Second-line anticonvulsant treatment of neonatal seizures

A video-EEG monitoring study

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Abstract—The authors conducted a randomized trial of second-line anticonvulsant treatments for neonates. The response to treatment was assessed using continuous video-EEG because the clinical diagnosis of seizure in neonates is known to be unreliable. Of 27 neonates with EEG-confirmed seizures, 5 were excluded because of protocol violations, and 11 responded to phenobarbitone in a dose of 40 mg/kg as first line. Three of five neonates treated with lignocaine responded. Six neonates were treated with benzodiazepines as second line: None responded, and their neurodevelopmental outcome was poor.

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Phenobarbitone remains the standard first-line treatment for neonatal seizures worldwide but is ineffective in many neonates.[1] Second-line anticonvulsant regimens vary widely but usually involve the benzodiazepines (diazepam, clonazepam, lorazepam, midazolam), phenytoin, or paraldehyde. Lignocaine is popular in some parts of Europe. Neonatal seizures have an adverse effect on neurodevelopmental progression and predispose to cognitive, behavioral, or epileptic complications in later life.

Only continuous EEG can reliably detect and measure the neonatal seizure burden because there is a poor correlation between the clinical and electrographic manifestations of seizure in the newborn.[2] Few second-line anticonvulsant treatments for neonates have been evaluated using EEG, and there are no previous studies using video-EEG. We designed an open randomized trial of midazolam and lignocaine as second-line anticonvulsant treatments for neonates who failed to respond to first-line phenobarbitone treatment.

Methods. *Subjects.* Neonates cared for at the Neonatal Intensive Care Units of King's College or Guy's Hospitals in London, UK, were eligible for the study, which had full ethical committee approval. Written parental consent was obtained in all cases. Neonates were eligible for the study if they were at high risk of developing seizures because of birth depression or cord blood acidosis, had abnormal movements suggesting seizures, or had meningitis. Neonates were studied as soon as possible after enrollment. Neonates who had already received a single loading dose of phenobarbitone were not excluded from the study.

Monitoring. A Telefactor Beehive video-EEG system (W. Conshohocken, PA) was used to record video and 12 channels of EEG. All neonates were monitored continuously for at least 24 hours after enrollment. If electrographic seizures were not detected during this time, recording was stopped. If seizures were present, monitoring was continued until seizure control was established or treatment was considered to have failed (at least 48 hours later). Physiologic information from routine intensive care monitoring was collected prospectively. Neonates in the intensive care units of both our hospitals are routinely sedated with midazolam, at a dose of 30 to 60 μg/kg/h. Neonates who were randomized to receive midazolam as treatment were given a much larger dose, whereas those who received lignocaine continued to be given background midazolam. Some neonates were also receiving continuous low-dose morphine as analgesia (10 to 20 μg/kg/h).

Treatment protocol. Phenobarbitone. All neonates whose seizures were confirmed by EEG were treated with phenobarbitone in a dose of up to 40 mg/kg. If this failed to abolish seizures or reduce the seizure burden by at least 80% within 12 hours of enrollment, the neonate was randomly assigned to receive midazolam or lignocaine as second-line anticonvulsant therapy. Serum levels were checked.

Second-line anticonvulsant therapy randomization. Neonates were assigned to IV treatment with midazolam or lignocaine according to an open randomized design. Midazolam was administered as a bolus dose of 60 μg/kg followed by an infusion of 150 μg/kg/h; lignocaine was administered as a bolus of 4 mg/kg over 20 minutes followed by an infusion of 2 mg/kg/h. Blood samples were collected to determine serum levels of both drugs.

If the assigned anticonvulsant failed to abolish or reduce seizure burden by at least 80% within 12 hours, anticonvulsant treatment was increased to either 300 μg/kg/h of midazolam or 4 mg/kg/h of lignocaine. If the increased dose of either drug failed to improve the seizure burden within 48 hours of enrollment, the clinical team on the Neonatal Intensive Care Unit took over management decisions. Clonazepam was the treatment usually chosen in this situation and was the treatment used if parents were not willing for their child to be given a drug chosen randomly.

