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Neonatal Convulsions Treated with Continuous, Intravenous Infusion of Diazepam

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ABSTRACT

Eight infants born at term in the years 1974-76, with neonatal convulsions due to severe perinatal asphyxia, were treated for 6-11 days with continuous intravenous infusion of diazepam. Doses of 1.0-1.5 mg per hour (mg/h) were usually required to stop the convulsions. In one infant 2.75 mg/h was needed. During the treatment, all infants had measurable serum concentrations of diazepam, half of them above 35 μmol/1. The convulsions stopped in all eight infants, and did not return after discontinuation of the infusion. Side-effects were noted in all infants, but they were all able to breathe adequately. At follow-up the psychomotor development was normal in all cases and there were no signs of neurological disorders, except in one patient, in whom mild epilepsy was observed.

Continuous infusion of diazepam should be given in doses of at least 1 mg/h (corresponding to around 0.3 mg/kg h) to stop convulsions in full-term infants efficiently and should be increased under close supervision and with monitoring of respiration and heart rate until treatment is effective.

INTRODUCTION

Neonatal convulsions remain a serious problem, and in recent studies (3, 4, 6, 7) the same grave prognosis has been found as in many earlier ones, that is, roughly half of the infants die or become handicapped and at most half survive without handicap. The main deciding factor for the prognosis is the background of the convulsions., i.e. the severity of the brain injury wnich causes them. It must always be an advantage to the infant if the fits are brought under effective control as early as possible. Each fit is often so short that measures started at the onset of a fit may not influence its duration. To prevent fits a continuous intravenous

infusion of an anticonvulsive drug can be given.

Benzodiazepines are effective anticonvulsants, particularly when given intravenously (7). Their metabolism differs in the neonatal period from that in later life (5). The clinical effect of continuous intravenous infusion of diazepam was studied in eight newborn infants with convulsions, and at the same time repeated measurements were made of the serum concentration of diazepam and of its main metabolite, N-desmethyldiazepam.

MATERIAL AND METHODS

In an investigation of infants with neonatal convulsions due to perinatal asphyxia, 8 infants - 2 girls and 6 boys - born at term in 1974-76 were subjected to a special study concerning the effects of diazepam therapy. The only reason for selecting these patients was that several blood samples for determination of the serum level of diazepam and of its metabolite N-desmethyldiazepam could be obtained.

In 6 of the infants the convulsions started during the first day of life, in one during the second day and in one during the sixth day. All infants were born within 2 weeks of the expected date and their birth weights varied between 2.930 and 4.450 kg.

A standard diazepam preparation (Stesolid ^{R}, Dumex Läkemedel AB, Helsingborg, Sweden, 5 mg/ml) was used and added to the infusion of isotonic glucose solution which the infant needed for other reasons. A new solution for infusion was prepared every 12 hours. Before the diazepam infusion was finally stopped, peroral phenobarbital therapy was started.

During the neonatal period the 8 infants were admitted to a neonatal intensive care unit where they were under the close observation of trained nurses and where their problems - e.g. respiration metabolism, nutrition, infections - were taken care of. After discharge they were repeatedly examined at the Outpatient Unit of the Department of Paediatrics, Uppsala, either by a paediatric neurologist or by a neonatologist. An EEG was performed at the age of one year before discontinuation of phenobarbital treatment and again at the age of two years. Those infants who showed a completely normal development and physical condition were checked after about two years by general paediatricians at child health centres. This examination included careful history-taking, particularly concerning development and symptoms suggesting fits, and

physical examination with emphasis on the psychomotor development and neurological status.

During the diazepam infusion, capillary blood was drawn and kept deep-frozen until analysed. The analyses, which were performed by gas chromatography (2), comprised diazepam and N-desmethyldiazepam determinations and were made at the laboratory of Dumex Läkemedel, Helsingborg, Sweden.

