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Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures

Nathalie L Maitre[1], **Ciaran Smolinsky**[1,*], **James C. Slaughter**[2], and **Ann R Stark**[1]

[1]Department of Pediatrics, Vanderbilt University, Nashville TN

[2]Department of Biostatistics, Vanderbilt University, Nashville TN

Abstract

Objective—Compare neurodevelopment after levetiracetam (LEV) and phenobarbital (PB) for neonatal seizures.

Study design—Retrospective study of infants who received antiepileptic drugs (AEDs) for neonatal seizures. Effect of cumulative exposure to LEV and PB on outcomes of death, cerebral palsy (CP), and Bayley Scales of Infant Development (BSID) scores were evaluated at 24 months corrected age. Analyses were adjusted for number of electrographic seizures and gestational age.

Results—In 280 infants with comparable seizure etiology and cranial imaging results, increased exposure to PB was associated with worse BSID cognitive and motor scores (8.1- and 9-point decrease per 100 mg/kg; p=0.01). The effect was less with LEV (2.2- and 2.6-point decrease per 300 mg/kg LEV (p=0.01). CP probability increased by 2.3-fold per 100 mg/kg PB and was not associated with increasing LEV.

Conclusion—Increased exposure to PB is associated with worse neurodevelopmental outcomes than LEV. Prospective studies of outcomes of neonatal exposure to AEDs are essential.

Introduction

Infants cared for in neonatal intensive care units (NICUs) are at high risk for adverse neurodevelopmental outcomes and contribute up to half of new cases of cerebral palsy, deafness, blindness, and cognitive impairments in the United States.(1–4) Infants at the highest risk include those with direct perinatal brain insults from ischemia, hemorrhage, trauma and infections, although genetic, metabolic or anatomic conditions also contribute.(5–7) While the origin of neonatal cortical dysfunction varies, the resulting altered electrophysiologic process is often manifested by a seizure disorder.(8,9)

Corresponding Author: Nathalie Maitre, MD, PhD, Division of Neonatology, The Monroe Carell Jr. Children's Hospital at Vanderbilt 11111, Doctor's Office Tower, 2200 Children's Way, Nashville, TN 37232-9544, Office: 615-936-5933, Fax: 615-343-1763, nathalie.maitre@vanderbilt.edu.

*The first two authors contributed equally to the manuscript

Antiepileptic drugs (AEDs), including phenobarbital, phenytoin, and benzodiazepines that are routinely used to manage neonatal seizures are poorly effective and not well studied in this population.(10) They are also used as adjuncts to other neuroprotective therapies to decrease destructive excitatory processes in the setting of brain injury.(11) They act primarily on gamma aminobutyric acid (GABA) receptors,(12–14), have been associated with neuronal apoptosis *in vitro* and in neonatal animal models and thus have potential risks in newborn infants.(15–17) In addition, although prolonged use of these agents has been associated with cognitive decline in older children and adults, their impact on neurodevelopmental outcomes of infants with neonatal seizures is unknown.(18) Newer AEDs, including levetiracetam, oxcarbamazepine, and topiramate, are increasingly used to treat neonatal seizures,(19,20) although evidence is equally limited on their effectiveness or effect on neurodevelopment.(21) The mechanisms of action of these drugs are only partially characterized.(22–25)

Our goal was to evaluate the impact of AED use on neurodevelopmental outcomes at 2 years corrected age in children treated for neonatal seizures with either a traditional GABA-ergic AED or a newer transmitter release-modifying AED, to help guide future prospective trials of these medications. We tested the hypotheses that neurodevelopmental outcomes, as measured by standardized scores and diagnosis of cerebral palsy, would be more favorable in patients who received levetiracetam compared to phenobarbital and that higher cumulative AED exposure would be associated with poorer outcomes.

