Brain-orientated intensive care treatment in severe neonatal asphyxia

Effects of phenobarbitone protection

N W SVENNINGSEN, G BLENNOW, M LINDROTH, P O GÄDDLIN, AND H AHLSTRÖM

Department of Paediatrics, Units of Neonatology and Neurology, University Hospital, Lund, Sweden

SUMMARY The effect of applying brain-orientated neonatal intensive care for term infants with severe neonatal asphyxia was studied. Such treatment included protective phenobarbitone administration together with assisted ventilation and other measures to counteract postasphyxial cerebral oedema and any abrupt changes in blood pressure and oxygenation. The mortality rate and incidence of long-term sequelae were reduced appreciably, resulting in a 0-1 year mortality rate of 14% (previously 50%) and an incidence of neurodevelopmental handicap at 18 months of 17% (previously 50%). It is important in the management of infants with severe asphyxia at birth to avoid blood pressure fluctuations and to control neuronal epileptic activity by the use of barbiturates and early ventilator treatment.

Some reports have shown that the long-term prognosis of infants who respond rapidly to resuscitation after neonatal asphyxia may not be as bad as might have been expected from the initial condition of the baby and the course of the disease. However, the more severely asphyxiated infant with inadequate respiration and abnormal motor activity after resuscitation eventually develops apnoeic spells and convulsions, and such infants have a high mortality rate and incidence of cerebral handicaps.¹⁻⁵ Consequently in any baby with severe asphyxia the risk of serious handicap is high. As the chance of handicap cannot be predicted it is difficult to decide to what extent resuscitative efforts should be applied. Mortality rate and incidence of long-term neurodevelopmental handicaps probably vary according to the practice followed by the individual hospital—for example, when to start and when to stop resuscitation. The increasing use of mechanical ventilation in many neonatal units has accentuated this problem as the doctor in charge has to decide if such treatment should be started.

The aim of our study was to evaluate the advantages of early administration of phenobarbitone in high dosage combined with vigorous treatment of shock and ventilatory support in term infants with severe neonatal asphyxia.

Material and methods

We studied 35 term (37 to 42 weeks' gestation) newborn infants with severe neonatal asphyxia treated in our neonatal intensive care unit during the 6-year period 1973 to 1979. During the first 3 years (May 1973 to October 1976) 16 infants (group A) were treated conservatively (treatment A). During the second 3 years (November 1976 to October 1979) 19 infants (group B) were treated in accordance with our special intensive care protocol (treatment B). Any infant with a CNS congenital malformation, other lethal malformation, or a chromosomal disorder was excluded from the study.

Criteria.

Severe neonatal asphyxia

This was considered present if insufficient respiration and severe hypotonia persisted after more than 30 minutes of intensive resuscitation. Most babies also had had signs of intrauterine asphyxia—such as abnormal fetal heart rate pattern on cardiotachygraphic registration and a fetal scalp pH below 7.20. Only term infants fulfilling these criteria were studied.

Neonatal management

The following procedures were common to groups A and B. General principles in our neonatal intensive care unit have been given earlier.^{6,7}

All infants were nursed in incubators in a neutral thermal environment with a humidity between 60 and 80%. Umbilical vein and artery catheters were inserted and the catheter position controlled by the use of an x-ray film. Chest and abdomen x-ray examinations were done on days 1 and 2, and thereafter according to the condition of the patient. They included: acid-base balance with arterial blood gas measurements, haemoglobin, platelets, prothrombin, blood glucose, serum electrolytes, C-reactive protein, leucocytes and blood cultures, serum creatinine, and blood urea. Electronic monitoring of heart rate, respiration, and skin temperature was made using SAAB-respimeter (SAAB, Linköping, Sweden) or HP cardiorespirograph (Hewlett-Packard, USA). During the last 2 years of the study transcutaneous oxygen tension ($TcPo_2$) was measured with a radiometer $TcPo_2$ -meter (Radiometer A/S, Copenhagen, Denmark). In 9 infants in group B arterial blood pressure was measured via the umbilical artery catheter. Fluid balance was calculated by continuous measurements of parenteral and peroral fluid supply and fluid output via stool and urine.

Electroencephalograms were recorded in all infants. In any infant with convulsions, a lumbar puncture to search for signs of meningitis or cerebrospinal fluid haemorrhage with cytological examination⁸ was also done. Head circumference was watched during treatment.

