Journal of Neonatal Biology
ISSN: 2167-0897

Yonglin et al., J Neonatal Biol 2016, 5:2
DOI: 10.4172/2167-0897.1000216

Case Report Open access

Use of Ambroxol and Treatment of *Klebsiella ozaenae* in Extremely Low Birth Weight Preterm: Case Report and Literature Review

Liu Yonglin, Qiao Yanmei, Yun Zhongming, Zhang Xiaopu and Bilal Haider Shamsi*

Pediatrics Department, Shenmu Hospital, Shenmu County, Yulin City, Shaanxi Province, P.R. China

***Corresponding author:** Bilal Haider Shamsi, Pediatrics Department, Shenmu Hospital, Shenmu County, Yulin City, Shaanxi Province, P.R. China (719300), Tel: 008615129310514; E-mail: drhydi@outlook.com

Rec date: December 07, 2016; **Acc date:** April 29, 2016; **Pub date:** May 05, 2016

Abstract

Introduction: Respiratory distress syndrome (RDS) is the most common respiratory complication occurring in preterm newborns due to deficiency of endogenous pulmonary surfactant. Ambroxol, is a promoter of fetal lung maturity and indicated as secretolytic therapy in bronchopulmonary diseases. *Klebsiella ozaenae*, whose antibiotic susceptibility data is limited, is associated with ozena; a primary atrophic rhinitis (AR), RTIs, cerebral abscess, meningitis, UTIs, and is one of the leading cause of (ICU) acquired pneumonia. This case study reports the use of post-natal intravenous amroxol to treat RDS, and use of cefoperazone sulbactam to treat *Klebsiella ozaenae* and *Pseudomonas aeruginosa*.

Case Presentation: A Chinese preterm, extremely low birth weight female (birth weight was 750 grams) was delivered by emergency caesarian section to a pregnancy-induced hypertensive G2P2 mother at 27 weeks' gestational age and was admitted in the pediatric ward because of severe dyspnoea with grunting respiration, tachypnoea, cyanosis and crackles in the lung fields. A working diagnosis of RDS was made and she was placed in incubator and neonatal continuous positive airway pressure (NCPAP) was applied immediately. She was managed with ambroxol for RDS and cefoperazone sulbactam for *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria and was successfully treated by 3 days' intravenous gamma globulin therapy and 10 days' antibiotics administration. On 67th day of hospitalization, baby was discharged with a body weight of more than 2100 grams.

Conclusions: The early application of NCPAP and ambroxol reduced the severity of this disease in preterm neonate and improved the clinical course of RDS. The combination of cefoperazone and sulbactam is effective against both of *K. ozaenae* and *Pseudomonas aeruginosa* bacteria.

Keywords: Respiratory distress syndrome; Ambroxol, *Klebsiella ozaenae*; Extremely low birth weight; Cefoperazone sulbactam

Introduction

Respiratory distress syndrome (RDS) is the most common respiratory disease of preterm neonates caused by deficiency of endogenous pulmonary surfactant needed for alveolar stability [1,2]. Although exogenous surfactant therapy has enhanced survival from RDS, chronic lung disease still is a potential cause of mortality and morbidity, thus there is a great need of newer treatments that may decrease lung injury in premature neonates [3]. Although glucocorticoids are effective in the prevention of RDS and in the treatment of chronic lung disease, the repetition of their dose causes aggregated side effects [4]. The studies show that repeated antenatal doses could lead to growth retardation, decreased fetal brain size and affected neuronal development [5]. Ambroxol, is a relatively new promoter of neonatal lung maturity and increasing number of studies described its role in the prevention of RDS [6]. The effectiveness of postnatal intravenous ambroxol in the treatment and the prevention of RDS need concern and more research [7]. This case is reported to study the role of post-natal intravenous ambroxol in the treatment of RDS and its effects on the course and severity of the disease.

