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Surfactant Administration in Preterm Infants: Drug Development Opportunities

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Abstract

Objective: To evaluate how frequently surfactant is used off-label in preterm infants.

Study design: We conducted a retrospective cohort analysis of prospectively collected administrative data between 2005 and 2015 from 348 neonatal intensive care units in the United States. We quantified off-label administration of poractant alfa, calfactant, or beractant in inborn infants <37 weeks gestational age. Off-label surfactant administration was defined according to the Food and Drug Administration (FDA) label.

Results: Of 110,822 preterm infants who received surfactant, 68,226 (62%) received surfactant off-label. The majority of infants who received surfactant off-label had a higher birth weight than label (40,716 [37%]), had a later gestational age than label (35,191 [32%]), or were intubated and administered surfactant followed by immediate extubation (INSURE) (32,310 [29%]). Poractant alfa was administered via INSURE more frequently than beractant or calfactant (16,688 [38%]; 7137 [20%]; 8485 [27%], respectively). An increasing number of infants received surfactant via INSURE from 2005 to 2015 (1697 [19%]; 3368 [36%]).

Conclusions: The majority of surfactant given to preterm infants is administered off-label. The uptrend in administration via INSURE coincides with increased supporting evidence. The gap between FDA labelling and current clinic practice exemplifies an opportunity for label expansion, which may require additional prospective or retrospective safety and/or effectiveness data for infants with later gestational age and higher birth weight.

Surfactant is one of the most frequently used medications in neonatal intensive care units (NICUs).¹ Beractant, calfactant, and poractant alfa, animal derived surfactants, are labeled

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for use in preterm infants by the Food and Drug Administration (FDA) for prevention and/or treatment of respiratory distress syndrome (RDS), one of the most common diseases in NICUs.^{2, 3} Prior to the 1970s, RDS was the most frequent cause of preterm death, but changes in practice, including the development of exogenous surfactant, have decreased death, severe RDS, and pulmonary air leak syndromes.^{4, 5} RDS remains common, affecting over 90% of infants born < 29 weeks GA and 2–10% of infants born 34 to 36 weeks.^{2, 3} The clinical surfactant trials from the late 1980s and early 1990s included infants 23 to 34 weeks gestational age (GA) and/or with birth weight 500 to 2000 g.^{5–10} Observational studies suggest that a proportion of surfactant use is outside of this population.^{3, 11, 12}

FDA label specifications vary for each type of animal-derived surfactant by GA, birth weight, postnatal age, and number of doses (Table 1).^{13–15} A large number of late preterm infants receive surfactant, suggesting off-label use, but the full breadth of off-label use has not been established.^{11, 12} Common to all 3 surfactant types are the requirements of risk for or diagnosis of RDS and administration during mechanical ventilation.^{13–15} The FDA requirement of mechanical ventilation may contribute to a large proportion of off-label use via INSURE, a technique that avoids mechanical ventilation through intubation, surfactant treatment, then rapid extubation back to non-invasive support.¹⁶

In an effort to better describe the off-label use of surfactant and to establish the foundation for label expansion, we characterized off-label surfactant administration to preterm infants. We hypothesized that the majority of surfactant use is off-label, primarily in infants with higher GA and birth weight as well as administration via INSURE.

Methods

We obtained data from the Pediatrix Medical Group Clinical Data Warehouse, which prospectively captures clinical information entered into an electronic health record system by clinicians at 348 neonatal intensive care units within the Pediatrix Medical Group, which operates in the United States.¹⁷ We extracted information on prenatal characteristics, demographics, and in-hospital clinical outcomes. We included all inborn infants <37 weeks GA discharged between 2005 and 2015 who received beractant, calfactant, or poractant alfa. We excluded NICUs that administered surfactant to less than 50 infants over the entire study period and excluded infants who received more than one type of surfactant.

