



Original Research

Drug-Induced Liver Injury in Critically Ill Children Taking Antiepileptic Drugs: A Retrospective Study



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ABSTRACT

Background: Antiepileptic drugs are among the leading causes of drug-induced liver injury (DILI). Due to critical illness, children admitted to intensive care units are more prone to DILI.

Objective: We attempted to elucidate the association between antiepileptic drug use and the associated factors resulting in DILI in a pediatric intensive care unit of a tertiary care hospital.

Methods: We carried out an observational retrospective study on children receiving antiepileptic drugs. Details on their demographic characteristics, drugs, serum levels of antiepileptic drugs and liver function tests, and hospital stay were recorded. Council for International Organizations of Medical Sciences definitions were adhered to when defining DILI. LiverTox (<https://livertox.nih.gov>) and DILIRank were used to assess the risks of hepatotoxicity of the concomitant drugs. Regression models were developed for predicting DILI.

Results: Five out of 9 patients taking phenobarbitone (55.6%), 9 out of 12 taking phenytoin monotherapy (75%), 7 out of 10 taking phenytoin/phenobarbitone (70%), all 3 receiving phenytoin/phenobarbitone/valproate sodium, and 1 with phenytoin/carbamazepine developed DILI either in the form of hepatocellular injury or liver biochemical test abnormalities. None of the patients had cholestatic or mixed type of liver injury. All the critically ill children received at least 2 concomitant drugs with hepatotoxic potential. Concomitant category B hepatotoxic drugs and toxic drug levels were significantly associated with increased risk of DILI. Similarly, a trend was observed for less-DILI-concern concomitant drug class and toxic drug levels when the drugs were analyzed by DILIRank classification.

Conclusions: A significant proportion of critically ill children taking antiepileptic drugs experience DILI. Guidelines recommending use of drugs with reduced risk of potential hepatotoxicity for various concomitant disease states in such children admitted to intensive care units receiving antiepileptic drugs are urgently needed.

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Introduction

Antiepileptic and anticonvulsant agents are among the commonly used drug classes in intensive care units (ICUs). Antiepileptic drugs (AEDs) are also initiated in ICUs as prophylactic drugs in patients with traumatic brain injury, meningitis, and brain neoplasms.¹ Febrile convulsions is a unique indication in children to

receive anticonvulsant drugs in pediatric ICUs (PICUs).² One-tenth of critically ill children were initiated AEDs acutely in ICU settings due to epileptic seizures.³ Almost 53% treated for a seizure attack were reported to have recurrent seizures in a PICU.⁴

Drug-induced liver injury (DILI) is defined as the xenobiotic-induced hepatic injury resulting in alteration of liver enzymes in the absence of other known causes.⁵ The majority of antiepileptic agents get metabolized in the liver and form a leading cause of DILI worldwide.^{6,7} DILI can range between asymptomatic elevations of liver enzymes and hepatic failure.⁹ Although hepatotoxicity is a common adverse event amongst the conventional AEDs, valproate has more hepatotoxicity than carbamazepine that

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has more than phenytoin.¹⁰ Children are particularly more susceptible to idiosyncratic hepatotoxicity than adults.¹¹ Particularly, children younger than age 2 years are vulnerable to developing DILI following sodium valproate.⁸ Patients admitted in ICUs are more likely to be observed with abnormal liver enzymes due to several reasons such as acute hepatitis, acute liver failure, and secondary sclerosing cholangitis that are unrelated to antiepileptic agents but rather to their critical illnesses.¹² Critically ill patients often have hypoxic, toxic, and inflammatory insults to the hepatocytes that can increase the risk of hepatotoxicity.¹³ LiverTox (<https://livertox.nih.gov>) is a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group to provide evidence-based up-to-date details on DILI for practising clinicians and researchers working on this field.¹⁴ Based on the cumulative evidence available for drug-induced hepatotoxicity, LiverTox has classified drugs into categories A, B, C, D, and T.¹⁵ Categories A and B have substantial case reports with adequate strength of associating the implicated drugs with liver injury. DILlrank is the largest reference rank dataset on drugs causing DILI, developed by the Food and Drug Administration (FDA) in the year 2016.¹⁶ DILlrank classifies 1036 FDA-approved drugs into most-, less-, no-, and ambiguous-DILI-concern drugs. It is vital to understand the hepatotoxic potentials of concomitant drugs administered in ICU setup, particularly in critically ill children receiving categories A and B drugs according to LiverTox or most/less-DILI concerns as per DILlrank classification. We envisaged the present study to assess the changes in liver function tests associated with primary antiepileptic agents belonging to the above categories and the associated factors for DILI in these critically ill children.

Methods

Study ethics and population

This study was carried out as a retrospective observational study after obtaining approval from our institution's ethics committees. Children admitted into the PICU between January 1, 2016, until December 31, 2018, were included in the study if they were administered any of the antiepileptic or anticonvulsant drugs with at least 1 assessment of serum liver enzyme levels and measurement of serum level of the concerned drug was carried out. Those children diagnosed without any primary liver disorders were included in this study.