Methods

Study design

We conducted a retrospective cohort study of all infants cared for in the Monroe Carell Jr Children's Hospital Neonatal Intensive Care Unit (NICU) at Vanderbilt who received phenobarbital (PB) and/or levetiracetam (LEV) from January 2007 through December 2010, identified through the electronic pharmacy record. We included all patients who (1) had at least one observed clinical seizure and who (2) received PB or LEV for a diagnosis of seizures, as documented in the electronic medical record. Outborn patients who received either AED prior to admission to the Vanderbilt NICU were excluded if either their initial seizure occurred more than 48 hours before transfer or if AED administration data at the referring hospital were unavailable. Institutional review board approval was obtained for access to the medical and pharmacy records.

Exposure measures

We used transport records and admission notes to determine total AED dose/kg administered prior to NICU admission. Cumulative AED dosage administered through hospital discharge, as documented in the pharmacy database, was calculated by using the algebraic sum of AED doses/body weight on each corresponding day and expressed in mg/kg. Exposure to PB and LEV was analyzed both as a continuous measure (cumulative dose) and as a categorical measure (exposed or non-exposed). AED were used in both intravenous and oral formulations. Oral PB is formulated in a 15% alcohol base while

intravenous PB contains 1% alcohol. LEV in oral and intravenous formulations contains only inactive ingredients.

Clinical characterization of subjects

We recorded clinical and demographic data, including sex, gestational age at birth (GA), birth weight, maternal education level, and race/ethnicity. Number of observed clinical seizures was obtained from the attending physician's medical record documentation. Number of EEG seizures was obtained from the pediatric neurologist's documented analysis of the EEG if performed. We used the number of EEG documented seizures as a proxy measure of seizure severity as it may be more predictive than type of seizure.(26) We reasoned that persistent or highly visible clinical seizures prompted providers to obtain EEGs, and EEG-documented epileptiform activity was in turn a more reliable marker of disease severity/persistence. We classified seizure etiology as perinatal hypoxia/ischemia, infection, infarct/aneurysm, hemorrhage, congenital malformation of the central nervous system, metabolic, or other based on medical and imaging records. For those infants with cranial imaging including cranial ultrasound examinations or magnetic resonance imaging, we further classified findings based on the reading by pediatric neuroradiologists as normal or abnormal. Abnormal findings were also categorized according to brain region affected: cortical, periventricular/intraventricular, deep nuclei, cerebellar, congenital malformation and other.

Treatment practices

Practices were inconsistent and varied widely due guidelines recommending PB as a first line treatment for neonatal seizures and availability of input from pediatric neurologists. Guidelines stating LEV should be used as a first-line agent for neonatal seizures in the Vanderbilt NICU were not published until 2012. PB was also the only antiepileptic used by neonatal transport teams across TN. At the time of the study the primary AED for treatment of neonatal seizures was PB per NICU treatment guidelines and LEV was added in most cases after failure of PB. Cases in which LEV was used as a first line treatment represent patients in which a pediatric neurologist was immediately consulted and LEV was started at their recommendation.

Outcomes measures

There were three outcomes of interest. (1) We ascertained death within the first two years of age. (2) We assessed neurodevelopmental outcomes as measured by motor, cognitive, and language performance on the Developmental Assessment of Young Children (DAYC) at 12 months(27) and the Bayley Scales of Infant Development (BSID), 3rd ed. at 24 months.(28) All assessments were performed by trained examiners in the Vanderbilt NICU Follow-up Clinic. The DAYC corroborates caregiver responses with child observation and challenge of developmental milestones in motor, cognitive, and communicative domains. For both the DAYC and BSID, standardized scores for adjusted age are expressed with a mean of 100 (SD 15). Only composite scores in all three domains were used as continuous variables for the analysis. We reported patients' corrected age scores on the DAYC and BSID assessments performed closest to twelve and twenty-four months corrected age, respectively.(3) We identified children with a diagnosis of cerebral palsy (CP) by two years

of age, made by pediatric specialists according to published criteria,(29,30) and scored for severity using the Gross Motor Function Classification System.(31)