Intravenous fluids

Intravenous fluids given were 10% glucose, generally with sodium-bicarbonate on day 1–2 (6 mmol/100 ml 10% glucose). Thereafter sodium, potassium, calcium, chloride, and 20% human albumin (AB Kabi, Sweden) were added according to fluid and electrolyte balance. The fluid amounts were 60–80 ml/kg per 24 hours on days 1–2, 80–100 ml/kg per 24 hours on days 2–3, and 100–120 ml/kg per 24 hours thereafter.

Antibiotics

Immediately after resuscitation cephalothin (100 mg/kg per 24 hours) was given. If septicaemia was diagnosed, treatment was changed to gentamicin (7 mg/kg per 24 hours) and cloxacillin (100 mg/kg per 24 hours) or carbenicillin (200 mg/kg per 24 hours). Serum concentrations of gentamicin were analysed once or twice a week.

Treatment A.

Intubation and ventilator treatment

If the infant had required endotracheal intubation, this was stopped immediately spontaneous breathing started. For correction of acidosis, sodium bicarbonate 5 ml per estimated kg body weight was given through an umbilical vein catheter at 10 to 20 minutes of age to any infant requiring endotracheal intubation. Ventilator treatment was started only if the baby did not obtain spontaneous respiration or if recurrent apnoeic attacks requiring mask and bag ventilation or severe respiratory insufficiency with hypercarbia ($Paco_2 > 9$ kPa) later occurred.

Blood transfusion

This was given to any infant with a level of haemoglobin below 140 g/l during the first 48 hours after birth.

Anticonvulsive treatment

If convulsions were recorded, an initial intravenous dose of diazepam (1 mg/kg) was given; for recurrent convulsions phenobarbitone (8 mg/kg per 24 hours in two doses intramuscularly or perorally) was given. If the convulsions did not respond, pyridoxine 100 mg in a single dose was given. If the convulsions still continued lidocaine (4–6 mg/kg per hour intravenously in 5.5% glucose infusion) was added.

Treatment B.

Intubation and ventilator treatment

If the baby had required intubation initially, the baby was extubated as soon as adequate spontaneous breathing had been established. Sodium-bicarbonate (5 ml/kg estimated body weight) and 30% glucose (2 ml/kg) were given via umbilical vein catheter at between 10 and 20 minutes after birth. Ventilator treatment was started after resuscitation if the baby did not show regular spontaneous breathing and adequate muscular tone with vigorous movements, and did not cry within 30 minutes after delivery.

Blood and plasma transfusions

All infants were given fresh frozen plasma within the first hours after delivery and thereafter daily for 3 days postnatally in a dosage of 10–15 ml/kg intravenously. Hypotensive infants in shock or with low haemoglobin concentrations (less than 150 g/l at age 0–24 hours) were given erythrocyte concentrate 10 mg/kg repeatedly. Infants with signs of haemorrhagic disorders (blood oozing from umbilicus or heel pricks) received antifibrinolytic drugs (Cyklokapron) and fresh blood exchange transfusion.

Barbiturate protection

In infants fulfilling the criteria for severe neonatal

asphyxia (*vide supra*) phenobarbitone treatment was started, generally within 60 minutes of delivery without awaiting clinical signs of convulsions. An initial intravenous dose of 10 mg/kg was given and then 4 hours later treatment with 10 mg/kg per 24 hours in two doses was started.

Brain oedema treatment

Bethametasone was started simultaneously in a dosage of 2 mg intravenously 6-hourly and frusemide in a dosage of 2 mg/kg intravenously 8-hourly. These drugs were tailed off over 48 to 96 hours.

Anticonvulsive treatment

If convulsions still occurred despite phenobarbitone intravenous diazepam (1–2 mg/kg) was administered. If convulsions still persisted lidocaine was given in an initial dose of 2 mg/kg intravenously, and thereafter 4–6 mg/kg per hour, tailed off over 24 to 36 hours.

Drug level monitoring

Serum concentration of phenobarbitone was measured 24–48 and 72–96 hours after starting treatment. On day 4 the treatment was tailed off over 4–6 days until the serum concentration was below 125 $\mu\text{mol/l}$ (3 mg/100 ml) before the baby was taken off the ventilator. In infants receiving diazepam the serum concentration of diazepam and N-desmethyldiazepam was measured before the baby was taken off the ventilator.