The genus *Klebsiella* comprises of non-motile, aerobic and facultatively anaerobic, Gram negative rods [8]. At the time of writing, the genus *Klebsiella* includes *K. pneumonia, sub specie pneumoniae, K. pneumoniae sub specie ozaenae, K. pneumoniae sub specie rhinoscleromatis, K. oxytoca, K. ornithinolytica, K. planticola, and K. terrigena* [9]. *K. pneumoniae* are amongst the most common causes of community-acquired and hospital-acquired infections [10]. *K. pneumoniae* is followed by *K. oxytoca*. *K. ozaenae* and *K. rhinoscleromatis* are rare, but can cause serious clinical syndromes (ozena and rhinoscleroma, respectively) [11]. The in vitro data on antibiotic susceptibility of *K. ozaenae* is very limited. The first report of plasmid mediated resistance to broad-spectrum cephalosporins was of an isolate of *K. ozaenae* [12,13]. There have been no succeeding reported isolates of ESBL producing *K. ozaenae* and no randomized trials in the treatment of *K. ozaenae* infections have been reported [14]. This case study reports the successful treatment of *Klebsiella ozaenae* accompanied with *Pseudomonas aeruginosa* in an extremely low birth weight neonate.

Case Presentation

A Chinese preterm, extremely low birth weight female (birth weight was 750 grams) was delivered by emergency caesarian section to a pregnancy-induced hypertensive G2P2 mother at 27 weeks' gestational age, having normal placenta and umbilical cord with clear amniotic fluid. She had no birth asphyxia and had spontaneous breathing at birth (APGAR scores were 8 in one minute and 10 in 5 minutes). She

developed moaning, frothing and peri-oral cyanosis with decreased reactivity, and was admitted in the pediatric ward. Examination revealed severe dyspnoea with grunting respiration, tachypnoea, cyanosis and crackles in the lung fields. She also had tachycardia and tender hepatomegaly. Heart rhythm was regular with no audible murmur. Muscle tone was reduced and neonatal reflexes were not elicited. Chest X-ray showed hyperinflation, right lower zone patchy consolidation with increased lung markings and obliteration of the costophrenic angle. Echocardiography was normal. AmnioStat-FLM test was negative. She was placed in incubator and neonatal continuous positive airway pressure (NCPAP) was applied immediately. She was managed with ambroxol 30 mg/kg/d, divided in three intravenous doses and theophylline therapy for 3 days which gradually resulted in smooth breathing. Intravenous nutrition therapy was started 2nd day after admission and the adjuvant naso-gastric tube feeding was started with preterm children formula on the fifth day. During the first 10 days of admission daily milk feeding was 20 ml/d and body weight dropped to 685 grams, until the 14th day of hospitalization when milk feeding was increased gradually to 80 ml/d and weight correspondingly increased to 900 grams. The 14th day, child became cyanosed with poor response and fever, transcutaneous oxygen desaturation ($TCSO_2$) dropped to 60%, WBC raised to 12.26×10^9/L, neutrophils 0.60, Hemoglobin 127 g/L and CRP 21 mg/L. 16th day and 18th day throat swab bacterial cultures were reported as *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria and was successfully treated by 3 days' intravenous gamma globulin therapy and 10 days' antibiotics administration (cefoperazone sulbactam). She was transfused with sedimented blood cells at a packed cell volume of 20%. Till 30th day milk feeding was added to 150 ml/d, weight became 1100 grams and intravenous infusion was stopped. At 41st day after admission normal oral feeding was started and daily milk feeding was increased to 360 ml/d with body weight 1900 grams. On 67th day of hospitalization, baby was discharged with a body weight of more than 2100 grams. The follow up visit after 2 years revealed height being 85 cm and weight 10 kg with normal nervous system development including hearing, vision and language skills. 3rd year follow-up showed height 90 cm and weight 11 kg with normal intelligence level (Figure 1).

Discussion

Respiratory distress syndrome, RDS, occurs in up to 83.0% of extremely low birth weight premature neonates and is one of the leading causes of child mortality [15]. Complicated RDS can cause pneumopericardium, patent ductus arteriosus, pulmonary hypertension and heart failure. Distressed breathing in children causes endothelial dysfunction, which is an early marker of atherosclerosis [16]. These cardiac conditions can later cause adult cardiovascular disease. It has been reported that cardiovascular mortality is higher among former preterm adults than those born at term which may be related to preterm RDS. This condition is referred to as cardiovascular perinatal programming [17]. Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscous or excessive mucus [18]. This is a mucoactive drug with secretolytic and secretomotoric properties that maintains clearance mechanisms of the respiratory tract, and plays an important role in the body's natural defence mechanisms. It stimulates type II pneumocytes for the synthesis and release of surfactant [19]. Surfactant acts as an anti-glue factor by decreasing the adhesion of mucus to the bronchial wall. Ambroxol is indicated as secretolytic therapy in bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport [20]. It facilitates expectoration and productive cough. Although in this case, before admission treatment was given to promote lung maturity but because of the low gestational age and the pregnancy-induced hypertensive mother, child developed RDS after admission to the hospital. The early application of NCPAP and ambroxol treatment, avoided the use of pulmonary surfactant (PS). In this work, the RDS at 24 hours of administration was successfully treated in the neonate with Ambroxol. This preventive effect coincides with earlier reports [21]. The need for CPAP was used as an index for severity (morbidity of RDS). Ambroxol reduced the need for CPAP and its mean pressure. Moreover, Ambroxol reduced the need for the initiation of mechanical ventilation during the course of illness. This coincides with the results of Wauer et al. [22].

