Surfactant Administration in Preterm Infants: Drug Development Opportunities

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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 for 2005-2015 from 348 neonatal intensive care units in the US. We quantified off-label administration of poractant alfa, calfactant, or beractant in inborn infants born at <37 weeks of gestational age (GA). Off-label surfactant administration was defined according to the Food and Drug Administration (FDA) label.

Results Of a total of 110 822 preterm infants who received surfactant, 68 226 (62%) received the surfactant off-label. The majority of infants who received surfactant off-label had a higher birth weight than those who received surfactant on-label (40 716 [37%]), had an older GA than those who received surfactant on-label (35 191 [32%]), or were treated with intubation and surfactant administration 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%], and 8485 [27%], respectively). An increasing number of infants received surfactant via INSURE from 2005 to 2015 (from 1697 [19%] to 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 labeling and current clinic practice exemplifies an opportunity for label expansion, which may require additional prospective or retrospective safety and/or effectiveness data for infants of older GA and higher birth weight. *(J Pediatr 2019;208:163-8).*

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Surfactant is one of the most frequently used medications in neonatal intensive care units (NICUs).[1] The animal-derived surfactants beractant, calfactant, and poractant alfa are labeled by the Food and Drug Administration (FDA) for use in preterm infants to prevent and/or treat respiratory distress syndrome (RDS), one of the most common diseases seen in the NICU.[2,3] Before the 1970s, RDS was the most frequent cause of preterm death, but changes in practice, including the development of exogenous surfactant, have decreased the rates of death, severe RDS, and pulmonary air leak syndromes.[4,5] RDS remains common, however, affecting >90% of infants born at <29 weeks gestational age (GA) and 2%-10% of infants born at 34-36 weeks GA.[2,3] The clinical surfactant trials from the late 1980s and early 1990s included infants born at 23-34 weeks GA and/or with birth weight 500-2000 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 I**).[13-15] A high proportion of late preterm infants receive surfactant, suggesting off-label use, but the full breadth of off-label use has not yet been established.[11,12] Common to all 3 surfactant types are the requirements of a risk for or diagnosis of RDS and

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
FDA	Food and Drug Administration
GA	Gestational age
INSURE	Intubation and surfactant administration followed by immediate extubation
NICU	Neonatal intensive care unit
RDS	Respiratory distress syndrome

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administration during mechanical ventilation.[13-15] The FDA requirement of mechanical ventilation may contribute to a large proportion of off-label use via intubation and surfactant administration followed by immediate extubation (INSURE), a technique that avoids mechanical ventilation through intubation, surfactant treatment, and then rapid extubation back to noninvasive 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 in preterm infants. We hypothesized that the majority of surfactant use is off-label, primarily in infants with older GA and higher 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 NICUs within the Pediatrix Medical Group, which operates in the US.[17] We extracted information on prenatal characteristics, demographics, and in-hospital clinical outcomes. We included all inborn infants at <37 weeks GA discharged between 2005 and 2015 who received beractant, calfactant, or poractant alfa. We excluded NICUs that administered surfactant to <50 infants over the entire study period and excluded infants who received more than 1 type of surfactant.

Off-label surfactant use was defined according to FDA labeling (**Table I**).[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, with birth weight <600 g or >1750 g, or at postnatal age >48 hours. Off-label poractant alfa use was defined as administration to infants with birth weight <600 g or >2000 g or at postnatal age >48 hours. Off-label calfactant use was defined as administration to infants with GA >29 weeks, with birth weight >1251 g, or at postnatal age >72 hours. Small for gestational age was defined as <10th percentile for age at birth as described by Olsen et al.[18] Because records of the method of surfactant administration were not 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 7 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 necessitating surgical intervention.[19] We defined BPD in infants of <32 weeks GA as receipt of supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure [CPAP], or mechanical ventilation) continuously from a corrected GA of $36^{+0\text{-}6/7}$ weeks. In infants of ≥32 weeks GA, BPD was defined by the receipt of supplemental oxygen or respiratory support (nasal cannula, CPAP, or mechanical ventilation) continuously from a postnatal age of 28-34 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 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.