Treatment with phenobarbitone was continued beyond the neonatal period, generally for 4 to 6 months, if an infant showed clinical signs of convulsions. In such infants the serum concentration of phenobarbitone was kept between 50 and 80 $\mu\text{mol/l}$ (1.2 and 1.8 mg/100 ml).

Follow-up examinations. Sono-encephalogram and skull transillumination as well as neurological evaluation were made before discharge from the neonatal unit.

At 5–6, 9–10, and 14–18 months neurodevelopmental examinations were performed in all babies. Ophthalmological examination and audiometric tests (at 10–18 months) were also performed in all.

Statistical methods. The χ^2 test has been used for group comparisons.

Results

Table 1 gives details of the infants. There were 16 group A and 14 group B infants with early neonatal asphyxia at delivery. In addition 5 group B infants with late neonatal asphyxia are presented separately. They had sudden cardiac arrest and apnoea several hours postnatally after a clinically apparently

Table 1 Clinical data of 35 infants with severe neonatal asphyxia

	Group A	Group B	
	Early asphyxia (n=16)	Early asphyxia (n=14)	Late asphyxia (n=5)
Birthweight (g)			
Mean	3366	3168	3482
Range	2380–4100	1970–4430	2940–4150
Gestational age (weeks)			
Mean	39.7	39.6	39.4
Range	37–42	37–42	38–42
Small for gestational age (–2 SD)	1	2	—
Boys: girls	12: 4	9: 5	3: 2
Mode of delivery			
Vaginal: vertex*	14 (6)	11 (3)	2
Breech	—	—	1
Caesarean section	2	5	2
Apgar scores mean (range)			
		P-value	
At 1 minute	1.5 (0–4)	NS	1.0 (0–4)
At 5 minutes	3.1 (0–5)	NS	2.7 (0–5)
At 10 minutes	4.6 (3–7)	NS	4.7 (1–5)
Number IPPV- treated infants	10 (62%)	11 (87%)	5 (100%)
Age at start of IPPV (hours)	8.5 (1–18)	0.9 (0.5–4)	21 (2–48)
Duration of IPPV (days)	9.4 (1–35) NS	12.5 (4–25)	5 (3–21)

* Vacuum extraction, forceps instrumental delivery in brackets. NS=not significant.

symptom-free period. All were term infants. One in group A and 2 in group B were small for gestational age. The boy/girl distribution was 12/4 and 12/7. Instrumental or caesarean section delivery had been made in 8 of 16 infants in group A and in 10 of 19 infants in group B.

Among the infants with early neonatal asphyxia 10 in group A and 7 in group B were inborn (that is delivered in the maternity hospital in Lund). During period A another 4 and during period B another 2 term infants with severe perinatal asphyxia did not respond to resuscitation and died shortly after delivery. These 6 infants were not included in the study. In our inborn population the total incidence of severe early neonatal asphyxia was 1.1 per thousand (14 of 12 653 liveborn infants) during period A and 0.8 per thousand (9 of 10 519 liveborn infants) during period B.

The degree of asphyxia as evaluated by Apgar score is also shown in Table 1. The mean Apgar score of infants in groups A and B with early asphyxia at delivery was not appreciably different, whereas group B infants with late neonatal asphyxia had only slightly reduced Apgar scores. In group A 10 (62%) of 16 infants were treated with intermittent positive pressure ventilation (IPPV). In these infants IPPV was started at a mean age of 8.5 hours

Table 2 Clinical data of 5 group B infants with late neonatal asphyxia

Sex	Birthweight (g)	Gestational age (weeks)	Delivery	Apgar score	Age at which respiratory and cardiac arrest took place (hours)	Age at which IPPV started (hours) and duration	Symptoms	Outcome
M	3180	41	Caesarean section (ablatio placentae)	6-9-9	12	13 (5 days)	Persistent fetal circulation. No convulsions	Normal
F	4020	40	Vertex	7-5-5	2	2.5 (6 days)	Meconium aspiration. No convulsions	Normal
M	4150	40	Breech	8-10-9	2	2.5 (3 days)	Meconium aspiration. Convulsions at 4 hours	Died day 3 (anoxic encephalopathy and meconium aspiration syndrome)
F	2940	39	Vertex	9-10-10	48	48 (10 days)	Group B streptococcal sepsis. Convulsions at 49 hours	Normal
M	3120	37	Caesarean section	9-9-9	8	9 (21 days)	Persistent fetal circulation. Renal vein thrombosis. General bleeding and intracranial haemorrhage. Convulsions at 5 hours	Infantile spasms. Moderate psychomotor retardation

