Thiopentone induced coma after severe birth asphyxia

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SUMMARY The aim of this study was to determine the feasibility of inducing a prolonged coma in severely asphyxiated newborn babies by the infusion of high dose thiopentone. In six severely asphyxiated babies the electroencephalograph (EEG) and blood pressure were monitored continuously. Thiopentone was infused at a rate sufficient to suppress completely the EEG providing the mean blood pressure remained above 35 mm Hg; it was continued until there was no evidence of cerebral oedema for 24 hours. In two the infusion was stopped prematurely because of hypotension that was unresponsive to treatment. In the other four a deep coma was maintained for a median duration of 127 hours. All developed pharmacodynamic tolerance to the thiopentone and showed non-linear elimination kinetics. Three babies died; the three survivors have moderate to severe handicap. It was concluded that with full intensive care it is possible to induce a deep coma; the outcome does not seem to be improved, however, and the incidence of complications was high.

Babies born without a heart beat who despite resuscitation do not start to breathe spontaneously within the first half hour after birth have a poor outcome.¹⁻³ In a large study babies with an Apgar score of three or less for more than 20 minutes had a mortality of 87% and the rate of cerebral palsy in survivors was 57%.⁴ Monitoring of heart rate and sonography are used to identify the fetus at risk of intrapartum asphyxia, but despite this some are born profoundly asphyxiated. Although death results from damage to organs other than the brain, long term morbidity is almost exclusively a consequence of impaired brain function.

There is debate about the management of post-asphyxial encephalopathy. Severe restriction of fluid intake to reduce production of cerebrospinal fluid and prevent cerebral oedema has not been shown to be beneficial and may result in depletion of intravascular volume and hypotension.⁵ Hyperventilation decreases raised intracranial pressure only by reducing cerebral blood flow; if there is associated hypotension from myocardial ischaemia or hypovolaemia hyperventilation may lead to further neuronal injury. Although steroids are often given, there is no evidence of a reduction in the cerebral oedema after hypoxia, ischaemia, or trauma.⁶ Hyperosmotic diuretics can decrease intracerebral interstitial fluid and lower intracranial pressure. When there is

increased vascular permeability from hypoxia, however, influx of hyperosmotic fluid may increase the intracranial water content further and lead instead to a rise in intracranial pressure.⁵

Barbiturates have been shown to induce a reversible depression of neuronal function, cerebral metabolic rate, and blood flow.⁷ These effects are dependent on dose until the electroencephalogram (EEG) is isoelectric when cerebral metabolic rate and blood flow are reduced by 50%.⁸ The reduced cerebral blood flow is associated with an increased cerebrovascular resistance and reduced cerebral blood volume. This may explain the accompanying reduction in intracranial pressure.⁸ In addition, it has been suggested that barbiturates stabilise lysosomal membranes, quench oxygen free radicals, reduce intracellular calcium concentrations, and modify amino acid and neurotransmitter release from the neurone.⁹

When given to animals before generalised cerebral ischaemia high doses of barbiturates protect the newborn and fetal brain.¹⁰⁻¹³ This effect, however, has not been found consistently after global cerebral ischaemia in mature animals.⁹ Barbiturates given before or sometime after cerebrovascular occlusions reduce the area of infarction in many species.¹⁴⁻¹⁶ In primates subjected to permanent middle cerebral artery occlusion the reduction in the size of the

infarction is proportional to the dose until there is maximal suppression of neuronal activity.^{17 18} A beneficial effect has been shown even when treatment with barbiturates was delayed up to two hours after the occlusion.^{14 15 18 19} When vascular occlusion has been followed by re-perfusion coma induced by the barbiturate, started after 30 minutes and maintained for 96 hours, provides nearly complete protection.²⁰

In view of these findings we designed a study to investigate the possibility of using treatment with high dose barbiturate for newly born babies who had sustained very severe intrapartum asphyxia.

Patients and methods

Babies born between May 1980 and December 1982 in the John Radcliffe Maternity Hospital, Oxford, were eligible for the study if there was no heart beat at birth and despite resuscitation they failed to establish spontaneous respiration within 20 minutes after birth. Babies with obvious lethal congenital malformations were excluded.

Thiopentone was selected as the most appropriate barbiturate because it is highly lipid soluble; thus high concentrations can be achieved in neurones within seconds of an intravenous bolus.

After resuscitation had been performed and a regular heart beat established the babies were transferred to the intensive care nursery. The possible benefits and side effects of an infusion of thiopentone were discussed with one or both parents as soon as possible and before starting the infusion. Their consent for this treatment was obtained. Umbilical arterial and venous catheters were inserted and the aortic blood pressure and the central venous blood pressure were monitored continuously. A two channel EEG was recorded continuously, using

a method described previously.²¹ If the mean aortic blood pressure was greater than 35 mm Hg an infusion of a 2.5% solution of thiopentone in water was started through the central venous catheter. A loading dose of 10 mg/kg of thiopentone was given over 30 minutes. In the next hour a further dose of 10 mg/kg was given. Thereafter, the rate of infusion of thiopentone was reduced to 2 mg/kg/h and subsequently adjusted to keep the EEG isoelectric.