Study procedure

Hospital records of eligible children were examined for the following details: demographic characteristics (eg, age and gender); diagnoses; laboratory investigations (eg, liver enzymes that included serum aspartate amino transferase [AST], alanine amino transferase [ALT], alkaline phosphatase [ALP], and gamma glutamyl transferase [GGT]); drug-related details (eg, dose, frequency, and duration); hospital stay; and outcome status (eg, dead or alive).

Definitions and classifications used

DILI has been classified according to the revised criteria by Council for International Organizations of Medical Sciences as follows: hepatocellular injury, ALT ≥ 2 upper limit of normal (ULN) reference range (RR) and R ≥ 5 ; cholestatic injury, ALP ≥ 2 ULN and R ≤ 2 ; mixed injury, ALT ≥ 3 ULN, ALP ≥ 2 ULN, and $2 < R < 5$. If ALT and ALP did not meet any of these criteria, it was called liver biochemical test abnormalities.¹⁷ The value of R was calculated using the formula (actual ALT/ALT ULN) / (actual ALP/ALP ULN). Our labo-

Table 1

List of antiepileptic drugs with their potential, degree, and concerns of hepatotoxicity as classified by drug-induced liver toxicity (DILI)rank and LiverTox*.

Antiepileptic drug	LiverTox category	DILlrank classification	
		Risk of DILI concern	Severity class
Carbamazepine	A	Most	7
Clonazepam	D	Less	3
Diazepam	E	Ambiguous	4
Divalproex sodium	Not classified	Most	8
Ethosuximide	E	Ambiguous	3
Felbamate	B	Most	7
Fosphenytoin	A	Most	8
Gabapentin	C	Less	3
Lacosamide	Not classified	Ambiguous	3
Lamotrigine	B	Most	7
Levetiracetam	C	Less	8
Lorazepam	Not classified	Ambiguous	3
Midazolam	Not classified	No	0
Oxcarbazepine	D	Less	3
Phenobarbitone	B	Less	3
Phenytoin	A	Most	8
Pregabalin	C	Less	0
Primidone	Not classified	No	0
Tiagabine	Not classified	Ambiguous	3
Topiramate	C	Less	3
Valproate sodium	A	Most	8
Vigabatrin	Not classified	Ambiguous	2
Zonisamide	D	Less	2

* LiverTox (<https://livertox.nih.gov>), a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group.

ratory provides age-specific reference ranges for liver function tests and these values were considered for assessing DILI.

LiverTox classifies the drugs based on the number of published cases with clear association with DILI into category A (≥ 50 cases); category B (12–49 cases); category C (4–11 cases); category D (1–3 cases), and category E (none). Those drugs that cause DILI only at higher than the recommended doses are categorized as T. Similarly, DILlrank classifies the drugs based on the reported concerns and severity of DILI. Table 1 lists the antiepileptic drugs based on the LiverTox and DILlrank categories. We classified ages of children per FDA classification into the following groups: neonate (birth–1 month), infant (1 month–2 years), children (2–12 years), and adolescents (12–16 years).¹⁵

Statistical analysis

Descriptive statistics was used for representing demographic characteristics. The χ^2 test for independence and Fisher exact probability test were used for the assessment of categorical variables wherever appropriate. Concomitant drugs with potential hepatotoxicity were classified as per LiverTox classification and DILlrank, and were assessed as categorical outcomes. Multivariable logistic regression analysis was used to assess the significance of association between the predictor variables (ie, age group, sex, antiepileptic drug, and number of LiverTox categories A and B drugs) in causing DILI. Only A and B of LiverTox categories were considered because other categories have limited evidence for their association with DILI. A similar regression analysis was carried out for DILlrank categories with the same predictor variables, and only the most- and less-DILI-concern concomitant drugs were included. The effect measures of variables in predicting DILI were expressed as odds ratio (95% CI). A *P* value ≤ 0.05 was considered significant. SPSS version 26 (IBM SPSS Statistics for Windows, Armonk, NY) was used for performing statistical tests.

Table 2
Regimen of the categories A/B line antiepileptic agents with concomitant antiepileptic drugs used in the study participants.

