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Efficacy of Continuous Intravenous Lidocaine in the Management of Clusters of Seizures

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Clusters of seizures, which has been defined as acute repetitive seizures in between which the patient regains consciousness, is a not uncommon event in clinical practice, and may present considerable health risks to patients. In this setting, continuous intravenous (iv) lidocaine treatment was performed in 22 patients whose cluster of seizures did not respond to rectal or intravenous diazepam (DZP). With cardiac and respiratory monitoring, the patients were administered an iv lidocaine dose of 1 to 4 mg/kg followed by continuous iv lidocaine (1 to 4 mg/kg/hr).

In 9 patients in whom episodes of convulsions recurred more than 3 times within 24 hours and who had no underlying disorder with normal development at onset, 7 patients experienced no relapse of seizures after the start of the treatment. Relapse occurred only once in one other patient after termination of lidocaine but disappeared after reinfusion, and one patient had no response.

In 17 episodes of 13 patients, who had been diagnosed with epilepsy and in whom the frequency of seizures disturbed their daily routine, seizures were terminated in 3 patients with 4 episodes. The incidence of seizures was decreased in 5 patients with 6 episodes, and there was an absence of response in 7 patients with 7 episodes.

Continuous iv lidocaine was particularly useful for clusters of seizures seen in infants with normal development and no underlying disorder. Lidocaine was less effective in patients with refractory epilepsy, although some cases were controlled completely. These results suggest that lidocaine treatment should be tried at an early stage in clusters of seizures.

Introduction

Clusters of seizures (CS) is a not uncommon event in clinical practice, and may present considerable health risks, leading to status epilepticus (SE) or neurological deficit, to patients[1)2)]. In this setting, rectal or intravenous diazepam (DZP) is used as a first-line treatment[1)], the same as for treatment of SE. However, this treatment is not always successful, probably due to its short duration of action. Therefore, there is a need for an alternative approach in patients with CS. Lidocaine has been used in treating SE or CS[3)~12)], because it can be used by continuous intravenous (iv) injection and showed no serious effects on respiration or the cardiovascular system. In this study, we describe the results of the use of continuous iv lidocaine for the management of CS in children and adolescents.

Subjects and Methods

Between 1992 and 1997, 22 patients who re-

Table 1 Clinical background of group A patients

Case	Age at CS (m)	Diagnosis at CS	FH	PH	DQ at CS
1	4	BIC	conv. DMD	conv.(3m)	101
2	5	CGE	−	−	normal
3	6	BIC	FC	CS(5m)	normal
4	13	FC-C	FC	−	normal
5	19	FC-C	FC	−	97
6	20	FC-C	FC	−	88
7	23	FC-C	−	−	normal
8	24	CGE	FC	−	99
9	38	FC-C	FC	−	100

CS: cluster of seizures, CGE: cryptogenic generalized epilepsy, BIC: benign infantile convulsion (Fukuyama), FC-C: complex febrile convulsion, conv.: single afebrile convulsion, DMD: Duchenne muscular dystrophy, FH: family history, PH: past history, DQ: developmental quotient.

quired hospitalization due to CS and who did not respond to rectal or iv DZP received continuous iv lidocaine. "Cluster" was not strictly defined in terms of frequency and duration but referred to where ; (1) the patient regained consciousness between seizures, (2) at the first episode seizures recurred more than 3 times within 24 hours, and (3) the incidence of seizures exceeded the usual level such that they disturbed the daily routine of the patient with epilepsy regardless of the total duration of clustering episode.

The patients were allocated to one of the two groups. Group A patients had been hospitalized due to the first episode of convulsions (including 2 cases with a second episode) and showed no neurological abnormality with normal development at onset (n=9). Group B patients had been diagnosed with epilepsy and treated with antiepileptic drugs (n=13, 17 episodes).

Results

1. Patient background

In group A, the mean age at hospitalization was 1 year and 4 months. Six patients had a family history of febrile convulsions and one patient had had nonfebrile convulsions in infancy. For seven patients, the CS was their first episode of seizures. And other 2 had had seizures 1 month before the CS. No patients had any other complicating medical history except seizures. These patients were diagnosed at the time of discharge as benign infantile convulsions[13] (BIC; 2 cases), complex febrile convulsions (FC-C; 5 cases) or cryptogenic generalized epilepsy (CGE; 2 cases) (Table 1).