RESULTS

The initial diazepam dose was 0.5 mg/h (6 patients) or 1.0 mg/h (2 patients). The lower dose was ineffective and had to be increased to 0.7-2.75 mg/h for all infants before the convulsions definitely disappeared. In one patient a dose higher than 2.0 mg/h was necessary; 1-1.5 mg/h was the highest dose needed in the other 7 patients.

When the infant had been convulsion-free for 12-24 hours, the dose was slowly decreased in steps of 0.1-0.25 mg/h with one or two such changes per 24 hours. One patient was treated for 3 days, one for 11 days, and the rest for 6-8 days. No fits occurred during infusion of the highest dose used in each patient, and all patients remained convulsionfree during the dose-decreasing phase and after infusion of the drug had been stopped. All patients showed obvious side-effects - they were drowsy and floppy to varying degrees. They also needed feeding through a gastric tube and initially parenteral fluid and nutrition. All 8 infants breathed spontaneously and assisted ventilation was not needed.

In two patients the first measurements of the serum diazepam and N-methyldiazepam concentrations were made within 2 hours after the start of the infusion; in one of them the serum diazepam level was 1.28 µmol/1; one of them never received more than 0.7 mg/h and the other two never more than 1 mg/h. In the other 5 one or several values exceeded 3.5 µmol/1, and 4 had at least one value above 35 µmol/1.

The highest diazepam concentrations were 80.5 µmol/1 (on a dose of 1.5 mg/h; birth weight 4.450 kg) and 55 µmol/1 (on a dose of 1.0 mg/h; birth weight 3.030 kg). The highest dose used among these 8 infants, 2.75 mg/h for 5 hours in a boy weighing 3.870 kg gave a maximum serum concentration of 21.7 µmol/1. The serum level of diazepam, at which the convulsions stopped, varied so much that no "anticonvulsant level" can be defined, but it seems

to be higher than the level of 0.5-1.2 µmol/l (150-350 ng/l) which is considered anticonvulsant in older children (3).

Fig. 1 summarizes all serum diazepam concentrations recorded in relation to the diazepam dose, expressed as mg per kg and hour (mg/kg h). From the figure it is obvious that a dose of 0.35 mg/kg h always gave a stable and high serum level. In full-term infants this corresponds to a dose of 1.0-1.5 mg/h.

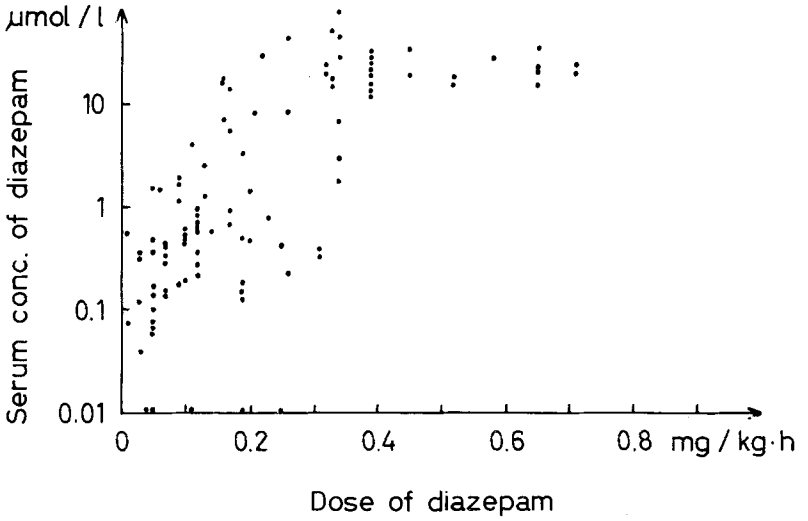

Fig. 1. Serum concentration of diazepam (log scale) in relation to the given doses of the drug in all eight infants.

