Letter to the Editor

USE OF SURFACTANTS

I read with interest the review article by Dr. Ramanathan, which evaluates the use of surfactants in the management of neonatal respiratory distress syndrome (nRDS)[1] and Corff et al., which examines the practical considerations in the selection and use of pulmonary surfactant therapy for nRDS.[2]

Dr. Ramanathan correctly points out that lucinactant, which contains a synthetic polypeptide that mimics the action of surfactant protein B (SP-B), has been examined in phase III clinical trials. However, he describes this new peptide as behaving more like SP-C than SP-B, which is not correct.

Of the four known surfactant proteins, SP-B appears to play the dominant role in stabilizing and enhancing the ability of phospholipids to lower surface tension. Infants who are congenitally deficient in SP-B develop lethal respiratory failure shortly after birth,[3] whereas those deficient in SP-C tend to develop chronic lung disease in early adulthood.[4] Lucinactant is a synthetic product containing a 21-amino acid synthetic peptide, sinapultide (KL_4), which mimics the actions of human SP-B.[5] Although earlier work by some investigators have suggested that this peptide forms a transmembrane helix and therefore more likely mimics SP-C,[6,7] this structural orientation was seen only in phospholipid *bilayers* and not in the physiologic phospholipid monolayer *in vivo*, where the sinapultide spatial structure resembles an amphipathic domain of SP-B.[8] Indeed, very recent data using ^{31}P NMR and ^{2}H NMR show that the KL_4 peptide lies parallel to the polar head groups under physiological conditions, and even in DPPC/POPG bilayers,[9] consistent with original observations by Cochrane et al.[8] We hypothesize that this unique spatial arrangement of the KL_4 peptide supports the results and significant clinical improvement in prevention and treatment of nRDS as already established in several clinical studies.[10,11]

Dr. Ramanathan also makes some statements about the quality of trials involving lucinactant on grounds that are debatable and can be easily repudiated. The clinical trials evaluating lucinactant were robust both in design and execution. The SELECT trial tested the hypothesis that lucinactant would be superior to a non-protein-containing synthetic surfactant.[12] Thus, the primary comparison was lucinactant against colfosceril palmitate. The SELECT trial final sample size was consistent with pre-specified trial design and the statistical conclusions from the trial are valid, given the robustness of the P values. It is important to understand that the power of a study is a concept that is more appropriate for study design and is meaningful before final analysis of the data. After the study is completed and final analysis is performed, power is not a factor that has an impact on the interpretation of statistically significant results. The issue of being underpowered is only meaningful if the results of the study are not statistically significant, where under powering might be one of the reasons for failing to meet the primary statistical assumptions. This fact is often misinterpreted by clinicians.

The STAR trial was designed to demonstrate noninferiority of lucinactant compared with poractant, and did in fact demonstrate this outcome with only half the number of initially planned subjects.[13] From a statistical point of view, early termination of this study could reduce its power and could have explained a statistically *non-significant* finding resulting from the analysis of this reduced sample. However, any statistically significant result would be valid and is even more convincing, given the smaller sample size. Indeed, noninferiority was demonstrated even at the 99% confidence limits.

Corff et al. comment on the more practical aspects of surfactant therapy suggesting the preparation time and complexity for the various surfactants may delay administration of the therapy to the infant. While currently available surfactants require warming to room temperature prior to administration, there is a lack of consistency and adherence to these warming requirments.[14] If surfactants are warmed according to manufacturers' instructions, all warming methods take a similar amount of time (see Table).

Table. Product Storage and Warming Specifications

Product	Storage	Warming
Beractant (Survanta; Ross Products Division, Abbott Laboratories Inc.)	Light-protected refrigerated storage 2°C–8°C	• Let stand at room temperature for ≥ 20 minutes, or warm by hand for ≥ 8 minutes • Artificial warming methods should not be used
Lucinactant (Surfaxin, Discovery Laboratories, Doylestown, PA		• Heat in warming cradle at 44°C for 15 minutes.
Poractant alfa (Curosurf; Dey Pharmaceuticals, Inc.)	Light-protected refrigerated storage 2°C–8°C	• Slowly warm to room temperature

The Surfaxin warming procedure supports predictable and consistent preparation and assures that warming of the product is conducted as specified in the label.

Corff et al. are correct in stating that there are drawbacks presently associated with surfactant administration. Aerosolized surfactants have been tested in animal models of respiratory distress syndrome. In addition, four small clinical studies have been performed to date. A recent feasibility study showed aerosolized lucinactant (Aerosurf) to be tolerable and safe.[15] The effectiveness of this form of treatment, however, requires further study, with the goal of optimizing the dose of aerosolized surfactant, developing the best delivery system and choosing a surfactant that maintains its activity once aerosolized.[16]

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DISCLOSURE Dr. Sinha is a paid consultant to Discovery Laboratories, Inc.