Drugs (n)	Age group (n)	Mean dose/kg (mg)	Route of administration, IV:PO (n)	Mean cumulative dose (mg)	Concomitant antiepileptic agent (n)
Phenobarbitone (9)	0–1 mo (3)	3.28	2:1	115	NA
	1 mo–2 y (3)	2.8	3:0	455	NA
	2–12 years (3)	2.3	0:3	586.7	Topiramate (2); lamotrigine (1)
Phenytoin (12)	0–1 mo (1)	2.5	1:0	300	NA
	1 mo–2 y (3)	3.01	3:0	750	Levetiracetam (2); oxcarbazepine (1)
Valproate (2)	2–12 y (8)	3.88	6:2	1263.9	Levetiracetam (3)
	2–12 y (2)	22.53	0:2	6800	Levetiracetam (1)
Phenytoin/phenobarbitone (10)	0–1 mo (1)	2.4/2.4	0:1	120/120	NA
	1 mo–2 y (8)	2.5/2.5	4:4	206/428.6	NA
	2–12 y (1)	2.7/3.1	1:0	1780/1610	Vigabatrin (1)
Phenytoin/phenobarbitone/valproate sodium (3)	2–12 y (3)	1.8/4.5/7.2	3:0	882.5/2360/9513	Levetiracetam (2); oxcarbazepine (1)
	phenobarbitone/Valproate sodium (1)	2–12 y (1)	8.7/8.7	0:1	250/3000
Phenytoin/valproate sodium (2)	2–12 y (2)	1.6/6.5	2:0	500/2200	Levetiracetam (1)
Carbamazepine/phenytoin (1)	2 y	17/10	0:1	2660/1680	NA
Valproate/ethosuximide (1)	2–12 y (1)	63/39	0:1	22,800/10,500	Levetiracetam (1)

IV = intravenous; NA = no additional; PO; by mouth.

Results

Demographic details

Forty-one patients were identified receiving drugs for seizure disorder out of the total 426 during the study period. Mean (SD) age was 3.9 years (3.8 years); body weight was 15.1 kg (13 kg); and male:female ratio was 26:15. Six had refractory status epilepticus; 5 had septic encephalopathy; 4 each had traumatic brain injury and cerebral palsy; 3 each had hydrocephalus with ventriculo-peritoneal shunt, encephalitis, and congenital heart disease; 2 each were diagnosed with hypoxic ischemic encephalopathy and metabolic disorder; and 1 each had astrocytoma with metastasis, glioblastoma, Treacher syndrome, DiGeorge syndrome, Down syndrome, hemophilia, chronic kidney disease on peritoneal dialysis, leukodystrophy, and metabolic disorder. Mean (SD) hospital stay of the study participants was 12.2 days (9.8 days).

Antiepileptic drug-related details

Eleven patients received phenytoin; 9 received phenobarbitone; 3 were administered valproate sodium; 10 children were administered phenytoin/phenobarbitone; 3 were given phenytoin/phenobarbitone/valproate sodium; and 1 each received phenytoin/valproate sodium, phenobarbitone/valproate and ethosuximide/valproate sodium, phenytoin/carbamazepine, and valproate sodium alone. Newer antiepileptic agents were administered with the aforementioned conventional antiepileptic drugs as follows: levetiracetam (n = 4 with phenytoin and n = 1 each with valproate sodium and phenytoin/phenobarbitone/valproate sodium), topiramate (n = 1 with phenobarbitone), vigabatrin (n = 1 with phenytoin/phenobarbitone), oxcarbazepine/levetiracetam (n = 1 each with phenytoin and phenytoin/phenobarbitone/valproate sodium), and topiramate/lamotrigine (n = 1 with phenobarbitone). A summary of the dose, route, frequency, and duration of the category A and B antiepileptic agents (phenytoin, phenobarbitone, valproate, and carbamazepine) along with the concomitant antiepileptic drugs for the various age groups are described in Table 2.

Serum levels of the antiepileptic drugs

Mean (SD) phenytoin levels amongst the study participants was 56.4 $\mu\text{mol/L}$ (46.6 $\mu\text{mol/L}$) (RR = 40–80 $\mu\text{mol/L}$). Eight samples of phenytoin were observed in the toxicity range with the mean (SD)

percent difference from the ULN of 37.9% (15.8%). Mean (SD) phenobarbitone serum levels was 149.9 $\mu\text{mol/L}$ (71.2 $\mu\text{mol/L}$) (RR = 65–172 $\mu\text{mol/L}$). Similar to phenytoin, 8 samples were in the toxicity range with the mean (SD) percent difference from the ULN being 28.6% (23%). Mean (SD) valproate sodium level was 259.2 $\mu\text{mol/L}$ (174.3 $\mu\text{mol/L}$) (RR = 350–700 $\mu\text{mol/L}$) and none were observed to be in the toxicity range.

Changes in the liver enzymes

Liver functions were checked on daily basis for all the patients on antiepileptic drugs. None of the children had either cholestatic or mixed type of hepatic injury. Similarly, no altered liver functions were observed in patients either receiving valproate alone or in combination with phenytoin, ethosuximide, or phenobarbitone. No significant differences ($P = 0.1$) were observed in the proportions of patients with hepatocellular injury or liver biochemical test abnormalities between the other antiepileptic drugs (Figure 1). Similarly, none of the patients taking valproate alone or in combination with phenytoin, phenobarbitone, or ethosuximide and phenytoin/carbamazepine showed elevation of GGT, whereas 6 out of 12 (50%) taking phenytoin, 7 out of 9 (77.8%) taking phenobarbitone, 8 out of 10 (80%) taking phenytoin/phenobarbitone, and all the patients who received phenytoin/phenobarbitone/valproate sodium showed such elevations. No statistically significant differences were observed in the aforementioned proportions showing GGT elevations ($P = 0.2$).

