Evaluating the Use of Medications Obtained Through Health Canada's Special Access Programme in Pediatric Status Epilepticus (SAP-P Status Epilepticus Study)

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Background

- Status epilepticus (SE): a convulsive seizure lasting > 5 minutes or a focal seizure lasting > 10 minutes
- Refractory status epilepticus (RSE): seizure not terminated with a 1st and 2nd line antiepileptic drug (AED)
- Few studies guide pharmacological management after failure of 1st and 2nd line AEDs
- 3rd line AEDs recommended in treatment of RSE are rectal paraldehyde, IV levetiracetam, IV valproic acid, and IV pentobarbital
- However, these 3rd line AEDs are only available through Health Canada's Special Access Programme (SAP) and their efficacy and safety are unknown
- SAP AED use in SE at BC Children's Hospital (BCCH) has not been reviewed

Objectives

- **Primary**: To describe the frequency of SAP AEDs used in pediatric SE at BCCH
- **Secondary**: To describe effectiveness and safety of SAP AEDs used in pediatric SE

Methods

- **Design**: Retrospective observational health record review
- **Inclusion**: Pediatric patients, aged 1 month to 19 years with a diagnosis of SE, admitted to BCCH between Jan 2008 to Sept 2018, who received ≥ 1 dose of SAP AED
- **Effectiveness**: Time to seizure termination, patient disposition, and number, dose, and duration of SAP AEDs used
- **Safety**: Adverse effects (AE) with a Naranjo score of ≥ 4 (probable to definite AE) were reported
- **Statistics**: Sample size of convenience, descriptive statistics

Results

Table 1. Patient Characteristics

	N = 49
Male (n (%))	27 (55)
Median age (range)	3 years (1 month – 16 years)
Median weight (range)	15.7 (6-65) kg
SE events (n)	58
Patients with ≥ 2 SE events (n (%))	6 (12)
Admissions to hospital (n)	53
Patients with ≥ 2 hospital admissions (n (%))	3 (6)
Known seizure disorder prior to admission (n (%))	32 (65)
Median AEDs prior to admission (range)	1 (0-4)
≥ 3 AEDs prior to admission (n (%))	13 (25)

Table 2. Patient Characteristics by SAP AEDs

	Paraldehyde	Levetiracetam	Valproic acid	Pentobarbital
	n = 29	n = 21	n = 7	n = 7
Known seizure disorder prior to admission (n (%))	22 (76)	12 (57)	4 (57)	3 (43)
Median AEDs prior to admission (range)	2 (0-4)	1 (0-3)	1 (0-4)	0 (0-4)
≥ 3 AEDs prior to admission (n (%))	10 (34)	3 (14)	1 (14)	1 (14)

Figure 1. Frequency of SAP AED Use (N = 58 events)

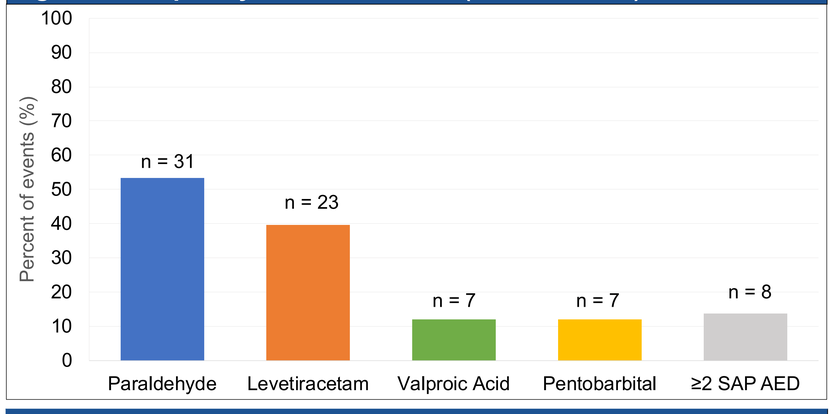

Table 3. Outcomes of SE Events (N = 58)

Median AEDs given for SE (range)	3 (0-15)
Treatment with ≥ 2 SAP AEDs (n (%))	8 (14)
Treatment with ≥ 2 days of SAP AEDs (n (%))	10 (17)
Median seizure duration (range)	135 minutes (10 minutes – 60 days)
Median seizure duration from 1st AED in hospital (range)	95 minutes (6 minutes – 60 days)
Median length of stay in hospital (range)	11 (1-88) days
Admissions requiring ICU (n (%))	36 (68)
Median length of stay in ICU (range)	4 (0-62) days
Mortality (n (%))	5 (10)

Table 4. Outcomes by SAP AEDs

	Paraldehyde	Levetiracetam	Valproic acid	Pentobarbital
	n = 31	n = 23	n = 7	n = 7
Median AEDs prior to SAP AED (range)	1 (0-4)	1 (0-3)	3 (0-7)	4 (3-7)
Treatment with ≥ 2 SAP AEDs (n (%))	2 (6)	5 (22)	6 (86)	5 (71)
Treatment with ≥ 2 days of SAP AEDs (n (%))	4 (13)	3 (13)	4 (57)	6 (86)
Median length of stay in hospital (range)	6 (2-85) days	14 (2-88) days	50 (10-88) days	55 (5-88) days
Admissions requiring ICU (%)	59	71	100	100
Median length of stay in ICU (range)	2 (1-41) days	7 (2-62) days	34 (2-62) days	48 (3-62) days
Mortality (n (%))	1 (3)	3 (14)	2 (29)	3 (43)

Table 5. Dose and Duration of SAP AEDs

	Paraldehyde	Levetiracetam	Valproic Acid	Pentobarbital
Median dose (range)	0.28 (0.1-0.5) mL/kg/dose	40 (17.5-60) mg/kg/day	32 (15-48) mg/kg/day	3 (1-5) mg/kg/hour
Median duration (range)	1 (1-9) day	1 (1-18) day	1 (1-21) day	18 (2-26) days

Table 6. Frequency of Adverse Effects of SAP AEDs

	Paraldehyde	Levetiracetam	Valproic acid	Pentobarbital
	n = 31	n = 23	n = 7	n = 7
Hyperammonemia	0	0	1 (14%)	0
Metabolic derangements	1 (3%)	0	0	1 (14%)
Pancreatitis	0	0	1 (14%)	0
Dermatologic change	0	0	0	1 (14%)
Hypotension	1 (3%)	0	0	3 (43%)
SAP AED discontinued due to AE	0	0	0	2 (29%)

Limitations

- Effectiveness confounded by heterogeneity in patient, seizure, and treatment characteristics
- Adverse effects confounded by simultaneous medications, physiologic effects of prolonged seizure, and co-morbidities

Conclusions

- Paraldehyde and levetiracetam were most frequently used
- Paraldehyde and levetiracetam were frequently used as 2nd line agents before phenytoin and phenobarbital
- Pentobarbital was associated with the highest frequency of adverse effects, while levetiracetam had the lowest
- Unable to assess effectiveness due to multiple confounders