In group B, the age at hospitalization ranged from 1 year 8 months to 22 years 11 months, with a mean age of 10 years and 7 months. Two patients had a family history of febrile convulsions and another 2 had a history of epilepsy. Only 2 patients showed normal development, whereas 5 patients showed mild and 6 patients showed severe retardation. Underlying causes of epilepsy were unknown origin in 6 patients; congenital factors in 5 patients including cortical dysplasia, tuberous sclerosis, chromosome abnormality, and MELAS (mitochondorial encephalomyopathy with lactic acidosis and stroke-like episode) ; and postnatal factors in 2 patients including sequelae of acute encephalopathy and Rasmussen syndrome. A number of patients presented in group B with neurological deficiets as listed in Table 2.

2. Clinical symptoms of seizure and treatment

In group A, generalized tonic and tonic-clonic seizures within a few minutes were noted by clinical observation, but secondary generalization of partial seizures was identified in 2 patients in whom simultaneous videotape-electroencephalography minitoring were possible. Factors that induced seizures in Group A were fever in 5 patients, diarrhea in 6 patients and 5 patients had both fever and diarrhea (Table 3), but physical status was good and no patients had evidence of encephalitis or encephalopathy. There was a time lag of 4 to 79 hours from the first seizure to the start of continuous iv lidocaine, during which 3 to 23 tonic-clonic seizures occurred. Each patient

Table 2 Clinical background of group B patients

Case	Age at CS (m)	Etiology of epilepsy	Classification of epilepsy	FH	DQ/IQ at CS	Neurological symptoms
1	20 31	anomalies syndrome	SGE	MR	72 64	minor anomalies
2	29	cortical dysplasia	SLRE	FC	150	hemiplegia
3	63	unknown	SLRE		71	
4	85	chromosomal abnormality	SGE		13	
5	97	cortical dysplasia	SLRE		51	hemiplegia
6	101 108	unknown	SGE		severe	ataxia
7	125	acute encephalopathy	SLRE		16	
8	140	Doose syndrome	SGE	EPI	<25	ataxia
9	152	unknown	SGE	FC	severe	ataxia
10	159 165 171	Rasmussen syndrome	SLRE	EPI	89	myoclonus
11	204	tuberous sclerosis	SLRE	TS	60	
12	228	unknown	SGE		border	
13	275	MELAS	SLRE		51	hemiplegia

SGE: symptomatic generalized epilepsy, SLRE: symptomatic localization-related epilepsy, EPI: epilepsy, FC: febrile convulsions, MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode, TS: tuberous sclerosis, MR: mental retardation.

Table 3 Clinical course & treatment of group A patients

Case	Related factor	Rota antigen	Time lag before lidocaine (hrs)	No of seizures before lidocaine	Loading dose of lidocaine (mg/kg)	Max. maintenance dose (mg/kg/hr)	Duration of lidocaine injection (hrs)	Outcome of lidocaine therapy
1	–	–	12	8	3	2	85	excellent
2	–	–	79	23	1	1	28/48	excellent
3	–	–	36	7	1	2	86	excellent
4	F D BA	–	4	6	2	1	66	excellent
5	F D	–	24	7	3	1	51	excellent
6	F D	–	10	5	2	1	19	excellent
7	F D	–	4	3	2	1	48	excellent
8	D	–	18	4	4	2	16	not effective
9	F D	–	12	11	2	1	48	excellent

F: fever, D: diarrhea, BA: bronchial asthma, excellent: no recurrence of seizures after lidocaine injection.

was treated with iv or rectal DZP before and after hospitalization but experienced relapsed seizures, and therefore DZP was judged ineffective (Table 3).