In most cases the serum level of N-desmethyldiazepam started to increase about 12 hours after the start of the infusion, and a high level, often still increasing, was recorded during the dose-decreasing phase. Unfortunately the concentration was not always measured after the infusion was stopped. The highest concentration measured was 9.74 µmol/1. This was recorded in the patient who never received more than 0.7 mg/h and, during the dose-decreasing phase, when he had been on 0.4 mg/h for 14 hours. Patients showing the highest serum levels of diazepam had the lowest levels of N-desmethyl-diazepam, and vice versa. No clear relation was observed between the severity of the clinical findings, i.e. the convulsions and the side-effects of the drug, and the serum levels of diazepam and N-desmethyldiazepam.

At follow-up, all patients were well, with normal psychomotor development and normal neurological findings. Only one patient had convulsions. This patient had required the highest dose and the longest diazepam therapy. When falling asleep he had a series of jerks lasting for at least half an hour, thus quantitatively exceeding the usual type of jerks occurring, when falling asleep. He also had epileptic potentials on his EEG, increasing during light sleep and coinciding with his jerks. In spite of the lack of other types of seizures he is considered to have a mild form of epilepsy and is being treated with carbamazepine. No seizures have been reported in any of the other patients and their EEGs are normal.

The diazepam dose and serum levels of diazepam and N-desmethyldiazepam are reviewed in a patient (birth weight 3.8 kg) with a mild respiratory disturbance after birth. On the 3rd day of life convulsions started. His convulsions stopped at a dose of 1.5 mg/h when this dose had been used for 24 hours.

DISCUSSION

Although all eight infants recovered with no or only mild sequelae, it cannot be concluded that this satisfactory outcome is due to the treatment used. It seems reasonable to suppose that an early and efficient treatment of the convulsions is advantageous to the infant.

The doses of diazepam used in this study are of the same magnitude as those used successfully by Thong et al. (8) for continuous intravenous infusion in convulsing infants. The serum concentrations are in reasonable agreement with those recorded by Langslet et al. (5) in newborn infants, who received a single intravenous injection of diazepam. As is obvious from the present study a dose of 0.7 mg/h in a full-term baby may in some cases be enough, but a dose of 1 mg/h is more likely to stop the seizures. If the treatment is not successful, the dose can be increased considerably. In this study the highest dose needed to stop the seizures was 2.75 mg/h. The serum concentrations of diazepam and its metabolite N-desmethyldiazepam, in these newborns, were extremely high compared with those reported in older children (1). Although the infants showed obvious side-effects, lasting several days longer than the duration of the therapy, none of them needed assisted ventilation.

Table 1. The administered doses of diazepam (mg/h and mg/kg h) and the serum concentrations of diazepam and N-desmethyldiazepam in one patient. The convulsions stopped entirely after 24 hours infusion of 1.5 mg/h.

DOSE				SERUM CONCENTRATION					
						Diazepam		N-Desmethyl-diazepam	
Date	Hour - Hour	mg/h	mg/kg h	Date	Hour	ng/ml	µmol/1	ng/ml	µmol/1
26.8	09.30-16.00	0.5	0.13	26.8	11.30	364	1.28	67	0.25
26.8	16.00	1.25	0.33	27.8	04.00	4463	15.67	115	0.42
27.8	17.00			27.8	16.00	5379	18.89	<25	<0.09
27.8	17.00	1.5	0.39	27.8	18.30	8673	30.45	<5	<0.02
				28.8	06.30	4034	14.16	<5	<0.02
				28.8	18.30	5643	19.81	50	0.18
				29.8	06.30	9811	34.45	25	0.09
				29.8	?	7164	25.15	40	0.15
30.8	10.00			30.8	06.30	4815	16.91	60	0.22
30.8	10.00-17.00	1.0	0.26	30.8	13.00	13042	45.79	126	0.47
30.8	17.00	0.8	0.21	30.8	20.00	2458	8.63	37	0.14
31.8	10.00			31.8	08.00	-	-	-	-
31.8	10.00	0.6	0.16	31.8	14.30	5037	17.69	123	0.45
01.9	13.00			01.9	03.00	2031	7.13	<25	<0.09
01.9	13.00-17.30	0.4	0.11	01.9	12.00	4815	16.91	231	0.85

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