Table I. Surfactant on-label definitions

Variables	Beractant	Poractant alfa	Calfactant
Birth weight, g	600-1750	600-2000	<1251
GA, wk	23-29	Any	<29
Postnatal age, h	<48	<48	<72
Mechanical ventilation required?	Yes	Yes	Yes
Diagnosis (or risk factors)	RDS	RDS	RDS

Statistical Analyses

The unit of observation for this study was the infant. We used standard summary statistics, including median (IQR) and count (percentage), to describe categorical study variables. We compared the distributions of study variables across categories using the Wilcoxon rank-sum, χ^2, and Fisher exact tests where appropriate. Observations with missing data were omitted from analysis, and imputation was not performed. All analyses were performed using Stata SE 14.2 (StataCorp, College Station, Texas) and assumed a significance level of $\alpha = 0.05$. This study was approved by the Duke Institutional Review Board without the need for written informed consent, because the data were collected without identifiers.

Results

We identified a total of 110 822 preterm infants who received beractant, calfactant, or poractant alfa, of whom 68 226 (62%) received surfactant off-label. Median GA and birth weight were higher in the infants who received off-label surfactant compared with those who received surfactant on-label (median GA, 32 weeks [IQR, 30-34 weeks] vs 27 weeks [IQR, 25-29 weeks], $P < .0001$; median birth weight, 1806 g [IQR, 332-2350 g] vs 946 g [IQR, 750-1190 g], $P < .0001$) (**Table II**). Of the 35 239 infants who received beractant, 24 844 (71%) were off-label recipients. Among the 44 444 infants who received poractant alfa, 24 790 (56%) did so off-label, and among the 31 139 infants who received calfactant, 18 592 (60%) did so off-label (**Table III**).

Of the 110 822 preterm infants studied, 32 310 (29%) received surfactant via INSURE. A total of 4624 infants (4%) had a GA and/or birth weight below FDA label specifications, and

Table II. Cohort characteristics

Characteristics	On-label use (N = 42 596), n (%)	Off-label use (N = 68 226), n (%)
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)
GA, wk		
<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 sex	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 delivery	31 887 (76)	49 414 (74)
Multiple gestation	5827 (14)	9748 (14)
Antenatal steroids	33 674 (79)	39 463 (58)

2413 (2%) received surfactant after the recommended postnatal age (eg, 48-72 hours postnatal). Most infants who received beractant or calfactant off-label had a higher than label-recommended GA (18 557 [53%] and 16 634 [53%], respectively) and/or birth weight (11 627 [33%] and 12 454 [28%], respectively). More infants received poractant alfa off-label via INSURE compared with beractant or calfactant (16 688 [38%], 7137 [20%], and 8485 [26%], respectively) (**Table III**). Most infants receiving off-label surfactant (55 084 [81%]) had a diagnosis of RDS. Only 6856 (9%) had another diagnosis, including 3030 (4%) with pneumonia, 3561 (5%) with persistent pulmonary hypertension of the newborn, 117 (0.2%) with meconium aspiration syndrome, and 148 (0.2%) with congenital diaphragmatic hernia. Among infants who received surfactant off-label, death occurred in 3513 (6%), BPD in 6283 (9%), BPD or death in 9568 (14%), air leak syndrome in 3898 (6%), and pulmonary hemorrhage in 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; from 546 (13%) to 283 (28%) for beractant, from 462 (31%) to 2358 (39%) for poractant alfa, and from 689 (22%) to 727 (32%) for calfactant (**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 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 below label group (600 g), from 290 of 437 infants (66%) in 2005 to 510 of 686 infants (74%) 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 31^{+0}-36^{+6} weeks) or late-preterm infants (GA 34^{+0}-36^{+6} 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 of 23-34 weeks and/or with birth weight of 500-2000 g, and subgroup analyses demonstrated the greatest 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 GA 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 fraction of inspired oxygen after surfactant administration, but inconsistent reduction in mortality and no

