

An Open Label Comparison of Calfactant and Poractant Alfa Administration Traits and Impact on Neonatal Intensive Care Unit Resources

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OBJECTIVE To compare calfactant (CA) and poractant alfa (PA) administration traits, short-term clinical responses, and resource use in the neonatal respiratory distress syndrome (RDS) setting. **METHODS** An open label series of 277 (213 PA and 64 CA) infants was evaluated for 445 administrations. Registered respiratory therapists collected patient, surfactant administration, and post-administration clinical data. Economic analysis involved labor costs of surfactant administration and usage, wastage, and product average wholesale price. Analysis utilized the Mann-Whitney rank sum test for differences in administration time and either the chi-square or Fisher's exact test for categorical variables.

RESULTS PA had a statistically lower bedside administration time than CA (3.8 minutes vs. 5.3 minutes; $P = .006$) and a higher percentage of doses administered in less than five minutes (58.9% vs. 4.3%; $P < .001$). Doses administered per patient were similar (1.67 vs. 1.72). PA and CA were similar in time to recovery (81.4% vs. 74.3%), percent desaturation (24.8% vs. 26.7%), and bradycardia (3.8% vs. 8.5%). Reflux was significantly higher (13.2% vs. 3.5%; $P < .001$) with CA. Economic analyses found total administration costs per dose were \$2.21 for PA and \$3.08 for CA. Mean wastage costs were \$141.21 for PA and \$337.34 for CA ($P < .001$).

CONCLUSIONS PA appeared to utilize fewer neonatal intensive care unit resources than CA due to reduced administration time and less wastage of drug product. Future studies should more closely evaluate time, resource, wastage, and post-administrative clinical effects to fully assess the impact of surfactant products in this setting.

KEYWORDS calfactant, pharmacoeconomics, poractant alfa, respiratory distress syndrome, surfactant

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INTRODUCTION

Treatment with pulmonary surfactant significantly reduces the morbidity and mortality

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associated with neonatal respiratory distress

ABBREVIATIONS AWP, average wholesale price; CA, calfactant; NICU, neonatal intensive care unit; PA, poractant alfa; PL, phospholipids; RDS, respiratory distress syndrome; RRT, registered respiratory therapist

syndrome (RDS)^{1,2} by reducing air-liquid surface tension in the alveoli and preventing

collapse.^{3,4} Among the treatment modalities utilized in the RDS setting, pulmonary surfactants demonstrate the best clinical and economic outcomes.⁵ To date, natural surfactants show greater clinical benefits in treating RDS than synthetic agents, including faster onset,⁵⁻¹⁰ fewer cases of pneumothorax,⁵⁻¹¹ reduced dependence on supplemental oxygen and positive-pressure ventilation,⁵⁻¹¹ and a lower mortality rate [relative risk 0.87 (95% CI, 0.76-0.98)].⁸ Natural surfactants may benefit from the presence of proteins not contained within currently available synthetic surfactants: surfactant-associated proteins B and C, which increase phospholipid (PL) stability and enhance PL interaction with the air-liquid interface.^{5,7}

Three natural surfactants are currently available in the United States: poractant alfa (PA; Curosurf, DEY, LP, Napa, CA), beractant (BA; Survanta, Ross Laboratories, St. Louis, MO), and calfactant (CA; Infasurf, Forest Laboratories, St. Louis, MO). PA and BA are compared in several published clinical trials that demonstrate relative advantages of PA when compared to BA in infant oxygenation,¹²⁻¹⁴ ventilatory requirements,¹²⁻¹⁴ need for redosing,¹³ incidence of complications such as patent ductus arteriosus,¹² and mortality up to 36 weeks postconceptional age in infants born at ≤ 32 weeks gestation.¹³ CA and BA are also compared in published clinical trials. Bloom et al. demonstrated a modest benefit in oxygen requirement with a longer sustained effect with CA compared to BA.¹⁵ However, to date, no studies directly compare PA to CA.