EEG analysis. A seizure was defined as the evolution of sudden, repetitive, evolving stereotyped forms with a definite beginning, middle, and end, lasting at least 10 seconds.[3] Neonatal status epilepticus was defined as continuous seizure activity for at least 30 minutes or recurrent seizures for >50% of the entire recording duration.[4] Seizure control was defined as complete ab-

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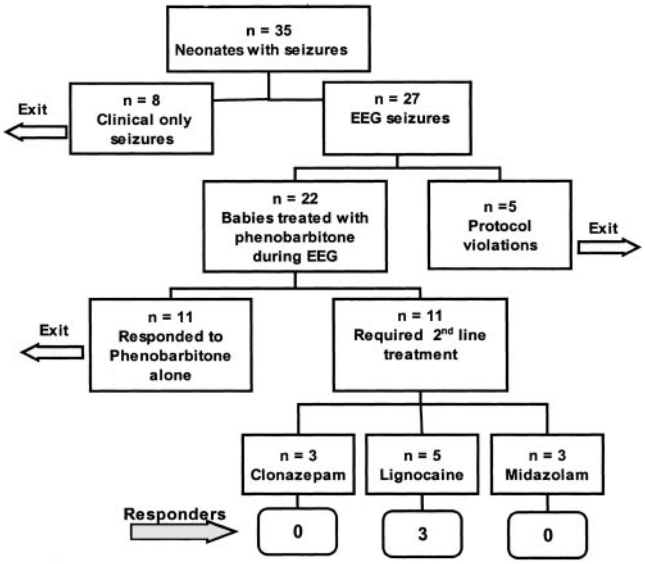

Figure. Study flow chart.

sence of any electrographic seizure activity. A major improvement was defined as a ≥80% decrease in pretreatment seizure burden. Seizure duration was measured from the second hour after treatment and during each subsequent hour of treatment.

For each seizure, duration, location, and type (i.e., electrographic or electroclinical) were analyzed in each neonate by two observers for each hour of the study. Interobserver agreement was assessed.

Endpoints. The primary endpoint in this study was control of electrographic seizures. By "control" we mean complete absence of seizure activity on the EEG or a reduction of >80% of pretreatment burden.

Neurodevelopmental assessment. All surviving neonates had an Amiel–Tison and Griffiths neurodevelopmental assessment at 1 year.

Results. Eighty-seven neonates were enrolled in this study. Fifty-two neonates did not have seizures. Thirty-five had either clinical or electrographic seizures (figure). Of these 35 neonates, 14 had been treated with at least 20 mg/kg of phenobarbitone (sometimes more) prior to enrollment.

"Clinical only" seizure group. In 8 of the 14 neonates who had already received one dose of phenobarbitone, there was no evidence of seizure activity on the EEG for up to 24 hours after enrollment. In these neonates, monitoring was discontinued at that point ("exit"; see the figure).

Phenobarbitone (first-line) responders. Twenty-seven neonates had seizure activity on the EEG at enrollment. Five neonates were excluded from the study because of protocol violations. The remaining 22 neonates received phenobarbitone treatment and had continuous EEG monitoring from enrollment. Eleven of the 22 neonates responded to this phenobarbitone treatment (table 1). Four of these neonates died. Of the seven remaining neonates, five were normal at follow-up and two had moderately abnormal neurodevelopmental outcomes.

Second-line treatment group. The 11 neonates who did not respond to a dose of 40 mg/kg of phenobarbitone were treated with midazolam, lignocaine, or clonazepam as second-line anticonvulsant treatment (table 2). Three neonates received clonazepam, five lignocaine, and three midazolam. Two neonates became seizure-free after treatment with 4 mg/kg/h of lignocaine and one had an 80% reduction in seizure burden. None of the other neonates responded to any second-line treatment at any dose.

The outcome of neonates who required second-line treatment for their seizures was generally poor (see table 2). Serum levels of anticonvulsants showed that all neonates had values that remained within the therapeutic range for each drug.

Discussion. We report continuous video-EEG monitoring during second-line anticonvulsant treatment in the newborn. Only a small number of neonates went on to receive a second-line anticonvulsant. The response to second-line treatment with benzodiaz-

Table 1 *Clinical, seizure, and outcome details of 11 neonates that responded to phenobarbitone therapy alone*

Case no.	PB, mg/kg	GA, wk	BW, g	AP[1]	AP[5]	Cord pH	Diagnosis	Pre PB	+ 2 h	+ 4 h	Outcome
1	40	41	4,380	5	6	7.07	Hypoxic ischemic encephalopathy	NM	840	0	Normal
2	40	41	3,980	4	5	7.08	Hypoxic ischemic encephalopathy	1,208	112	0	Normal
3	40	29	908	7	9	7.2	Intracranial hemorrhage	3,600	73	0	Died
4	20	33	1,460	4	9	N/A	Intrauterine growth retardation, twin	1,762	0	0	Normal
5	20	34	2,122	1	2	6.88	Myopathy, ventilator dependent	1,280	0	0	Died
6	40	40	4,240	2	5	0	Hypoxic ischemic encephalopathy, severe meconium aspiration	1,800	0	0	Died
7	20	40	2,680	9	9	7.13	Benign neonatal seizures	197	0	0	Normal
8	20	39	4,600	1	5	6.8	Hypoxic ischemic encephalopathy	1,040	0	0	Moderate
9	40	33	1,200	0	0	N/A	Intrauterine growth retardation	2,149	0	0	Normal
10	20	28	684	5	2	7.21	Intracranial hemorrhage, severe respiratory distress	1,260	133	0	Died
11	20	40	3,944	0	0	7.22	Hypoxic ischemic encephalopathy	1,700	0	0	Moderate

PB = phenobarbitone; GA = gestational age; BW = birth weight; AP[1] and AP[5] = Apgar scores at 1 and 5 min; Pre PB = seizure duration in seconds during the 1 h prior to phenobarbitone treatment; + 2 h (4 h) = seizure duration in seconds during a 1-h period 2 h (4 h) after treatment; NM = not monitored in this period.