Concomitant drugs with hepatotoxic potential

Several drugs with potential to result in hepatotoxicity were administered concomitantly with antiepileptic drugs (Table 3). Irrespective of age group, there were minimum of 2 and maximum of 15 such drugs in the study population. Due to the number of constraints, statistical analyses for the differences in LiverTox categories were carried out only for phenytoin, phenobarbitone, and phenytoin/phenobarbitone groups; and no significant differences (P values = 0.3, 0.7, and 0.6, respectively) were observed. Assessment of hepatotoxicity potential for the concomitant drug with DILrank lead to a similar observation as summarized in Table 3. Nearly half of the concomitant drugs with hepatotoxic potential were antimicrobial drugs followed by drugs for stress ulcer prophylaxis (Table 4). However, we also observed certain differences between the LiverTox and DILrank classifications for certain drugs (Table 5).

Table 3
Potential hepatotoxic drugs administered with categories A/B antiepileptic drugs.

Category A/B antiepileptic drug	Age group	Concomitant hepatotoxic drugs	Category A/B*	Antiepileptic drug (n) [†]	Age group (n) [‡]
Phenobarbitone (9)	0-1 mo (3)	Ampicillin (C)-2; ranitidine (B)-2; cefotaxime (D)-1; ceftazidime (D)-1; acetazolamide (D)-1; omeprazole (B)-1; cefuroxime (D)-1; ceftriaxone (B)-1; ketamine (B)-1; enoxaparin (D)-1; vancomycin (C)-1; paracetamol (T)-1; meropenem (D)-1	B-5; C-3; D-6; T-1	MC,8-1; LC,5-4; LC,4-2; LC,3-5; LC,0-2	3 (2-6)
	1 mo-2 y (3)	Ampicillin (C)-1; cefotaxime (D)-1; acyclovir (D)-2; vancomycin (C)-2; omeprazole (B)-2; ceftriaxone (B)-1; metronidazole (C)-2; paracetamol (T)-2; amoxicillin-clavulanate (A)-1; meropenem (D)-1	A-1; B-3; C-5; D-3; T-2	LC,5-2; LC,4-3; LC,3-4; LC,0-1	4 (4-5)
	2-12 y (3)	Paracetamol (T)-2; amoxicillin-clavulanate (A)-1; lamotrigine (B)-1; topiramate (C)-2; ceftazidime (D)-1; omeprazole (B)-1; clonazepam (D)-1; ranitidine (B)-2; cefotaxime (D)-2; clindamycin (B)-1; cefepime (D)-1; fluconazole (B)-1	A-1; B-6; C-2; D-5; T-2	MC,8-1; MC,7-1; LC,5-5; LC,4-1; LC,3-6;	3 (3-9)
Phenytoin (12)	0-1 mo (1)	Amiodarone (A)-1; paracetamol (T)-1; meropenem (D)-1; omeprazole (B)-1; enoxaparin (D)-1; ampicillin (C)-1; cefotaxime (D)-1	A-1; B-1; C-1; D-3; T-1	MC,8-1; LC,5-1; LC,4-1; LC,3-3	6
	1 mo-2 y (3)	Paracetamol (T)-3; mebendazole (D)-1; ketamine (B)-1; ranitidine (B)-1; vancomycin (C)-1; fluconazole (B)-1; metronidazole (C)-1; levetiracetam (C)-1; ceftriaxone (B)-3; omeprazole (B)-3; enoxaparin (D)-1; cimetidine (B)-1; baclofen (D)-1; nifedipine (B)-1; ciprofloxacin (B)-1; meropenem (D)-1	B-12; C-3; D-4; T-3	MC,8-2; LC,8-1; LC,5-1; LC,4-6; LC,3-6; LC,2-1; LC,0-2	7 (3-8)
	2-12 y (8)	Paracetamol (T)-5; hydroxyurea (C)-1; omeprazole (B)-5; meropenem (D)-5; amoxicillin (B)-1; fluconazole (B)-2; clindamycin (B)-3; levetiracetam (C)-3; ceftriaxone (B)-2; vancomycin (C)-3; acyclovir (D)-1; ranitidine (B)-1; ketamine (B)-1; cefotaxime (D)-2; ondansetron (D)-2; captopril (B)-2; nifedipine (D)-2; acetazolamide (D)-1; cefepime (D)-1; amlodipine (C)-1; labetalol (C)-2; risperidone (C)-1; atenolol (D)-1; trimethoprim-sulfamethoxazole (A)-1; voriconazole (B)-1; etoposide (C)-1; metronidazole (C)-1; ceftazidime (D)-1	A-1; B-18; C-13; D-9; T-5	MC,8-6; LC,8-3; LC,7-4; LC,5-4; LC,4-9; LC,3-14; LC,0-4	4 (3-15)
Valproate sodium (2)	2-12 y (2)	Omeprazole (B)-2; vancomycin (C)-1; paracetamol (T)-1; levetiracetam (C)-1; ceftriaxone (B)-1; clindamycin (B)-1	B-4; C-2; T-1	LC,8-1; LC,4-4; LC,0-1	3

