The Lancet · Saturday 12 January 1980

ARTIFICIAL SURFACTANT THERAPY IN HYALINE-MEMBRANE DISEASE

TETSURO FUJIWARA, HARUO MAETA, SHOICHI CHIDA, TOMOAKI MORITA, YOSHITANE WATABE, TADAAKI ABE

Departments of Pædiatrics, Anæsthesiology, and Surgery, Akita University School of Medicine, Akita 010, Japan

Summary Ten preterm infants severely ill with hyaline-membrane disease (HMD) were given artificial surfactant endotracheally. Oxygenation and alveolar-arterial oxygen gradients improved, the levels of inspired oxygen and peak respirator pressure could be reduced, and many of the radiological abnormalities resolved. Acidosis and systemic hypotension were also reversed. In nine infants a patent ductus arteriosus became evident after recovery from HMD, necessitating further assisted ventilation. Eight infants survived, including five of six with birthweight less than 1500 g; two died of unrelated causes. Postnatal tracheal instillation of artificial surfactant may prove a useful treatment for severe HMD.

Introduction

IN hyaline-membrane disease (HMD) the underlying process is believed to be a deficiency of alveolar surfactant which results in progressive neonatal atelectasis.[1,2] An obvious form of treatment is therefore to administer surfactant through the airways. There have been experimental and clinical trials with an aerosol of dipalmitoyl lecithin,[3] the principal component of pulmonary surfactant, but this agent has proved uniformly ineffective.[4,5] By contrast, "natural" surfactant, delivered to the lung of fetal animals before the onset of breathing, does seem to compensate for a deficiency of alveolar surfactant.[6,7]

Owing to side-effects and variable specific surface activity,[5] "natural" surfactant cannot be used in man, so we have developed an artificial surfactant with properties closely resembling those of pulmonary surfactant.[5] It consists of a mixture of naturally occurring surfactant lipids and synthetic lipids containing dipalmitoyl lecithin and phosphatidyl glycerol in the phosphorus molar ratios of 1:0·65:0·12. This surfactant improved pulmonary mechanics in premature rabbits[8] and protected their immature lungs from injuries due to intermittent positive-pressure ventilation.[9] After extensive studies to establish the safety of this surfactant as a drug, we have tried it in ten infants severely ill with hyaline-membrane disease.

Patients and Methods

We studied ten infants with HMD admitted consecutively to the intensive-care unit within 20 hours of delivery. Informed consent was obtained from one or both parents. Two infants were born in the hospital and eight were transferred from elsewhere. They had a mean (±SEM) gestational age of 30·2±0·6 weeks (range 28–33) and a mean birthweight of 1552±104 g (range 1150–2143). Table I shows the provenance of the infants. Early diagnosis in cases 1, 2, 3, and 5 was aided by tests on amniotic fluid. Infants born outside our hospital were attended in the ambulance by one of us. Before treatment with surfactant all were observed on the ventilator with unchanged settings. That the infants were not improving before surfactant administration was shown by comparison of P_aO_2, P_aCO_2, and pH 10–20 min before the procedure with those 30–90 min earlier. There were no significant differences. Further details of the infants are in table II. HMD was diagnosed by clinical and radiological criteria.[10] The infants were managed in servo-regulated incubators without humidification. All had radial-arterial catheters in place for monitoring of arterial PO_2, PCO_2, acid-base balance, and blood-pressure. Alveolar-arterial oxygen tension gradients ($AaDO_2$) were calculated from the alveolar air equation.[11] All infants were ventilated according to the guidelines of Reynolds,[10] with the MVP-10 pædiatric neonatal ventilator (Bio-Med) in two cases and with the electro-controlled respirator (Fukuda, Tokyo) in the remainder.

