



References on the Administration of Anticonvulsive Agents Using ALZET® Osmotic Pumps

1. Carbamazepine

Q5784: K. Deseure, *et al.* Differential drug effects on spontaneous and evoked pain behavior in a model of trigeminal neuropathic pain. *J Pain Res* 2017;10(279-286)

ALZET Comments: Carbamazepine, baclofen, clomipramine; DMSO, PEG, Ethyl Alcohol, Acetone; SC; Rat; 2ML1; Controls received mp w/ vehicle; animal info (7 weeks old); dimethyl sulfoxide, propylene glycol, ethyl alcohol, and acetone at a ratio of 42:42:15:1; post op. care (morphine 5 mg/day); behavioral testing (Facial grooming); Therapeutic indication (Trigeminal neuralgia, neuropathic pain);

Dose (30 mg/day carbamazepine (the first-line drug treatment for trigeminal neuralgia), 1.06 mg/day baclofen, 4.18 mg/day clomipramine, and 5 mg/day morphine);.

Q0269: S. M. Cain, *et al.* High resolution micro-SPECT scanning in rats using ¹²⁵I beta-CIT: Effects of chronic treatment with carbamazepine. *Epilepsia* 2009;50(8):1962-1970

ALZET Comments: Carbamazepine; DMSO; propylene glycol; ethyl alcohol; acetone; SC; Rat; 2ML2; 14 days; Controls received mp w/ vehicle; animal info (adult, male, Sprague-Dawley, 160-270 g); functionality of mp verified by serum drug levels; 42% DMSO used; identified 3 mg/kg/day as the highest dose that could be reliably administered via minipumps over a 14-day period at 37 degrees Celsius, pg. 1969.

P5195: H. C. Doheny, *et al.* A comparison of the efficacy of carbamazepine and the novel anti-epileptic drug levetiracetam in the tetanus toxin model of focal complex partial epilepsy. *British Journal of Pharmacology* 2002;135(6):1425-1434

ALZET Comments: Carbamazepine; levetiracetam; DMSO; Propylene glycol; ethanol, saline; IP; Rat; 7 days; Controls received mp/ vehicle; functionality of mp verified by drug serum levels; dose-response (text p.1428); carbamazepine was dissolved in 42.5% DMSO/42% Propylene glycol/15% ethanol. Levetiracetam was dissolved in saline; 2-day recovery period given using coiled PE-40 tubing; epilepsy; anticonvulsant.

2. Deprenyl

P9373: F. Chenu, *et al.* Long-term administration of monoamine oxidase inhibitors alters the firing rate and pattern of dopamine neurons in the ventral tegmental area. *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY* 2009;12(4):475-485

ALZET Comments: Clorgyline; phenelzine; deprenyl; SC; Rat; 2, 21 days; Controls received mp w/ saline; enzyme inhibitor (MAO, monoamine oxidase); animal info (male, Sprague Dawley, 250-300 g.).

P5438: J. M. Mejia, *et al.* Monoamine oxidase inhibition during brain development induces pathological aggressive behavior in mice. *Biological Psychiatry* 2002;52(8):811-822

ALZET Comments: Chlorgyline; Deprenyl; Saline; SC; Mice (pregnant); 2002; 2004; 6 weeks; Controls received mp w/ vehicle; teratology; enzyme inhibitors (monoamine oxidase inhibitors); 2002 pumps were replaced w/ 2004 pumps after 2 weeks to complete a 6 week infusion; agents infused singly or concomitant in the same pump.

P4227: W. Loscher, *et al.* Anticonvulsant efficacy of L-deprenyl (selegiline) during chronic treatment in mice: continuous versus discontinuous administration. *Neuropharmacology* 1998;37(1587-1593)

ALZET Comments: Deprenyl, L-; Water, distilled; SC; mice; 2002; 2004; 2,4 weeks; controls received mp w/saline; functionality of mp verified by residual volume; comparison of daily i.p. injections vs. mp; good methods (p. 1588); anticonvulsant; also called selegiline.

P3400: M. C. Carrillo, *et al.* The optimal dosage of (-) deprenyl for increasing superoxide dismutase activities in several brain regions decreases with age in male Fischer 344 rats. *Life Sci* 1993;52(1925-1934)

ALZET Comments: Deprenyl; Saline; SC; Rat; 3 weeks; controls received mp w/saline; dose-response.