(continued on next page)

Table 3 (continued)

Category A/B antiepileptic drug	Age group	Concomitant hepatotoxic drugs	Category A/B*	Antiepileptic drug (n) [†]	Age group (n) [‡]
Phenytoin/phenobarbitone (10)	0–1 mo (1)	Ampicillin (C)-1; meropenem (D)-1; omeprazole (B)-1	B-1; C-1; D-1	LC,3-2; LC,4-1	4
	1 mo–2 y (8)	Ibuprofen (A)-1; ranitidine (B)-5; atenolol (B)-2; acetazolamide (D)-1; ampicillin (C)-3; ceftazidime (D)-1; meropenem (D)-3; vancomycin (C)-4; paracetamol (T)-2; ceftriaxone (B)-4; acyclovir (D)-2; hydralazine (A)-3; labetalol (C)-2; nifedipine (B)-2; captopril (B)-1; omeprazole (B)-3; cefuroxime (D)-1; labetalol (B)-1; amiodarone (A)-1; ketamine (B)-1; HCTZ (D)-1; cefotaxime (D)-1	A-5; B-19; C-9; D-10; T-2	MC,8-6; LC,7-1; LC,5-7; LC,4-9; LC,3-12; LC,2-1; LC,0-5	6 (3-9)
	2–12 y (1)	Clonazepam (D)-1; acetazolamide (D)-1; paracetamol (T)-1; vancomycin (C)-1; fluconazole (B)-1; cefepime (D)-1; omeprazole (B)-1; ciprofloxacin (B)-1; meropenem (D)-1; sildenafil (D)-1; ceftazidime (D)-1	B-3; C-1; D-6; T-1	MC,8-2; MC,7-1; LC,3-5; LC,4-1; LC,0-1	9
Phenytoin/phenobarbitone/valproate (3)	2–12 y (3)	Meropenem (D)-2; vancomycin (C)-2; levetiracetam (C)-2; omeprazole (B)-2; ketamine (B)-1; ceftazidime (D)-1; fluconazole (B)-1; nifedipine (B)-1; ranitidine (B)-1; cefepime (D)-1; captopril (B)-1; paracetamol (T)-1; aspirin (T)-1; ceftriaxone (B)-1; acyclovir (D)-1	B-8; C-4; D-3; T-2	MC,8-1; LC,8-2; LC,7-1; LC,5-1; LC,3-5; LC,0-3	7 (6–11)
Phenobarbitone/valproate (1)	2–12 y (1)	Ketamine (B)-1; labetalol (C)-1; hydralazine (B)-1; ceftriaxone (B)-1; paracetamol (T)-1; acyclovir (D)-1; atenolol (D)-1; amlodipine (C)-1; captopril (D)-1; enalapril (D)-1	B-3; C-2; D-4; T-1	MC,8-1; LC,7-2; LC,5-1; LC,4-2; LC,3-1; LC,0-1	8
Phenytoin/valproate sodium (2)	2–12 y (2)	Amoxicillin-calvulanate (A)-1; acyclovir (D)-1; ranitidine (B)-2; paracetamol (T)-2; levetiracetam (C)-1; cefotaxime (D)-1	A-1; B-2; C-1; D-2; T-2	LC,8-1; LC,5-4	4.5 (4–5)
Carbamazepine/phenytoin (1)	2 y	Omeprazole (B)-1; ceftriaxone (B)-1; clindamycin (B)-1; paracetamol (T)-1; ibuprofen (A)-1; ceftazidime (D)-1; clonazepam (D)-1; ondansetron (D)-1	A-1; B-3; D-2; T-1	LC,7-1; LC,4-2; LC,3-4	8
Valproate/ethosuximide (1)	2–12 y (1)	Clonazepam (D)-1; omeprazole (B)-1; vancomycin (C)-1; clindamycin (B)-1; cefotaxime (D)-1; levetiracetam (C)-1; fluconazole (B)-1	B-3; C-2; D-2	MC,8-1; LC,8-1; LC,5-1; LC,4-1; LC,3-2; LC,0-1	7

DILI = drug-induced liver injury; HCTZ = hydrochlorothiazide; MC = most-DILI concern; LC = less-DILI concern.

* LiverTox (<https://livertox.nih.gov>), a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group.

[†] Severity class classified between 0 and 8 according to Food and Drug Administration.

[‡] Excluded the category T because this class of drug is likely to result in DILI only at high doses.