Statistical Analysis

We analyzed cumulative exposure to AEDs rather than single comparisons between two groups that would have included only 30 surviving infants in the LEV alone group, and only 18 with DAYC and 7 with BSID scores. Continuous variables were summarized using the median, 25th, and 75th percentiles. Categorical variables were summarized using percentages. Separate linear regression models were fit to determine if DAYC and BSID scores were associated with exposure to PB or LEV while controlling for confounding variables. Logistic regression was used to estimate the association of CP with PB or LEV exposure while controlling for gestational age and severity of seizure disorder. In each regression model, we modeled the expected dose-response relationship between PB (or LEV) and developmental scores by including an indicator variable for receiving any dose of PB (or LEV) plus an additional covariate for the actual dose of PB (or LEV) received. Such an approach allowed us to test for three types of association: the effect of getting any dose versus none, the dose-response relationship in subjects receiving any dose, and any overall effect of PB (or LEV) on the outcome by testing both associations simultaneously. We conducted the overall test first using a significance level of 0.05. If the overall test was significant, then the two step-down tests were performed using a significance level of 0.025. For the dose-response relationship, we report the expected change in DAYC and BSID scores per 100 mg/kg increase in PB and 300 mg/kg increase in LEV, which represented approximately one third of the range of cumulative doses for each AED.

Results

Patient characteristics

During the study period, 280 infants met inclusion criteria. Of these, 106 received only PB, 33 received only LEV, and 141 received both drugs. Because most infants had received both AEDs, the number of infants receiving only LEV or only PB was small and groups were analyzed by cumulative exposure (Figure 1A). Thus, 247 infants comprised the group receiving any PB and 174 comprised the group receiving any LEV with an overlap of 141 patients. These groups did not differ in median gestational age (38 weeks) or birth weight (Table 1). We detected no significant differences between groups regarding sex, race/ethnicity or maternal education level. Median cumulative doses (interquartile range) were 60 mg/kg (37,87) and 360 mg/kg (152,675) for PB and LEV, respectively.

Seizures—The groups that received any PB or any LEV did not differ in seizure etiology or number of observed clinical seizures (Table 2). EEGs were recorded in 205 of 247 (91%) infants who received any PB and for 171 of 174 (98%) infants who received any LEV. Seizure severity, as indicated by the number of electrographic seizures, did not differ between groups.

Outcomes—Of the 280 infants in this study, 68 (24%) died by two years of age. When subjects with similar seizure severity and gestational age were compared, there was no

evidence that any exposure or cumulative exposure to either AED was associated with death.

DAYC scores were available for 62% of surviving patients and BSID scores were available for 32% (Figure 1B). The availability of scores was similar in the group with any PB and the group with any LEV exposure. There were no statistically significant differences in gestational age, etiology, imaging characteristics or seizure severity between the infants who had follow-up and those who did not. At 12 months, patients who received any PB or any LEV had similar median corrected age. DAYC scores were within the average range in all domains (Table 2). At 24 months, corrected age median BSID scores were within one standard deviation of the mean of 100 (in the low normal range) but there were wide differences reflected in the range of scores (Table 2). After adjusting for seizure severity and gestational age, neurodevelopmental outcomes at 12 months of age showed negative effects of increasing PB and LEV exposure only in motor domains ($p= 0.007$ and $p= 0.01$ respectively, see supplementary materials). At 24 months, increased exposure to PB was associated with decreasing cognitive and motor scores, with a decrease of 8 points in BSID cognitive score ($p=0.01$), and a decrease of 9 points in BSID motor score ($p=0.023$) for every 100 mg/kg of PB exposure. In the case of LEV, increased exposure was significantly associated with decreasing cognitive and motor scores, with a decrease of 2.2 points in BSID cognitive score ($p=0.001$), and a decrease of 2.6points in BSID motor score ($p=0.001$) for every 300 mg/kg of LEV exposure.

Similar decreases in communication BSID scores were observed for both PB and LEV but were less clinically meaningful. Receiving any PB versus none was associated with lower BSID language score ($p=0.024$), but there was no evidence of a dose relationship. In the case of LEV, BSID communication score decreased 2.3 points for every 300 mg/kg LEV ($p=0.001$).