In the neonatal intensive care unit (NICU), time is often critical, particularly when treating RDS in very low birth weight preterm infants. Health care professionals in this setting place significant importance on medications that afford easy preparation and quick administration and exert a rapid onset of action. Surfactant therapies that best meet these criteria and exhibit a lower incidence of adverse effects may reduce health care resource consumption and enhance outcomes. Additionally, in an era of heightened emphasis on cost efficiency,¹⁶⁻¹⁸ economic differences that result from differences in vial size and product wastage could also play a role in determining a product's place on a health system's formulary. At the time of this evaluation, there are no published surfac-

tant studies that focus primarily on practical administrative measures such as these.

This pilot evaluation was conceived to provide important preliminary information about differences that may exist between PA and CA as a prelude to further investigation. The primary objective was to compare the technical administration traits of PA and CA in treating premature neonates with RDS in the NICU setting. Secondary objectives included comparing their impact on short-term clinical effects and resources utilized.

METHODS

In order to observe potential differences in the technical aspects of administration between PA and CA, very low birth weight preterm infants were enrolled in a sequential, non-randomized, open label study at the Pennsylvania Hospital NICU of the University of Pennsylvania Health System from October 2001 to May 2004. PA was used exclusively from October 2001 to August 2003 and CA was used exclusively from September 2003 to May 2004. PA was resumed for routine use after the completion of the study. Approval was obtained from the institutional review board as a non-consent study because of the observational nature of the evaluation.

All infants who were intubated and required surfactant therapy for RDS during the investigational period were included in the study. There were no exclusions for any concomitant conditions or disease states, as these variables were not expected to affect the administration of surfactant therapy. Consistent with product labeling, PA was dosed at 2.5 mL/kg initially, then at 1.25 mL/kg for additional doses.¹⁹ CA was dosed at 3 mL/kg for all doses.²⁰ Each dose was administered intratracheally by a registered respiratory therapist (RRT) in two aliquots, according to manufacturer dosing recommendations.^{19,20}

The Pennsylvania Hospital NICU is a 45-bed Level III unit. There is a dedicated RRT staff of at least one RRT at all times. The RRTs have from 8 to 26 years of experience, and all are highly skilled in administering various surfactant products. Because of the RRT familiarity with different surfactant products, the study design did not include a "learning

curve” when changing surfactant products. The same RRT staff was present for both phases of the study.

RRTs administered the surfactant following the same standard dosing procedures. Both surfactants were administered with the same ancillary supplies and equipment. At the time of surfactant administration, the RRTs recorded temporal, clinical, and pharmaceutical data in a standard data collection table. Patient information included gender, gestational age, and birth weight. After administration, the infants were observed for five to fifteen minutes to record the incidence of any short-term clinical effects. The RRTs documented their own time and clinical descriptions; because this was an observational study, formal time and motion studies with objective third party observers were not done. Infants were administered additional doses of surfactant if they remained intubated and were still receiving supplemental oxygen ($\text{FiO}_2 \geq 0.30$) more than twelve hours after the previous dose, at the discretion of the attending neonatologists. All infants did not receive a repeat dose if FiO_2 was ≥ 0.30 , but there were no changes in attending staff or repeat dosing strategies during the study.

The primary outcome measures of the study were the time of drug administration to the infant, and the following short-term clinical effects: time to recovery; number of surfactant doses administered; reflux up the endotracheal tube or into the pharynx; oxygen desaturation, defined as pulse oximetry $< 90\%$; and bradycardia, defined as heart rate < 100 beats per minute during administration. Secondary outcome measures included the number of vials used for each administration and unused product remaining within the single-dose vials (which was discarded after one use, per manufacturer recommendations).^{19,20}

Statistical differences in administration time between the PA and CA groups were tested using the Mann-Whitney rank sum test. Administration time was further categorized into < 5 minute and ≥ 5 minute intervals. Recovery times were also subsequently categorized into < 1 minute and 1-5 minute intervals. Categorized variables including the clinical outcome observations of desaturation, reflux, and bradycardia were tested using either the chi-square or Fisher’s exact test. Statistical significance

Table 1. Study population

	PA	CA
Number of patients	213	64
Mean # doses per infant	1.67	1.72
Birth weight (g)*	1410 \pm 676	1649 \pm 875
Gestational age (wks)*	29.4 \pm 3.5	30.2 \pm 4.2

CA, calfactant; PA, poractant alfa

*mean \pm SD

was defined as $P < .05$.