P3067: D. D. Mousseau, *et al.* Effects of age and chronic antidepressant treatment on [3H]tryptamine and [3H]dihydroalprenolol binding to rat cortical membranes. *Cell. Molec. Neuro* 1993;13(1):3-13

ALZET Comments: Imipramine HCl; Desipramine HCl; Clomipramine HCl; Tranylcypromine HCl; Phenelzine sulfate; Clorgyline HCl; Deprenyl HCl; SC; Rat; 2002; 2ML4; 14,28 days; antidepressant; controls received mp with vehicle; drug concentrations determined from Greenshaw program.

3. Levetiracetam

Q8196: C. H. Fu, *et al.* Early Seizure Activity Accelerates Depletion of Hippocampal Neural Stem Cells and Impairs Spatial Discrimination in an Alzheimer's Disease Model. *Cell Rep* 2019;27(13):3741-3751 e4

Agents: Levetiracetam **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;

ALZET Comments: Dose (75 mg/kg/day); Controls received mp w/ vehicle; animal info (); levetiracetam aka LEV; neurodegenerative (Alzheimer's);

Q7955: P. M. Casillas-Espinosa, *et al.* Disease-modifying effects of a novel T-type calcium channel antagonist, Z944, in a model of temporal lobe epilepsy. *Prog Neurobiol* 2019;182(101677

Agents: Z944; levetiracetam **Vehicle:** saline, normal, propylene glycol and DMSO buffered; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 1, 4 weeks;

ALZET Comments: "Dose ((Z944 60 mg/kg/day), (levetiracetam 200 mg/kg/day)); 40% propylene glycol, 40% DMSO, and 20% normal saline solution used; Controls received mp w/ vehicle; animal info (11 weeks, male, Wistar); behavioral testing (Sucrose preference, Elevated plus maze, Open field, Morris water maze, Forced swim test); Z944 is a highly potent and selective T-type Ca²⁺ channel antagonist; neurodegenerative (Temporal lobe epilepsy); Therapeutic indication (continuous levetiracetam infusion significantly reduced the average number of seizures and the seizure severity in comparison to vehicle treated animals, but without affecting the latency to the first seizure. Z944 treatment after SE significantly prolonged the latency to develop the first spontaneous seizure and also reduced the average number of seizures in comparison to the vehicle treated counterparts); "

Q6467: R. P. Haberman, *et al.* Heightened cortical excitability in aged rodents with memory impairment. *Neurobiol Aging* 2017;54(144-151

Agents: Levetiracetam **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

ALZET Comments: Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Aged, male Long-Evans rats);

Q4492: M. Levesque, *et al.* The anti-ictogenic effects of levetiracetam are mirrored by interictal spiking and high-frequency oscillation changes in a model of temporal lobe epilepsy. *SEIZURE-EUROPEAN JOURNAL OF EPILEPSY* 2015;25(18-25

Agents: Levetiracetam **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 2 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-300g); cardiovascular; "These pumps deliver a continuous dosing over 2 weeks, circumventing the need for repetitive invasive blood sampling." pg 19;

Q5035: A. R. Ko, *et al.* Blockade of endothelin B receptor improves the efficacy of levetiracetam in chronic epileptic rats. *Seizure* 2015;31(133-40

Agents: Levetiracetam; SB202190; BQ788 **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 1003D; **Duration:** 3 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 7 days); pumps replaced between trials;

4. Phenobarbital

R0242: W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. *Epilepsia* 2007;48(7):1245-1258



ALZET Comments: Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4,2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments); half-life (p. 1247) table 1 (18 compounds); animal info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.

P0494: F. J. Hock, *et al.* A novel method for the administration of the enzyme inducer phenobarbital to rats via an osmotic minipump. IRSC Med. Sci. : Biochem 1984;12(8):661

ALZET Comments: Phenobarbital; SC; Rat; 2002; 8 days; Comparison of phenobarb. consumed po in drinking water vs. mp infusion; author states advantages of mp use.

P0447: T. P. Davis, *et al.* Centrally acting drugs alter in vitro B-endorphin processing in the rat. Eur. J. Pharmacol 1984;100(249-251

ALZET Comments: Chlorpromazine; haloperidol; phenobarbital; promethazine; SC; Rat; 2001; 8 days; Comparison of agents effects.

P0401: W. Kuhn, *et al.* A new method for kinetic studies of drug interactions in experimental animals during steady state: controlled-rate application of valproic acid, phenobarbital and their combinations via implanted osmotic minipumps in the mouse. Arzneimittelforschung 1983;33(11):1579-1582

ALZET Comments: Phenobarbital, sodium; Valproate, sodium; Water; SC; mice (pregnant); 2001; 2002; 1 and 2 weeks; no stress see p. 1580, 1582; 1-2 pumps/animal; VPA and PB used singly and in combination in mp.