A total of 159 patients (75% of surviving patients) were assessed for CP at two years of age, and the proportion of infants assessed was similar in the LEV and PB groups. No significant association was found between exposure to any LEV or cumulative LEV exposure and the diagnosis of CP. Controlling for gestational age and severity of seizure disorder, receiving PB was associated with CP ($p=0.018$). The probability of developing CP increased by 2.3 fold for every 100 mg/kg increase in PB (Figure 4).

Discussion

Our study suggests that exposure to any PB for the management of neonatal seizures, at equivalent gestational ages and disease severity, was associated with poorer neurologic outcomes compared to exposure to any LEV. Furthermore, our results show a relationship between increasing cumulative AED exposure and severity of neurologic impairment. This is true for standardized measurements of cognitive and motor development as well as development of CP.

Our findings may reflect a relationship between neurotoxicity of PB and poor neurodevelopmental outcomes, as has been well documented in animal models. PB exposure

equivalent to doses used to manage seizures in humans has been shown to induce neuronal apoptosis in the developing rat brain, whereas LEV, even at high doses, does not induce cell death.(15,32) PB, but not LEV, has also been shown to interfere with maturation of synaptic connections.(33) The links between laboratory studies and use of these drugs in human infants are difficult to establish due to the lack of studies on AED use and either neuroimaging or biochemical findings in the neonatal setting. Studies in infants briefly exposed to PB *in utero* prior to delivery demonstrated no significant cognitive or motor deficits by two years of age compared to non-exposed controls.(34,35) However, studies in pediatric populations showed significant impairments related to PB exposure after birth on various measures of development and with widely varying lengths of follow-up.(36) Our results support the association between PB exposure and occurrence of major motor and cognitive impairments in early childhood. Also, because the oral PB given to infants is mixed in an alcohol base, it is possible that some of the negative effects observed on neurodevelopment could be due to a very low cumulative exposure not present in infants treated with LEV.

Alternatively, our findings may reflect a positive association between LEV and improved outcomes. In rat models, LEV has been shown to reduce neuronal apoptosis following hypoxic injury. In this model, LEV also has an anti-inflammatory effects on astrocytes and microglia, mediated in part through TGF-Beta induction(37,38). Furthermore, receptors for LEV appear in the human brain as early as 26 weeks gestation, reaching near-adult levels by 37 weeks, a window of development in which stabilization of synaptic connections and modulation of inflammation may favor plasticity.(39) Prenatal exposure to LEV does not appear to result in decreased developmental quotient.(40)

Another consideration in explaining the difference in outcomes in PB vs. LEV exposed neonates is the issue of nonequivalent dosing. Doses of LEV, PB, and other AEDS needed to control seizures in neonates are not yet well-established, and comparatively larger cumulative amounts of PB may lead to detrimental neurodevelopmental consequences. This may be especially true in neonatal patients whose gestational age and illness may affect the metabolism and volume distribution of AEDs.(41,42) Circulating levels of these AEDs can be measured but optimal levels in neonates (particularly preterm infants) are variable and the correlation with efficacy is insufficient.(43–46) Additionally, although we attempted to control for severity of seizure disorder by stratifying patients according to number of EEG documented seizures, it is possible that cumulative AED effects may have been influenced by disease severity but not manifest on EEG. Disease severity is always a confounding factor, especially in a retrospective study and may explain our findings, even though we carefully assessed for matching etiologies between groups and attempted to control for severity of the seizure disorder. However, LEV was mostly a second line agent in this cohort, used when PB did not control seizures. If disease severity alone accounted for our results, infants treated with LEV and PB should have had more severe disease and worse outcomes than those treated with PB alone, regardless of exposure.