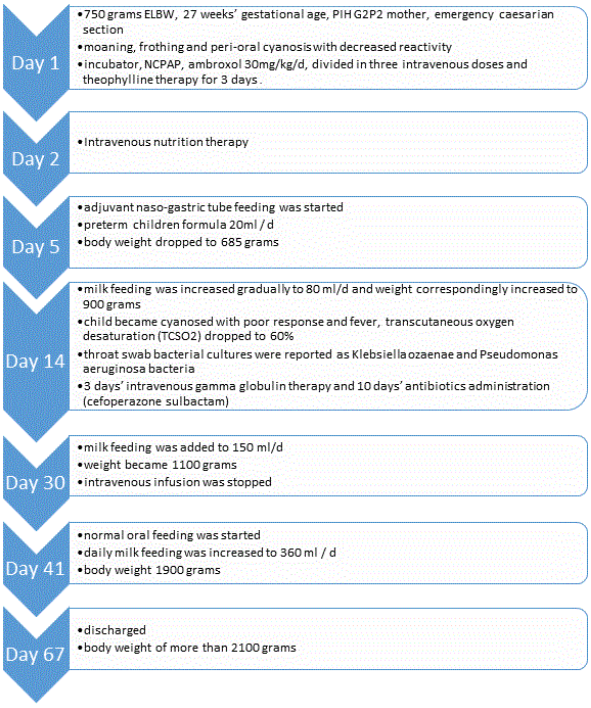

Figure 1: Schematic representation of the baby's hospital stay.

Ambroxol also reduced the oxygenation index (OI) which shows a better gas exchange, a lower mean airway pressure (MAP) and a lower fraction of inspired oxygen (FIO2) endorsing earlier studies [23,24]. This reflects a reduced peak inspiratory pressure (PIP) and peak expiratory end pressure (PEEP), as well as reduced inspiratory time, verifying the already reported study by Elsayed [25]. Ambroxol efficacy is probably dependent not only on lung pathology, but also on the dose administered and the duration of administration. Our choice of 30 mg/kg/day was the dose already reported yet, larger doses could also be used safely [26]. The Ambroxol used in this study was safe and caused no complications which is in accordance to the reported researches [27]. Moreover, its administration is simple in comparison with surfactant administration and is cheaper.

Biggest toil in treating premature children is infection, particularly hospital-acquired infections which are also one of the main reasons of death [28]. Signs of infection must be closely monitored and timely treated [2]. *Klebsiella ozaenae* is associated with ozena; a primary atrophic rhinitis (AR), RTIs, cerebral abscess and meningitis, and

UTIs. Sources for clinical samples of *Klebsiella ozaenae* are respiratory tract (RT; nasopharyngeal samples), urinary tract (UT) and blood [29] and the spectrum of disease caused by this organism is very extensive [30]. *Klebsiella ozaenae* is one of the leading cause of (ICU) acquired pneumonia. The in vitro data on antibiotic susceptibility of *K. ozaenae* is very limited and there have been no randomized trials in the treatment of *K. ozaenae* infections so, treatment is said to be based on antibiotic susceptibility results and the site of infection. The use of ciprofloxacin, intravenous aminoglycosides, trimethoprim/sulfamethoxazole and piperacillin are already reported for the treatment of *K. ozaenae* [31,32] but in case of neonates, the side effects may limit the selection of antibiotics. In this report, on the 14th day of hospital admission the patient developed cyanosis with poor responses, fever of 38, TCSO2 dropped to 60% and increased blood WBC and CRP. 16th day and 18th day throat swab bacterial cultures were reported as *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria. The culture and sensitivity was confirmed with multiple laboratory analysis and thus according to the susceptibility, intravenous cefoperazone sulbactam and gamma globulin therapy was given. Cefoperazone is a third generation cephalosporin antibiotic and Sulbactam is an irreversible inhibitor of β-lactamase [33,34]. In the combination of cefoperazone and sulbactam, cefoperazone exerts its bactericidal effect by inhibiting the bacterial cell wall synthesis, and sulbactam acts as a beta-lactamase inhibitor, to increase the antibacterial activity of cefoperazone against beta-lactamase-producing organisms. The outcome was successful against both of the cultured bacteria i.e. *Klebsiella ozaenae* and *Pseudomonas aeruginosa*. Early postnatal protein deficiency could affect the development of cell differentiation and myelination of the brain, resulting in irreversible cognitive, motor and behavioral abnormalities [35,36]. The caloric requirements of the neonate during the disease process were fulfilled initially as total parenteral nutrition and later partial parenteral nutrition respectively.