A pharmacoeconomic analysis was also conducted to determine the costs associated with each therapy. The cost of surfactant administration was determined by multiplying the RRT wage (\$35/hour for Philadelphia area; \$0.58/minute)²¹ by the time spent by the RRT. The cost of wasted drug was determined by subtracting the amount of the surfactant dose given from the amount of surfactant in the vial dispensed, then multiplying by the per-mL cost for each product, which was determined using average wholesale price (AWP 2005). For PA, AWP was \$327.60 for a 1.5-mL vial and \$641.34 for a 3-mL vial.²² For CA, AWP was \$732.12 for a 6-mL vial.²² For patients receiving PA who required both 3-mL vials and 1.5-mL vials, the cost per mL of the 1.5-mL vial was used to calculate wastage costs.

RESULTS

A total of 277 patients were evaluated: 213 in the PA group and 64 in the CA group. The patient data and dosing characteristics have been summarized in Table 1. The average gestational age of the study population was 29.4 \pm 3.5 weeks in the PA group and 30.2 \pm 4.2 weeks in the CA group. Average birth weight was 1410 \pm 676 grams for the PA group and 1649 \pm 875 grams for the CA cohort. Infants in the PA group received a mean of 1.67 doses per patient. Infants in the CA group received a mean of 1.72 doses per patient.

With respect to time-in-motion observations, there was a significant difference in average surfactant administration time between groups for the 141 administrations for which time was recorded (95 PA, 46 CA) (Figure 1). Mean surfactant administration time per dose of PA was 3.8 minutes, compared to 5.3 minutes for CA ($P = .006$). Furthermore, there was a signifi-

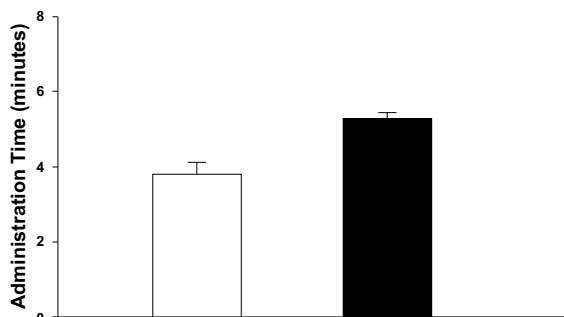


Figure 1. Mean surfactant administration time (mean \pm SEM).

□ = poractant alfa; ■ = calfactant.

$P = .006$

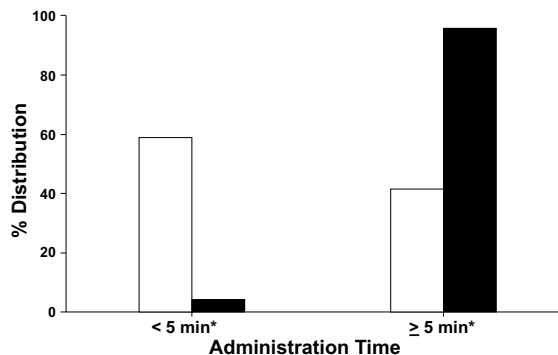


Figure 2. Distribution of surfactant administration time.

□ = poractant alfa; ■ = calfactant.

* $P < .001$

cant difference in the percentage of doses that were administered in less than five minutes (Figure 2). In the PA treatment group, 58.9% of the surfactant doses were administered in less than five minutes, whereas only 4.3% of CA doses were administered in that time ($P < .001$). There was no difference in preparation time for the two surfactant products.

Clinical observations were also made during the initial five- to fifteen-minute period after surfactant administration to gauge tolerability (Figure 3). A significant difference in the incidence of reflux between the two treatment groups was observed (PA 3.5% vs. CA 13.2%; $P < .001$). There was also a trend toward fewer episodes of bradycardia with PA (PA 3.8% vs. CA 8.5%; $P = .05$). In addition, a lower incidence of desaturation was observed with this surfactant, although the difference was not significant. In terms of time for recovery after administration (Figure 4), PA showed a greater percentage of patients with a recovery time of less than one minute, although it was not significant (PA 81.4% vs. CA 74.3%).