(range 1 to 18). In group B 11 (87%) of 14 infants were treated with IPPV starting early according to treatment B criteria at a mean age of 0.9 hours (range 0.5 to 4) after birth. The delay in starting IPPV in some group B infants was mainly related to transportation of outborn infants. In the 3 infants not treated with IPPV in group B, sufficient spontaneous ventilation and oxygenation had been established at arrival in the neonatal intensive care unit. Despite starting earlier, IPPV was not continued significantly longer in group B than in group A. The 5 group B infants with late neonatal asphyxia were started on IPPV after resuscitation because they fulfilled our criteria for severe neonatal asphyxia. Their clinical data and diagnoses are shown in Table 2.

Mortality. As shown in Table 3 the total mortality (at age 0-12 months) was significantly lower in group B (14%) than in group A (50%). In group A 5 infants died in the neonatal period with anoxic

encephalopathy at necropsy examination. Cerebral oedema in 3 of these infants, and intraventricular haemorrhage in the remaining 2 were major additional findings. Postnatal deaths occurred at 1½, 3, and 3½ months of age in group A and at 7 and 11 months of age in group B infants. These 5 infants all had severe anoxic encephalopathy with corticocerebral atrophy at necropsy. All had shown clinical symptoms of severe cerebral sequelae—that is convulsions, retarded psychomotor development, and tetraplegia or hemiplegia.

Handicaps in surviving infants. As shown (Table 4) the higher survival rate in group B did not result in

Table 3 Mortality rate

	Group A	Group B	
	Early asphyxia (n=16)	Early asphyxia (n=14)	Late asphyxia (n=5)
Liveborn infants	16 (10)	14 (11)	5 (5)
Mortality 0-28 days	5 (4)	0	1 (1)
Mortality 28 days-1 year	3 (3)	2 (2)	0
Total mortality	8 (50%)	2 (14%)	1 (20%)
P-value	P<0.05		

No of infants treated with IPPV shown in brackets.

Table 4 Handicap rate in infants after severe neonatal asphyxia and surviving the first year of life

	Group A	Group B	
	Early asphyxia (n=16)	Early asphyxia (n=14)	Late asphyxia (n=5)
Survivors at 1 year	8 (50%)	12 (86%)	4 (80%)
Neurodevelopmental sequelae in survivors	4 (50%)	2 (17%)	1 (25%)
CP	1	—	—
CP+PMR	1	1	—
CP+PMR+convulsions	2	—	—
PMR+convulsions	—	1	1
Rate of handicap			
In survivors	4 (50%)	10 (83%)	3 (75%)
In total liveborn	4 (25%)	10 (71%)	3 (60%)
P-value	P<0.01		

CP = cerebral palsy, PMR = psychomotor retardation.

an increased rate of neurodevelopmental handicaps (17%) compared with group A (50%). On the contrary in relation to the total number of infants the incidence of normal survivors after early severe asphyxia was 71% in group B compared with only 25% in group A ($P < 0.01$). In infants with early neonatal asphyxia at birth the following handicaps were found:

Group A

One infant had moderate diplegia only, one hemiplegia with moderate psychomotor retardation, and 2 infants severe dyskinetic cerebral palsy, and convulsive disorders (infantile spasms in one case).

Group B

One infant had severe tetraplegia and psychomotor retardation, and one infant with moderate psychomotor retardation had hemiconvulsions at age 2 years.

In infants with late neonatal asphyxia only 1 of 4 survivors developed abnormally with infantile spasms at age 4 months, later developing slight psychomotor retardation but no seizures. The normal survivors were at least 18 months (range 18 months–6 years) at the last follow-up examination.

Convulsions and phenobarbitone treatment. Neonatal convulsions occurred in 87% of group A infants (Table 5). In group B phenobarbitone treatment was started as soon as intensive care treatment had been decided on. Yet in 3 infants convulsions had started before phenobarbitone treatment was instituted and

Figure Phenobarbitone serum levels in group B infants.

9 infants had convulsions despite it. However, recurrent neonatal convulsions occurred much more often in group A (63%) than in group B infants (21%).

Convulsive disorders were still present after the neonatal period in 5 of 11 group A infants compared with only 3 of 14 group B infants.

