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Clonazepam Pharmacokinetics and Therapeutic Efficacy in Neonatal Seizures

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Summary. Eighteen newborns (gestational age 28 to 42 weeks and post-natal age 0.5 to 44 days) suffering from convulsions not controlled by phenobarbital were treated with clonazepam 0.1 mg/kg (8 cases) or 0.2 mg/kg (10 cases) administered by slow intravenous infusion. The plasma half-lives in these 'phenobarbital pretreated neonates' were of the same order of magnitude as those reported in adults (20-43 h).

Post-natal age did affect clearance, which was 50-70% less than in adults and older children. At the end of the infusion period, plasma clonazepam ranged from 28 to 117 ng/ml in the 0.1 mg/kg group and from 99 to 380 ng/ml in the 0.2 mg/kg group. In the former an immediate therapeutic response was observed in 7 out of 8 cases, and in the latter a significant and somehow delayed effect on convulsion was present only in 6 cases. The data suggest that optimal therapeutic response might already have been achieved with the 0.1 mg/kg dose. Higher doses and toxic concentrations of clonazepam may be detrimental to complete control of seizures and may expose the newborn to an unnecessary risk of adverse events.

Key words: clonazepam, neonates, convulsions; therapeutic effect, pharmacokinetics

Clonazepam is a benzodiazepine derivative frequently used in the treatment of neonatal seizures. Its efficacy is remarkable in status epilepticus, in which intravenous administration of 0.1-0.2 mg/kg will often relieve the clinical disorder [2, 5, 12].

Despite its extensive use in newborns and infants, little or no information appears to have been published on the pharmacokinetic profile of clonazepam in this age group.

Such information would not only be of theoretical value, but it would also be of practical interest, since in adults and children it is known that the drug has an apparent plasma half-life of 20 to 40 h [7, 8, 13], with the attendant possibility of accumulation and side effects, such as motor impairment (ataxia and hypotonia) and severe drowsiness in 20 to 60% of cases [1, 5, 12].

The optimal clinical response has been associated with plasma clonazepam concentrations ranging from 15 to 80 ng/ml [1, 4, 8, 9], and it has been shown that levels above 120-150 ng/ml may increase seizure frequency or lead to the development of other type of seizures [5, 9, 10]. For these reasons it was considered important to evaluate the pharmacokinetic profile of clonazepam in neonates being treated for neonatal seizures following perinatal asphyxia or infection.

Patients and Methods

Studies were done in 18 neonates (12 boys and 6 girls), of 28 to 42 weeks of gestational age (GA), and of a postnatal age (PNA) of 0.5 to 44 days, hospitalized in the Service de Médecine et Réanimation Néonatales of Maternité Régionale A. Pinard in Nancy. They all were suffering from severe convulsive episodes, following perinatal asphyxia in 16 cases and infections in 2 cases. Status epilepticus was present in 5 cases and in the other 13 seizure activities were represented by clonic movements, mumbling and ictal apnoea. In all patients, previous treatment with phenobarbitone (PB) had either been ineffective or was only partly effective.

Informed consent was obtained from the parents for repeated capillary blood sampling.

Methods

Clonazepam (CZP) was administered by slow venous infusion over 5 min in the dose of 0.1 mg/kg to 8 patients, and 0.2 mg/kg to 10 patients. In one case only (Case 2) the 0.1 mg/kg dose followed 7 days of repeated treatment with clonazepam 0.3 to 0.6 mg/kg/24 h. Capillary blood samples (from 8 to 12 for each newborn) were taken from the heel at the end of the slow venous infusion at various times between 0.5 and 120 h. The blood (~500 µl) was immediately centrifuged and the plasma frozen until analysed.

Plasma concentrations of clonazepam were determined by the GC method of de Silva et al. [3].

Pharmacokinetic analysis was carried out by means of the PHARM program [6]. The parameters analysed were concentration at the end of the infusion period, distribution half-life ($t_{½}$), terminal elimination half-life ($t_{½\beta}$), apparent volume of distribution (V_Z), total body clearance (CL) and AUC extrapolated to infinity ($AUC_{0-\infty}$).

Results

Observations on Neonates Receiving 0.1 mg/kg

There were 6 boys and 2 girls, of GA 31 to 42 weeks and PNA 0.5 to 40 days (Table 1).

