Comparison of the Pharmacoeconomics of Calfactant and Poractant Alfa in Surfactant Replacement Therapy

Michael M. Zayek, MD; Fabien G. Eyal, MD; and Robert C. Smith, BScPharm, MS

OBJECTIVE To compare the pharmacy costs of calfactant (Infasurf, ONY, Inc.) and poractant alfa (Curosurf, Chiesi USA, Inc., Cary, NC).

METHODS The University of South Alabama Children's and Women's Hospital switched from calfactant to poractant alfa in 2013 and back to calfactant in 2015. Retrospectively, we used deidentified data from pharmacy records that provided type of surfactant administered, gestational age, birth weight, and number of doses on each patient. We examined differences in the number of doses by gestational ages and the differences in costs by birth weight cohorts because cost per dose is based on weight.

RESULTS There were 762 patients who received calfactant and 432 patients who received poractant alfa. The average number of doses required per patient was 1.6 administrations for calfactant-treated patients and 1.7 administrations for poractant alfa-treated patients, $p = 0.03$. A higher percentage of calfactant patients needed only 1 dose (53%) than poractant alfa patients (47%). The distribution of the number of doses for calfactant-treated patients was significantly lower than for the poractant alfa-patients, $p < 0.001$. Gestational age had no consistent effect on the number of doses required for either calfactant or poractant alfa. Per patient cost was higher for poractant alfa than for calfactant in all birth weight cohorts. Average per patient cost was \$1160.62 for poractant alfa, 38% higher than the average per patient cost for calfactant (\$838.34). Using poractant alfa for 22 months is estimated to have cost \$202,732.75 more than it would have cost if the hospital had continued using calfactant.

CONCLUSION Our experience showed a strong pharmacoeconomic advantage for the use of calfactant compared to the use of poractant alfa because of similar average dosing and lower per patient drug costs.

ABBREVIATIONS FDA, Food and Drug Administration; GA, gestational age; RDS, respiratory distress syndrome;

KEYWORDS calfactant; Curosurf; Infasurf; pharmacoeconomics; poractant alfa; surfactant

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Introduction

Currently there are 3 lung surfactant replacement products in the United States that are Food and Drug Administration (FDA) approved for treatment of newborn infants with respiratory distress syndrome (RDS), a severe and potentially fatal cause of respiratory failure in the first few days of life. Two of the products, calfactant (Infasurf; ONY, Inc., Amherst, NY) and beractant (Survanta; Abbvie, North Chicago, IL) are FDA approved for prevention of RDS (i.e., are indicated for therapy before any symptoms). Calfactant, beractant, and poractant alfa (Curosurf; Chiesi USA, Inc., Cary, NC) are FDA approved for treatment of RDS. Our institution used both poractant alfa and calfactant in the years between 2003 and 2011 and found no differences in the ultimate clinical outcomes of mortality, chronic lung disease, or acute pulmonary complications.

One of the advantages that the manufacturer claims for poractant alfa is that using its surfactant results in

only a small percentage of patients requiring more than 1 dose.¹ The expectation that University of South Alabama Children's Hospital would experience a similarly reduced frequency of single dose usage was one of the factors that led us to change from calfactant to poractant alfa in 2013. We used poractant alfa exclusively for the next 22 months but did not observe a reduction in the rate of multiple doses needed in our patients. In 2015, we returned to using calfactant. This report describes the patterns of dosing in neonatal patients before, during, and after the switch from calfactant to poractant alfa and back to calfactant, as well as the pharmacoeconomic impact of those dosing patterns.

Materials and Methods

The data from the pharmacy records of University of South Alabama Children's Hospital provided the birth weight, gestational age (GA), and number of surfactant doses administered to each patient from February 2010

Figure 1. Comparison of the average number of doses of calfactant and poractant alfa.

through February 2016, a 6-year period. USA Children's & Women's Hospital delivers 3000 patients per year, and the neonatal intensive care unit (NICU) is a 70-bed level IIIB unit with over 1000 admissions per year. We included all patients who were treated with surfactant. Poractant alfa was the surfactant used from July 24, 2013, to June 7, 2015. Calfactant was used before and after the poractant alfa era. No patient identifiable data were used.

