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PREVENTION OF INTRAVENTRICULAR HAEMORRHAGE IN PRETERM INFANTS BY PHENOBARBITONE*
A Controlled Trial

STEVEN M. DONN DIETRICH W. ROLOFF
GARY W. GOLDSTEIN

Department of Pediatrics, Sections of Newborn Services and Pediatric Neurology, and Department of Neurology, University of Michigan Medical Center, Ann Arbor, Michigan 48109, U.S.A.

Summary Sixty infants with birth-weights less than 1500 g and who were less than 6 h old were randomly assigned to a group given phenobarbitone or a control group. Intravenous phenobarbitone was given in doses sufficient to achieve anticonvulsant serum levels within 12–18 h. Maintenance therapy was continued for one week. Periventricular/intraventricular haemorrhage (IVH) occurred in 13·3% (4/30) of the phenobarbitone group and in 46·7% (14/30) of the control group. The occurrence of risk factors related to IVH was similar in the two groups. Phenobarbitone may reduce the incidence of IVH in small preterm infants.

Introduction

THE reported incidence of periventricular/intraventricular haemorrhage (IVH) in preterm infants is 40–43%.[1,2] Haemorrhages usually occur on the 2nd or 3rd postnatal day[3] and may by asymptomatic.[1,2] The major sites of involvement are the periventricular germinal matrix and the lateral ventricles.[4] Prevention of IVH has been based upon good supportive care and avoidance of risk factors associated with IVH, such as the rapid infusion of sodium bicarbonate.[5] Specific intervention has not been studied in a controlled manner.

The potential neuroprotective benefits of barbiturates[6-23] have been investigated in animal experiments and in uncontrolled studies in adults. We investigated the use of phenobarbitone for the prevention of IVH in preterm infants in a randomised, controlled study. We chose to evaluate phenobarbitone rather than a short-acting barbiturate because of the availability of pharmacokinetic data on this drug and extensive experience with its use in neonates.

Methods

The investigation was approved by the Committee for Clinical Research and Investigation Involving Human Beings, University of Michigan Medical Center. Informed consent was obtained from a parent of each infant before enrolment in the study, which took place from April, 1980, to March, 1981.

Infants were eligible for the study if they weighed less than 1500 g at birth, had no obvious congenital malformations, were admitted to our neonatal intensive-care unit within the first 6 h of life, and had mothers who had not taken barbiturates during pregnancy.

Infants were randomly assigned by lottery (sampling without replacement) to treatment or control groups. The treatment group received phenobarbitone according to the following protocol: two loading doses of 10 mg/kg each were administered intravenously 12 h apart; maintenance doses of 2·5 mg/kg every 12 h were begun 12 h after the second loading dose and were continued intravenously, intramuscularly, or orally for 6 days. Steady-state serum concentrations were achieved on the 3rd postnatal day and dosages were adjusted to maintain levels in the 20–30 μg/ml range. At the end of the 7th day therapy was stopped.

We performed bedside cranial ultrasonography by means of a portable real-time sector scanner (Mark III Real-Time Imager, Advanced Technology Laboratories, Bellevue, WA 98005 U.S.A.) and a trans-fontanelle approach[24] on fifty-one of the sixty infants on the 3rd, 4th, or 5th postnatal day. The nine remaining infants died before the 3rd postnatal day and a postmortem examination was performed. Ultrasound scans were interpreted by at least two ultrasonographers, who did not know which infants had received phenobarbitone. In three cases the ultrasonographers did not agree on the presence of IVH; computed axial tomography (EMI 1005 Head Scanner, EMI Medical, U.S.A.) was performed in these infants. Neuroradiologists were also not informed about which infants had received phenobarbitone. Studies were repeated whenever an infant had clinical or laboratory evidence suggestive of IVH. Haemorrhages were graded according to the system proposed by Papile et al.[1]

We reviewed the case-reports after discharge or death of the infants to determine the variables which may have influenced the development of IVH.[25-27]

Results

Two-tailed Student's *t*-test analyses did not demonstrate any significant differences in birth-weights, gestational ages, or Apgar scores between the two groups. Nor were there any significant differences in sex distribution or survival rates as determined by χ^2 analysis (table I). Postmortem examination was performed on fourteen of the fifteen who died. Seven of the dead infants had IVH. We did not believe that IVH had been the main cause of death in these infants. Death in the fourteen infants was attributed to hyaline membrane disease (seven cases), sepsis (six cases), and bronchopulmonary dysplasia with sepsis (one case). In addition, there were no statistically significant differences between the groups with respect to mode of delivery or place of delivery (inborn versus transport).