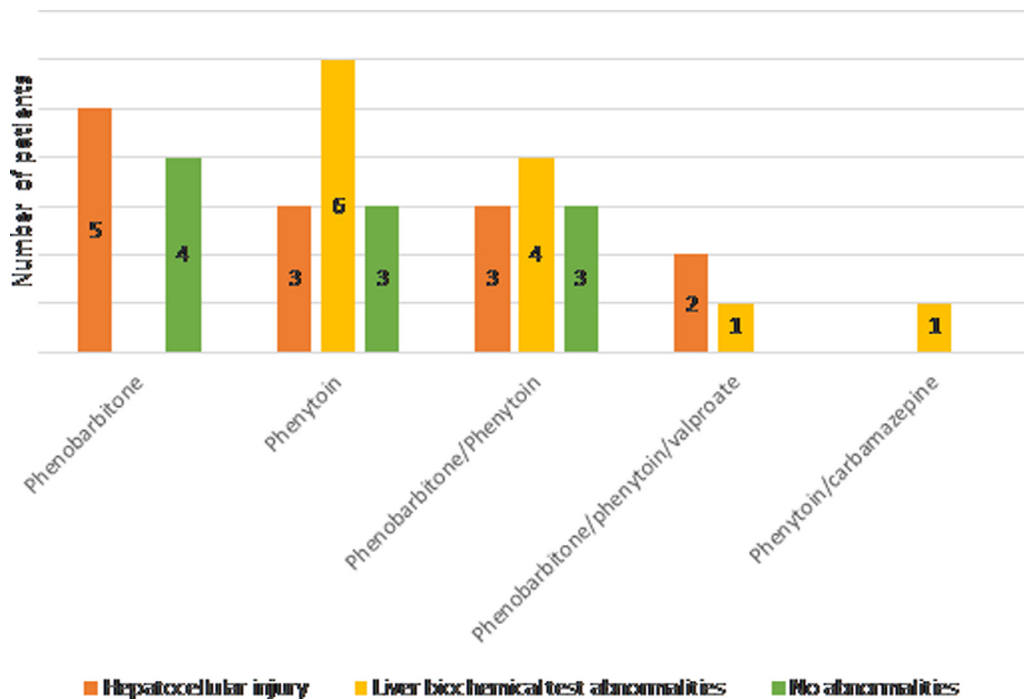


Figure 1. Hepatocellular injury and liver biochemical test abnormalities among the study participants. No significant differences were observed in the proportion of patients with any of the types of liver injury between the antiepileptic drugs.

Table 4

Total number of concomitant drugs with potential hepatotoxicity amongst the study cohort.

Drug class (%)	Drug	LiverTox* category	DILLrank concern; severity class	No. of children† (%)	
Antimicrobials (56.1)	Acyclovir	D	Not classified	8 (4.4)	
	Amoxicillin-clavulanate	A	Not classified	3 (1.7)	
	Ampicillin	C	LC; 3	8 (4.4)	
	Cefepime	D	LC; 3	4 (2.2)	
	Cefotaxime	D	LC; 5	10 (5.6)	
	Ceftazidime	D	LC; 3	7 (3.9)	
	Ceftriaxone	B	LC; 4	15 (8.3)	
	Clindamycin	B	LC; 3	7 (3.9)	
	Fluconazole	B	MC; 8	7 (3.9)	
	Meropenem	D	LC; 3	9 (5)	
	Metronidazole	C	LC; 3	7 (3.9)	
	Vancomycin	C	LC; 0	16 (8.9)	
	Drugs for SUP (21.1)	Omeprazole	B	LC; 4	24 (13.3)
		Ranitidine	B	LC; 5	14 (7.8)
Cardiovascular drugs (17.8)		Atenolol	D	LC; 4	4 (2.2)
	Captopril	B	LC; 7	5 (2.8)	
	Enoxaparin	D	LC; 3	3 (1.7)	
	Hydralazine	B	LC; 3	4 (2.2)	
	Labetalol	C	MC; 8	6 (3.3)	
	Nifedipine	B	LC; 3	6 (3.3)	
Others (5)	Acetazolamide	D	MC; 8	4 (2.2)	
	Ketamine	B	LC; 0	6 (3.3)	
	Ondansetron	D	LC; 7	3 (1.7)	

DILI = drug-induced liver injury; LC = Less-DILI concern; MC = Most-DILI concern; SUP = stress ulcer prophylaxis.

* LiverTox (<https://livertox.nih.gov>), a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group.

† Total number may exceed the total sample included because each child received multiple drugs.

Multivariable logistic regression analysis

A multivariable logistic regression model was developed for predicting the risk of hepatocellular injury or liver biochemical test abnormalities compared with children with normal liver enzymes (Table 6). Presence of concomitant category B hepatotoxic drugs (odds ratio = 2; 95% CI, 1–3.3) and toxic drug levels (odds ratio = 10; 95% CI, 1.4–1000) were associated with increased risks of DILI. A similar regression model for DILLrank categories was

developed and none of the evaluated factors were observed to be statistically significant (Table 7) although a trend was noted for the number of less-DILI-concern concomitant drugs ($P=0.06$) and toxic drug levels ($P=0.09$).

