Neuropathology was assessed as the number of FJB positive cells in 10 brain regions: dorsal CA1, dorsal CA3, hilus, ventral CA1, ventral CA3, amygdala, thalamus, and the parietal, entorhinal and piriform cortices.

Results: At 30, 60 and 120 min after the start of SE, MDZ treatment significantly reduced both seizure power as well as EEG spike frequency for several hours. However, at all three time points, MDZ did not completely terminate electrographic SE and had no significant effect on neuronal death. However, when data for MDZ treatment were combined from all three delay times, a small but significant reduction in global neuronal death was detected when compared to vehicle treatment.

Conclusions: These data demonstrate that treatment of OP-induced SE by MDZ can reduce seizure intensity even when delayed by as much as 120 min. However, this treatment alone was insufficient to completely stop seizures and resulted in a minimal reduction in cell death, indicating the need for better treatment options that enhance neuronal survival following OP exposure.

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Rapid intranasal delivery of diazepam utilizing prodrug/enzyme formulations: a promising drug delivery strategy for outpatient treatment of seizure emergencies

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Background: Diazepam is effective in interrupting status epilepticus and halting acute repetitive seizures. It is imperative to achieve a therapeutic concentration of diazepam as quickly as possible, because 1) seizures become increasingly difficult to control when treatment is delayed, so a short window of opportunity exists when rescue therapy with benzodiazepines, such as diazepam, is maximally effective; and 2) the risk of life-threatening complications and permanent neuronal damage increases with prolonged seizure activity. Substantial effort and resources have been dedicated to developing a safe, rapid-acting diazepam nasal spray that can be administered in emergency situations or prophylactically by patients who experience auras. However, formulating an aqueous solution of diazepam for a nasal spray device has been challenging because the drug has very low solubility. This solubility issue can be circumvented by co-administering a hydrophilic prodrug of diazepam with a converting enzyme. Besides addressing solubility, this strategy leads to an increase in the chemical activity gradient that drives drug absorption.

Methods: A pharmacokinetic study in rats was performed. Single doses of a hydrophilic diazepam prodrug, avizafone (equivalent to diazepam at 0.500, 1.00, and 1.50 mg/kg), and a converting enzyme, human *aminopeptidase B*, were administered intranasally. Resulting diazepam concentrations were measured in plasma samples and in whole brain homogenates at time points ranging from 2 to 90 minutes.

Results: Both diazepam and a transient open ring intermediate were readily absorbed through the nasal mucosa, with first order absorption rate constants 0.122 ± 0.022 min^{-1} for the intermediate and 0.0689 ± 0.0080 min^{-1} for diazepam. For the low, medium, and high dose levels respectively, bioavailablities were 77.8 ± 6.0, 112 ± 10, and 114 ± 7 %; maximum plasma concentrations were 71.5 ± 9.3, 388 ± 31, and 355 ± 187 ng/mL; and times to peak plasma concentration were 5, 8, and 5 min.

Conclusions: Our results demonstrate that practically insoluble diazepam can be delivered intranasally with rapid and complete absorption by co-administering avizafone with aminopeptidase B. Therapy based on this aqueous drug formulation approach is expected to result in swift rescue from seizure emergencies, with an excellent safety profile.

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Novel Use of the 'Photosensitivity Model of Epilepsy' to Identify the Rapidity of Anti-Epileptic Drug (AED) CNS Penetration: Implications for Future Choice in iv Treatment of Status Epilepticus (SE)

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Background: The overall 40-70% efficacy rate for status epilepticus (SE) treatment by AEDs is not optimal; *time* required to abort seizures is key. The conventional human Phase-IIa "Photosensitivity Model in Epilepsy" has been successfully utilized to identify efficacy of single *oral* doses of potential new AEDs, including Levetiracetam-(LEV) and brivaracetam-(BRV); both suppressed EEG photosensitivity response at ≥1h. In order to assess differences in time to effect of intravenous neuroactive AEDs, the Model's procedure needs to be conducted every few minutes. The conventional 'Model' involves simultaneous, intermittent (regular, hourly intervals x12hr) photic-induced EEG + blood sampling for concurrent AED concentration. EEG measurements are time-intensive, requiring 7-10min of operational activity (3-eye conditions at separate flash frequencies [2-60 Hz]) per photic-stimulation-result. 'The Model' methodology has not yet been applied to i.v. AEDs, where EEG effect is anticipated in <30min.

Methods: The 'Model' needed to become more time efficient; we adapted it:

i. by studying AED-produced change in each volunteer-patient's EEG upper limit/threshold only (Kasteleijn-Nolst Trenité DG, Reed RC. Epilepsy Curr 2013; 13 (Suppl 1).
ii. by limiting 3 eye conditions to a "best one" (via screening photosensitivity-data);