In addition to clinical observations, economic factors were also considered. Since preparation time was not significantly different between surfactants, costs were only calculated for administration time of each dose (Figure 5). Administration costs per dose were \$2.21 for the PA group and \$3.08 for the CA group. A significant difference in cost due to drug wastage between the groups was also noted (Figure 6). Mean wastage cost per dose in the PA group was \$141.21, while mean wastage cost in the CA group was \$337.34 ($P < .001$). This resulted in a cost savings of \$196.13 per dose delivered.

DISCUSSION

This exploratory study was the first to compare CA and PA. The goal was to evaluate the technical aspects of administration with initial short-term clinical observations and economic implications of two surfactant products. Observations indicated that PA was associated with a shorter average administration time compared to CA, fewer incidences of reflux, and trends favoring time to recovery, incidence of desaturation, and bradycardia. PA appeared to offer a cost savings compared to CA based on cost of administration and drug wastage.

Several valuable observations can be made based on this analysis. A significantly shorter surfactant administration time is observed with PA, and this disparity may be due partly to the higher PL concentration in that surfactant: PA contains 99% PL, at a concentration of 80 mg PL/mL, whereas CA consists of 95% PL at a concentration of 35 mg PL/mL.^{19,20} The higher PL concentration in PA allows for a smaller volume and facilitates more rapid administration. The percentage of doses administered within five minutes is greater in infants receiving PA than with CA. This difference in administration time can be clinically significant for both the RRT providing care in a stressful environment and the distressed, physiologically labile infant receiving ventilatory support. The higher PL concentration also affords administration of a more potent dose (200 mg/kg). Ramanathan et al.¹³ reports that administration of a larger initial dose of PA (200 mg/kg) results in a significantly greater percentage of infants who are successfully treated with only one dose compared to a smaller PA dose of 100 mg/kg

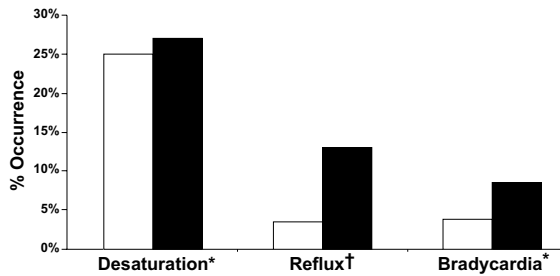


Figure 3. Clinical observations after administration.

□ = poractant alfa; ■ = calfactant.

* $P = .05$

† $P < .001$

(73% vs. 59%; $P < .002$). Fewer instances of redosing indicate faster clinical resolution of RDS, which results in reduced resource utilization and increased cost savings. Another factor that may play a role in the observed difference in administration time is the viscosity of the products. A less viscous surfactant may be reasonably expected to have a quicker administration time, as well as other desirable administrative or clinical effects.²³

The differences in PL concentration that result in a corresponding lower dosage volume associated with PA may also account for the reduced adverse effects seen with PA in this study. The significantly lower percentage of infants who refluxed surfactant into the endotracheal tube or pharynx with PA is likely due to the larger volume of surfactant administered with CA and possibly also a difference in viscosity. These differences, although slight, may be clinically important. Reflux may contribute to obstruction of the endotracheal tube or tracheobronchial tree, which may predispose the neonate to development of distended terminal airways, pulmonary interstitial emphysema or pneumothorax,²⁴ decreased arterial saturation, and bradycardia.⁷ Furthermore, reflux disrupts the administration of pulmonary surfactant, delaying the time it takes the drug to reach its site of action. This adverse effect may result in drug loss, greater resource utilization, and discomfort to the infant. Such maldistribution of surfactant may also impede the neonate's recovery from RDS. Indeed, infants appear to experience a quicker recovery time with PA (Figure 4). With less reflux, the delivery of care is effectively coupled with greater tolerance and ease of administration.