IVH occurred in 13·3% (4/30) of infants in the phenobarbitone group and 46·7% (14/30) of infants in the

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TABLE I—BIRTH DATA, APGAR SCORES, AND SURVIVAL

—	Phenobarbitone (N=30)	Control (N=30)
Birth-weight (g):		
Mean±SD	1101±243	1037±208
Range	720–1460	690–1390
Gestational age (weeks):		
Mean±SD	28.9±1.9	28.6±1.9
Range	26–34	26–33
Sex:		
Male	16	13
Female	14	17
Apgar score:		
1 min	3·4±2·0	3·8±2·3
5 min	5·8±2·1	5·7±2·2
*Delivered in our hospital**	26	24
Survived	24	21

None of the differences between the phenobarbitone and control groups was significant.
*Inborn.

TABLE III—RESPIRATORY AND METABOLIC DATA IN BOTH GROUPS

—	Phenobarbitone (N=30)	Control (N=30)
Oxygen therapy only	2	5
Continuous distending pressure	3	4
Mechanical ventilation	25	21
Thoracostomy drainage	7	5
Hyperoxia (PaO_2>120 mm Hg)	22	19
Hypoxia (PaO_2<40 mm Hg)	16	19
Hypercapnia ($PaCO_2$>60 mm Hg)	12	14
Hypocapnia ($PaCO_2$<30 mm Hg)	12	14
Bicarbonate therapy	21	16
Hypotension	15	17
Volume expansion	12	11
	22	18

None of the differences between the two groups was significant.

untreated group ($p<0·01$, $\chi^2=7·94$). The incidence of IVH in the control group was similar to that diagnosed by computed tomography cited in previous reports.[1,2]

Table II gives the clinical and laboratory data on the eighteen infants with IVH. Patient 18 died before receiving the second loading dose of phenobarbitone and thus a steady-state concentration had not been achieved.

Both groups required the same degree of ventilatory support. The percentage of infants in each group experiencing at least one episode of hyperoxia, hypoxia, hypercapnia, hypocapnia, acidosis, or hypotension was similar (table III). Hypotension was defined as a systolic blood-pressure at least 10 mm Hg below the expected value,[28] or clinical evidence of impaired perfusion. Pressures were measured every hour by the non-invasive doppler technique ('Dinamap', Model 84712005, Critikon, Tampa, Florida) or by direct umbilical-artery manometry. Sodium bicarbonate and blood-volume expanders (blood or colloid, 10 ml/kg, infused within 30 min) were administered to both groups with comparable frequency. Though differences in these factors might have been expected, the close similarities between the groups emphasises the findings of Lazzara et al. that only half the cases of haemorrhage can be correctly predicted from clinical findings.[29]

The mean steady-state serum phenobarbitone concentration, determined in twenty-five infants, was 26·6±6·5 μg/ml (range 15·9–39·6 μg/ml). Five infants died before maintenance therapy had been initiated. Seizures were not observed in any of the infants in the treatment group; in one infant in the control group seizures developed after IVH had been diagnosed and phenobarbitone was then given. None of the infants on phenobarbitone became hypotensive.

Five eligible infants admitted to the neonatal intensive-care unit during the study period were not enrolled. One infant died before random allocation to treatment, and the parents of four infants did not consent to the study.

Discussion

The results of this randomised, controlled study suggest that phenobarbitone may reduce the incidence of IVH in preterm infants. The following mechanisms of neuroprotection mediated by barbiturates have been proposed: decreased cerebral metabolic rate,[6-11] decreased catecholamine release,[12-14] "free-radical" inactivation,[15] decreased intracellular and extracellular oedema,[16-18] anticonvulsant effect,[19,20] decreased intracranial pressure,[21] sedative effect,[22] and enzyme induction.[23] Since the pathogenesis of IVH is complex, the benefits provided by phenobarbitone probably involve several of these mechanisms.