A limitation of our study was that few infants received only one AED. Thus, 141 infants were included in both groups, limiting our ability to draw conclusions about associations with specific drugs. Furthermore, our study did not examine neurodevelopmental outcomes

for infants who received PB for reasons other than seizures, such as induction of hepatic metabolism. Another limitation is that patients with neonatal seizures are often followed by neurologists and developmental specialists rather than our NICU follow-up clinic and their outcomes were unavailable for analysis. Thus, test scores were available in only 2/3 of infants at 12 months and 1/3 at 24 months, and only 2/3 had CP assessments at 24 months available at 24 months. Most importantly, our study is limited by its retrospective design that precludes attribution of direct causality between AED exposure and negative cognitive and motor outcomes. Despite the stated limitations, this study remains one of the first and largest to examine neurodevelopmental outcomes using validated measures up to two years of age for patients treated with AEDs during the neonatal period. Most randomized controlled trials that support the negative effects of PB on cognitive and motor abilities have been conducted in adult populations, and those in children are limited by small sample sizes and short duration of follow-up.

In conclusion, we have shown that increasing exposure to PB is associated with worse outcomes at 2 years of age and that LEV may be associated with improved outcomes compared to PB. Although our evidence and that of others suggests that use of AEDs may adversely affect neurodevelopment, untreated epileptic disorders are known to increase the risk of cognitive defects. Our findings highlight the need for prospective trials to investigate both the comparative efficacy of various AEDs in controlling neonatal seizures as well as the long-term effects of exposure to these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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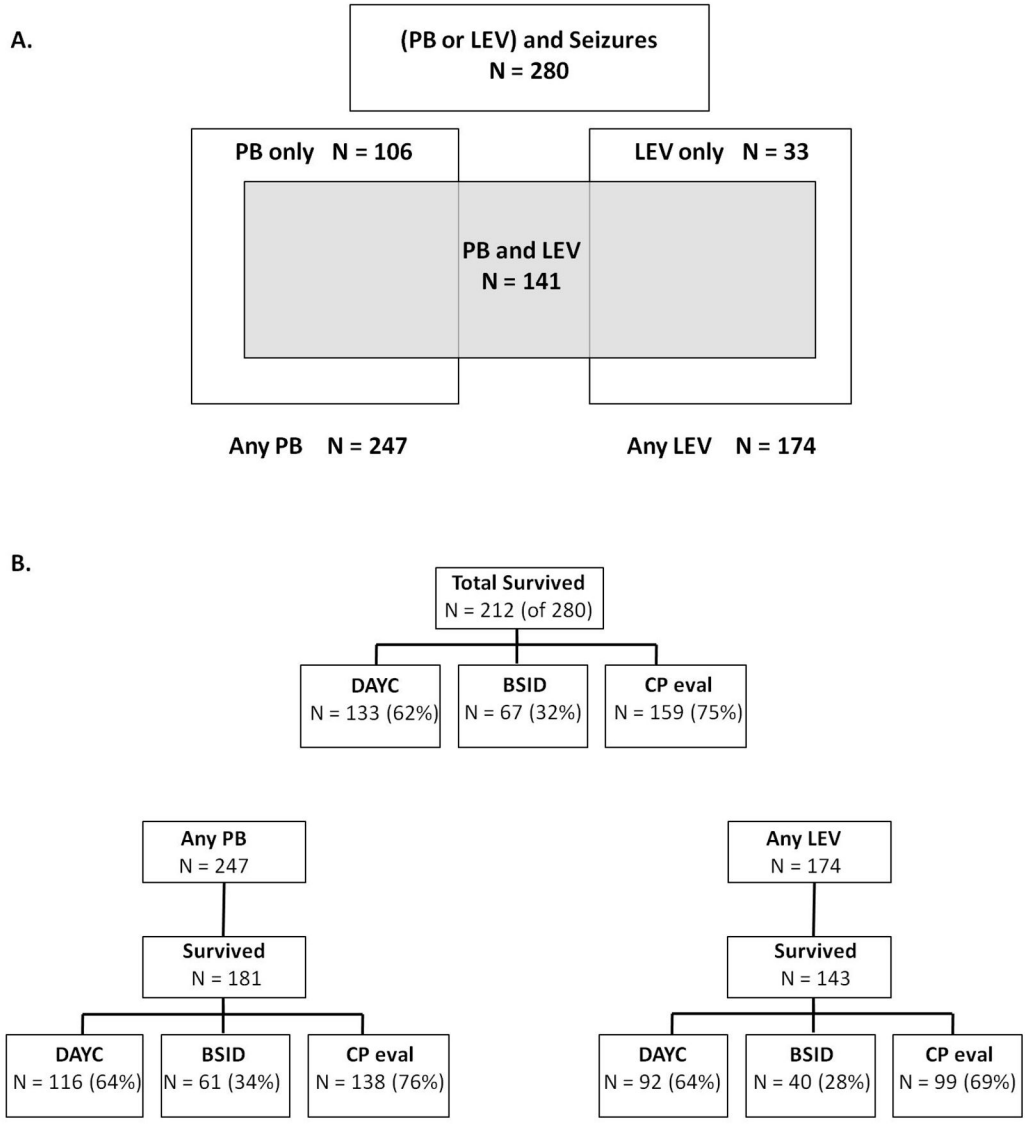