Phenobarbitone serum concentrations were regularly measured in group B infants and the maximum levels obtained are shown in the Figure. Although the initial dose was equal in all cases the maximum level generally obtained on day 2 or 3 differed widely, as did the disappearance rate after stopping phenobarbitone. Apart from these pharmacokinetic peculiarities of phenobarbitone, we noted that in infants with serum concentrations greater than 225 $\mu\text{mol/l}$ (5.2 mg/100 ml) there was invariably a decrease of heart rate below 100 per minute as well as decreased beat-to-beat variability (to less than 5) in infants monitored with a cardiorespirograph. In 6 group B infants blood pressure monitoring showed a decrease of mean arterial blood pressure from 40–50 to 30–35 mmHg within 15 minutes after intravenous phenobarbitone infusion.

Discussion

Several experimental studies have indicated that barbiturate can ameliorate the effects of various types of brain hypoxia or ischaemia even when administered in the phase of resuscitation.^{9–12} This has led to clinical trials of barbiturate therapy after cardiac arrest in adults and these have given contradictory results.^{11 13–15} In one report a lower rate of mortality and brain damage was found in the

Table 5 Convulsions in infants with severe asphyxia

	Group A	Group B	
	Early asphyxia	Early asphyxia	Late asphyxia
	(n = 16)	(n = 14)	(n = 5)
Neonatal convulsions	14 (87%)	8 (57%)	4
Age at which convulsions started (hours)			
Mean	7.5	6.6	16
Range	1–18 hrs	3–10 hrs	4–48 hrs
Phenobarbitone treatment			
All infants	14	14	5
Before convulsions	0	7	2
After convulsions	14	1	2
Recurrent neonatal convulsions	10 (63%)	3 (21%)	2
Diazepam or lidocaine or both	7	3	2
Rate of postnatal convulsive disorders	5/11 (=46%)	3/14 (=21%)	1/4
In survivors	2/8 (=25%)	1/12 (=8%)	1/4
In infants dying postnatally	3/3	2/2	—

offsprings of rhesus monkey mothers treated by barbiturate before birth.¹⁶ In the present study our aim was to evaluate the outcome of phenobarbitone treatment in the neonatal period as protection against brain lesions in severely asphyxiated newborn infants.

There are several possible mechanisms whereby barbiturate may exert a protecting effect^{12 14 17-22}—for example by a sedative effect, by a reduced cerebral metabolic rate of oxygen (CMRO₂) known to follow barbiturate administration, by the anticonvulsive effect *per se*, by prevention of cerebral oedema and reduction of intracranial hypertension, or by a membrane stabilisation effect. The suggested ability of phenobarbitone to inhibit lipid peroxidation²³ has recently been disproved.²⁴

Recent reports indicate that in asphyxiated pre-term newborn infants the autoregulation of cerebral blood flow in relation to blood pressure is lost leading to a pressure passive cerebral blood flow.^{18 25} Consequently there is a considerable risk of cerebral haemorrhage due to sudden rise in blood pressure often occurring during infant care (for example, at suctioning, handling, feeding, etc.) or during seizures. (In our study 2 infants who died early in the neonatal period actually had cerebral haemorrhage at necropsy in addition to anoxic encephalopathy.) For the same reason the risk of ischaemic cerebral lesions due to sudden drop in blood pressure is also high in neonatal asphyxia.^{25 26} From continuous measurements of blood pressure in some babies in our study it was obvious that the rather high barbiturate concentrations obtained ameliorated sudden rapid blood pressure changes—for example during endotracheal tube suctioning or lumbar puncture. In this context animal studies showing that during stress CMRO₂ will increase to about twice the pre-stress value should be taken into consideration.²⁷ Thus sedation may be crucial in the treatment of seriously ill newborn infants.

It is well known that seizures under certain circumstances may give rise to brain damage.^{20 27} Therefore the anticonvulsive effect of barbiturate *per se* may also be an important protective factor. Postasphyxial seizures are common after severe neonatal asphyxia, in some reports occurring in more than half of the cases.^{4 5 28 29} Furthermore, in these studies several children with neurodevelopmental handicaps initially had had prolonged seizures. In the postasphyxial state convulsions probably have a deleterious effect since CMRO₂ increases if there is impaired circulation and ventilation, finally leading to curtailed cerebral energy balance.^{30 31} Furthermore, Wasterlain²⁰ showed that even short-lasting but recurrent seizures in newborn rats are followed by reduction in brain size and DNA content. Thus it

is important to prevent prolonged or recurrent seizures after neonatal asphyxia. Despite early anti-convulsive treatment several group B infants still had seizures. However, recurrent seizures were avoided to a large extent in this group (Table 5).