With cardiac and respiratory monitoring, the patients in group A were administered an iv lidocaine dose of 1 to 4 mg/kg followed by continuous iv lidocaine (1 to 2 mg/kg/hr). Case 8 had no control of seizures with continuous iv lidocaine for 16 hours, and this was replaced with iv phenytoin (PHT), but seizure control remained difficult. Case 2 experienced relapse after termination of continuous iv lidocaine for 28 hours; the infusion was given again for 48 hours, and there was no further relapse. The other 7 patients experienced no relapse of seizures after the start of the treatment, and continuous iv lidocaine was terminated after 19 to 86 hours, and the course was unevent-

Table 4 Treatment and outcome of group B patients

Case	Type of seizures	Loading dose of lidocaine (mg/kg)	Max. maintenance dose (mg/kg/hr)	Duration of lidocaine injection (hrs)	Outcome of lidocaine therapy
1	GTS	2	1	48	excellent
	GTS	2	1	48	good
2	SPS	2	2.8	55	not effective
3	SPS/sGTCS	3	4	53	not effective
4	GTS	2	4	432	good
5	SPS/sGTCS	2	3	46	good
6	GTS		1	124	excellent
	GTS	2	2	148	excellent
7	non-convulsive	4	ND	–	not effective
8	non-convulsive	3.5	1	97	not effective
9	GTS	2	4	7	not effective
10	SPS/sGTCS	4	2	260	good
	SPS/sGTCS	4	1.5	209	excellent
	SPS/sGTCS	4	1.5	258	good
11	CPS	4	2	18	not effective
12	GTS	3	4	60	not effective
13	sGTCS	2.5	2	79	good

GTS: generalized tonic seizures, sGTCS: secondary generalized tonic-clonic seizures, SPS: simple partial seizures, CPS; complex partial seizures, non-convulsive: non-convulsive status epilepticus.

ful thereafter.

In group B, various types of seizure were observed: generalized brief tonic seizures lasting for several ten seconds in 7 patients, secondarily generalized seizures in 6 patients, simple partial seizures in 6 patients, non convulsive status with cluster of generalized tonic-clonic seizures in 2 patients, and complex partial seizures in 1 patient. The patient with nonconvulsive SE was included in our series because their level of consciousness changed and there were some periods of time in which the patient became conscious. There were no clear factors that induced CS in group B. The patients in group B were administered an iv lidocaine dose of 1 to 4 mg/kg followed by continuous iv lidocaine (1 to 4 mg/kg/hr). Seizures terminated in 3 patients with 4 episodes, and after termination of the treatment no relapse was seen. Incidence of seizures was decreased in 6 episodes, and there was an absence of response in 7 episodes; patients required iv PHT or continuous iv barbiturate (BT) under mechanical ventilation (Table 4).

3. Factors affecting the treatment outcome

Of the 9 patients in Group A, only the patient with CGE did not respond to lidocaine and seizures continued for a period, but the subsequent course after termination of seizures was uneventful. Compared with responders, there were no differences in time lag until the start of lidocaine, intravenous dose of lidocaine, or dose of continuous iv lidocaine in this patient.

In group B, comparison between responders and non-responders showed no differences in age at onset of CS, the presence or absence of developmental deterioration or of neurological complications, time lag, intravenous dose of lidocaine, or dose of continuous lidocaine infusion (Table 5).

4. Outcome

In group A, all patients except one who was lost to follow-up were followed for a mean of 24.5 months. Seven patients developed normally and experienced no relapse of convulsions, although one patient showed borderline development re-

Table 5 Clinical features as a predictive factor of outcome in group B patients

Age	< 10 y vs > 10 y	NS
IQ	severe vs normal/mild	NS
Neurological complication	(+) vs (−)	NS
Time lag of lidocaine treatment	< 12 hrs vs > 12 hrs	NS
Loading dose	> 2 mg/kg vs < 2 mg/kg	NS
Max. dose of maintenance injection	> 2 mg/kg/hr vs < 2 mg/kg/hr	NS

NS: not significant.

tardation and had one episode of convulsions. In group B, patients continued to have repeated epileptic seizures afterwards, indicating refractory epilepsy.

Discussion

Convulsive SE is characterized by a prolonged seizure (lasting longer than 30 minutes by definition), and is therefore a medical emergency because the stress on the respiratory and cardiovascular systems and metabolism may lead to sequelae or death. The treatment strategy has been reasonably well established, and most patients respond well to the recommended first-line treatment of iv DZP or other benzodiazepine. In patients refractory to DZP, PHT and general anesthesia with continuous iv BT is used under intensive respiratory and cardiac care[1].

