Purpose: To determine whether the treatment with high-dose oral diazepam could control dyskinesia in anti-NMDA receptor encephalitis, we analyzed therapeutic efficacy of high-dose diazepam in dyskinesia associated with anti-NMDA receptor encephalitis.

Methods: We reviewed the cohort data of patients diagnosed with anti-NMDA receptor encephalitis who were admitted to Seoul National University Hospital between January 2012 and July 2018 with moderate to severe dyskinesia. Diazepam was administered orally or via a nasogastric tube, 3 to 6 times a day. We assessed the treatment effect by comparing dyskinesia severity using a grading system at the initiation of diazepam treatment, on the first day of high-dose diazepam, and after one week of treatment with high-dose diazepam.

Results: Thirty-three patients with anti-NMDA receptor encephalitis and dyskinesia were treated with high-dose oral diazepam (ranging from 6 mg to 180 mg), along with immunotherapy. The severity of dyskinesia improved significantly (p-value<0.001), from median grade 3.5 (ranging from 2 to 4) to median grade 2 (ranging from 0 to 4), after one week of high-dose diazepam. No patients had serious adverse events except mild sedation.

Conclusions: We have treated the dyskinesia with high-dose oral diazepam in number of cases, and the treatment was effective and safe. This study suggests that oral administration of high-dose diazepam could be a promising treatment option for the management of severe dyskinesia in anti-NMDA receptor encephalitis.

doi:10.1016/j.yebeh.2019.08.060

Epilepsy & Behavior 101 (2019) 106786

Assessment of antiseizure and neuroprotective effects of novel compounds in a delayed-treatment rat model of organophosphate (OP) exposure

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Background: It is well-known that exposure to organophosphates (OP), including nerve agents, results in status epilepticus (SE) and neuronal damage in the brain. Early control of seizure activity reduces mortality and damage. In the event of a mass release, treatment is likely to be greatly delayed compared to what would occur in a hospital setting. Therefore, there is a pressing need for treatments that can be administered after a significant delay and in a pre-hospital situation. The CounterACT Neurotherapeutic Screening (CNS) Program has now tested 9 externally submitted and 8 internally chosen compounds for this purpose.

Methods: Male, Sprague Dawley rats (150-200 g) were implanted for electroencephalogram (EEG) recordings. SE was induced by diisopropyl fluorophosphate (DFP). One hour after SE onset, rats were co-administered midazolam (MDZ) and a test compound or MDZ alone. EEG was recorded for 24 hr, followed by perfusion, tissue collection and labeling with Fluoro-Jade B. Neurons positive for Fluoro-Jade B were counted in 10 brain regions: dorsal CA1, dorsal CA3, hilus, ventral CA1, ventral CA3, amygdala, thalamus, and the parietal, entorhinal and piriform cortices. All data were analyzed quantitatively with blind procedures.

Results: Of the externally submitted compounds, compared to MDZ alone, significant anti-seizure effects were found for two compounds. These compounds reduced both seizure power and seizure duration. Each of these compounds also reduced neuronal death, compared to when MDZ was administered alone. In the same protocol, these data were compared to: (1) ganaxolone (with MDZ), which had a minimal effect on seizures, and (2) bumetanide (also with MDZ), which had no effect on seizures. Both of these latter compounds also had no effect on neuronal death.

Conclusions: These data demonstrate that MDZ-induced suppression of OP-mediated SE can be enhanced by co-administration of other compounds, even when both compounds are administered at a long-delay (i.e., 1 hr) after SE onset. Furthermore, this delayed treatment can significantly reduce neuronal death. This screening program will continue to search for other compounds that may provide better treatment of OP-induced SE.

doi:10.1016/j.yebeh.2019.08.061

Epilepsy & Behavior 101 (2019) 106787

Development of Antiepileptic Drugs Box for Status Epilepticus Fast Track (SE BOX)

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Background and Objective: Status epilepticus (SE) is one the most concerned issue in patient treatment. Due to it can lead to disability and mortality. Hence, the most important key is to control the seizure within 1 hour after patient had symptom. The principle of SE treatment is to shorten the time to receive the treatment. Physician must be able to give an early diagnose (Time to diagnosis) and start medicine immediately (Time to Treatment). This study aims to root cause analysis SE service problems and development SE BOX for ready to use.

Methods: The study design was action research phase I, we root cause analysis about problems of SE service by collected data from electronic hospital database between 1st October 2017 and 30st September 2018 at Srinagarind hospital.

Results: The important problems of SE service from root cause analysis 19 patients with SE were delay of treatment such as the mean time to diagnosis was 272 minutes (0-53 hours) and mean time to treatment was 32 minutes (0-80 minutes). The average waiting time of stat dose was 13.24 minutes and the percent achievement of 20 minutes guarantee time was 82.6%. However, this waiting time was collected only in pharmacy department not include the delivery time to carry the medicine to wards. Moreover, from drug information service data there were 17 questions about IV antiepileptic drug which were asked by physicians and nurse the most stability/compatibility, dose/administration, ADR/side effect respectively. From those issues, there are many steps and these can lead to the delay of treatment. As a result, Integrated Epilepsy Research Group is developing the system of antiepileptic drugs to be ready-to-use by preparing SE Box. The box consists of 4 drugs; Phenytoin injection (6 vials), Phenobarbital injection (5 amp),

Sodium valproate injection (6 vials) and Levetiracetam injection (8 vials) encloses with all drug information sheets to serve information which health care provider need before drug administration.