Furthermore, larger volumes of surfactant may be associated with transient hypercapnia

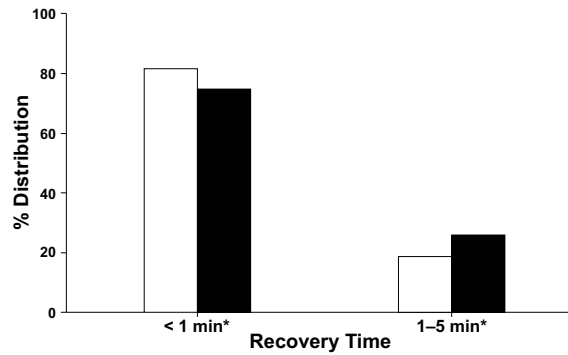


Figure 4. Time for recovery after administration.

□ = poractant alfa; ■ = calfactant.

* $P > .05$

and a decrease in oxygenation. When administering surfactant to very low birth weight neonates, the transient hypercapnia that is associated with the administration of the surfactant appears to have an impact on cerebral blood flow and its autoregulation.^{25,26} It would be desirable to minimize the fluctuation in PaCO_2 that has been shown to be associated with the administration of surfactants. Additionally, less volume could cause less of a surface-active effect with respect to the disturbance of ventilation for the brief period of time that the surfactant is being administered and then distributed in the lungs. Thus, a smaller volume may have an impact on these parameters, and its effects should be evaluated in controlled clinical trials.

Differences in composition and viscosity may have other consequences as well. Rüdiger et al. observe that preterm infants who develop bronchopulmonary dysplasia have a significantly lower percentage of several compounds, including polyunsaturated fatty acid-containing phospholipids and plasmalogen, a minor surfactant lipid, in their lungs.²⁷ These compounds contribute to lower surfactant viscosity at low surface tension levels.²⁸ PA contains a relatively high proportion of these components compared to other available surfactants, although CA's relative concentration is not available to compare directly to PA's.²⁸ A direct viscosity comparison between PA and CA should be considered for future research.

Other favorable short-term clinical trends associated with PA include time to recovery, percentage of infants experiencing oxygen desaturation, and bradycardic events. Oxygen desaturation and bradycardia are undesir-

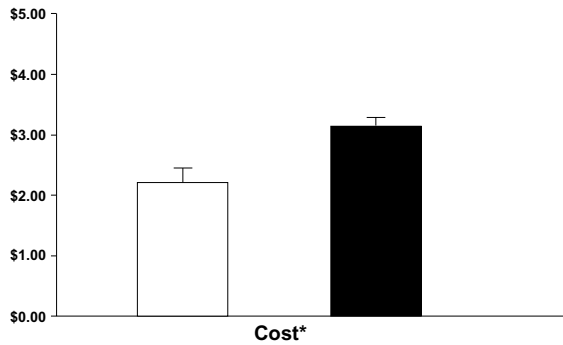


Figure 5. Total administration cost per dose (total mean cost \pm SEM).

□ = poractant alfa; ■ = calfactant.

* $P > .05$

able side effects because they impair oxygen delivery, incur further NICU intervention and resource utilization, and place unwarranted stress on the infant. Although not directly statistically comparable, the rate of bradycardia associated with PA in this analysis (3.8%; Figure 3) is lower than the 5.2% rate of bradycardia observed in a postmarketing study of more than 900 preterm infants by Lamboley-Gilmert et al.²⁹ The rate of transient desaturation (15.7%) in their analysis is lower than the rate of desaturation observed in the present analysis (25%; Figure 3), but this may be due in part to the fact that Lamboley-Gilmert and colleagues defined desaturation as the decrease of oxygen saturation below 85%, whereas in this study, desaturation was defined as less than 90%.

Financial benefits may be observed when considering administration time and drug wastage. The key driver to savings in this analysis was less waste of PA, resulting in a significant mean cost-savings per dose of \$196.13. Marsh et al.³⁰ performed a similar study comparing the vial sizes, drug waste, and cost savings of PA and BA and also found that vial size was a key cost driver.