Administration of Artificial Surfactant

Lyophilised artificial surfactant[5] was suspended in physiological saline (19 μmol lipid phosphorus/ml) and about 10 ml of this fluid was put into the endotracheal tube. Mean age at this point was 12·3±(SEM) 2·8 h, range 4–33. During the instillation, which took about 20 s, the infant was held in many positions to facilitate entry of the instillate into each lobar and segmental bronchus. Then 100% oxygen was blown into the lungs with an anæsthetic bag. The dose of surfactant was about 150 μmol lipid phosphorus/kg. After completion of this treatment each infant was ventilated with a respirator. To evaluate the acute effects of supplementary surfactant, we compared the P_aO_2, P_aCO_2, and acid-base balance, and the radiographic findings, 45 min or less before surfactant treatment with those up to 3 h after surfactant treatment, the initial respirator settings and fractional inspired oxygen (F_iO_2) remaining unchanged. Neither bicarbonate nor diuretics were given during this study period. Between 20 min and 3 h after administration of surfactant, it was usually possible to reduce the F_iO_2 to 0·4 and the respirator pressure by 5–10 cm H_2O.

The radiographic severity of HMD was graded 1–5 by Bomsel's criteria as modified by Matsumura.[12] Significant left-to-right shunting was diagnosed by (1) clinical signs (precordial murmur, bounding femoral pulses, hyperactive precordium, apnœa, bradycardia) and (2) progressive pulmonary plethora and œdema on radiographs with echocardiographic evidence of increasing left-atrial to aortic-root dimension ratio (LA/AO

TABLE I—PROVENANCE OF INFANTS AND OBSERVATION PERIODS

Case no.	Age on arrival	Observation period on IPPV (h)	Age at surfactant instillation (h)
1	Inborn, 20 min.	8	13
2	Outborn, 3 h	2	7
3	Outborn, 1 h	2	4
4	Outborn, 10 h	2	15
5	Outborn, 2 h	2	6
6	Outborn, 3 h	1·5	6
7	Outborn, 3·5 h	1	6
8	Outborn, 17 h	1·5	20
9	Outborn, 6 h	2	14
10	Inborn 30 min	1	33

IPPV=intermittent positive-pressure ventilation.

ratio). Pulmonary changes due to patent ductus arteriosus were graded as follows: 0, within normal limits; 1, slightly increased pulmonary vascular markings; 2, more prominent pulmonary vasculature; 3, hazy pulmonary vessels, some ill-defined homogeneous shadows of water density, interval cardiomegaly; 4, "white-out"—massive cardiomegaly, indistinguishable from severe hyaline-membrane disease.

Results

Clinical data and the outcomes are summarised in table II.

Clinical Effects

Soon after instillation of surfactant the peripheral circulation seemed to increase in all infants. Grunting, when present, ceased quickly and the chest looked more compliant. On auscultation of the chest, all infants had predominantly vesicular breath sounds. Of the seven infants with no bowel sounds before surfactant, all had bowel sounds within an hour afterwards. There was a diuresis in all but one.

Blood-pressure

Continuous measurement of blood-pressure was possible in six infants. The mean systolic was 37±(SEM)5 mm Hg, range 25–50, before surfactant, and within 6 h it was 59±4 mm Hg, range 48–70 ($p<0.02$).

Blood-gas Tensions and pH

Arterial PO_2 (fig. 1) increased from 45±7 mm Hg, range 17–89, to 212±46 mm Hg, range 61–464 ($p<0.005$), in 67±15 min, range 20–180. During the same period the arterial PCO_2 fell from 50±4 mm Hg, range 38–68, to 33±2 mm Hg, range 23–38 ($p<0.005$), and the pH rose from 7·129±0·051, range 6·810–7·293, to 7·305±0·044, range 7·045–7·638 ($p<0.05$).