Conclusion: SE BOX may be suitable for resolve the problems of SE service to reduce the waiting time and improve effectiveness of SE treatment; however the benefit of SE BOX need more study.

Keywords: status epilepticus; SE, AED

doi:10.1016/j.yebeh.2019.08.062

Epilepsy & Behavior 101 (2019) 106788

Intranasal midazolam as initial in-hospital treatment for status epilepticus: A pharmaco-EEG cohort study

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Background: To evaluate the efficacy and tolerability of intranasal midazolam (in-MDZ) as first line in-hospital therapy in patients with status epilepticus (SE) during continuous EEG recording.

Methods: Medical records of all patients treated with in-MDZ during EEG recording between August 2015 and April 2018 were retrospectively reviewed. Data on medical history, etiology and semiology of SE, as well as anticonvulsive medication, efficacy, and safety of in-MDZ was collected. Time to end of SE regarding administration of in-MDZ and beta-band effects were independently analysed by two board certified epileptologists on EEG and with frequency analysis.

Results: In total, 42 patients (mean age 52.7 ± 22.7 years; 23 female) were treated with a median dose of 5 mg in-MDZ (range 2.5-15 mg, mean 6.4 mg, SD 2.6) for SE. Most of the patients suffered from non-convulsive status epilepticus (n = 24; 55.8%). In total, 24 (57.1%) patients were responders as SE stopped after administering in-MDZ without any other drug being given in-between. On average, SE ceased on EEG five minutes and five seconds after application of in-MDZ (median 04:56 mins; range 00:29 mins -14:53 mins; SD 03:13mins). Frequency analysis showed an increased beta-band on EEG after application of in-MDZ at four minutes and seven seconds on average (median 03:50; range 02:20 - 05:40; SD 01:09 mins). Adverse events were recorded in six patients (14.3%) with nasal irritations in five (11.9%) and prolonged sedation in one (2.6%) patient.

Conclusions: This pharmaco-EEG based study showed that in-MDZ is effective and well-tolerated for initial treatment of SE. EEG and clinical effects occur within 04:07 and 5:05 mins on average. Intranasal administration of midazolam appears to be an easily applicable and rapidly effective alternative to buccal and intramuscular application as first line treatment if an intravenous route is not available.

doi:10.1016/j.yebeh.2019.08.063

Epilepsy & Behavior 101 (2019) 106789

Effect of ZX008 (Fenfluramine HCl Oral Solution) on Total Seizures in Dravet Syndrome

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Objective: Assess ZX008 (fenfluramine) effect on total seizure frequency in patients with Dravet syndrome.

Background: Dravet syndrome (DS) is a rare, severe, treatment-resistant, developmental epileptic encephalopathy. In a Phase 3, randomised, double-blind, placebo-controlled trial, ZX008 significantly reduced convulsive seizure (CS) frequency (defined as tonic-clonic, hemiclonic, tonic, atonic, clonic, and focal motor seizures). We present secondary analyses of total seizure (TS) frequency (defined as CS plus absence or atypical absence, myoclonic, atonic, and focal seizures without clear observable motor signs).

Methods: Patients (2-18y) with DS, and CSs not controlled by current anti-epileptic drug regimen were enrolled. Following a 6-week baseline period, patients were randomised 1:1:1 to placebo, ZX008 0.2 mg/kg/day (ZX008/0.2), or ZX008 0.8 mg/kg/day (ZX008/0.8; maximum 30 mg/day), and treated for 14 weeks, including 2-week titration. Caregivers recorded seizure number and type daily via electronic diary.

Results: A total 119 patients were randomised (10.1% UK, mean age 9 ± 4.7y). Baseline median monthly TS frequency ranged from 40.7–53.9 across groups. ZX008 significantly reduced TS frequency in a dose-related manner during 14 weeks' treatment. Median TS frequency reductions were 13.1% with placebo, 34.3% with ZX008/0.2 ($p = 0.031$), and 70.1% with ZX008/0.8 ($p < 0.001$). Median non-CS seizure subtype reductions (combined) were 55.6% with placebo and 75.1% with ZX008/0.8 ($p < 0.035$), including a 54.8 and 78.6% reduction in absence and 34.8 and 64.0% reduction in myoclonic seizures, respectively. Seizure freedom was experienced by 3 (7.5%) subjects with ZX008/0.8, 3 (7.7%) with ZX008/0.2, and none with placebo. Median longest seizure-free interval was significantly longer in ZX008 groups vs placebo. ZX008 was generally well-tolerated, and no cases of FDA-defined cardiac valvulopathy were observed; neither were there echocardiographic findings or clinical symptoms suggesting pulmonary hypertension.

Conclusions: In addition to significantly reducing convulsive seizures, ZX008/0.8 mg/kg/day also significantly reduced other