Figure 1. Study population and follow-up

1A: Study population by type of AED received

1B: Availability of outcomes by type of AED received

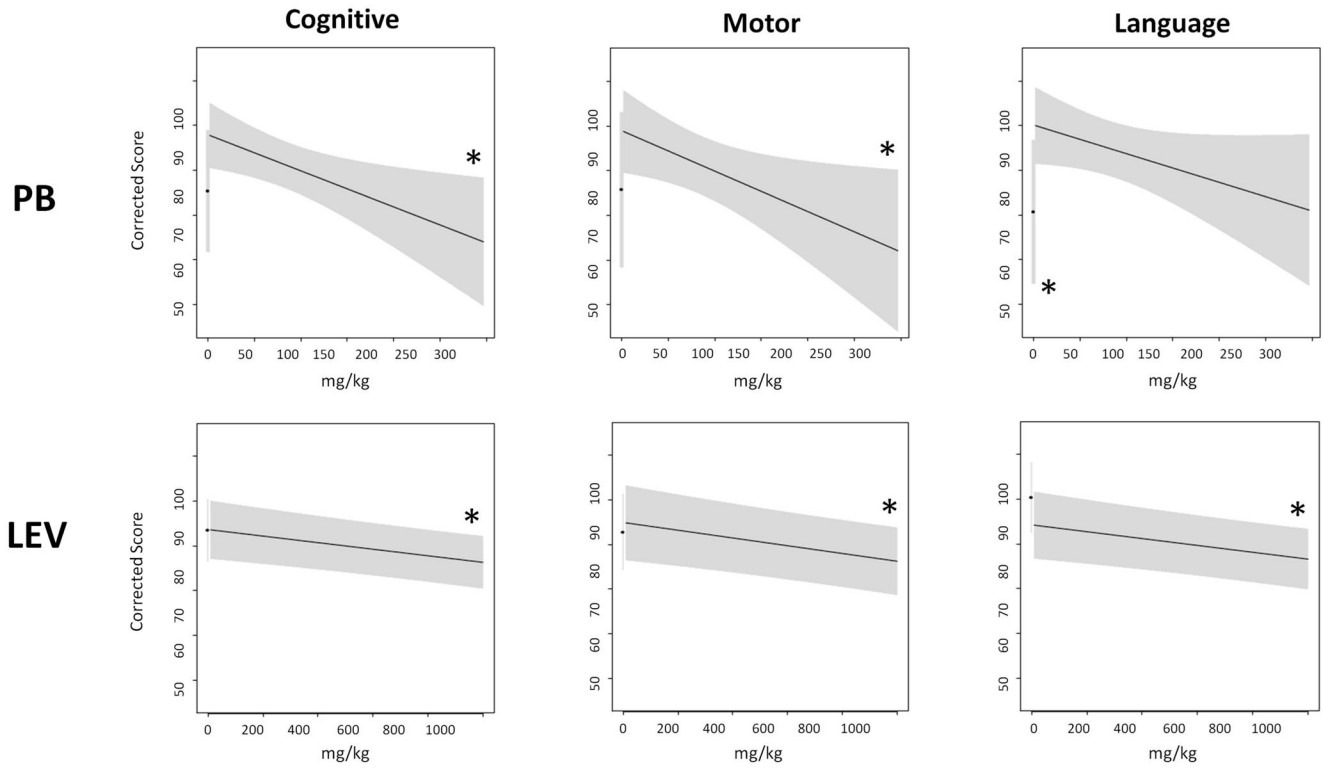

Figure 2. Increasing cumulative AED exposure is associated with worse 24-month BSID III scores

Single point with standard deviation error bar represents patients not receiving AED of interest at all; line represents increasing cumulative exposure.