Even when a seizure is short, if it is repeated it can have a major impact on the life of the patient. If the patient remains unconscious between seizures, he or she can be treated in line with the strategy for SE. However, some patients with CS quickly regain consciousness after a seizure ends, with little residual physical effects, which can make treatment rather difficult. For example, in BIC seizures tend to repeat several times in a few days and patients used to be conscious during the episode[13]. Similar repeated seizures are sometimes seen in patients with chronic epilepsy. The approach to treatment in such patients should differ from that for convulsive SE. DZP is not always successful in the treatment due to its short duration of action. PHT has a more sustained action, however, repeat iv administration is needed to achieve a good sustained response, and it can be difficult to maintain stable serum PHT levels. In addition, PHT induces severe vessel pain when administered iv and tends to cause phlebitis, which may be an obstacle in infants in whom obtaining iv access is difficult. For continuous iv BT, systemic management including monitoring and support of respiration and blood pressure is essential.

Lidocaine has been used in a wide range of age groups since its first application to treat convulsive SE by Bernhard et al in 1955, and the efficacy and safety of lidocaine has been proven[3]. Lidocaine is a fast-acting and short-lasting anticonvulsant, and control of serum levels is easy, even with continuous infusion. Heart rate monitoring is needed because of possible induction of arrhythmias, but the level of consciousness is not affected, and the effect on respiratory and hemodynamics is minimal; because of these merits lidocaine is considered to be the second-line drug following DZP for treatment of SE.

In the present study, we evaluated the usefulness of continuous iv lidocaine in patients in whom seizures which lasted from 20 or 30 seconds to a few minutes occurred repeatedly in a short period of time. These patients did not satisfy the definition of SE because they were conscious between seizures. In group A patients, who had no evident underlying causes, and in whom seizures developed in infancy, 7 out of 9 patients had no relapse after the first lidocaine infusion. Relapse occurred only once in one other patient but disappeared after reinfusion, and one patient had no response. During continuous infusion, sleep and waking rhythm was maintained,

Table 6 Studies of lidocaine in status epilepticus/intractable seizures

		intractable epilepsy/cluster of seizures				status epilepticus			
		C	P	N	W	C	P	N	W
Miyata[4]	EPI	3		1		3			
	sympt					8		1	
Watanabe[5]	EPI		1	1	1	1		3	
	sympt	1	4	3		2	3	2	
Sata[6]	EPI	3				1			
	sympt			1		1	4		
Takahashi[8]	EPI					14		8	
	sympt					6		10	
	n	7	5	6	1	36	7	24	0
	(%)	(36.8)	(26.3)	(31.6)	(5.3)	(53.7)	(10.4)	(35.8)	

C: completely stop, P: partially effective, N: not effective, W: worsening, EPI: epilepsy case, sympt: acute symptomatic seizure.

and patients were able to go about their daily routine as usual. Iv doses were relatively lower than those reported previously[4)~12)]. No arrhythmia was found by heart rate monitoring and no other side effects were found.

The patients in group B had a variety of underlying diseases and had been treated with antiepileptic drugs. Only 4 out of 17 episodes showed a marked response to lidocaine; this was a markedly lower response rate than in Group A. The patients who had no response together with a patient with decreased incidence of seizures received a second round of medication of continuous iv midazolam, PHT, and BT. Comparison between responders and non-responders showed no differences in underlying disease, seizure type, or age at onset of clustered seizures.

Studies on the usefulness of lidocaine have been performed in a wide variety of age groups with a range of underlying diseases, including SE, CS, or intractable epilepsy. This may explain why very different response rates have been reported. In Japan, Miyata et al[4)], Watanabe et al[5)], Sata et al[6)], Tanabe et al[7)], Takahashi[8)], reported studies in a group of patients (Table 6), while some reports have presented a single case study [14)~16)].