Discussion

We carried out the present study to assess the incidence and the associated factors for DILI in critically ill children receiv-

Table 5

Discrepancies between the LiverTox^{*} and drug-induced liver injury (DILI) rank classifications in classifying certain concomitant drugs in the study participants.

Drug	LiverTox category	DILlrank classification	
		DILI concern	Severity class
Acetazolamide	D	Most	8
Acyclovir	D	Not mentioned	
Amoxicillin-clavulanate	A	Only amoxicillin has been categorized as less-DILI concern and the severity class is 5. There is no mention for amoxicillin-clavulanate	
Divalproex sodium	Not categorized	Most	8
Hydralazine	A	Less	3
Labetalol	C	Most	8
Trimethoprim-sulfamethoxazole	A	Only trimethoprim has been categorized as less-DILI concern with the severity class 4. There is no mention for trimethoprim-sulfamethoxazole	

* LiverTox (<https://livertox.nih.gov>), a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group.

Table 6

Summary results of multivariable logistic regression analysis for the factors predicting the risk of hepatocellular injury and liver biochemical abnormalities with LiverTox^{*} categories of antiepileptic drugs.

Predictive factors	Hepatocellular injury/LBA [†]
Category A concomitant hepatotoxic drugs	0.5 [0.2–1.3]; 0.1
Category B concomitant hepatotoxic drugs	2 [1–3.3]; 0.05 [‡]
Age group: 0–1 mo [§]	5 [0.5–50]; 0.2
Age group: 1 mo–2 y [§]	2.5 [0.6–10]; 0.2
Male sex	0.4 [0.1–1.7]; 0.2
Category B antiepileptic drugs [§]	0.5 [0.1–3.3]; 0.5
Category A/B antiepileptic drugs [§]	2 [0.2–10]; 0.5
2 category A antiepileptic drugs [§]	ND
2 category A/B antiepileptic drugs [§]	0.2 [0.01–20]; 0.3
Drug level in the toxic range [#]	10 [1.4–1000]; 0.03 [‡]

LBA = liver biochemical test abnormalities; ND = not determined.

* LiverTox (<https://livertox.nih.gov>), a database conceptualized by the National Library of Medicine, National Institute of Diabetes and Digestive and Kidney Diseases and the Drug-Induced Liver Injury Network study group.

[†] Values are presented as odds ratio [95% CI]; *P* value.

[‡] Statistically significant.

[§] In reference to age group 2–12 y.

^{||} In reference to female sex.

[§] In reference to category A monotherapy.

[#] In reference to drug levels in the normal range.

ing antiepileptic drugs. Five out of 9 patients taking phenobarbitone (55.6%), 9 out of 12 taking phenytoin monotherapy (75%), 7 out of 10 taking phenytoin/phenobarbitone (70%), all 3 receiving phenytoin/phenobarbitone/valproate sodium, and 1 with phenytoin/carbamazepine developed DILI either in the form of hepatocellular injury or liver biochemical test abnormalities. None of the patients had cholestatic or mixed type of liver injuries. Similar number of patients receiving each of the above antiepileptic drug/s also showed elevations of GGT. Minimum 2 drugs with hepatotoxic potential were identified concomitantly with antiepileptic agents. Concomitant category B hepatotoxic drugs and toxic drug levels were associated with significantly increased risks of DILI with antiepileptic drugs. Similarly, a trend was observed for the less-DILI-concern concomitant class of drugs and toxic drug levels per DILlrank classification. Differences might exist between the DILlrank and LiverTox classifications of drugs that needs further exploration.

Sepsis and respiratory infections are the most common causes for admissions and consequent mortality in PICUs.^{16,17} Antimicrobial agents such as third-generation cephalosporins (eg, cefotaxime, ceftriaxone, and ceftazidime), aminopenicillins, amino-

Table 7

Summary results of multivariable logistic regression analysis for the factors predicting the risk of hepatocellular injury and liver biochemical abnormalities with drug-induced liver injury (DILI) rank classification of antiepileptic drugs.

Predictive factor	Hepatocellular injury/LBA [*]
Most-DILI-concern concomitant hepatotoxic drugs	0.7 [0.3–1.7]; 0.5
Less-DILI-concern concomitant hepatotoxic drugs	1.3 [1–1.7]; 0.06
Age group 0–1 mo [†]	3.3 [0.4–50]; 0.2
Age group of 1 mo–2 y [†]	2 [0.4–10]; 0.4
Male sex [‡]	0.4 [0.1–1.7]; 0.2
Ambiguous/Most-DILI-concern antiepileptic drugs [§]	ND
2 most/less-DILI-concern antiepileptic drugs [§]	0.1 [0.005–3.3]; 0.2
Most/less-DILI-concern antiepileptic drugs [§]	0.8 [0.1–5]; 0.8
2 most-DILI-concern antiepileptic drugs [§]	ND
Less-DILI-concern antiepileptic drugs [§]	0.2 [0.04–1.4]; 0.1
Drug level in the toxic range	5 [0.7–50]; 0.09

LBA = liver biochemical test abnormalities; ND = not determined.