TABLE II—SUMMARY OF DATA ON PATIENTS WITH IVH

Patient	Birth-weight (g)	Gestational age (wk)	Age at diagnosis (h)	Method of diagnosis	Grade of IVH	Survived	Ventriculo-megaly	Serum phenobarbitone (μg/ml)
Controls:								
1	690	26	5*	PM	II	–	–	..
2	1040	28	72	US	III	–	+	..
3	920	28	7*	PM	IV	–	+	..
4	1280	32	90	US	I	+	–	..
5	1060	30	39*	PM	III	–	+	..
6	1220	30	70	US	II	+	+	..
7	1390	30	55	CT	I	+	–	..
8	1290	33	46	US	I	+	–	..
9	1115	30	52	US	I	+	–	..
10	800	26	37	US	III	+	+	..
11	800	26	37	US	II	–	–	..
12	790	26	27*	PM	II	–	–	..
13	740	26	9*	PM	II	–	–	..
14	755	27	56	US	II	+	–	..
Phenobarbitone:								
15	1050	29	78	US	III	+	+	22·7
16	720	26	51	US	IV	+	+	15·9
17	880	27	49	CT	II	+	–	26·0
18	900	27	17*	PM	II	–	–	..

PM = postmortem examination; US = cranial ultrasonography; CT = computed tomography. *Age at death.

We felt that it was reasonable to begin this investigation with anticonvulsant doses of phenobarbitone, since the resultant serum level should have predictable and slight side-effects and might still provide neuroprotection. The dosage schedule selected was based on the report of Lockman et al.[30] Since IVH often occurs before 24 h of age,[31] we limited the study to infants to whom we could administer phenobarbitone before they were 6 h old. We timed the dose intervals so as to achieve loading 12 h after the start of phenobarbitone treatment. This schedule should establish the desired phenobarbitone serum level before the time at which IVH is most likely to occur.[3] Eight infants (five treatment, three control) died before they were 18 h old; IVH occurred in one treated infant and in three controls. The statistical significance of the difference between the two groups is not changed if these patients are removed from the analysis. However, the relatively high incidence of early IVH indicates that dosages and dose intervals should be more closely investigated. Side-effects were not evident in any of the infants on phenobarbitone. In particular, respiratory depression and hypotension were no more common in treatment infants than in control infants (table III).

Although a brief course of phenobarbitone treatment in the neonatal period has no known long-term effects upon cognitive development, we intend to follow-up the infants in this study. We will evaluate infant development and cognitive function, and perform routine medical and neurological assessments. The ability of phenobarbitone to prevent IVH in the population studied is promising, since it suggests that the occurrence of haemorrhage can be modified by drug therapy in the first hours of life. However, before we can recommend phenobarbitone treatment of infants at risk for IVH we need to know what the long-term outcome is in those who have received phenobarbitone treatment as infants.

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Requests for reprints should be addressed to S. M. D., Box 007, L3018 Women's Hospital, Ann Arbor, Michigan 48109, U.S.A.

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VIPERGIC NERVES IN THE PENIS

J. M. POLAK J. GU*
S. MINA S. R. BLOOM

Departments of Histopathology and Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS

Summary High concentrations of vasoactive intestinal polypeptide (VIP) were detected by immunocytochemistry and radioimmunoassay in thirty surgical specimens of male external genitalia. VIP was found exclusively in fine autonomic nerves. VIPergic nerves were most densely concentrated in the penis around the pudendal arteries and in the erectile tissue of the corpus cavernosum. Considerable numbers of VIP nerve fibres were also seen in the vas deferens and epididymis. VIP is known to exert regulatory actions on blood-flow, secretion, and muscle tone. Its presence in considerable amounts in the male genital tract suggests that this newly discovered peptide neurotransmitter may be important in the nervous control of male external genitalia.

Introduction

VASOACTIVE intestinal polypeptide (VIP) is a newly discovered regulatory peptide composed of 28 aminoacids.[1] It relaxes smooth muscle and is a powerful vasodilator. It also stimulates secretion in the pancreas and intestine.[2] VIP has been demonstrated, by the use of specific antibodies, in autonomic nerves supplying many peripheral tissues.[3] VIPergic nerves form a major part of the newly recognised class of non-adrenergic non-cholinergic (peptidergic) nerves. Despite these discoveries, little attention has been paid to the

*J. G. is a visiting colleague from Peking Medical College, Peoples' Republic of China.

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