TABLE II—CLINICAL DATA ON STUDY INFANTS

Case	Sex	GA (wk)	BW (g)	Intrapartum problems	During IPPV before surfactant					Chest X-ray grading	Outcome
					F_iO_2	P_aO_2 (mm Hg)	P_aCO_2 (mm Hg)	pH	$AaDO_2$ (mm Hg)		
1	M	28	1400	Placenta prævia	0·80	41	38	7·022	491	5	Lived, subglottis stenosis, PDA spontaneously closed at age 20 days
2	M	28	1150	C-section; placenta prævia	0·35	34	40	7·253	176	3	Lived, BPD (stage 3) PDA surgically ligated at age 4 months
3	M	29	1180	C-section; premature onset of labour	0·65	30	56	7·293	374	5	Lived, PDA spont. closed at age 6 days
4	F	32	1182	ROM	0·80	56	68	6·939	455	5	Lived, PDA spont. closed at age 4 days
5	M	32	1740	—	0·90	64	40	7·246	520	5	Died at age 36 h, œsophagotomy
6	M	30	1426	ROM 1·5 h	1·00	89	48	7·191	575	5	Died of sepsis at age 30 days PDA, histological BPD
7	M	28	1340	C-section; placenta prævia	1·00	39	47	7·110	627	5	Lived, PDA surgically ligated at age 12 days
8	F	30	1424	—	1·00	19	55	6·810	639	5	Lived, PDA surgically ligated at age 9 days
9	M	32	1900	—	1·00	17	64	7·136	632	5	Lived, PDA surgically ligated at age 55 h
10	M	33	2143	—	0·60	58	42	7·292	292	5	Lived, PDA spont. closed at age 4 days

Abbreviations: GA=gestational age; BW=birth weight; IPPV=intermittent positive pressure ventilation; ROM=premature rupture of membranes; PDA=patent ductus arteriosus. C=cæsarian.

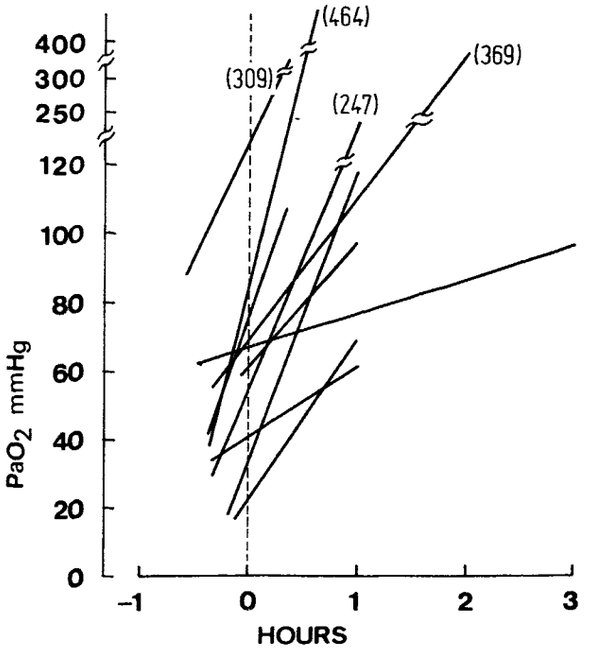

Fig. 1—Changes in P_aO_2 within 45 min before and within 3 h after administration of artificial surfactant.

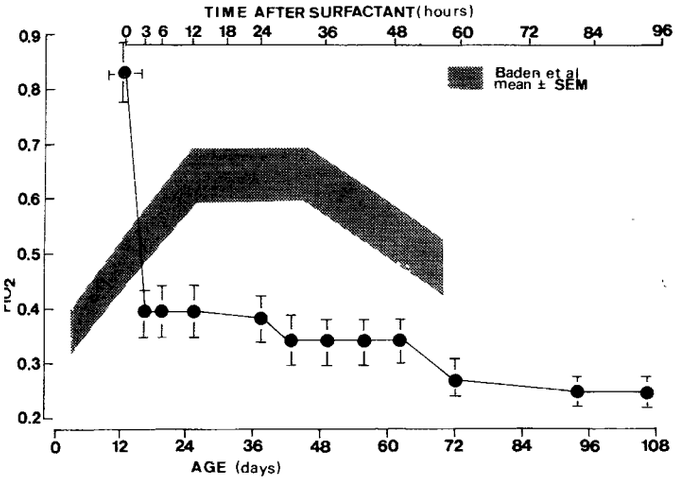

Fig. 2—Changes in F_iO_2 during the first 108 h of life.