Table III. Off-label surfactant use

Variables	Beractant (N = 35 239), n (%)	Poractant alfa (N = 44 444), n (%)	Calfactant (N = 31 139), n (%)	Total (N = 110 822), n (%)
Total off-label	24 844 (71)	24 790 (56)	18 592 (60)	68 226 (62)
Birth weight <label	2091 (6)	2438 (5)	N/A*	4529 (4)
Birth weight >label	11 627 (33)	12 454 (28)	16 635 (53)	40 716 (37)
GA <label	95 (0.3)	N/A*	N/A*	95 (0.1)
GA >label	18 557 (53)	N/A*	16 634 (53)	35 191 (32)
INSURE†	7137 (20)	16 688 (38)	8485 (27)	32 310 (29)
Postnatal age >label	1551 (4)	1182 (3)	227 (1)	2413 (2)

N/A, not applicable.
*On-label by definition.
†Identified as surfactant administration without mechanical ventilation.

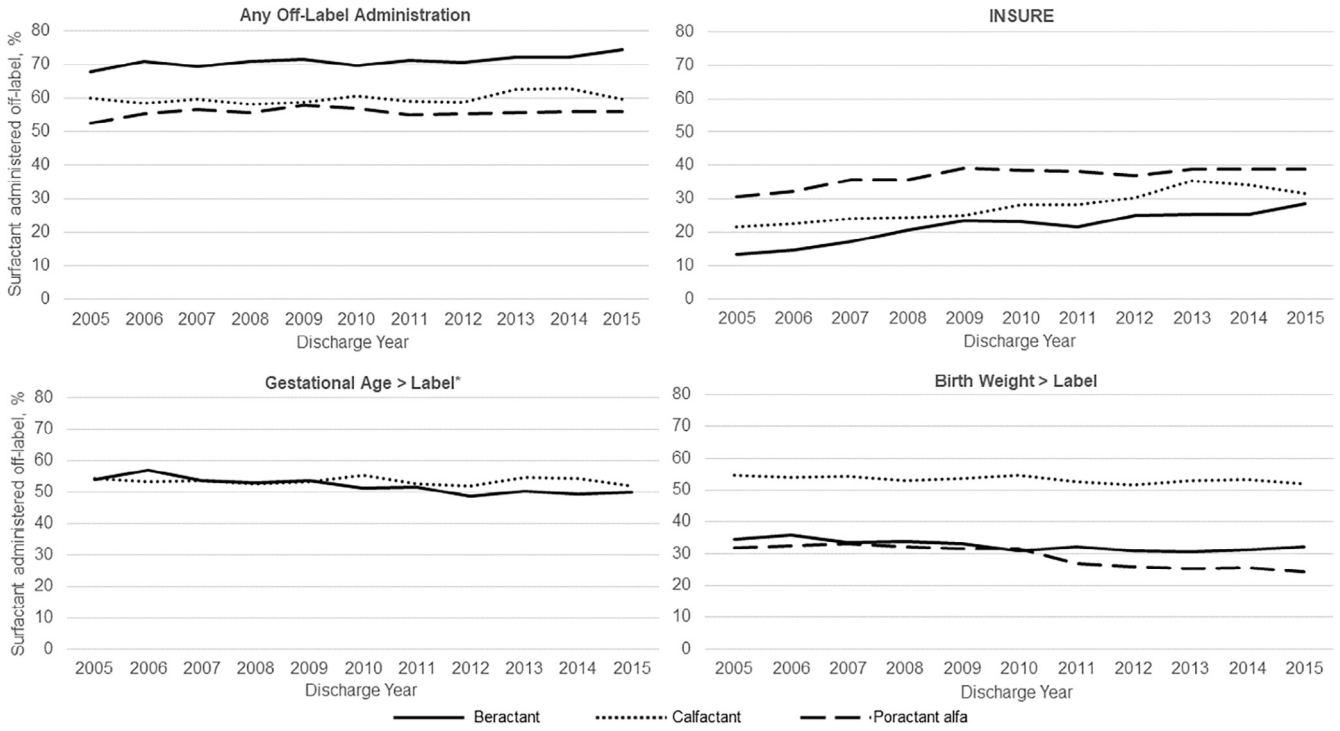

Figure. Percentage surfactant administered off-label to preterm infants by year. *Poractant alfa label does not specify GA.