Off-label surfactant use was defined according to FDA labeling (Table 1).^{13–15} Off-label administration included beractant, calfactant, or poractant alfa given via INSURE or for any diagnosis other than RDS. Off-label beractant use was defined as administration to infants with GA < 23 weeks or > 29 weeks, birth weight < 600 g or > 1750 g, or postnatal age > 48 hours after birth. Off-label poractant alfa use was defined as administration to infants with birth weight < 600 g or > 2000 g, or postnatal age > 48 hours. Off label calfactant use was defined as administration to infants with GA > 29 weeks, birth weight > 1251 g, or postnatal age > 72. Small for gestational age (SGA) was defined as <10th percentile for age at birth as described by Olsen.¹⁸ Because no record of method of surfactant administration was available in the dataset, we identified infants who received surfactant but no mechanical ventilation as a surrogate to identify infants who received surfactant via INSURE. We

reviewed diagnoses of interest recorded by the clinician at the time of surfactant administration, including RDS, pneumonia, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn, and meconium aspiration syndrome. We report the frequency of in-hospital outcomes including bronchopulmonary dysplasia (BPD), air leak syndromes (pneumothorax and pulmonary interstitial emphysema) within seven days of surfactant dosing, death, sepsis (defined as bacteremia with an organism not typically considered a contaminant), intraventricular hemorrhage grade III or IV, and necrotizing enterocolitis requiring surgical intervention.¹⁹ We defined BPD in infants < 32 weeks GA as receiving supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) continuously from a corrected GA of 36 0/7 to 36 6/7 weeks. In infants ≥ 32 weeks GA, BPD was defined by the receipt of supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) continuously from a postnatal age of 28 to 34 days.¹¹ The definition required continuous respiratory support or supplemental oxygen to more clearly define infants with BPD compared with those with a transient need for oxygen. Infants who were classified as not having BPD included those who died before the test period or were discharged before the test period. The composite outcome of BPD or death was defined as the diagnosis of BPD and/or all-cause in-hospital mortality.

Statistical Analyses

The unit of observation for this study was the infant. We used standard summary statistics, including medians (interquartile ranges) and counts (percentages), to describe categorical study variables. We compared distributions of study variables across categories using Wilcoxon rank sum, Chi square, and Fisher exact tests where appropriate. Observations with missing data were omitted from analysis and no imputation was performed. All analyses were performed using Stata SE 14.2 (StataCorp, College Station, TX) and assumed a significance level of $\alpha = 0.05$. The study was approved by the Duke Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

Results

We identified 110,822 preterm infants who received beractant, calfactant, or poractant alfa. Of these, 68,226 (62%) received surfactant off-label. Median GA and birth weight were higher in the infants who received off-label surfactant (median GA 32 weeks, interquartile range 30–34 and median birth weight 1806 g, interquartile range 1332–2350) – than infants who received surfactant on-label (gestational age 27 weeks, 25–29, $P < .0001$; birth weight 946 g, 750–1190, $p < 0.0001$) (Table 2). Of the 35,239 infants who received beractant, 24,844 (71%) were off-label recipients. Among 44,444 infants, 24,790 (56%) received poractant alfa off-label and of 31,139 infants, 18,592 (60%) received calfactant off-label (Table 3).

Of the 110,822 preterm infants, 32,310 (29%) received surfactant via INSURE. A total of 4624 (4%) infants had a GA and/or birth weight below FDA label specifications and 2413 (2%) infants received surfactant after the recommended postnatal age (e.g., 48 to 72 hours

postnatal). Most infants who received beractant or calfactant off-label had a higher than label gestational age (18,557 [53%]; 16,634 [53%], respectively) and/or birth weight (11,627 [33%]; 12,454 [28%]). Most infants received poractant alfa off-label via INSURE (16,688 [38%]), more than beractant (7137 [20%]) or calfactant (8485 [26%]) (Table 3). Most infants receiving off-label surfactant (55,084 [81%]) had a diagnosis of RDS. Only 6,856 (9%) had other diagnoses: 3,030 (4%) had a diagnosis of pneumonia, 3,561 (5%) had persistent pulmonary hypertension of the newborn, 117 (0.2%) had meconium aspiration syndrome, and 148 (0.2%) had congenital diaphragmatic hernia. Among infants who received surfactant off-label, death occurred in 3513 (6%), BPD 6283 (9%), BPD or death 9568 (14%), air leak syndrome 3898 (6%), and pulmonary hemorrhage 867 (1%).