For comparison, the F_iO_2 values reported by Baden et al.[11] for the infants with HMD are superimposed on the figure, with permission from Dr Baden and the American Academy of Pediatrics.

F_iO_2 and Respirator Inspiratory Pressure

We were able to lower the inspired oxygen concentration from an average of 81±7%, range 35–100, to 38±5%, range 21–60 ($p<0.01$) within 3 h of administration of surfactant (fig. 2). Likewise the peak inspiratory pressure could be reduced from 30±2 cm H_2O, range 20–45, to 22±2 cm H_2O, range 15–35 ($p<0.02$) within 6 h of surfactant.

$AaDO_2$

Fig. 3 shows the changes in $AaDO_2$ during the first 108 h of age. It fell from an initial 474±49 mm Hg, range 176–639, to 189±29, range 62–260 ($p<0.005$) 3 h after surfactant and 120±18 mm Hg, range 56–184 ($p<0.001$), at 30 h. For comparison, the $AaDO_2$ values

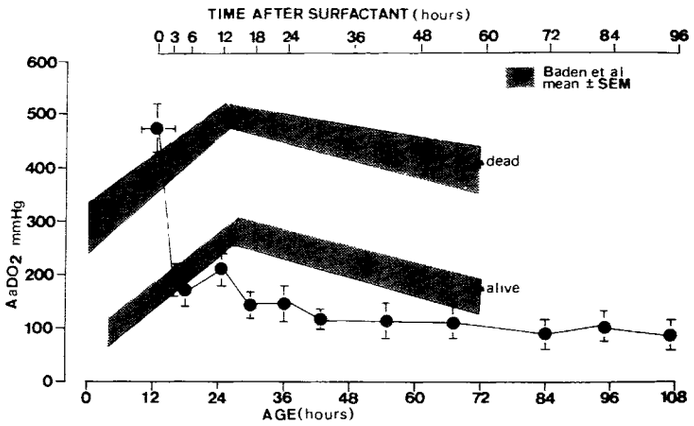

Fig. 3—Changes in $AaDO_2$ during the first 108 h of life.

For comparison, the $AaDO_2$ values reported by Baden et al.[11] for the infants with HMD who survived and those who died, are superimposed on the figure with permission from Dr Baden and the American Academy of Pediatrics.

reported by Baden et al.[11] for infants with HMD who survived and those who died are superimposed.

Chest Radiographs

Radiographic resolution was much more abrupt than usual, with all traces of HMD disappearing in most patients. The time for nearly complete radiological clearing of HMD averaged 6 h after surfactant, range 1·5–23. In two patients (cases 3 and 9) the 2 h post-surfactant chest film suggested that the surfactant was not distributed equally throughout the lungs. In case 3, the right lower lobe was well-inflated while the right upper field and the left lung still showed pulmonary changes typical of HMD; complete clearing of the HMD was observed on the 4th day of life. In case 9 the 2 h post-surfactant film showed a well-inflated right lung but an atelectatic left lung. By the 6th day of life the atelectatic lung was clear.

Subsequent Clinical Course

In nine infants a patent ductus arteriosus became clinically evident. The mean time at which the murmur was heard was 35 h of life, range 21–96, and 21 h after surfactant, range 2–94. The mean time of onset of pulmonary plethora after resolution of the HMD was 36 h of life, range 20–53. The PDA closed spontaneously in four infants (cases 1, 3, 4, 10), one of whom (case 1) needed prolonged respiratory support. Other infants with PDA (cases 2, 6, 7, 8) also required days or weeks of ventilation.

Fig. 4 shows the changes in radiographic HMD grading after surfactant, together with other indices throughout the clinical course. After recovery from HMD the $AaDO_2$ remained nearly normal, as did P_aO_2. Fig. 5 shows the effect of artificial surfactant in one case with subsequent pulmonary œdema due to a large PDA. Three infants (cases 7, 8, 9) had their PDA ligated, were weaned off the respirator, and are doing well. An increased LA/AO ratio correlated well with clinical and radiological evidence of increasing shunt.