If the mean aortic blood pressure fell below 35 mm Hg and the central venous blood pressure was less than 12 cm H₂O plasma was infused. If the mean aortic blood pressure fell below 30 mm Hg the infusion of thiopentone was stopped, but if it did not rise above 35 mm Hg in the subsequent half hour an infusion of dopamine was started at 2 µg/kg/min, increasing to a maximum of 10 µg/kg/min. When the mean aortic blood pressure was above 35 mm Hg the infusion of thiopentone was restarted.

All babies received intermittent positive pressure ventilation, and arterial blood gases were measured at least four hourly. The oxygen tension was maintained between 6.6 and 11.3 kPa (50–85 mm Hg) and the carbon dioxide tension between 3.7 and 4.6 kPa (28–35 mm Hg). The intake of non-colloid fluid was 60 ml/kg/24h, given intravenously.

An ultrasound scan of the brain was performed daily. Myocardial function was assessed by electrocardiograph (ECG) daily and by echocardiography. Blood glucose concentration was measured three hourly, plasma thiopentone concentration six hourly, and plasma electrolyte concentrations and liver function tests daily.

The infusion of thiopentone was continued until there was a 24 hour period with no evidence of raised intracranial pressure based on clinical examination and cerebral ultrasonography. Babies who died had a postmortem examination, which

Table 1 Clinical characteristics of the patients

Case No	Sex	Gestation (weeks)	Weight (g)	Duration of labour		Method of delivery	Time from birth to onset of		First blood pH
				First stage (h)	Second stage (min)		Heart beat (min)	Respiration (min)	
1	M	40	4270	4.5	23	SVD	2	25	7.05*
2	M	41	3430	10.5	30	KFRD	10	20	7.00*
3	M	41	3400	30.3	60	KFRD	5	120	6.59*
4	F	40	3230	3.8	51	NBFD	10	90	6.89†
5	F	40	3480	11.5	77	Ventouse	20	Never	6.87*
6	F	41	3740	Cord prolapse		Ventouse failed; LSCS	3	150	6.75†

SVD=Spontaneous vaginal delivery.

KFRD=Kejiland's forceps rotational delivery.

NBFD=Neville Barnes forceps delivery.

LSCS=lower segment caesarean delivery.

*Arterial blood taken after resuscitation and treatment with bicarbonate.

†Umbilical arterial blood.

included a histological examination of the brain. A clinical examination, intellectual assessment by the Griffiths scale, and assessment of visual and auditory function was carried out on the surviving babies at the age of 3 years.

Results

Altogether, 15 522 babies were born during the 32 months of the study. Six babies fulfilled the criteria for entry, which represented an incidence of 0.4/1000 live births each year.

The clinical characteristics of the babies studied are summarised in Table 1. Two patients (cases 3 and 4) were monitored by cardiotocography during labour and had evidence of fetal distress. Case 3 had a fetal tachycardia of ≥ 180 beats/min, with loss of variability for three hours before delivery. Case 4 had late decelerations in heart rate for two hours followed by a fetal bradycardia of less than 60 beats/min for 35 minutes before delivery. There was meconium staining of the liquor during the labour of cases 2 and 5. Cases 1, 2, and 4 had the umbilical

cord tightly around their necks at the time of delivery.

The median time between birth and starting the infusion of thiopentone was 115 minutes, with a range of 60–140 minutes. The maximum plasma thiopentone concentrations measured during each 24 hour period during and after the stopping of the infusion are shown in Figure 1. In cases 2 and 5 the infusion was stopped after five and 30 hours, respectively, because of hypotension that was unresponsive to an infusion of dopamine. The remaining four babies completed the study. The median duration of the infusion of thiopentone in these babies was 127 hours, with a range of 86–169 hours. In all four progressively increasing plasma concentrations of thiopentone were required to maintain an isoelectric EEG. Neurological examination during the barbiturate coma was uninformative; even deep tendon, occipitocervical, and corneal reflexes were abolished. The pupils remained constricted and were non-reactive to light.

After stopping the infusion the rate of thiopentone elimination was measured in cases 3, 4, and 6

Fig. 1 Plasma thiopentone concentrations in the six infants from the onset of infusion.

Fig. 2 Clearance of thiopentone in case 3, 4, and 6 after stopping the continuous infusion.

(Fig. 2). The rate of thiopentone clearance was not constant, rather it slowly increased with time, indicating the presence of non-linear elimination kinetics. Cases 3 and 6 began to show clinical evidence of cerebral activity (movement in response to a noxious stimulus) at plasma thiopentone concentrations of less than 187 and 165 $\mu\text{mol/l}$ 101 and 107 hours, respectively, after the infusion had been stopped. Case 4 sustained brain death and showed no clinical evidence of cerebral activity when the serum thiopentone concentrations were unrecordable.