Both surfactants are suspensions in saline and stored refrigerated. A key difference is the cost to the institution derived from the number of single-dose vials used per patient and the price of those vials. An initial and a repeat dose of calfactant are the same 105 mg/kg (3 mL/kg) body weight. Calfactant comes in 3- and 6-mL vials. The number of vials of calfactant needed per dose is a single 3-mL vial for patients ≤ 1 kg, a single 6-mL vial for patients 1.001 to 2 kg, and a combination of vials for patients > 2 kg. Poractant alfa dosing is more complex because the initial dose is 200 mg/kg (2.5 mL/kg), but repeat doses are 100 mg/kg (1.25 mL/kg). Poractant alfa comes in 1.5- and 3-mL vials. For initial doses, the number of vials of poractant alfa is a single 1.5-mL vial for patients ≤ 0.6 kg, a single 3-mL vial for patients 0.601 to 1.2 kg, and a combination of vials for patients > 1.2 kg. For repeat doses, the number of vials of poractant alfa required is a single 1.5-mL vial for patients ≤ 1.25 kg, a single 3.0-mL vial for patients 1.2501 to 2.5 kg, and a combination of vials for patients > 2.5 kg.

Costs are presented as the amount paid by the hospital per vial when describing the actual per patient costs and "as if" when we calculated what the difference in costs would have been had we continued to use calfactant during the 22 months when poractant alfa was used.

Comparisons between the surfactants used unpaired t tests and χ^2 distributions. A p value of < 0.05 was used as indicating a significant difference.

Results

During the 72 months, we reviewed charts of 1194

Figure 2. Distribution of the total number of doses required for calfactant and poractant alfa. The calfactant dose distribution is significantly less than the poractant alfa distribution: χ^2 , 16.8; p = 0.0008.

patients who received surfactant therapy, an average of 16.6 per month. Calfactant was administered to 762 patients over 50 months, an average of 15.2 per month; poractant alfa was administered to 432 patients over 22 months, an average of 19.6 per month. The average number of doses of calfactant was 1.6 per patient, slightly, but significantly, fewer than the 1.7 dose per patient for poractant alfa (Figure 1).

A higher percent of patients received a single dose of calfactant, 53%, than poractant alfa patients, 47%; (Figure 2). A higher percentage of patients treated with poractant alfa required 2 or 3 total doses than calfactant-treated patients, and an equal percentage of patients in each treatment group received more than 3 doses. The difference in distribution of the number of doses is statistically significant, p = 0.0008.

The average number of doses per patient was examined among the different GA groups (Table 1). GA was unavailable for 7 (1.6%) of poractant alfa-treated patients and for 15 (2.0%) of calfactant-treated patients. GA for the total study population was not significantly correlated with the average number of doses for either calfactant or poractant alfa. The average number of doses was significantly higher in calfactant patients in the < 24 -week GA group and significantly lower in the 29- to 32-week GA group. The average number of calfactant doses per patient was equal to or lower than the number of poractant alfa doses per patient in the other GA groups.

Birth weight determines the size and number of vials needed for each dose of the surfactants. Birth weight was not available for 4 (0.9%) of the poractant alfa-treated patients and for 8 (1.0%) of the calfactant-treated patients. Table 2 shows the average vial usage per patient and the average cost per patient for that usage for each birth weight cohort. For calfactant, initial and retreatment doses are the same; for poractant alfa, a repeat dose is half the amount of the initial dose and

Table 1. Comparison of the Average Number of Doses per Patient in Gestational Age Cohorts

Gestational Age, wk	Poractant Alfa			Calfactant			p value
	n	Percent	Average Dose	n	Percent	Average Dose	
<24	59	14	1.4	86	12	1.7	0.008
24–25	58	13	1.4	91	12	1.5	0.323
26–28	109	25	1.5	174	23	1.5	1.000
29–32	123	28	2.0	195	26	1.3	< 0.001
33–37	62	14	2.0	180	24	2.0	1.000
≥38	14	3	2.7	21	3	1.9	0.071
Total	425	100	1.7	747	100	1.6	0.018

that difference is accounted for in the calculations of the average cost per patient. Per patient costs were lower for calfactant in all birth weight cohorts. The average per patient cost of poractant alfa was \$1160.62 and for calfactant \$838.34. Using poractant alfa averaged an increase of \$322.28 over using calfactant, an increase of 38.4% per patient.

Since the patient mix was similar, but not identical, during the periods when the 2 surfactants were used, we compared the actual per patient costs that the hospital experienced during the 22 months during which poractant alfa was exclusively used to the projected surfactant costs if we had used calfactant for those patients instead (Table 3). We calculated that use of poractant alfa increased drug costs by \$477.02 per patient or a total of \$202,732.75 during the poractant alfa usage.