Over the study period, off label surfactant administration remained stable overall – 5454 infants (62%) in 2005 and 5502 (59%) in 2015 – as well as the percentage off-label by type of surfactant – 2759 (68%) beractant recipients in 2005 and 739 (74%) in 2015, 790 (53%) poractant alfa recipients in 2005 and 3397 (56%) in 2015, and 1905 (60%) calfactant recipients in 2005 and 1367 (60%) in 2015. An increasing number of infants received surfactant via INSURE over time: from 1697 (19%) in 2005 to 3368 (36%) in 2015. The percentage of off-label administration via INSURE increased for all surfactant types over the study period – infants receiving beractant via INSURE changed from 546 (13%) to 283 (28%), poractant from 462 (31%) to 2358 (39%), and calfactant from 689 (22%) to 727 (32%) (Figure). The percentage of infants with GA and/or birth weight higher than label remained stable throughout the study period for all surfactant types, except for the percentage of infants who received poractant alfa off-label with birth weight higher than label decreased from 480 of 1502 (32%) to 1470 of 6061 (24%) (Figure). Off-label surfactant administration increased over the study period in the birth weight < label group (600 g) from 290 of 437 (66%) infants in 2005 to 510 of 686 (74%) infants in 2015.

Discussion

We found that a majority of preterm infants who receive surfactant are given the drug off-label. As previously suspected, a large proportion of surfactant use was in moderate (GA between 31 0/7 weeks – 33 6/7 weeks) or late-preterm infants (GA between 34 0/7 and 36 6/7 weeks) and infants with birth weight greater than label (1251 – 2000 g).¹¹ Surfactant trials from the era of FDA approval included infants with GA between 23 and 34 weeks and/or with birth weight between 500 and 2000 g, and subgroup analyses demonstrated the largest decrease in mortality for infants with GA < 30 weeks or birth weight < 1250 g.^{5, 10} Pathophysiology suggests infants with respiratory distress syndrome would respond to surfactant regardless of gestational age or birth weight. The American Academy of Pediatrics strongly recommends surfactant administration to infants < 30 weeks GA who are mechanically ventilated because of severe RDS but also states surfactant replacement is effective for larger and more mature preterm infants with established RDS.⁵ Objective evidence is limited for late preterm infants. Retrospective observational studies demonstrate decreased FiO₂ after surfactant administration, but inconsistent reduction in mortality and no significant difference in length of stay, need for mechanical ventilation, or duration of non-invasive support.^{20–23} Several moderate sized randomized controlled trials in a 2007 Cochrane review and a 2015 meta-analysis favoring early INSURE included infants with

GA 25–35 weeks as discussed below, but subgroup analysis did not focus on late preterm infants.^{24–28}

Clinical practice for surfactant has shifted in the 30 years since FDA approval. The preterm infant population now includes lower gestational ages, a high proportion with maternal steroid exposure, and many who are initially stabilized with CPAP.²⁹ For example, very few infants who received surfactant off-label had a birth weight < label, but this number increased over the study period. This may also be attributed to label differences between calfactant and poractant alfa (Table 1). Calfactant has no lower birth weight limit and there has been a shift towards poractant alfa administration and away from other surfactant types during this time period, but our findings could also reflect more widespread resuscitation of infants at the edge of viability.¹¹ Techniques have been developed recently that avoid mechanical ventilation through intubation, surfactant treatment, then rapid extubation back to non-invasive support (INSURE) and other minimally invasive surfactant therapy techniques.¹⁶