One subject was suffering from status epilepticus and the other 7 had severe and frequent clonic seizures accompanied in two cases (Nos. 3 and 6) by ictal apnoea. All were effectively unresponsive to PB. Administration of clonazepam led to cessation of seizures within 1 h in 6 cases and a significant reduction in seizure frequency in an additional patient with full control in 24 h. Only in one case (No. 2) was there no effect of clonazepam. Phenytoin (PHT) was prescribed to her. Antiepileptic treatment was continued with PB alone in 4 cases and with PB + PHT in a further 4 (Nos. 1, 2, 3 and 6). Diazepam (DZP) was given to 2 cases (Nos. 1 and 2).

No appreciable side effects were observed in 7 cases, and hypotonia was present in Case 5.

At the end of the slow venous infusion plasma clonazepam ranged from 28 ng/ml to 117 ng/ml, and 30 min later it was 18 to 60 ng/ml. In most cases clonazepam was still found (3 to 8 ng/ml) 72 h after injection.

In the four cases in whom it could be measured the apparent distribution half-life ranged from 0.40 to 1.32 h, the elimination half-life varied from 19.4 to 140 h, and the apparent V_Z was 1.5 to 11.0 l/kg (Table 3). Clearance values were rather variable at 0.025 l/h/kg to 0.063 in neonates below 7 days of PNA and of 0.140 and 0.150 l/h/kg in two infants of

Table 1. Clinical details and therapeutic outcome in the neonates treated with clonazepam 0.1 mg/kg

Case	Sex	G.A. [weeks]	B.W. [g]	Aetiology	P.N.A. [days]	Type of seizures	EEG	AEDs Treatment		Clinical effects	Side-effects
								Before CZP	After CZP		
1 MJ	M	35	2300	A.F.D.	0.5	Status epilepticus	Low voltage irritative	PB	PB, DZP, PHT	Stop seizures - 1 h	None
2 VF	F	39	3000	A.F.D.	9.0	Clonic	Low voltage very irritative	PB[a]	PB, DZP, PHT	None	None
3 LS	M	41	4000	A.F.D.+ C.F.D.	2.5	Clonic+ Apnoea	Low voltage irritative	PB	PB, DZP, PHT	Stop seizures - 1 h apnoea reduced	None
4 PG	M	41	3960	A.F.D.	2.5	Clonic	Low voltage rhythmic	PB	PB	Stop seizures - 1 h	None
5 LJ	M	42	3120	C.F.D.	0.5	Clonic	Low voltage hypoactive	PB	PB	Stop seizures - 1 h	hypotonia
6 MP	M	32	2400 (2500)	Infection	25	Clonic+ Apnoea	Low voltage irritative	PB	PB - PHT	Stop seizures - 1 h	None
7 BA	F	31	1480 (2000)	Infection	40	Clonic	Irritative	PB	PB	Stop seizures - 1 h crisis at 24 h - then stop	None
8 WC	M	40	3100	A.F.D.	1.0	Clonic	Low voltage rhythmic	PB	PB	Stop seizures - 1 h	None

P.N.A. : Postnatal age
G.A. : Gestational age
B.W. : Birth weight (in brackets the weight on the day of injection for Cases 6 and 7)
A.F.D. : Acute fetal distress
C.F.D. : Chronic fetal distress
AED : Antiepileptic drug
[a] Patient 2 received CZP 0.3–0.6 mg/day for 5 days

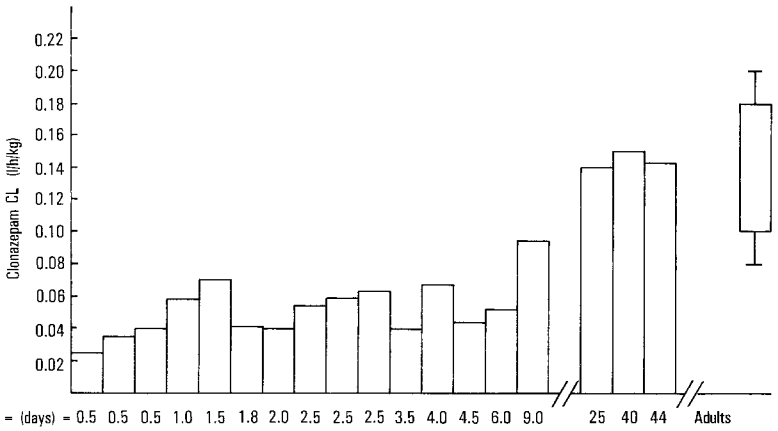

Fig. 1. Relationship between total body clearance of clonazepam and postnatal age in 18 newborns suffering from neonatal convulsions who were also given phenobarbital