The difference in administration cost per patient (Figure 5) is likely a conservative estimate of cost savings. In the level three NICU that served as this study's setting, specialized RRTs are responsible for administering surfactant to the infants. However, in some hospitals or in certain circumstances, neonatologists or neonatal nurse practitioners may be required to directly administer the surfactant therapy. Applying neonatologist or specialty nurse wage

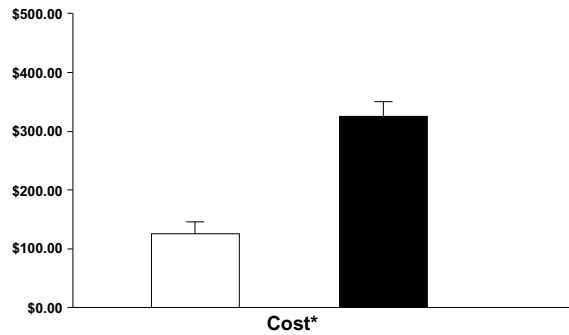


Figure 6. Mean wastage cost per dose (mean wastage cost \pm SEM).

□ = poractant alfa; ■ = calfactant.

* $P < .001$

data would increase the economic disparities. Additionally, there is a less tangible opportunity cost associated with taking a physician away from practice to perform the technical task of surfactant administration.

The endpoints explored herein reflect important aspects of surfactant therapy that should be considered in future studies. Future assessments of surfactants should take into account the impact of preparation and administration time, recovery time, and product wastage. It would also be valuable to examine other factors, such as rates and costs of redosing and re-intubation, as well as preparation and administration time that takes into account all aspects of the drug delivery process, such as delivery time of the drug to the unit from the pharmacy or an automated dispensing machine. A study of this nature would allow an examination of the relative time span between the physician order and drug administration. Other areas of interest for investigation that may affect surfactant administration include analyses considering gestational age, weight, or disease severity. Furthermore, this study was not designed or powered to analyze long-term clinical differences between PA and CA, such as mortality or chronic lung disease. Due to the lack of comparative studies between these two surfactants, an investigation of this manner would be useful and relevant, albeit difficult, as it has been estimated that measurement of a statistically significant reduction in mortality would require a sample size of more than several thousand patients.³¹

Due to the nature of the study design, this exploratory analysis has several limitations that

must be acknowledged. The primary limitation is the use of a sequential, non-randomized, open label design, which invites the possibility of change in clinical practice over the time period of the study, as well as potential bias of the clinicians in favor of either drug. Due to the observational design and less of design control, the surfactants were used exclusively for different lengths of time, which results in an unequal amount of data between treatment groups. It would be ideal for future studies to be randomized, double-blind, and involve parallel-treatment groups over the same length of time. Another limitation is the use of AWP to determine costs because institutional costs vary based upon individual contracts; the actual institution costs for this analysis were unavailable throughout the entire study period. Since this analysis was conducted at a single institution, the results may not accurately reflect other regions that may have different policies or practices.

Furthermore, power to determine significant statistical differences between the short-term clinical outcomes was not determined *a priori*. Therefore, in this study, a type II error may have occurred if the number of infants enrolled was not sufficient to detect a significant difference.

Several potential variables associated with the study design and its limited control merit mention. As the study involved surfactant administration by different RRTs over a period of years, there may be variability between the individual RRT administration times and techniques. It is also possible that as an individual RRT becomes more adept with surfactant administration, the time required for drug administration decreases. Although it would be difficult to eliminate this variable entirely, it might be minimized by conducting a trial with parallel treatment groups that measures the consistency of RRT administration times. Another potential variable involves the re-use of partially used vials. Although the manufacturers state that the surfactant vials are for single-use,^{19,20} some institutions draw up multiple doses from the same vial. Because the manufacturer's recommendations were followed in this study, the results might differ from those in institutions that utilize vials for multiple doses; they may have different economic results, as they would likely incur less overall

wastage. Yet another variable that may affect drug wastage and cost is the availability of a smaller CA vial. At the time of the study, CA was only available as a 6-mL vial. A 3-mL vial has since become available. A sensitivity analysis was performed to determine the impact of this new size, as well as several other variables.