Table 2 *Clinical, seizure, and outcome details of 11 neonates that required second-line anticonvulsant therapy*

Case no.	GA, wk	BW, g	AP^1	AP^5	Cord pH	Diagnosis	Pre PB	+ 2 h	+ 4 h	Second-line drug	Pre second	+ 2 h	+ 4 h	+ 6 h	Outcome
12	42	3,562	7	9	6.85	Hypoxic ischemic encephalopathy	NM	3,600	3,600	Midazolam	3,600	1,560	3,600	3,600	Mild
13	40	4,414	3	3	N/A	Hypoxic ischemic encephalopathy	NM	NM	NM	Midazolam	1,173	1,642	1,515	2,107	Died
14	41	3,628	9	10	7.24	Arteriovenous malformation	NM	1,573	2,398	Midazolam	2,398	282	1,575	1,606	Moderate
15	41	3,855	4	6	6.8	Hypoxic ischemic encephalopathy	NM	NM	NM	Lignocaine	3,600	0	3,600	73	Died
16	41	3,540	7	7	7.33	Hypoxic ischemic encephalopathy	NM	50	757	Lignocaine	1,365	0	0	89	Severe
17	41	3,172	2	0	N/A	Hypoxic ischemic encephalopathy	NM	145	210	Lignocaine	587	393	488	319	Severe
18	37	4,796	1	1	N/A	Hypoxic ischemic encephalopathy	2,217	788	155	Lignocaine	319	339	834	1,958	Died
19	25	795	7	9	N/A	Intracranial hemorrhage, meningitis	NM	1,816	3,600	Lignocaine	3,600	142	0	0	Severe
20	38	2,650	1	4	6.6	Hypoxic ischemic encephalopathy	3,371	1,037	1,361	Clonazepam	1,361	486	1,976	1,684	Moderate
21	36	2,886	3	4	7.26	Hypoxic ischemic encephalopathy	NM	NM	NM	Clonazepam	843	408	118	196	LTF
22	26	700	3	6	7	Reduced end-diastolic flow, premature	2,008	2,744	3,600	Clonazepam	3,600	3,600	3,600	3,600	Died

GA = gestational age; BW = birth weight; AP^1 and AP^5 = Apgar scores at 1 and 5 min; Pre PB = seizure duration in seconds during the 1 h prior to phenobarbitone treatment; + 2 h (4 h) = seizure duration in seconds during a 1-h period 2 (4) h after treatment; Pre second = seizure duration in seconds during the 1-h period immediately before second-line treatment was commenced; + 2 h (4 h, 6 h) = seizure duration in seconds during a 1-h period 2 (4, 6) h after treatment with second-line treatment; NM = not monitored in this period; LTF = lost to follow-up.

epines was disappointing. Clonazepam and midazolam did not affect the seizure burden. Three of five neonates responded to lignocaine therapy after 12 hours of treatment and only at the maximum dose. The temporal response to the higher dose and the fact that seizures continued far longer in the group given benzodiazepines suggest that our results were not due to chance.

Over half of the neonates we studied responded to phenobarbitone therapy, in contrast to earlier studies.[1,2] Lignocaine has a narrow therapeutic range and can induce seizures in high doses. The drug can accumulate and so cannot be infused over very prolonged periods. Midazolam did not reduce seizures in the three neonates studied, and clonazepam did not prove to be an ideal anticonvulsant for neonates either. We were unable to reproduce the good results reported in older children with status epilepticus.

Our results confirm those of others, which show that phenobarbitone is effective only in about one-third to one-half of neonates with seizures. Based on previous experience, we believe that phenobarbitone is most effective in neonates with well-preserved background EEG patterns.[2] The combination of a high seizure burden and a severely abnormal background EEG makes it probable that phenobarbitone will fail and outcome will be adverse.

Our results show that treatment with midazolam or clonazepam does not achieve seizure control in neonates with high seizure burdens. Lignocaine (and, by inference, phenytoin) may reduce the seizure burden, but the outcome may not be improved. The search for an effective anticonvulsant regimen in the newborn must continue.

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