Table 2. Clinical details and therapeutic outcome in the neonates treated with clonazepam 0.2 mg/kg

Case	Sex	G.A. [weeks]	B.W. [g]	Aetiology	P.N.A. [days]	Type of seizures	EEG	AEDs treatment		Clinical effects	Side-effects
								Before CZP	After CZP		
9 CE	F	37	2240	A.F.D.	1.5	Status epilepticus	Very abnormal	PB	PB, PHT, PGB	None - reduction seizures with progabide - stop 72 h	None
10 BF	F	32	2060	A.F.D. (I.V.H.)	0.5	Status epilepticus	Very abnormal	PB	PB, PHT, DZP	None	None
11 RS	M	28	1740	Left heart Hypoplasia-ischaemia	3.5	Clonic	Irritative	PB	PB	Decrease 7 h stop day 14	None
12 LG	M	41	3000	A.F.D.	6.0	Clonic+ mumbling	Low voltage irritative	PB	PB - DZP	Stop - 12 h	None
13 ZJ	M	40	3420	A.F.D.	2.5	Clonic	Very abnormal	PB - PHT	PB - PHT	Stop 1 h - then 1 fit at 48 h - then stop	Hypotonia
14 GA	M	30	1720 (3000)	Pneumo-pathy hypoxia	44	Clonic	Low voltage irritative	PB	PB - DZP	Stop 1 h - then 1 fit at 48 h - then stop	None
15 CS	F	42	3350	C.F.D.	2.0	Tonic+ mumbling	Low voltage spikes	PB - DZP	PB - DZP	Stop - 1 h	None
16 OL	F	39	3000	A.F.D.	4.0	Clonic	Low voltage irritative	PB	PB	Stop - 1 h	None
17 VG	F	41	2280	C.F.D.+ A.F.D.+ I.C.H.	4.5	Status epilepticus +apnoea+ hypotonia	Very abnormal	PB - DZP	PB - PHT - PGB	None - decrease with progabide - stop day 10	None
18 BA	M	42	3680	A.F.D.	1.5	Status epilepticus +mumbling	Very abnormal	PB - DZP	PB - PHT	Stop - 7 h	None

P.N.A. : Postnatal age
G.A. : Gestational age
B.W. : Birth weight (in brackets the weight on the day of injection for Case 14)
A.F.D. : Acute fetal distress
C.F.D. : Chronic fetal distress
I.V.H. : Intraventricular haemorrage
I.C.H. : Intracranial haemorrage
PGB : Progabide
AED : Antiepileptic drug

Table 3. Pharmacokinetic parameters of clonazepam in neonates

Dose [mg/kg]	Case	G.A. [weeks]	P.N.A. [days]	Co [ng/ml]	$t_{½\alpha}$ [h]	$t_{½\beta}$ [h]	V_Z [l/kg]	AUC [ng/ml/h]	CL [l/h/kg]
0.1	1	35	0.5	86	1.28	81	4.1	2873	0.035
	2	39	9.0	28	-	19[a]	2.7[a]	1048[a]	0.094[a]
	3	41	2.5	40	1.31	140	11.0	1859	0.054
	4	41	2.5	38	-	29	2.6	1587	0.063
	5	42	0.5	30	-	43	1.5	3958	0.025
	6	32	25	24	-	30	5.9	722	0.140
	7	31	40	46	1.32	24	5.1	672	0.150
	8	40	1.0	117	0.40	28	2.3	1710	0.058
0.2	9	37	1.5	186	0.10	28	2.8	2887	0.070
	10	32	0.5	150	-	74	4.4	4905	0.040
	11	28	3.5	380	0.19	36	2.1	4873	0.040
	12	41	6.0	190	2.10	34	2.6	3818	0.052
	13	40	2.5	181	0.16	23	1.9	3409	0.059
	14	30	44	99	-	22	5.0	1309	0.153
	15	42	2.0	150	0.17	39	2.2	4413	0.040
	16	39	4.0	140	0.22	26	2.5	2983	0.067
	17	41	4.5	250	0.27	29	1.8	3909	0.044
	18	42	1.8	n.a.	-	49	2.9	4947	0.041

n.a. = not available
[a] Elimination kinetics evaluated after repeated treatment

PNA 25 and 40 days (Fig. 1). In Case 2, who had received 6 days of repeated treatment with clonazepam and PB, the clearance was 0.094 l/h/kg. In this patient case, who did not respond to the treatment, the plasma clonazepam level at the end of the slow intravenous infusion was low (28 ng/ml) and the disappearance rate was quite rapid ($t_{½\beta} = 19.4$ h).