The major side effects were dose dependent cardiovascular and respiratory depression. The loading dose of thiopentone suppressed all spontaneous respiratory effort; all babies received intermittent positive pressure ventilation, the median period being 9.5 days, with a range of 3–20 days. In addition, four babies had early respiratory problems attributed to asphyxial lung injury. Soon after birth all six babies had ECG and ultrasound evidence of myocardial ischaemia or infarction. In all the heart rate and blood pressure fell after the beginning of the infusion of thiopentone (Fig. 3). In two (cases 2 and 5) an infusion of dopamine was used to support myocardial function. All six babies had clinical evidence of acute tubular necrosis and all had initial low plasma calcium concentrations (less than 1.5 mmol/l (6mg/100ml)); two (cases 3 and 6) had one

Fig. 3 Rate of infusion and plasma concentrations of thiopentone for case 3 in relation to heart rate and blood pressure.

Table 2 Outcome of the patients

Babies who survived.

Case No	Age at last examination (years)	Clinical findings			
		Motor	Sensory	Intellectual	Other
1	5	Mild spastic diplegia	—	Moderate retardation	—
2	4	Severe dystonic cerebral palsy	—	Normal	—
6	3	Severe spastic quadriplegia	—	Severe retardation	Epilepsy; microcephaly

Babies who died.

Case No	Age at death	Post mortem findings			
		Brain	Heart	Kidney	Liver
3	8 months	Severe atrophy. Neuronal cell loss. Gliosis involving cerebral cortices, basal ganglia, thalamus, hypothalamus, and brain stem	Normal	Normal	Normal
4	13 days	Severe necrosis of the neurons of cerebral cortex, basal ganglia, thalamus, hypothalamus, corpus callosum, cerebellum, and brain stem	Normal	Vascular congestion	Normal
5	5 days	Anoxic haemorrhages. Early neuronal necrosis, involving cerebral hemispheres, basal ganglia, thalamus, hypothalamus, and brain stem	Biventricular infarction	Acute tubular necrosis	Centrilobular necrosis

hypoglycaemic episode (less than 1.1 mmol/l (19.8 mg/100 ml)). Three babies died (cases 3, 4, and 5), and three survived with serious disabilities (cases 1, 2, and 6). The outcome of the babies is tabulated in Table 2.

Discussion

The poor outcome of the survivors of this study was disappointing. The explanation may lie in the delay from the onset of cerebral ischaemia to the administration of the thiopentone. In the babies the neuronal ischaemia must have begun during labour and it is therefore difficult to determine the exact time of onset for each baby. Only two babies had cardiac tocographic monitoring during labour: both had evidence of fetal distress for more than two and a half hours before delivery. In addition, there was a delay from birth to the administration of thiopentone. During this time resuscitation was performed, the baby transferred to the intensive care nursery, catheters placed in the aorta and inferior vena cava, monitoring of pressure begun, and parental consent obtained. The total time from the onset of neuronal ischaemia to administration of thiopentone may have been up to four hours. Animal studies have shown a beneficial effect from thiopentone only when it was administered up to two hours after the onset of neuronal ischaemia.

The major side effect of the infusion of thiopentone

was cardiovascular suppression. It has been shown that this myocardial toxicity will be potentiated if the myocardium is compromised or if intravascular volume is depleted. There was clinical evidence of myocardial ischaemia in all six babies studied, and cardiovascular suppression was evident in all six immediately after administering the first dose of thiopentone. If episodes of hypotension and thus further cerebral ischaemia are to be avoided in very severely asphyxiated babies it is important to monitor both arterial and central venous blood pressures before starting the infusion of thiopentone. In addition, it is necessary to assess cardiac function regularly by clinical examination, ECG, and echocardiography.

To keep the EEG suppressed the serum thiopentone concentrations had to be progressively increased. A similarly rapid onset of pharmacodynamic tolerance has been described previously in adult patients,²² but its mechanism is unknown. The rapid development of tolerance makes continuous recording of the EEG mandatory as it provides the only guide to the necessary rate of infusion of the thiopentone. Thiopentone is almost completely metabolised by a hepatic microsomal system, with only 0.3% being recovered unaltered in human urine.²³ When used in low doses (5 mg/kg)—for example, as a bolus for the induction of anaesthesia—thiopentone shows first order kinetics with a half life in neonates double that of adults (16

hours and eight hours, respectively).²³ In this study after prolonged administration thiopentone showed non-linear kinetics, and initially there was a very slow clearance of thiopentone from the blood. This non-linearity is probably a consequence of the saturation of the hepatic enzyme system that oxidises thiopentone to an inactive carboxylic acid metabolite. This has important therapeutic implications: when the infusion is stopped after a prolonged period the subjects remained comatose for many days. Intensive care must continue during this time, and it is impossible to make a detailed assessment of neurological function. Such a long period of coma and uncertainty immediately after a difficult delivery is stressful both to the parents and to the medical and nursing staff caring for the baby.

This study shows that treatment with high dose thiopentone is possible in the newborn after severe intrapartum asphyxia but that it requires full intensive care and extremely close medical and nursing supervision. When begun one to two hours after birth the outcome does not seem to be improved and the incidence of complications is high.

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