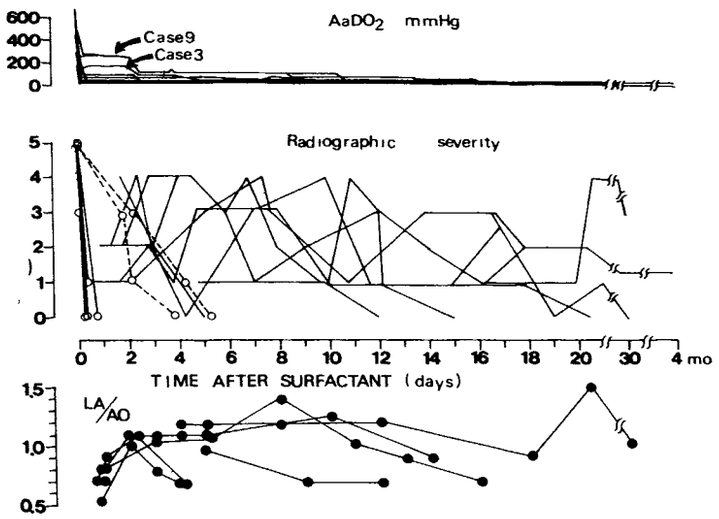

Fig. 4—Changes in $AaDO_2$, radiographic grading of HMD and pulmonary œdema due to a PDA, and LA/AO ratios following administration of artificial surfactant throughout the course of HMD.

o——o indicates radiographic grading of HMD.
o- - -o indicates radiographic grading of HMD in patients 3 and 9 (see text).
—— indicates radiographic grading of pulmonary œdema due to PDA.

Duration of Respiratory Care

The duration, after administration of surfactant, of inspired oxygen at a concentration of more than 60% was 2·2±1·1 h, range 0–12. The mean total durations of intermittent positive-pressure ventilation (IPPV), intermittent mandatory ventilation (IMV), and CPAP were 2·8 d (range 0–11), 8 d (range 0–20), and 4·3 d (range 0–13), respectively. The mean total duration of endotracheal intubation was 13±3·3 d (range 1·5–30).

Complications and Outcome

None of the infants had alveolar rupture. Artificial surfactant seemed to have no adverse effects. Eight infants, including five of six weighing less than 1500 g at birth, survived. Two infants died of unrelated causes. In case 5 the infant died at 36 h of life with post-operative complications after surgical correction of œsophageal atresia with tracheo-œsophageal fistula (Vogt IIIb). The necropsy revealed a well-inflated lung free of HMD. The other infant (case 6) died with *Serratia* sepsis on the 30th day of life before surgical ligation of the ductus was possible; histologically the alveoli were generally aerated without hyaline membranes, but there were some focal pulmonary changes compatible with bronchopulmonary dysplasia (BPD). The ductus was widely patent. His recurrent pulmonary œdema had been only partly controlled by fluid restriction, frusemide, digoxin, indomethacin, and ventilatory support. During the acute phase of HMD, he had been ventilated with a peak inspiratory pressure of 35 and end-expiratory pressure of 3 cm H_2O with 100% oxygen for 6 h and 55% oxygen for 12 h. In one infant (case 2) the typical appearance of BPD (Northway's stage 3) developed on the 15th day of life. He had been exposed to less than 40% oxygen for 2 h and IPPV with a peak inspiratory pressure of 20 cm H_2O for 6 h during the acute phase of HMD. At $3\frac{1}{2}$ months of age pulmonary insufficiency developed after an episode of upper-respiratory-tract infection. The PDA was ligated at 4 months, and 3 days postoperatively he was breathing air spontaneously. This infant still has some radiological evidence of BPD, but is progressing well. The other seven are progressing normally.