Nearly a third of infants in our cohort received surfactant off-label via INSURE and the proportion who received surfactant via INSURE increased over the study period. Over time, a gap has expanded between current evidence on INSURE and FDA labeling. INSURE was developed in Scandinavia about 25 years ago, has been studied in other populations, and has been reviewed in meta-analyses in recent years.^{16, 24, 27} A 2007 Cochrane review showed decreased need for mechanical ventilation, incidence of oxygen use at 28 days, and incidence of air leak syndromes in the overall population. A 2015 meta-analysis of INSURE versus CPAP added studies from the earlier Cochrane review and subtracted studies with prolonged mechanical ventilation. It showed a trend toward decreased BPD, mortality, and air leak. The American Academy of Pediatrics includes INSURE in its most recent clinical report, recommending consideration of immediate CPAP instead of routine prophylactic surfactant administration, and if it is likely mechanical ventilation will be needed early surfactant administration followed by rapid extubation is preferable to prolonged ventilation.³⁰

In our cohort, poractant alfa was administered more often via INSURE than the other surfactant types. Adverse effects of surfactant administration include transient bradycardia, hypotension, airway obstruction, and oxygen desaturations, which may limit the success of rapid extubation, especially if sedatives are used for intubation.^{13–15, 28} Selective use of poractant alfa for INSURE may be explained by favorable characteristics of poractant alfa, such as lower dosing volume, higher initial dose, and fewer total doses, that may decrease the frequency of transient vital sign instability.¹³

FDA labelling is an important step in ensuring medications are safely prescribed to children. Clinical trials overseen by the FDA require a standard of transparent data collection and adherence to protocol not guaranteed in other clinical trials. Although the term “off-label” does not equate to improper, illegal, contraindicated, or investigational, instances of off-label medication use in infants have been associated with increased mortality, morbidity, and adverse events.^{31–33} There has been considerable effort to conduct studies on dosing, safety, and effectiveness of drugs in an effort to expand evidence-based practice and FDA labeling.

^{34–36} Ideally, FDA labeling reflects or contributes to best evidence. Legislation to this end has led to an increasing number of neonatal and pediatric label changes or approvals.^{33, 35, 37} The FDA does not regulate individual prescribing practices. Practitioners have the ultimate responsibility to understand available current evidence, society guidelines, and FDA label content whenever a medication is prescribed. Off-label prescribing occurs for a wide range of reasons – a complete lack of data, incomplete information on effectiveness or safety in children, or FDA labeling that is not reflective of recent evidence.^{33, 38}

Clinical practice has evolved over the last 30 years since beractant, calfactant, and poractant alfa were labelled, creating a gap between evidence and the FDA label. The gap between the FDA label and clinical practice can partially be explained by the costly and lengthy supplemental drug applications that must be submitted by the proprietor. Legislation, such as the Best Pharmaceuticals for Children Act, seeks to decrease such barriers. One avenue for expanding FDA labeling in pediatric populations is extrapolation of effectiveness data from other age ranges. Dosing and safety data may not be extrapolated, so additional prospective clinical trials are often needed. Retrospective data, if available, may sometimes be used instead or in support of clinical trials. For example, label expansion of a specific pediatric ibuprofen formulation used safety and effectiveness data from secondary subgroup analyses of prior studies.^{39, 40} Often, adult data is extrapolated down to the pediatric age range if one may assume that there are similar disease progressions, responses to intervention, and similar exposure-response relationships between the two groups. Remifenantil and methylphenidate are examples of extrapolation within pediatrics. Remifenantil was extrapolated down from 2–18 to 0–1 years and methylphenidate was extrapolated up from children into adolescence.³⁹ Because the largest number of infants who received surfactant off-label had a higher birth weight and/or GA than label, one approach to more inclusive FDA labeling may involve extrapolation up to a higher GA and birth weight. As surfactant is not a systemically active drug, pharmacokinetic studies would not be necessary, but additional prospective or retrospective safety data may be needed.