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REPLY

I welcome the comments by Dr. Sunil Sinha on my review article.[1] To answer his comment on the peptide that is present in the synthetic surfactant lucinactant, it is not just how this peptide has been shown oriented at the air-liquid interphase. It is important to understand that overall composition of surfactant is much more important than phospholipids or surfactant proteins (SPs), including SP-B. It is well known that SP-B deficiency results in severe respiratory failure. In patients with SP-B deficiency, not only SP-B protein is deficient, but, SP-C is also misprocessed, resulting in increased amounts of pro SP-C, rather than mature SP-C. To date, natural surfactants appear to be better than synthetic surfactants. In all of the comparative trials published to date, natural surfactants have been shown to be associated with a significant decrease in mortality. Natural surfactants vary in the proportion of lipids and SPs. Calfactant has a much higher amount of phospholipids and SP-B when compared to beractant. Yet, 4 large, randomized comparative trials involving more than 2,000 preterm infants showed no differences between these 2 surfactants.[2,3] Poractant alfa is the only surfactant that has shown a decreased mortality when compared with synthetic or natural surfactants, and decreased need for additional doses in comparative studies.[4,5] Likely reasons for these include higher proportion of phospholipids, adequate amounts of both SP-B and SP-C, and highest amount of anti-oxidant phospholipid, namely, plasmalogens. I disagree with Dr. Sinha's assessment that trials comparing lucinactant with beractant or poractant alfa have established significant clinical improvement in prevention and treatment of neonatal respiratory distress syndrome (RDS). There are no trials comparing lucinactant with other natural surfactants in the "prevention" of RDS. The SELECT trial by Moya et al.[6] was a rescue trial, due to the fact that the mean time of surfactant administration was 27 minutes. Meta-analysis of surfactant trials compared prophylaxis trials defined as surfactant administration within 15 minutes of age, and treatment trials as surfactant administration from 2 to 24 hours of age. To my knowledge, there are no trials comparing prophylaxis with

very early rescue treatment. In the SELECT trial,[6] there were no differences in any of the 13 outcomes reported between lucinactant and beractant. The SELECT trial also chose the primary outcome as RDS-related death at 14 days, which is not a clinically important outcome. All cause mortality at 36 weeks postmenstrual age was not different between lucinactant- and beractant-treated groups.

Regarding his comments on statistics, it is important to be aware that all too often studies are reported that are simply too small to have adequate power to detect the hypothesized effect. In other words, even when a difference exists in reality it may be that too few study subjects have been recruited. The result of this is that P values are higher and confidence intervals wider than would be the case in a larger study and the erroneous conclusion may be drawn that there is no difference between the groups. This phenomenon is well summed up in the phrase, 'absence of evidence is not evidence of absence.' In other words, an apparently null result that shows no difference between groups may simply be due to lack of statistical power, making it extremely unlikely that a true difference will be correctly identified. It is not uncommon for conclusions to be made arbitrarily on the basis of convenience, available resources, or limited number of subjects enrolled in studies terminated before the calculated sample size is achieved. The primary outcome chosen in the STAR trial[7] is also not a clinically relevant outcome. These investigators chose survival without oxygen requirement or on mechanical ventilation at 28 days of age. However, this primary outcome has been shown to be a poor predictor of both short- and long-term outcomes in preterm infants. They also chose -14.5% difference to achieve statistical noninferiority, based on a poractant alfa study published 17 years ago.[8] Furthermore, the size of the effect should be large enough to be clinically relevant. The absolute difference in their primary outcome was –4.7%. Infants less than 1000 g are at increased risk for bronchopulmonary dysplasia (BPD) and adverse neurodevelopmental outcomes. Almost two thirds of the population was less than 1000 g in the STAR trial. In infants between 600 and1000 g, 51.9% were alive without BPD at 36 weeks postmenstrual age in lucinactant group as compared to 55.6% in the poractant alfa treated group. In the STAR trial, no statistical differences were noted in 16 outcome variables reported between lucinactant and poractant alfa. In fact, mortality or BPD was 35.3% in the lucinactant group, and 33.1% in the poractant alfa group. Similarly, BPD alone was 35.3% with lucinactant and 29.8% with poractant alfa. However, both these results are not statistically significant. It is incorrect, based on these results, to conclude that treatment with lucinactant is associated with "significant clinical improvement in prevention and treatment of RDS." One should not totally discount a trial simply because of inadequate sample size, but should carefully consider its results in the context of prior trial results. Noninferiority trials are intended to show whether a new treatment has at least as much efficacy as the standard. It is extremely crucial to use the treatment, in the case of the STAR trial, poractant alfa, as it had been studied. STAR investigators did not use the initial dose of 200 mg/kg of poractant alfa. Many studies have shown significant differences in outcome using same surfactant, but with different doses. Even a difference with a 60-mg/kg dose has been shown to be associated with a lower incidence of BPD.[9] Interventions and outcome measures in noninferiority trials should be similar to those trials that established the efficacy of the reference treatment. One should avoid measures that might dilute true differences between treatments, thereby enhancing the risk of erroneously concluding noninferiority.[10]

Dr. Sinha also commented on the article by Corff KE et al.[11] He stated that "if surfactants are warmed according to manufacturers' instructions, all warming methods take a similar amount of time". None of the natural surfactants take more than 8 minutes, in comparison to 15 minutes warming time recommended for lucinactant. In the SELECT trial, mean time to administer lucinactant was 27 minutes, and for beractant, it was 26 minutes. All of the previously published prevention trials using beractant administered beractant within 10-15 minutes of age. It is unclear as to why it took nearly double the time to administer beractant in the SELECT "prevention" trial. Timing of administration was not reported in the STAR trial.

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