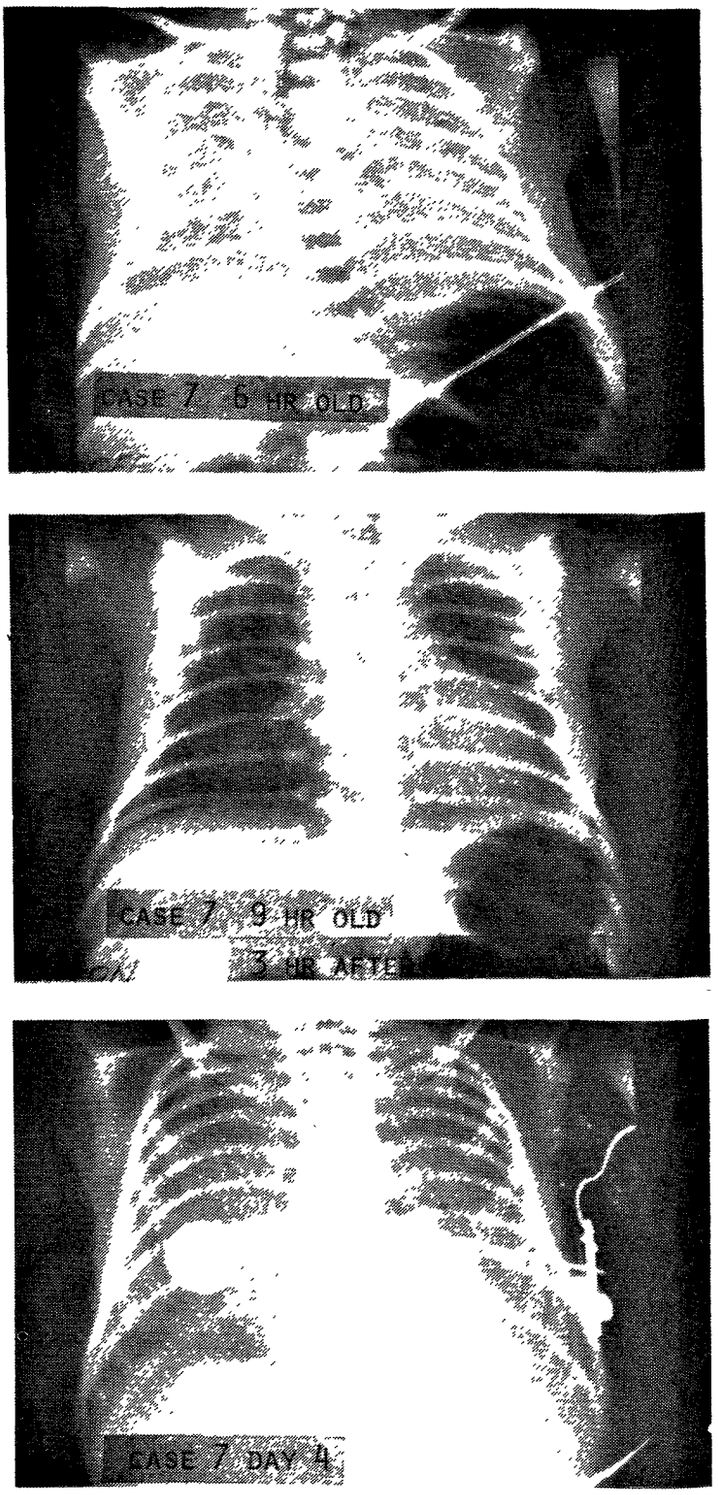

Fig. 5—Chest radiographs of a 28 wk gestation, 1340 g infant with severe HMD and pulmonary œdema secondary to large shunting PDA (case 7, table II).

Upper: severe HMD (grade 5) at age 6 h.
Middle: 3 h after administration of surfactant, at age 9 h.
Lower: interval cardiomegaly with increased pulmonary blood flow and pulmonary œdema on day 4.