The purposes of this report is to sensitize practitioners about the early diagnosis and management of the unusual organism *K. ozaenae*, and to validate the use of postnatal I.V ambroxol for the management of RDS.

Conclusion

Early administration of intravenous ambroxol can produce a positive efficacy for the prevention of RDS in preterm infants. The early application of NCPAP and Ambroxol reduced the severity of this disease in preterm neonate and improved the clinical course of RDS and in turn prevented future cardiac complications. The combination of cefoperazone and sulbactam is effective against both of *K. ozaenae* and *Pseudomonas aeruginosa* bacteria. The arrangement of symptomatic, supportive and specific treatment, with enthusiastic clinical and nursing care, is the key to successful rescue of the extremely low birth weight preterm neonates.

References

1. Kamath BD, Macguire ER, McClure EM, Goldenberg RL, Jobe AH (2011) Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. Pediatrics 127: 1139-1146.
2. Whitsett JA (2012) The molecular basis of pulmonary surfactant–lessons from newborn infants. Hamdan Medical Journal 5: 263-271.
3. Willson DF, Notter RH (2011) The future of exogenous surfactant therapy. Respir Care 56: 1369-1386.
4. Han S, Yu Z, Guo X, Dong X, Chen X, et al. (2011) Intratracheal instillation of corticosteroids using surfactant as a vehicle for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome. The Cochrane Library 4.
5. Porto AMF, Coutinho IC, Correia JB, Amorim MMR (2011) Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 12: 342-343.
6. Chen XQ, Wu SH, Guo XR, Zhou XY (2012) Effects of antenatal application of ambroxol and glucocorticoid on lung morphometry and signal transduction of bone morphogenetic protein in the fetal rat. Mol Med Rep 6: 63-68.
7. Ni-ya N (2011) Ambroxol and dexamethasone to promote fetal lung maturation in clinical observation. Chinese and Foreign Women Health 3: 14-15.
8. Munoz-Dávila M, Yagüe G, Albert M, García-Lucas T (2012) Comparative evaluation of Vitek 2 identification and susceptibility testing of Gram-negative rods directly and isolated from BacT/ALERT-positive blood culture bottles. Eur J Clin Microbiol Infect Dis 31: 663-669.
9. Kumar A, Chakraborti S, Joshi P, Chakrabarti P, Chakraborty R (2011) A multiple antibiotic and serum resistant oligotrophic strain, Klebsiella pneumoniae MB 45 having novel dfrA 30, is sensitive to ZnO QDs. Ann Clin Microbiol Antimicrob 10: 19-20.
10. Jones RN (2010) Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 51 Suppl 1: S81-87.
11. Endailalu YW, Sealy P, Michael M, Al Khalloufi K, Nabhani H (2012) Klebsiella ozaenae sepsis in a young healthy male. Malays J Pathol 34: 153-156.
12. Sougakoff W, Goussard S, Gerbaud G, Courvalin P (1988) Plasmid-mediated resistance to third-generation cephalosporins caused by point mutations in TEM-type penicillinase genes. Rev Infect Dis 10: 879-884.
13. Kliebe C, Nies B, Meyer J, Tolxdorff-Neutzling R, Wiedemann B (1985) Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. Antimicrob Agents Chemother 28: 302-307.
14. Paterson DL, Siu KL, Chang FY Klebsiella species (K. pneumoniae, K. oxytoca, K. ozaenae and K. rhinoscleromatis). Antimicrobe.
15. Tagare A, Chaudhari S, Kadam S, Vaidya U, Pandit A, et al. (2013) Mortality and morbidity in extremely low birth weight (ELBW) infants in a neonatal intensive care unit. Indian J Pediatr 80: 16-20.
16. Brunetti L, Francavilla R, Scicchitano P, Tranchino V, Loscialpo M, et al. (2013) Impact of sleep respiratory disorders on endothelial function in children. Scientific World Journal 2013: 719456.
17. Mercuro G, Bassareo PP, Flore G, Fanos V, Dentamaro I, et al. (2013) Prematurity and low weight at birth as new conditions predisposing to an increased cardiovascular risk. Eur J Prev Cardiol 20: 357-367.
18. Le J, Li J, Wen H, Chen B, Hong Z, et al. (2014) Rapid and sensitive determination of ambroxol hydrochloride injection by Raman spectroscopy combined with chemometric models. Analytical Methods 6: 1096-1100.
19. Paleari D, Rossi GA, Nicolini G, Olivieri D (2011) Ambroxol: a multifaceted molecule with additional therapeutic potentials in respiratory disorders of childhood. Expert Opin Drug Discov 6: 1203-1214.
20. Tirouvanziam R, Conrad C, Herzenberg L (2012) Methods of improving or preserving lung function in a patient with a pulmonary disorder. In Book Methods of improving or preserving lung function in a patient with a pulmonary disorder.
21. Seifart C, Clostermann U, Seifart U, Müller B, Vogelmeier C (2005) Cell-specific modulation of surfactant proteins by ambroxol treatment. Toxicology and applied pharmacology 203: 27-35.
22. Wauer RR, Schmalisch G, Böhme B, Arand J, Lehmann D (1992) Randomized double blind trial of Ambroxol for the treatment of respiratory distress syndrome. Eur J Pediatr 151: 357-363.

