. With early recognition, management, and possible prevention of these circulatory disturbances (PDA, hypotension), it may be possible to increase the significance of surfactant treatment further, and facilitate uncomplicated recovery.

In order to optimize the effects of surfactant therapy, future refinement will also be needed in our understanding of surfactant preparations, instillation techniques including pre- and postsurfactant ventilation, and weaning guidelines, dose, dose schedule, and patient selection.

The isolation and characterization of three surfactant proteins (SP-A, -B and -C) has considerably changed our understanding of the nature and properties of pulmonary surfactant and its metabolism. In the 1990s, we shall have a second or third generation surfactant consisting of synthetic lipids and proteolipid apoproteins (SP-B, -C) that are produced by recombinant DNA technology or direct chemical synthesis.

REFERENCES


DISCUSSION

Dr. Roloff: Are your trials done with one dose or with multiple doses?

Dr. Fujiwara: At present we use a single dose. We have studied more than 500 patients in our own center and in three multicenter studies involving 50 collaborating centers, and one dose has been used in more than 90% of the patients. A multicenter randomized study comparing single versus multiple doses is under way in Japan.

Dr. Merchant: How do you decide whether to administer surfactant?

Dr. Fujiwara: We have recently completed a randomized clinical trial comparing very early versus late therapy. Inasmuch as the prevalence of RDS in our center is about 35% in babies less than 29 weeks' gestation, we might treat 65% normal babies if all are treated early. We therefore employ a rapid surfactant test, the Pattle stable microbubble test, in gastric aspirates obtained at birth. We have confirmed that this test is as reliable as other established tests such as the L/S ratio or the immunologic quantification of surfactant-associated proteins in predicting RDS. The great advantage is that it only takes 10 min to get a result. We therefore use this test to identify babies in need of early surfactant prophylaxis, and it has been used in all our trials.
Dr. Kienast: If a second dose of surfactant is to be given, what is the preferred interval following the initial dose?

Dr. Fujiwara: We rarely find it necessary to give a second dose but in a few cases we have given one at around 24–36 h of age. This is in contrast to the findings of the Shapiro study. One reason might be that their babies were smaller than ours. Another important variable could be the quality of surfactant used. Quality control of surface activity of the surfactant used is very important, whether single or second dose strategy is used.

Dr. Dawes: You have shown that your kind of surfactant is excellent. The problem I have is understanding why, after such surfactant treatment, some babies still die. Is there another pathological problem within your infant population such as pulmonary hypoplasia? It may be that your surfactant treatment is 95 or 100% effective and that you are underestimating its true performance. Have you a method for measuring independently what is due to lack of surfactant and what is due to pulmonary hypoplasia?

Dr. Fujiwara: Surfactant therapy is not a panacea. Premature babies with RDS have many pathophysiological conditions besides surfactant deficiency as you rightly point out. The advantage of surfactant therapy is that it not only treats the surfactant deficiency but it also unmasks the relative contribution of several other factors to the complex pathophysiology of RDS. Other problems with oxygenation include transitional fetal circulation and myocardial dysfunction with or without tricuspid regurgitation.

Dr. Marini: One common problem is persistent ductus arteriosus. How do you manage this, and does treatment for PDA reduce the frequency of IVH?

Dr. Fujiwara: In our center we use an oral dose of mefenamic acid, a potent prostaglandin synthetase inhibitor. We found no difference in the frequency of PDA between surfactant-treated and control babies in our multicenter trial. Multiple regression analysis showed no significant interaction between PDA and IVH.

Dr. Marini: In our studies of the “rescue” administration of surfactant we found that there was an immediate and good improvement in gas exchange but pulmonary compliance took much longer to improve. In reptilians there are no alveoli but a lot of surfactant-like material in their bag-like lungs (1). Could surfactant facilitate oxygen transport in ways other than by reducing surface tension?

Dr. Fujiwara: We certainly cannot treat all aspects of the immature lung with surfactant alone. However, treatment with surfactant is also beneficial in restoring pulmonary stability and in reducing ventilator pressures and FIO\textsubscript{2}, thereby lessening the incidence of barotrauma, oxygen toxicity, and BPD. IVH is reduced as well because there are fewer risk factors for its occurrence.

Dr. Dawes: I take it that the purpose of giving surfactant is to provide a period during which there is enough surfactant for the newborn lung to start working until the system that normally regulates its supply comes into operation. Have you looked at methods of accelerating the natural process?

Dr. Fujiwara: Dr. Jobe and his associates are testing the efficacy of antenatal treatment with glucocorticoid and thyrotrpin releasing hormone in animal models and have found that pretreatment with these hormones enhances the efficacy of exogenous surfactant. To my knowledge no one has yet applied this concept in the clinical setting.

Dr. Marini: We have been using ambroxol for many years to enhance surfactant production after birth, at the suggestion of Wauer from Germany. This compound stimulates the production of surfactant by the type 2 pneumocytes. In a multicenter study (2) we found that it reduced the severity of RDS and caused a reduction in mortality. However, the effects are not so dramatic as with surfactant therapy and it takes about 36 h before surfactant-like
material appears in tracheal aspirates. It seems possible that it might be beneficial to give both ambroxol and surfactant at birth, so that when the exogenous surfactant is wearing off, the ambroxol stimulation will be taking effect. I do not think glucocorticoids should be used immediately after birth. Experience in the past has shown an increased incidence of IVH. I am also concerned about thyroid hormones because, although you enhance pulmonary maturation, you lower the levels of superoxide dismutase and this may increase the hazard of oxygen toxicity.

I have one further question: What is the clearance rate of your surfactant and is it cleared more slowly than naturally occurring surfactant? This is important in relation to the function of macrophages.

**Dr. Fujiwara:** The clearance rates of several different surfactant preparations have been extensively studied by Jobe in animal models. His studies show that Surfactant TA (our preparation) stays in the lungs longer than other surfactants. A recent report by Sherman suggests that if pulmonary macrophages are loaded with excess surfactant lipids there may be a reduction in pulmonary host defenses. We have no evidence of increased infection and no other groups have found this either, using different surfactants. However, this is potentially an important issue, and I think at the moment it is best to use the minimum effective dose of good quality surfactant, say 100 mg/kg, to minimize any possible macrophage problem.

**REFERENCES**