Discussion

The improvements after surfactant administration were in line with results in animals[6–9] and we do not think they were spontaneous. The infants were making little progress until they received surfactant, whereupon the radiological appearances, arterial oxygenation, acid-base balance, and $AaDO_2$ all improved rapidly; in addition, the babies needed less oxygen and less ventilator pressure. These trends point to improved lung function. The progressive hypoxia of acute HMD has been attributed by Chu et al.[3] to acidosis, systemic hypotension, and progressive pulmonary ischæmia, but they seemed to be reversed by surfactant administration; this observation supports the theory[1,2] that HMD is the consequence of alveolar surfactant deficiency at birth.

In animals,[7,9,13] supplementary surfactant protects the very immature lung from injuries due to IPPV—which are a major complication of HMD. We note the absence of alveolar rupture, the major complication of severe HMD with or without CPAP[14,15] or mechanical ventilation.[15]

It is noteworthy that a single dose of artificial surfactant seemed effective throughout the course of HMD. This may be because the biological half-life is long, or because the material somehow promotes the synthesis of natural surfactant. The first possibility is supported by work in newborn rabbits showing that endogenous lipid, once secreted, remains for at least 4 days in the alveolar space.[16]

Why was the incidence of PDA so high in this series? Jones and Pickering[18] report that increased survival of infants with HMD may increase the apparent incidence of PDA; those who die of HMD usually have a PDA, but die before it becomes clinically evident. We do not think the artificial surfactant could have been responsible for either the PDA or the pulmonary œdema. As judged by the LA/AO ratios, the shunts were sufficient on their own to account for the pulmonary œdema; and our work in animals gives no suggestion that the material promotes œdema. It is, incidentally, so free of adverse effects that we have been unable to determine the intraperitoneal LD_{50} in animals.

Severe HMD complicated by a large shunting PDA remains an extraordinarily difficult condition to treat.[17,18] Although surgical ligation often controls the heart-failure, many infants go on to die from their lung disease.[19–21] In contrast to previous reports,[18–22] most of the infants in our series, despite having varying degrees of pulmonary œdema, had nearly normal $AaDO_2$ with optimal blood gases while on the respirator with air. Hypoxia due to lung disease is therefore unlikely to be the major factor in the maintenance of a PDA in these infants. A possible explanation is that our artificial surfactant was preventing progressive lung disease.

Spontaneous or surgical closure of the large shunting PDA helped us in weaning infants from the respirator. In the two infants (cases 2 and 6) who did not undergo surgical ligation of the ductus there was evidence of bronchopulmonary dysplasia. Three main factors have been implicated in the pathogenesis of BPD—oxygen toxicity,[23] mechanical trauma from prolonged respirator therapy,[24] and congestive heart-failure secondary to left-to-right shunting through a PDA.[19] In our cases oxygen toxicity and high respirator pressure could be excluded, and the likely cause was chronic pulmonary œdema due to the large shunting PDA. In one of them (case 2) an added fluid load[25] may have potentiated the effect of pulmonary œdema. Our findings thus support the notion[18–22] that BPD and other complications of prolonged intubation may be prevented by early PDA ligation.

In our view these early results with artificial surfactant are sufficiently encouraging to justify further trials.

We thank Dr S. Suzuki, Dr T. Mori, Dr T. Mitsuhata, and the nursing staffs for their invaluable help in this study. We also thank Prof. T. Shozawa and Dr M. Sageshima for the pathology reports.

Requests for reprints should be addressed to T.F., Department of Pædiatrics, Akita University School of Medicine, Akita, 010, Japan.