Large doses of barbiturate may cause cardiac failure.¹⁵ Besides a moderate bradycardia (85 to 105 beats per minute) and decrease of beat-to-beat variability we noted only a moderate decrease in blood pressure. If cerebral autoregulation is abolished in asphyxiated infants such a decrease in blood pressure could lead to a reduction in brain perfusion and lower cerebral oxygen availability. However, this is counterbalanced by the reduction in CMRO₂ induced by barbiturate.¹⁷

Barbiturate blood levels varied widely but in all cases levels well above the therapeutic range considered anticonvulsant in older individuals (50–120 µmol/l (1.2–2.9 mg/100 ml)) were reached. At levels above 200 µmol/l (4.8 mg/100 ml) no infant had seizures. However, respiratory insufficiency occurred at levels 150–180 µmol/l (3.6–4.3 mg/100 ml). It is possible that the phenobarbitone administration thereby may have prolonged ventilator treatment in some infants. From studies of Jalling³² it is known that the phenobarbitone half-life in the newborn is long and variable. It was not possible to keep to a fixed treatment schedule as our asphyxiated newborn infants in several cases showed unpredictable pharmacokinetics (Figure). Repeated measurements of serum levels must be done during treatment, and heart rate and blood pressure should be monitored continuously.

Brain swelling is common in asphyxiated newborn infants, and was found in 3 infants at necropsy in our study. In accordance with earlier studies³³⁻³⁵ we therefore added steroids and IPPV to our intensive care treatment. The hyperosmotic glucose solution given initially in group B should counteract cerebral oedema more rapidly than steroid treatment which does not reduce intracranial pressure in less than 12 to 24 hours. Eventually the presumed membrane stabilising ability of barbiturate may also help to diminish the brain oedema.^{14 19 22}

The impact of disturbances in carbohydrate turnover in perinatal asphyxia is unknown. Experimental studies have repeatedly shown that hypoglycaemia reduces resistance to anoxia and seizures in the newborn period.^{20 36 37} There is experimental evidence implying that blood glucose concentrations considered adequate in physically well infants may be inadequate in cases of asphyxia.³⁶ Furthermore, it has been claimed that perinatal asphyxia may play a role in early onset of neonatal hypoglycaemia, especially in term infants.³⁸ On the other hand, experimental studies indicate that the brain lactate

accumulation after anaerobic metabolism may be a deleterious factor, brain lesions being less common in animals starved before experimental hypoxia.^{39 46} However, these studies have dealt with metabolic events before and during the asphyxial period. The consequence of administration of glucose in the resuscitation period in newborns has not been defined. In this context the impending heart failure due to depletion of cardiac glycogen stores must also be considered.⁴⁰

Not only is adequate oxygenation crucial; the PCO_2 level is of considerable importance too. Cerebral blood flow varies directly with the CO_2 tension⁴¹ and it has been shown that slight or moderate hypercarbia will increase the rate of intraventricular haemorrhage in newborn infants.⁴² Hyperventilation transiently and quickly lowers the intracranial pressure.^{43 44} In the present study we aimed at and obtained in most cases an arterial PCO_2 level in the range of 2.8 to 4.5 kPa (21 to 33 mmHg) within the first hours of IPPV treatment. As glomerular filtration rate is much lower in neonatal asphyxia⁴⁵ diuretics were included in the initial intensive care treatment to avoid fluid overload.

Owing to the fact that we had few patients and were not able to achieve a double-blind design, evaluation of our study should be cautious. However, this brain-orientated intensive care regimen including phenobarbitone protection seemed to improve the outlook for this group of patients in whom the prognosis would otherwise have been bad. Whether this regimen can be used in severely asphyxiated low birthweight infants cannot be decided without further clinical trials. Finally, we want to stress that the resources of a neonatal intensive care unit with experience in assisted ventilation and blood pressure monitoring is necessary for this kind of treatment until further experience is gained.

This work was supported by grants from Margareta-hemmet, First of May Flower Research Foundation, Jerring Research Foundation, and Swedish Medical Research Foundation grants Nos 29X-4732 and 14X-02872.