A strength of this study is the large, broad population analyzed. Our study also had a number of limitations, mainly related to the retrospective observational design. There was probable underestimation of administration via INSURE. We defined INSURE narrowly as surfactant administration without any mechanical ventilation as our dataset did not allow for a more distinct definition, but some infants could have received an initial dose via INSURE and subsequent doses with mechanical ventilation. Our methodology also did not allow quantification of the degree of overlap in individuals based on GA, birth weight, or method of surfactant administration. Although we determined the overall percentage of infants who received surfactant off-label, we could not estimate how many infants who received surfactant via INSURE also had GA or birth weight higher than label. We did not compare off-label in-hospital outcomes with infants who received surfactant on-label or birth weight matched infants who did not receive surfactant, because due to underlying differences in the populations, comparison would not have been meaningful. A minor limitation is the restriction to preterm infants, but few indications for surfactant therapy exist in older children in other settings.^{41, 42} Finally, our study was limited by the inability to review common adverse reactions of surfactant administration such as transient bradycardia, hypotension, airway obstruction, and oxygen desaturations.

In conclusion, the majority of surfactant use in preterm infants is off-label. This primarily reflects administration in later GA and higher birth weight populations than included in labeling or clinical trials, as well as evidence-based administration via INSURE. The gap between FDA labelling and current clinic practice exemplifies an opportunity for label expansion, which may require review of prospective or retrospective safety and/or effectiveness data for infants with later gestational age and higher birth weight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE:

Percentage Surfactant Administered Off-label to Preterm Infants by Year

*Poractant alfa label does not specify gestational age

Table 1:

Surfactant On-Label Definitions

	Beractant	Poractant alfa	Calfactant
Birth Weight (g)	600 – 1750	600 – 2000	< 1251
Gestational Age (w)	23 – 29	Any	< 29
Postnatal Age (h)	< 48	< 48	< 72
Mechanical Ventilation Required?	Yes	Yes	Yes
Diagnosis (or risk factors)	RDS	RDS	RDS

Table 2:**Cohort Characteristics**

	On-Label Usage N = 42,596 (%)	Off-Label Usage N = 68,226 (%)
Birth Weight (g)		
<600	1901 (4)	4592 (7)
601–750	8854 (21)	1318 (2)
751–1000	13,344 (31)	3401 (5)
1001–1250	10,011 (24)	5292 (8)
1251–1750	6662 (16)	17,749 (26)
>1750	1789 (4)	35,867 (52)
Gestational Age (w)		
<24	1843 (4)	1826 (3)
24–26	15,849 (37)	4668 (7)
27–29	17,845 (42)	9456 (14)
30–33	6532 (16)	29,099 (42)
34–36	527 (1)	23,177 (34)
Small for Gestational Age	45,357 (13)	6764 (10)
Male	22,985 (54)	39,967 (59)
Race/Ethnicity		
Caucasian	19,206 (45)	38,196 (56)
Black	11,538 (27)	11,768 (17)
Hispanic	8423 (20)	13,054 (19)
Other	2133 (5)	2706 (4)
Cesarean Section	31,887 (76)	49,414 (74)
Multiple Gestation	5827 (14)	9748 (14)
Antenatal Steroids	33,674 (79)	39,463 (58)

Table 3:

Off-label Surfactant Use

	Beractant N = 35,239 (%)	Poractant alfa N = 44,444 (%)	Calfactant N = 31,139 (%)	Total N = 110,822 (%)
Total Off-Label	24,844 (71)	24,790 (56)	18,592 (60)	68,226 (62)
Birth Weight < Label	2091 (6)	2438 (5)	N/A ^a	4529 (4)
Birth Weight > Label	11,627 (33)	12,454 (28)	16,635 (53)	40,716 (37)
Gestational Age < Label	95 (0.3)	N/A ^a	N/A ^a	95 (0.1)
Gestational Age > Label	18,557 (53)	N/A ^a	16,634 (53)	35,191 (32)
INSURE ^b	7137 (20)	16,688 (38)	8485 (27)	32,310 (29)
Postnatal Age > Label	1551 (4)	1182 (3)	227 (1)	2413

^aOn-label by definition^bIntubation, surfactant treatment, then rapid extubation, which was identified as surfactant administration without mechanical ventilation