REFERENCES

1. Avery EM, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959; **97:** 517–23.
2. Strang LR. Neonatal respiration, p. 181, Oxford: Blackwell, 1977: 181.
3. Chu J, Clements JA, Cotton EK, Klaus MH, Sweet AY, Tooley WH. Neonatal pulmonary ischemia. *Pediatrics* 1967; **40:** 709–82.
4. Ikegami M, Hesterberg T, Nozaki M, Adams FH. Restoration of lung pressure volume characteristics with surfactant: comparison of nebulization versus instillation and natural versus synthetic surfactant. *Pediat Res* 1977; **11:** 178–82.
5. Fujiwara T, Tanaka Y, Takei T. Surface properties of artificial surfactant in comparison with natural and synthetic surfactant lipids. *IRCS Med Sci* 1979; **7:** 311.
6. Enhörning G, Grossmann G, Robertson B. Tracheal deposition of surfactant before the first breath. *Am Rev Resp Dis* 1973; **107:** 921–27.
7. Adams FH, Towers B, Osher AB, Ikegami M, Fujiwara T, Nozaki M. Effects of tracheal instillation of natural surfactant in premature lambs. 1. Clinical and autopsy findings. *Pediat Res* 1978; **12:** 841–48.
8. Fujiwara T, Maeta H, Chida S, Morita T. Improved pulmonary pressure-volume characteristics in premature newborn rabbits after tracheal instillation of artificial surfactant. *IRCS Med Sci* 1979; **7:** 312.
9. Fujiwara T, Maeta H, Chida S, Morita T. Improved lung-thorax compliance and prevention of neonatal pulmonary lesion in prematurely delivered rabbit neonates subjected to IPPV after tracheal instillation of artificial surfactant. *IRCS Med Sci* 1979; **7:** 313.
10. Reynolds EOR. Management of hyaline membrane disease. *Br Med Bull* 1975; **31:** 18–24.
11. Baden M, Bauer CR, Colle E, Klein G, Taeusch HW, Stern L. A controlled trial of hydrocortisone therapy in infants with respiratory distress syndrome. *Pediatrics* 1972; **50:** 526–34.
12. Matsumura T, Ogawa J. A controlled clinical trial of CDP-choline in idiopathic respiratory distress syndrome. *Acta Neonat Jap* 1977; **13:** 210–21.
13. Nilsson R, Grossmann G, Robertson B. Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. *Pediat Res* 1978; **12:** 249–55.
14. Hall RT, Rhodes PG. Pneumothorax and pneumomediastinum in infants with idiopathic respiratory distress syndrome receiving CPAP. *Pediatrics* 1975; **55:** 493–96.
15. Ogata ES, Gregory G, Kitterman JA, Phibbs RH, Tooley WH. Pneumothorax in the respiratory distress syndrome. Incidence and effect on vital signs, blood gases and pH. *Pediatrics* 1976; **58:** 177–83.
16. Jobe A, Gluck L. The labelling of lung phosphatidylcholine in premature rabbits. *Pediat Res* 1979; **13:** 635–40.
17. Lees MH. Commentary: patent ductus arteriosus in premature infants—a diagnostic and therapeutic dilemma. *J Pediat* 1975; **86:** 132–34.
18. Jones RWA, Pickering D. Patent ductus arteriosus complicating the respiratory distress syndrome. *Arch Dis Child* 1977; **52:** 274–81.
19. Gay JW, Daily WJR, Meyer BHP, Trump DS, Cloud DT, Molthan ME. Ligation of the patent ductus arteriosus in premature infants: report of 45 cases. *J Pediat Surg* 1973; **8:** 677–83.
20. Cook RWI, Gribbin B, Grunning AJ, Pickering D. Ligation of patent ductus arteriosus in the very low birthweight newborn infant. *Arch Dis Child* 1978; **53:** 271–75.
21. Nelson RJ, Thibeault DW, Emmanouilides GC, Lippmann M. Improving the results of ligation of patent ductus arteriosus in small pre-term infants. *J Thorac Cardiovasc Surg* 1976; **71:** 169–78.
22. Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small pre-term infants. *J Pediat* 1978; **93:** 647–51.
23. Edwards DK, Dyer WM, Northway WH, Jr. Twelve years' experience with bronchopulmonary dysplasia. *Pediatrics* 1977; **59:** 839–46.
24. Taghizadeh A, Reynolds EOR. Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. *Am J Path* 1976; **82:** 241–58.
25. Brown E, Stark A, Sosenko I, Lawson EE, Avery ME. Bronchopulmonary dysplasia: possible relationship to pulmonary edema. *J Pediat* 1978; **92:** 982–84.