References

- Steiner H, Neligan G. Perinatal cardiac arrest. Quality of the survivors. *Arch Dis Child* 1975; **50**: 696-702.
- Scott H. Outcome of very severe birth asphyxia. *Arch Dis Child* 1976; **51**: 712-6.
- Thomson A J, Searle M, Russell G. Quality of survival after severe birth asphyxia. *Arch Dis Child* 1977; **52**: 620-6.
- deSouza S W, Richards B. Neurological sequelae in newborn babies after perinatal asphyxia. *Arch Dis Child* 1978; **53**: 564-9.
- Mulligan J C, Painter M J, O'Donoghue P A, MacDonald H M, Allen A C, Taylor P M. Neonatal asphyxia. II. Neonatal mortality and long-term sequelae. *J Pediatr* 1980; **96**: 903-7.
- Carlsson J, Svenningsen N W. Respiratory insufficiency syndrome (RIS) in preterm infants with gestational age of 32 weeks and less. *Acta Paediatr Scand* 1975; **64**: 813-21.
- Lindroth M, Svenningsen N W, Ahlström H, Jonson B. Evaluation of mechanical ventilation in newborn infants. I. Techniques and survival rates. *Acta Paediatr Scand* 1980; **69**: 143-9.
- Blennow G, Svenningsen N W, Gustafson B, Sundén B, Cronquist S. Neonatal and prospective follow-up study of infants delivered by vacuum extraction (VE). *Acta Obstet Gynecol Scand* 1977; **56**: 186-94.
- Bleyaert A L, Nemoto E M, Safar P, et al. Thiopental amelioration of postischemic encephalopathy in monkeys. *Acta Neurol Scand [Suppl]* 1977; **56**: Supplement 64, 144-5.
- Fisher D E, Paton J B, Behrman R E. The effect of phenobarbital on asphyxia in the newborn monkey. *Pediatr Res* 1975; **9**: 181-4.
- Michenfelder J D, Milde J H, Sundt T M, Jr. Cerebral protection by barbiturate anesthesia. *Arch Neurol* 1976; **33**: 345-50.
- Brann A W, Montalvo J M. Barbiturates and asphyxia. *Pediatr Clin N Am* 1970; **17**: 851-62.
- Renck H. Barbiturate protection against ischemic brain damage. *Scand J Clin Lab Invest* 1980; **40**: 209-10.
- Marshall L F, Shapiro H M. Barbiturate control of intracranial hypertension in head injury and other conditions: iatrogenic coma. *Acta Neurol Scand* 1977; **56**: Supplement 64, 156-72.
- Breivik H, Safar P, Sands P, et al. Clinical feasibility of trials of barbiturate therapy after cardiac arrest. *Crit Care Med* 1978; **6**: 222-44.
- Cockburn F, Daniel S, Dawes G, et al. The effect of phenobarbital anesthesia on resuscitation and brain damage in fetal rhesus monkeys asphyxiated on delivery. *J Pediatr* 1969; **75**: 281-91.
- Nilsson L, Siesjö B K. The effect of phenobarbitone anaesthesia on blood flow and oxygen consumption in the rat brain. *Acta Anaesthesiol Scand* 1975; Supplement 57, 18-24.
- Gardiner R M. Cerebral blood flow and oxidative metabolism during hypoxia and asphyxia in the newborn calf and lamb. *J Physiol* 1980; **305**: 357-76.
- Astrup J, Nordström C-H, Rehncrona S. Rate of rise in extracellular potassium in the ischemic rat brain and the effect of pre-ischemic metabolic rate. Evidence for a specific effect of phenobarbitone. *Acta Neurol Scand* 1977; **56**: Supplement 64, 148-9.
- Wasterlain C G. Neonatal seizures and brain growth. *Neuropediatrics* 1978; **9**: 213-28.
- Steen P A. Barbiturate protection against ischemic brain damage. *Scand J Clin Lab Invest* 1980; **40**: 205-7.
- Simeone F A, Frazer G, Lawner P. Ischemic brain edema: comparative effects of barbiturates and hypothermia. *Stroke* 1978; **10**: 8-12.
- Demopoulos H B, Flamm E S, Seligman M L, Jørgensen E, Ransohoff J. Antioxidant effects of barbiturates in model membranes undergoing free radical damage. *Acta Neurol Scand* 1977; **56**: Supplement 64, 152-3.
- Smith D S, Rehncrona S, Siesjö B K. Inhibitory effects of different barbiturates on lipid peroxidation in brain tissue *in vitro*. *Anesthesiology* 1980; **53**: 186-94.