significant difference in length of stay, need for mechanical ventilation, or duration of noninvasive support.[20-22] Several moderate-sized randomized controlled trials in a 2007 Cochrane Review and a 2015 meta-analysis favoring early INSURE included infants of 25-35 weeks GA as discussed below, but subgroup analysis did not focus on late-preterm infants.[23-27]

Clinical practice for surfactant has shifted in the 30 years since FDA approval. The preterm infant population now includes those with lower GA, a high proportion with maternal steroid exposure, and many who are initially stabilized with CPAP ventilation.[28] For example, very few infants who received surfactant off-label had a birth weight below label, but this number increased over the study period. This may also be attributed to label differences between calfactant and poractant alfa (**Table I**). Calfactant has no lower birth weight limit, and there has been a shift toward the use of poractant alfa and away from other surfactant types during this period, but our findings could also reflect more widespread resuscitation of infants at the edge of viability.[11] Recently developed techniques avoid mechanical ventilation through intubation, surfactant treatment, then rapid extubation back to noninvasive support (INSURE) and other minimally invasive surfactant therapy techniques.[16]

Nearly one-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 approximately 25 years ago, has been studied in other populations, and has been reviewed in meta-analyses in recent years.[16,23,26] A 2007 Cochrane review showed a 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 trends toward decreased BPD, mortality, and air leak. The American Academy of Pediatrics includes INSURE in its most recent clinical report, recommending the consideration of immediate CPAP instead of routine prophylactic surfactant administration, and if the need for early mechanical ventilation is likely, surfactant administration followed by rapid extubation is preferable to prolonged ventilation.[29]

In our cohort, poractant alfa was administered via INSURE more often 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.[13-15,27] The 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 labeling is an important step in ensuring that 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.[30-32] Considerable effort has been expended to conduct studies on the dosing, safety, and effectiveness of drugs in an effort to expand evidence-based practice and FDA labeling.[33-35] 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.[32,34,36] 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, including a complete lack of data, incomplete information on effectiveness or safety in children, or FDA labeling not reflective of recent evidence.[32,37]

Clinical practice has evolved over the last 30 years since beractant, calfactant, and poractant alfa were labeled, creating a gap between evidence and the FDA label. The gap between the FDA label and clinical practice can be explained in part 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 the 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 previous studies.[38,39] Often adult data are extrapolated down to the pediatric age range if it is assumed that disease progression, responses to intervention, and exposure-response relationships are similar in the 2 groups. Remifenantil and methylphenidate are examples of extrapolation within pediatrics. Remifenantil was extrapolated down from 2-18 years to 0-1 years, and methylphenidate was extrapolated up from children into adolescents.[38] Because the largest proportion of infants who received surfactant off-label had a higher birth weight and/or GA than those who received surfactant on-label, one approach to more inclusive FDA labeling may involve extrapolation up to an older GA and a higher birth weight. Because surfactant is not a systemically active drug, pharmacokinetic studies are not necessary, but additional prospective or retrospective safety data may be needed.

A strength of this study is the large, broad population analyzed. The study also has some limitations, mainly related to its retrospective observational design. Administration via INSURE likely was underestimated. 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 a GA or birth weight above label. We did not compare off-label in-hospital outcomes with those of infants who received surfactant on-label or birth weight-matched infants who did not receive surfactant, because this comparison would not have been meaningful owing to underlying differences in the populations. A minor limitation is the restriction to preterm infants, but few indications for surfactant therapy exist in older children in other settings.[40,41] 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 are included in labeling or clinical trials, as well as evidence-based administration via INSURE. The gap between FDA labeling 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 GA and higher birth weight. ■

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