* Values are presented as odds ratio [95% CI]; *P* value.

[†] In reference to age group 2–12 years.

[‡] In reference to female sex.

[§] In reference to most-DILI-concern antiepileptic monotherapy.

^{||} In reference to those drug levels in the normal range.

glycosides, meropenem, and vancomycin are commonly used in critically ill children in ICUs.^{18,19} We observed similar antimicrobial agents used in our study participants. With the exception of aminoglycosides, all other groups of antimicrobial drugs have been documented with DILI.¹⁵ Surprisingly, antimicrobial agents constitute the major class of drugs causing DILI as well as chronic liver damage according to registry studies.²⁰ Antiepileptic drug classes are the second leading group of implicated in causing DILI.²¹ Hence, the risk of DILI is certainly higher when such drug combinations are used out of necessity in PICUs. In the present study, we observed that all critically ill children received at least 1 antimicrobial drug with hepatotoxic potential. Similarly, drugs used for stress ulcer prophylaxis (SUP) such as ranitidine and omeprazole are also potentially hepatotoxic and should better be avoided at least when a most-DILI-concern as per DILlrank or category A LiverTox antiepileptic drug is administered to critically ill children. A recent network meta-analysis refuted any therapeutic benefits with all the drug classes that are used for SUP in critically ill adults, but there is dearth of evidence in pediatric populations.²² Sucralfate is as efficacious as proton pump inhibitors and histamine-2 receptor blockers for SUP at least in reducing the overt upper gastrointestinal bleeding.²² Sucralfate is a no-DILI-concern drug according to DILlrank classification and so shall be considered as a safe alternative to other drugs for SUP in critically ill children receiving antiepileptic drugs with greater risks of hepatotoxicity. With regard to the antimicrobial drugs, the choice is limited owing to the development of widespread resistance. On the other hand, most of the recent antiepileptic agents such as levetiracetam, lamotrigine, lacosamide, oxcarbazepine, pregabalin, gabapentin, and vigabatrin are associated with lower risks of DILI, and on considering the framework of similar efficacy to conventional antiepileptic drugs, should be preferred over the first-line antiepileptic drugs in children admitted into ICUs receiving concomitant drugs with hepatotoxic potential. Levetiracetam and lacosamide are also available intravenously and can be alternatives in status epilepticus.²³ A systematic review estimated that the efficacy of levetiracetam as an alternative to phenytoin in status epilepticus ranges between 44% and 94%.²⁴ A recent randomized clinical trial in children concluded that levetiracetam is equivalent to phenytoin in status epilepticus.²⁵ Hence, such drugs shall be preferred over the conventional antiepileptic agents in children at high-risk for DILI.

DILI from antiepileptic drugs can be either idiosyncratic or dose-related.²⁶ Idiosyncratic reactions are more common with the aromatic ring containing antiepileptic agents such as carba-

mazepine, phenytoin, and phenobarbitone and valproate.²⁷ We observed a greater risk of DILI with the antiepileptic drug levels in the toxicity range. Dose-DILI effect relationship has been well elucidated based on the quantum of metabolites especially for valproate sodium.²⁸ Polymorphisms in certain metabolizing enzymes were identified to be associated with antiepileptic agents-induced DILI.²⁹ Future studies should focus on identifying individuals with high-risk alleles predisposing DILI in critically ill patients. It is a great challenge for the treating physicians to maintain conventional antiepileptic agents within a narrow therapeutic window.³⁰ The recent antiepileptic agents have an advantage in this regard and shall be an alternative for children with unstable levels of conventional antiepileptic drugs.

The study is limited in not following up with the status of liver enzymes in patients after their transfer out from ICU; baseline duration of antiepileptic therapy was not available, and scores for assessing the severity of illness could not be used as complete details required for such scorings were not available from the hospital records.

Conclusions

We observed significant proportion of critically ill children who are taking antiepileptic drugs experience DILI either in the form of hepatocellular injury or liver biochemical test abnormalities. Guidelines recommending concomitant drugs with less/absent risk of potential hepatotoxicity in children admitted into ICUs who are receiving antiepileptic agents are the need of the hour.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Dr Kannan Sridharan was responsible for conceptualization of the study, the formal analysis, methodology, project administration, software, and writing the original draft. Dr Kannan Sridharan, Dr Amal Al Daylami, Dr Reema Ajjawi and Dr Husain Al Ajooz performed data curation and were responsible for the investigation, gathering resources, and review and editing of the manuscript.

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