- ²⁵ Lou H C, Lassen N A, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 1979; **94**: 118–21.
- ²⁶ Vannucci R C, Duffy T E. Cerebral metabolism in newborn dogs during reversible asphyxia. *Ann Neurol* 1977; **1**: 528–34.
- ²⁷ Siesjö B K. *Brain energy metabolism*. New York: Wiley, 1978: 56–100.
- ²⁸ André M, Vert P, Debrulle Ch. Diagnostic et évolution de la souffrance cérébrale chez les nouveau-nés ayant présenté des signes d'hypoxie foetale. Etude prospective. *Arch Fr Pediatr* 1978; **35**: 23–36.
- ²⁹ Brown J K, Purvis R J, Forfar J O, Cockburn F. Neurological aspects of perinatal asphyxia. *Dev Med Child Neurol* 1975; **16**: 567–71.
- ³⁰ Blennow G, Brierley J B, Meldrum B S, Siesjö B K. Epileptic brain damage: the role of systemic factors that modify cerebral energy metabolism. *Brain* 1978; **101**: 687–700.
- ³¹ Meldrum B S, Vigouroux R A, Brierley J B. Systemic factors and epileptic brain damage. Prolonged seizures in paralyzed artificially ventilated baboons. *Arch Neurol* 1973; **29**: 82–7.
- ³² Jalling B. Plasma concentrations of phenobarbital in the treatment of seizures in newborns. *Acta Paediatr Scand* 1975; **64**: 514–24.
- ³³ Volpe J J. Perinatal hypoxic-ischemic brain injury. *Pediatr Clin N Am* 1976; **23**: 383–97.
- ³⁴ Brown J K. Infants damaged during birth. Perinatal asphyxia. In: Gairdner D M T, ed. *Recent advances in paediatrics*, fifth edition. London: Churchill, 1976: 59–87.
- ³⁵ Hahn J F. Cerebral edema and neurointensive care. *Pediatr Clin N Am* 1980; **27**: 587–92.
- ³⁶ Holowach-Thurston H, Hauhart R E, Jones E M. Anoxia in mice: reduced glucose in brain with normal or elevated glucose in plasma and increased survival after glucose treatment. *Pediatr Res* 1974; **8**: 238–43.
- ³⁷ Vannucci R C, Duffy T E. Carbohydrate metabolism in fetal and neonatal rat brain during anoxia and recovery. *Am J Physiol* 1976; **230**: 1269–75.
- ³⁸ Gutberlat R L, Cornblath M. Neonatal hypoglycemia revisited. *Pediatrics* 1975; **58**: 10–7.
- ³⁹ Myers R E. Lactic acid accumulation as cause of brain edema and cerebral necrosis resulting from oxygen deprivation. In: Korobkin R, Guilleminault C, eds. *Advances in perinatal neurology*. Vol. 1. New York: Spectrum Publishers, 1979: 85–114.
- ⁴⁰ Lees M H. Perinatal asphyxia and the myocardium. *J Pediatr* 1980; **96**: 675–8.
- ⁴¹ Purves M J. *The physiology of the cerebral circulation*. London: Cambridge University Press, 1972: 173–99.
- ⁴² Kenny J D, Garcia-Prats J A, Hilliard J L, Corbet A J S, Rudolph A J. Hypercarbia at birth: a possible role in the pathogenesis of intraventricular hemorrhage. *Pediatrics* 1978; **62**: 465–7.
- ⁴³ Milligan D W A. Positive pressure ventilation and cranial volume in newborn infants (abstract). *Arch Dis Child* 1980; **55**: 317.
- ⁴⁴ Miller J D. Effects of long term controlled ventilation in intracranial hypertension. In: Lundberg N, Pontén U, Brock M, eds. *Intracranial pressure*. Vol. 2. Berlin: Springer, 1975: 467–70.
- ⁴⁵ Svenningsen N W. Single injection polyfructosan clearance in normal and asphyxiated neonates. *Acta Paediatr Scand* 1975; **64**: 87–95.
- ⁴⁶ Rehnörom S, Rosén I, Siesjö B K. Brain lactic acidosis and ischaemic damage. *J Cerebral Blood Flow Metab* 1981; **1**: 297–311.

Correspondence to Dr N W Svenningsen, Neonatal Intensive Care Unit, Department of Paediatrics, University Hospital, S-221 85 Lund, Sweden.

Received 24 August 1981