Shaded area represents 95% confidence interval

Only composite scores are shown for all domains

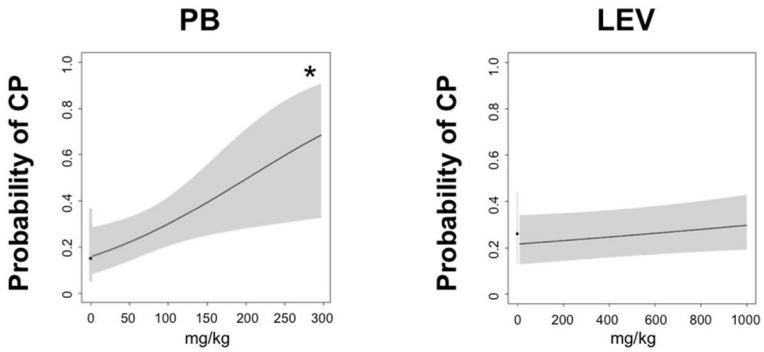

Figure 3. Increasing cumulative PB but not LEV exposure is associated with increased probability of cerebral palsy

Shaded area represents 95% confidence interval

Table 1

Characteristics of study population

	Any PB N=247	Any LEV N=174	PB + LEV N=141	All N=280
Clinical characteristics				
Gestational Age at birth in weeks median (IQR)	38 (35,39)	38	38 (37,39)	38 (35,39)
Number of clinical seizures (%)				
1	21	11	11	20
2–10	64	64	66	62
more than 10	15	25	23	17
Number of electrographic seizures (%)				
none	72	55	56	69
1	4	7	6	6
2–10	12	21	20	14
Etiology of seizures (%)				
Hypoxia/Ischemia	40	38	39	39
Infection	6	7	6	7
Infarct	11	14	16	11
Hemorrhage	23	19	19	22
Cong. malformation	5	7	5	6
Metabolic	6	6	6	6
Other	15	17	12	17
Imaging Characteristics				
Cranial Ultrasound findings by location (%)	**N=158**	**N=99**	**N=83**	**N=174**
Ventricles	36	30	31	35
Cortex	38	35	40	36
Cerebellum	4	5	4	5
Deep nuclei	7	8	10	6
Other	0	0	0	0
Malformation	5	9	6	7
MRI Findings by location (%)	**N=176**	**N=158**	**N=126**	**N=208**
Ventricles	27	24	25	25
Cortex	64	63	66	62
Cerebellum	8	9	9	8
Deep nuclei	23	23	26	22
Other	26	27	27	26
Malformation	9	12	9	11

IQR: interquartile range

Table 2

Neurodevelopmental outcomes at 12 and 24 months by type of AED received

	Any PB N=247	Any LEV N=174	PB + LEV N=141	All N=280
DAYC median (IQR)				
Cognitive	97 (85,104)	97 (85,107)	97 (85,107)	95 (87,107)
Motor	88 (68,97)	89 (68,99)	88 (68,99)	88 (68,97)
Communication	96 (83,100)	94 (85,98)	94 (86,98)	94 (83,100)
BSID median scores (IQR)				
Cognitive	85 (70,95)	85 (60,93)	85 (70,90)	85 (70,95)
Motor	85 (65,96)	85 (69,94)	84 (57,93)	85 (60,94)
Language	89 (71,97)	82 (67,95)	86 (69,96)	86 (68,97)
CP (%)	27	16	30	26
Death (%)	27	18	20	24

IQR: Interquartile range

CP: Cerebral Palsy

BSID: Bayley Scales of Infant Development 3d ed., corrected age scores

DAYC: Developmetnal Assessment of Young Children, corrected age scores