When the results of these reports are combined, excluding the one by Tanabe et al[7)] which did not specify the difference between SE and CS, a marked response (symptoms disappeared and not recurrent) was seen in 36 patients (53.7%), and symptoms were ameliorated in 7 patients (10.4%) or there was no response in 24 patients (35.8%) out of 67 patients with SE. A marked response was found in 19 of 30 patients with epilepsy (63.3%) and 17 of 37 patients with acute symptomatic SE (45.9%) ; therefore there was no marked difference based on patient background. For 19 patients with refractory seizures or cluster of seizures, a marked response was seen in 7 patients (36.8%), amelioration of symptoms in 5 patients (26.3%), and no change or deterioration in 7 patients (36.8%) ; the response rate was lower than that of patients with SE (statistically not significant). When analysis was limited to epileptic patients, there was a marked response in 6 out 10 patients, while a marked response was only seen in 1 out of 9 patients with acute symptomatic convulsions. The most common dosage of lidocaine was iv 2 mg/kg followed by continuous iv of 1 to 6 mg/kg/hr (4 mg/kg/h for most cases). Adverse effects were generally mild or none in most patients, and included drowsiness, dizziness[5)], muscle hypotonia, bradycardia, and visual and auditory hallucinations[6)].

In 2 studies of lidocaine performed abroad, one

by Hellström-Westas et al[9)~10)] which reported severe seizures in newborn infants, and Pascual et al[11)~12)] which reported SE in adults, the combined response rate was 38～92%. However, there have been no studies in a large group of children to date.

In previous reports, the number of patients with clustered epileptic seizures (group B in our report) was low and they had a variety of clinical manifestations. Therefore it is difficult to draw any conclusions about the specific indications for lidocaine. However, our results clearly indicate that in patients in whom normal life is disrupted by clustering of epileptic seizures, maintenance levels of lidocaine may provide good control of seizures, and restore normalcy to their daily lives.

We found only 2 cases which corresponded to our group A patients in the literature, one each with Rota infection and benign infantile partial epilepsy reported by Sata et al[6)] and their CS responded well to iv lidocaine. Group A patients had transient CS with a mild disease state, and symptoms were expected to disappear within a few days. But commonly-used rectal or intravenous DZP may not be effective in such patients. PHT and BT therapy, which are regarded as second-line treatments for SE, can place a burden on patients, and are not appropriate for these groups of patients even if it can control CS. Continuous infusion of lidocaine, which neither alters consciousness nor affects daily routine, should therefore be considered in such patients.

Conclusion

Lidocaine provides an effective means of control of CS, since it is effective in cases refractory to DZP, gives stable serum levels, and does not require respiratory or hemodynamic management. Lidocaine was particularly useful for CS seen in infants with normal development and no underlying disorder. Lidocaine was less effective for CS in patients with refractory epilepsy arising from an underlying disorder, although some cases were controlled completely. Therefore lidocaine treatment should be tried at an early stage in CS.

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けいれん発作群発に対するリドカイン持続静注の有効性について

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けいれん発作を反復する群発状態は，日常生活を障害し，発作重積状態に移行したり，神経学的後遺症を残す可能性があり，早急に対処すべき症候である．けいれん発作群発を呈し，ジアゼパムの直腸内または静脈内投与が無効であった22症例に対して，リドカイン持続静注療法を試みた．

「群発」は繰り返すけいれん発作の間欠期に意識が回復する状態とし，発作頻度は①初回けいれん発作の場合には24時間以内に3回以上，②てんかん症例では，日常的な発作頻度を超え通常の生活に支障を来す状態，と規定した．リドカインは1～4mg/kgを静注後，1～4mg/kg/hrで持続静注を行った．

初回発作で基礎疾患のない，神経学的に正常な9症例は平均年齢1歳4カ月で，熱性けいれんの家族歴が高かった．7例ではリドカイン開始後に発作の再燃はなく，中止による再発を認めなかった．1例では発作消失したが中止後に再発し，リドカイン再導入して消失した．1例ではリドカイン無効であった．てんかんの1歳8カ月から22歳までの13例では，17エピソードの発作群発に対して，発作消失3例4エピソード，発作減少5例6エピソード，無効7例7エピソードであった．有効例と無効例とを比較して，年齢，発達障害，神経学的合併症の有無，リドカイン使用量について比較したが，差を認めなかった．両群とも呼吸，循環動態，意識水準，睡眠覚醒リズム，食事摂取などに明らかな影響を認めなかった．

ジアゼパム抵抗性の発作群発状態に対して，リドカイン持続静注は基礎疾患のない，発達正常な乳幼児に対してきわめて有用であった．基礎疾患を有し，てんかんとして治療中の発作群発状態には有効率が低いが，副作用なく著効例もあるため，エピソードの早期に試みる方法である．