23. Zhuang WZ, Chen DM, Shi YX (2003) Effects of Ambroxol on Prevention of Respiratory Distress Syndrome in Premature Babies. Acta Universitatis Medicinalis Secondae Shanghai 6: 020.
24. Yun-Ping Z, Yao-Guang J (2001) Investigative progress in prophylaxis and treatment of ARDS with ambroxol [J]. Journal of Traumatic Surgery 2: 042.
25. Elsayed HF, Elkhaiouby MI, Elsharkawey SM, Elnemr MA (2006) Evaluation of the Role of Postnatal Ambroxol in the Prevention and Treatment of Respiratory Distress Syndrome in Preterm Neonates. Sultan Qaboos Univ Med J 6: 41-44.
26. Pozzi E, Luisetti M, Spialtini L, Coccia P, Rossi A, et al. (1989) Relationship between changes in alveolar surfactant levels and lung defence mechanisms. Respiration 55: 53-59.
27. Laoag-Fernandez JB, Fernandez AM, Maruo T (2000) Antenatal use of ambroxol for the prevention of infant respiratory distress syndrome. J Obstet Gynaecol Res 26: 307-312.
28. Wenzel RP, Edmond MB (2001) The impact of hospital-acquired bloodstream infections. Emerg Infect Dis 7: 174-177.
29. De Champs C, Vellin JF, Diancourt L, Brisse S, Kemeny JL, et al. (2005) Laryngeal scleroma associated with Klebsiella pneumoniae subsp. ozaenae. J Clin Microbiol 43: 5811-5813.
30. Tang LM, Chen ST, Hsu WC, Chen CM (1997) Klebsiella meningitis in Taiwan: an overview. Epidemiol Infect 119: 135-142.
31. Tang LM, Chen ST (1994) Klebsiella ozaenae meningitis: report of two cases and review of the literature. Infection 22: 58-61.
32. Stoor P, Söderling E, Grenman R (1999) Interactions between the bioactive glass S53P4 and the atrophic rhinitis-associated microorganism Klebsiella ozaenae. J Biomed Mater Res 48: 869-874.
33. Thornsberry C (1985) Review of in vitro activity of third-generation cephalosporins and other newer beta-lactam antibiotics against clinically important bacteria. Am J Med. 79: 14-20.
34. Buynak JD (2006) Understanding the longevity of the beta-lactam antibiotics and of antibiotic/beta-lactamase inhibitor combinations. Biochem Pharmacol 71: 930-940.
35. Tschopp O, Yang ZZ, Brodbeck D, Dummler BA, Hemmings-Mieszczak M (2005) Essential role of protein kinase B? (PKB?/Akt3) in postnatal brain development but not in glucose homeostasis. Development 132: 2943-2954.
36. Campagnoni AT (1988) Molecular biology of myelin proteins from the central nervous system. J Neurochem 51: 1-14.