Discussion

In the management of the formulary of an institution, economics become important when multiple options are available for pharmaceutical products with

equivalent effectiveness, side effects, and safety. A large, greater than 50,000 patients, retrospective study identified no difference in efficacy outcomes of survival and bronchopulmonary dysplasia or safety outcomes related to the use of beractant, calfactant, or poractant alfa.¹ We also retrospectively examined outcomes in our surfactant-treated population after changing from calfactant to poractant alfa in 2012 and observed no improvement in survival and no decrease in the incidence of bronchopulmonary dysplasia or other major complications of prematurity.²

Chiesi USA, the marketer of poractant alfa, promotes a very low rate of multiple doses, only 12% to 27% of patients requiring multiple doses in the 5 studies cited on their website³ and replicated in Figure 3.^{4–8} During the period of this report, the decision to retreat a patient, and how often retreatment was necessary, was at the discretion of the clinician responsible for the care of the patient and was not guided by a rigid protocol. The change to poractant alfa in our institution did not result in a decrease in the average doses per patient or the total doses used in the NICU, nor did the percentage of our patients requiring only a single dose approach the

Table 2. The Mean Number of 1.5- and 3.0-mL Vials of Poractant Alfa Used per Patient and the Average per Patient Cost of Those Vials and the Mean Number of 3.0- and 6.0-mL Vials of Calfactant Used per Patient and the Average per Patient Cost of Those Vials

Birth Weight Cohorts, g	Poractant Alfa				Calfactant			
	n	1.5 mL	3 mL	Average Patient Cost in USD	n	3 mL	6 mL	Average Patient Cost*
<500	50	1.5	0	442.62	58	1.5	0	429.05
500–999	156	0.6	0.8	624.68	245	1.5	0	417.45
1000–1499	81	0.8	1.6	1112.50	154	0	1.3	647.43
1500–1999	68	0.7	2.5	1611.32	94	0	1.3	624.74
2000–2499	29	0.2	2.8	1641.50	87	2.0	2.0	1506.21
2500–2999	16	2.4	3.4	2842.40	60	2.2	2.2	1648.59
≥3000	28	1.3	4.7	3081.34	56	0.2	4.0	2075.02
Total	428	0.9	1.6	1160.62	754	0.9	1.2	838.34

USD, United States dollars

Table 3. Comparison of Differences in Total Cost of Surfactant by Birthweight Cohort if Calfactant Had Been Used at USA Children's & Women's Hospital Between July 24, 2013, and June 7, 2015, When Poractant Alfa Was Actually Used

Birth Weight Cohorts, g	n	Actual per Patient Cost in USD: Poractant Alfa	Calculated per Patient Cost in USD: Calfactant*	Different in Cost per Cohort
<500	50	459.78	409.50	2514.00
500–999	156	640.54	409.50	36,042.24
1000–1499	81	1137.62	629.20	41,182.02
1500–1999	68	1644.50	629.20	69,040.04
2000–2499	29	1728.64	1514.00	6224.56
2500–2999	16	2667.43	1665.40	16,032.48
>3000	28	3122.65	1990.60	31,697.40
Total	428			202,732.75

USA, University of South Alabama; USD, United States dollars

* Calculation of calfactant cost uses dosing experience presented in Table 2 for each birth weight cohort.

range promoted for poractant alfa. We reviewed each of the studies cited in Figure 3 to try to identify factors that made single dosing so much more common than in our own experience with poractant alfa. Two of the studies in Figure 3 compared poractant alfa to another surfactant, beractant, Dizdar et al⁴ and Ramanathan et al.⁷ The other 3 were examining alternative methodologies for dosing poractant alfa. All of the studies cited in Figure 3 were complex, randomized controlled trials and were a small select population whose supervision and management may have been different from patients who were not recruited into the clinical trial. Four of the studies recruited between 0.3 and 11 patients per site per month. Only Dizdar et al⁴ had a larger rate of inclusion of 8.8 patients per month at its single site.