Variables tested included the acquisition cost of the products, a new vial size for CA, and labor costs. The first variable examined for the sensitivity analyses was the AWP cost of the products. Holding the cost of PA constant, it was determined that the AWP cost of the 6-mL vial of CA would have had to be \$303 for the wastage costs to be equal. This was less than half the actual AWP price. It was also determined that the AWP cost of the 6-mL vial of CA would have had to be \$360 for the cost difference to no longer be statistically significant. With the recent introduction of a 3-mL vial for CA,²⁰ it was next decided to go back and replace the use of 6-mL vials with 3-mL vials where appropriate and recalculate the cost difference. The mean wastage cost dropped to \$169.47, which was not statistically different from the PA mean wastage cost of \$141.21.

Finally, sensitivity analyses were performed around the use of other health care professionals instead of administration by only RRTs. At the time of writing, the median neonatologist salary in the Philadelphia area was \$200,207 per year.³² Assuming a 40-hour workweek, this would average \$96.25/hr (\$1.60/min), nearly three times the RRT rate. If administration were performed by only neonatologists, the mean cost would have been \$6.08 for PA and \$8.48 for CA. A median salary in the Philadelphia area for neonatal nurse practitioners was \$85,094,³² which translates into \$0.68/min. The total cost for neonatal nurse practitioners to administer PA would have been \$2.58, and \$3.60 for CA.

Ideally, a large, randomized, controlled trial comparing parallel treatment groups over an equal length of time would firmly define the differences between these products, although it would be difficult to carry one out with adequate sample size and power. The results obtained in this analysis should aid in future study direction regarding hypothesis generation, endpoints, and study design, and introduce a new perspective on variables to be con-

sidered when selecting a surfactant for clinical application. Evaluation of existing surfactants and new formulations in this manner as they become available would assist the clinician in assessing the costs and benefits of individual surfactant preparations.

This pilot study was an exploratory evaluation to determine how PA and CA compared with respect to their technical aspects of administration, short-term clinical observations, and the implications of any differences observed. These observations come with some limitations, based primarily on the study design, but the results imply that there may be areas of difference between PA and CA in drug administration time and short-term clinical outcomes.

CONCLUSIONS

The results of this initial pilot evaluation indicate that PA appears to involve less time for administration than CA with significantly fewer instances of reflux. Furthermore, the trends appear to favor PA with respect to time to recovery, percent desaturation, and bradycardia, and PA consumes significantly less staff time and administration costs. PA is associated with less product waste based on unused surfactant remaining in vials during the dates of the study. Considering the limitations of this evaluation, the results of this exploratory investigation suggest that there may be differences in administration time and, thus, cost between PA and CA, as well as differences in the incidence of short-term clinical observations. Prospective, randomized controlled trials are needed to further establish potential differences that exist between these surfactant products' technical, clinical, and financial outcomes.

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REFERENCES

- Schwartz RM, Luby AM, Scanlon JW, Kellogg RJ. Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500 g. *N Engl J Med* 1994;330:1476-80.
- Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: Systemic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
- Ishisaka DY. Exogenous surfactant use in neonates. *Ann Pharmacother* 1996;30:389-98.
- Merrill JD, Ballard RA. Pulmonary surfactant for neonatal respiratory disorders. *Current Opin Pediatr* 2003;15:149-54.
- Gal P, Ransom JL. Acute respiratory distress syndrome. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:557-75.
- Halliday HL. Natural vs synthetic surfactants in neonatal respiratory distress syndrome. *Drugs* 1996;51:226-37.
- Nguyen TN, Cunsolo SM, Gal P, Ranson JL. Infasurf and Curosurf: Theoretical and practical considerations with new surfactants. *J Pediatr Pharmacol Ther* 2003;8:97-114.
- Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD000144. DOI: 10.1002/14651858.CD000144.
- Suresh GK, Soll RF. Lung surfactants for neonatal respiratory distress syndrome: Animal-derived or synthetic agents? *Pediatr Drugs* 2002;4:485-92.
- Vermont-Oxford Neonatal Network. A multicenter, randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. *Pediatrics* 1996;97:1-6.
- Halliday HL. History of surfactant from 1980. *Biol Neonate* 2005;87:317-22.
- Malloy CA, Nicoski P, Muraskas JK. A randomized trial comparing beractant and poractant treatment in neonatal respiratory distress syndrome. *Acta Paediatr* 2005;94:779-84.

13. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K, et al. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. *Am J Perinatol* 2004;21:109-19.
14. Speer CP, Gefeller O, Groneck P, Laufkotter E, Roll C, Hanssler L, et al. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Arch Dis Child* 1995;72:F8-13.
15. Bloom BT, Kattwinkel J, Hall RT, Delmore PM, Egan EA, Trout JR, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome. *Pediatrics* 1997;100:31-38.
16. Baumer AM, Clark AM, Witmer DR, Geize SB, Vermeulen LC, Deffenbaugh JH. National survey of the impact of drug shortages in acute care hospitals. *Am J Health Syst Pharm* 2004;61:2015-2022.
17. Becker C. A dose of higher costs. With drug manufacturers being hit with new fees from distributors, providers and GPOs face new pricing pressures. *Mod Healthc* 2004;34:4-7.
18. Hoffman JM, Shah ND, Vermeulen LC, Hunkler RJ, Hontz KM. Projecting future drug expenditures – 2005. *Am J Health Syst Pharm* 2005;62:149-67.
19. Curosurf [prescribing information]. Napa, CA: DEY, L.P.; 2002.
20. Infasurf [prescribing information]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2003.
21. Salary.com™ Job Salaries & Compensation Survey Software [homepage on the Internet]. Needham, MA: Salary.com. Available at: <http://www.salary.com/>. Accessed June 9, 2005.
22. 2005 Drug Topics Red Book, 109th ed. Montvale, NJ. Thomson PDR; 2005.
23. King DM, Wang Z, Palmer HJ, Holm BA, Notter RH. Bulk shear viscosities of endogenous and exogenous lung surfactants. *Am J Physiol Lung Cell Mol Physiol* 2002;282:L277-284.
24. Hentschel R, Jorch G. Acute side effects of surfactant treatment. *J Perinat Med* 2002;30:143-148.
25. Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: Review of the literature and results of new analyses. *Pediatrics* 1993;92:775-786.
26. Kaiser JR, Gauss CH, Williams DK. Surfactant administration acutely affects cerebral and systemic hemodynamics and gas exchange in very-low-birth-weight infants. *J Pediatr* 2004;144:809-814.
27. Rudiger M, von Baehr A, Haupt R, Wauer RR, Rustow B. Preterm infants with high polyunsaturated fatty acid and plasmalogen content in tracheal aspirates develop bronchopulmonary dysplasia less often. *Crit Care Med* 2000;28:1572-1577.
28. Rudiger M, Tolle A, Meier W, Rustow B. Naturally derived commercial surfactants differ in composition of surfactant lipids and in surface viscosity. *Am J Physiol Lung Cell Mol Physiol* 2005;288:L379-383.
29. Lamboley-Gilmert G, Lacaze-Masmonteil T, Neonatologists of the Curosurf post-marketing French study. The short-term outcome of a large cohort of very preterm infants treated with poractant alfa (Curosurf) for respiratory distress syndrome: A postmarketing phase IV study. *Pediatr Drugs* 2003;5:639-645.
30. Marsh W, Smeeding J, York JM, Ramanathan R, Sekar K. A cost minimization comparison of two surfactants—beractant and poractant alfa—based upon prospectively designed, comparative clinical trial data. *J Pediatr Pharmacol Ther* 2004;9:117-125.
31. Tarnow-Mordi WO, Soll RF. Artificial versus natural surfactant—can we base clinical practice on a firm scientific footing? *Eur J Pediatr* 1994;153 Suppl 2:S17-S21.
32. Salary.com Job Salaries & Compensation Survey Software [homepage on the Internet]. Needham, MA: Salary.com. Available at: <http://www.salary.com/>. Accessed November 17, 2005.