Observations on Neonates Receiving 0.2 mg/kg

The group comprised 6 boys and 4 girls of GA 28 to 42 weeks and of PNA 0.5 to 44 days (Table 2). Four subjects suffered from status epilepticus, 5 from frequent clonic seizures and 1 from tonic seizures. Ictal apnoea was present in Case 17, and mumbling in Cases 13, 15 and 18.

As in the other group none had really responded to PB, and in 4 cases DZP and/or PHT had also been administered without success. The administration of clonazepam led to full control of seizures within 1 h in 4 cases (Nos. 13, 14, 15 and 16) and within 7–12 h in 2 other cases (Nos. 12 and 18). In one patient a decrease in seizures but not full control was observed after 7 h (Case 11). In 3 patients (Nos. 9, 10 and 17) clonazepam had no therapeutic effect; in two of them there was clinical improvement on adding Progabide (60 mg/kg/day), a new GABA agonist with antiepileptic activity.

In all a satisfactory response was observed in 7 cases out of 10; no appreciable side-effect was noticed in 9 cases, and severe hypotonia was evident in Case 13.

In this group plasma clonazepam concentrations ranged from 99 to 380 ng/ml at the end of the intravenous infusion, and from 52 to 124 ng/ml 30–40 minutes later; 72 h after dosing clonazepam was still present in most cases in concentrations of 10–20 ng/ml.

As reported in Table 3, the distribution half-life varied from 0.1 to 2.1 h, and the terminal half-life from 22.5 to 74 h. Clearance values were less dispersed than in the previous group, ranging from 0.040 to 0.070 l/h/kg in 9 neonates with a PNA below 7 days and 0.153 l/h/kg in the infant (Case 15) of PNA 44 days. The apparent volume of distribution ranges from 1.8 to 4.4 l/kg.

Discussion

The pharmacokinetic data obtained in newborns suffering from neonatal convulsions, who had previously been treated with a phenobarbitone, indicate that in most cases the plasma half-life of clonazepam lay between 20 and 40 h, values very similar to those observed in epileptic children and adults [5, 8]. A half-life over 40 h was observed in only 5 cases, 2 premature and 3 full term neonates, all treated within the first 2.5 days of extrauterine life.

The rapid distribution half-life found here is in good agreement with the rapid onset of therapeutic activity usually observed with the drug.

Gestational age did not appear to influence the disposition of clonazepam in phenobarbital-exposed

newborns. The finding is similar to that previously reported for diazepam in neonates treated with barbital, in whom a clear difference in the elimination rate of the benzodiazepine between premature and full term neonates was completely abolished by 2-3 days exposure to the inducing effect of phenobarbitone on the hepatic drug metabolizing enzyme systems [10].

On the whole, however, the clearance of clonazepam was considerably reduced with respect to the values described for epileptic children (0.130-0.180 l/h/kg) and adults (0.08-0.240 l/h/kg) [8]. A clear effect of postnatal age on this parameter was evident (Fig. 1).

In terms of safety both doses were well tolerated, with only one case in each group showing marked hypotonia. As to therapeutic outcome 87% of the patients treated with 0.1 mg/kg responded favourably within 1 hour whereas a good response was observed only in 40% of subjects in the 0.2 mg/kg group. Thus, although the number of subjects finally relieved to clonazepam in the two groups was not statistically different, the response appeared somehow delayed in the high dose group.

The plasma clonazepam concentrations at the end of the infusion in 0.1 mg/kg group were all within the range considered as therapeutic, but they were over the toxic level in 8 out of 10 cases in the 0.2 mg/kg group. It cannot be stated whether the less rapid response observed in the higher dose group was due to more severe pathology or to "toxic" clonazepam concentrations, but it should be remembered that an increase in seizure frequency associated with plasma clonazepam levels exceeding 150 ng/ml has been described in epileptic children and adults [5, 9, 10].

On the basis of the present data it appears that the therapeutic response is already optimal with the 0.1 mg/kg dose. With a higher dose the neonate is unnecessarily exposed to toxic concentrations of clonazepam, which risk interfering with motor and respiratory functions, and also prolonging a convulsive condition which may have important sequelae on the future development of the child.

We propose to initiate the treatment of neonatal convulsive states with a dose of clonazepam not exceeding 0.1 mg/kg and slowly to increase the dose if no response is observed within 6-8 h. Monitoring plasma clonazepam concentrations should be encouraged since it may greatly help in optimizing the therapeutic outcome.

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