Single dose success rates vary among centers and published studies. A low rate of single dosing of poractant alfa, 37%, was reported in a large, prospective single site study of 415 surfactant-treated patients in which poractant alfa and beractant were used in alternating months.⁹ A large, 2168-patient multicenter poractant alfa study, published more than 2 decades ago, comparing 200 mg/kg dose of poractant alfa to a 100-mg/kg dose, reported only 31% of the high dose patients required a single dose.¹⁰ However, a more recent study by Jeon et al¹¹ reported consecutive periods of surfactant use of 3 different surfactants, poractant alfa, calfactant, and beractant, which included all surfactant-treated patients at a single site treating 6.9 patients per month and observed a high rate of single dosing for 3 surfactants: poractant alfa, 77%; calfactant, 83%; and beractant, 83%.¹¹

The failure to observe high rate of single dosing is not unique to our study. The rate of single dosing appears to depend on the site, not the surfactant. The similarity of the pattern of usage between calfactant and poractant alfa observed in this report replicates 1 of the 2 previous reports comparing the usage be-

tween these 2 surfactants. In addition to Jeon et al,¹¹ Gerdes et al¹² reported calfactant patients averaging 1.72 doses and poractant alfa patients averaging 1.67 doses.¹² The Gerdes et al¹² experience is almost identical to the average per patient dosing of 1.6 for calfactant patients and 1.7 for poractant alfa patients observed in this experience.

A pharmacoeconomic advantage for poractant alfa over calfactant was advanced by Gerdes et al¹² because they observed a difference of 1.6 minutes in the average time to administer a dose, converting this spared time to a decreased administration cost of \$0.79 per patient. In their results, they identified more “wastage” of calfactant, defined as the amount of material in a single-dose vial that was not used compared to poractant alfa. However, in their discussion they stated that the difference in wastage was not statistically different when calfactant use included both a 3-mL and a 6-mL vial. Both products are presented in single-use vials and this “wasted” amount cannot be used for future doses. Gerdes et al¹² did not report an actual quantitative comparison of the cost of the surfactants because their institutional costs were unavailable for analysis. The fact that the average number of doses per patient was 1.67 for poractant alfa and 1.72 for calfactant and the absence of cost of drug data make their conclusion of a possible pharmacoeconomic advantage for poractant alfa over calfactant unsupported by appropriate data.

The calculation of the cost per patient in this experience shows what is inevitable if the usage per patient is similar with calfactant or poractant alfa—the costs per patient are going to be determined by the difference in price between the 2 products. Poractant alfa requires more drug, 200 mg/kg versus 105 mg/kg for the first dose, so even though the cost when calculated on a per milligram of surfactant is almost similar, the cost for the first dose is much higher using poractant alfa than calfactant. The costs of repeat doses of calfactant and

Figure 3. Partial reproduction of poractant alfa promotional data on single-dose success on its website in April 2017.

CUROSURF demonstrates consistently high rates of single-dose success			
Single-dose success in clinical studies			
CLINICAL STUDY	N*	GESTATIONAL AGE	CUROSURF (200 mg/kg) SINGLE-DOSE SUCCESS [†]
Dizdar EA, et al. 2011 ⁴	126	Median 28 wks	88%
Sandri F, et al. 2010 (treatment arm) ⁵	103	Mean 27.0 ± 1.0 wks	78%
Dani C, et al. 2004 ⁶	27	<30 wks	74%
Ramanathan R, et al. 2004 ⁷	293	Mean 28.7 ± 2.0 wks	73%
Verder H, et al. 1999 ⁸	60	25-29 wks	88%
* Total number of infants randomized			
† Single dose success is defined as no need for repeat doses of Curosurf® (poractant alfa)			

poractant alfa are more similar because the amount of the repeat dose in mg/kg is similar. For a hospital with a low rate of multiple dosing, the cost differential between calfactant and poractant alfa will be greater than observed here because a higher percentage of the doses administered will be initial doses, not repeat doses.

Conclusions

The single-site data presented here show a strong pharmacoeconomic advantage for calfactant compared to poractant alfa. The reason for the higher cost of poractant alfa is because its initial dose of 200 mg/kg is almost twice as large as the initial 105-mg/kg dose of calfactant.

We did not observe the promotional claim, “consistently high rates of single dose success,” with poractant alfa. Single-dosing rates for both calfactant and poractant alfa vary substantially in the available literature. This is the third comparison of poractant alfa and calfactant dosing in which the rate of single dose and/or average number of doses is similar.

ARTICLE INFORMATION

Affiliations Department of Pediatrics (MMZ, FGE) University of South Alabama School of Medicine, Department of Pharmacy (RCS), University of South Alabama Children's and Women's Hospital, Mobile, Alabama

Correspondence Michael M. Zayek, MD; mzayek@health.southalabama.edu

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