P0311: I. M. Kapetanovic, *et al.* Phenobarbital pharmacokinetics in rat as a function of age. Drug Metab. Disp 1982;10(6):586-589

ALZET Comments: Phenobarbital; Water; IP; Rat; 5 days; bolus injec. vs. mp infusion.

5. Promethazine

P0447: T. P. Davis, *et al.* Centrally acting drugs alter in vitro B-endorphin processing in the rat. Eur. J. Pharmacol 1984;100(249-251

ALZET Comments: Chlorpromazine; haloperidol; phenobarbital; promethazine; SC; Rat; 2001; 8 days; Comparison of agents effects.

6. Tiagabine

R0177: A. Pitkanen. Efficacy of current antiepileptics neurodegeneration in epilepsy to prevent models. Epilepsy Research 2002;50(1-2):141-160

ALZET Comments: Vigabatrin; Tiagabine; SC; Rat; 2 months; Neuroprotection; pump use mentioned on p. 147 and 155; long-term study.

P4724: A. Cleton, *et al.* Pharmacokinetic-pharmacodynamic modelling of tiagabine CNS effects upon chronic treatment in rats: lack of change in concentration-EEG effect relationship. European Journal of Pharmacology 2000;12(141-150

ALZET Comments: Tiagabine;; Saline;; IV (jugular);; Rat;; 2ML2;; 14 days;; Controls received mp w/ vehicle; functionality of mp verified by plasma levels; dose-response (graph p. 145); comparison of IV injections vs. mp; Tiagabine is a GABA uptake inhibitor; seizure prevention; Epilepsy;.

P3415: T. Halonen, *et al.* Tiagabine prevents seizures, neuronal damage and memory impairment in experimental status epilepticus. Eur. J. Pharmacol 1996;299(69-81



ALZET Comments: Tiagabine; Propylene glycol; SC; Rat; 2ML1; 7 days; functionality of mp verified by in vitro testing and residual volumes; dose-response; half-life (p. 70); compound stable for one week (see p. 78); stability.

7. Valproic Acid

Q6273: Z. Wang, *et al.* Infusion of Valproic Acid Into the Renal Medulla Activates Stem Cell Population and Attenuates Salt-Sensitive Hypertension in Dahl S Rats. *Cell Physiol Biochem* 2017;42(3):1264-1273

ALZET Comments: Valproic acid; IR (intra-renal); Rat; 2ML2; 10 days; Dose (50mg/Kg/d); Controls received mp w/ vehicle; animal info (male Dahl salt-sensitive rats, SS-13BN);

Q6267: P. Farzanehfar, *et al.* Can Valproic Acid Regulate Neurogenesis from Nestin+ Cells in the Adult Midbrain? *Neurochem Res* 2017;42(8):2127-2134

ALZET Comments: Valproic acid; Saline; CSF/CNS (left midbrain); Mice (transgenic); 1002; 2 weeks; 4 weeks; Dose (0.25 mg/μl); Controls received mp w/ vehicle; animal info (NestinCreERT2 C57BL/6 mice); ALZET brain infusion kit 1 used; Brain coordinates (3.0 mm posterior to Bregma, 1.5 mm lateral to the midline, and 4.0 mm below the surface of the brain); neurodegenerative (Parkinson's disease);

Q4357: C. Z. Chang, *et al.* Valproic acid attenuates intercellular adhesion molecule-1 and E-selectin through a chemokine ligand 5 dependent mechanism and subarachnoid hemorrhage induced vasospasm in a rat model. *Journal of Inflammation-London* 2015;12(U1-U11)

ALZET Comments: Valproic acid; PBS; Rat; 5 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 300-400g); ischemia (cerebral); dose-response (pg 4-6); behavioral testing (modified limb-placing test); cardiovascular; bp measured using tail cuff;

Q4323: R. C. Bates, *et al.* Increasing pro-survival factors within whole brain tissue of Sprague Dawley rats via intracerebral administration of modified valproic acid. *JOURNAL OF PHARMACOLOGICAL SCIENCES* 2015;128(193-201)

ALZET Comments: Valproic acid-PEG; CSF/CNS (caudate putamen); CSF/CNS (sagittal fissure); Rat; 2004; 25 days; Animal info (male, Sprague Dawley, 275-300g); ALZET brain infusion kit 1 used; behavioral testing (elevated plus maze, open field test); wound clips used;

Q6725: W. H. Lu, *et al.* Valproic acid attenuates microgliosis in injured spinal cord and purinergic P2X4 receptor expression in activated microglia. *J Neurosci Res* 2013;91(5):694-705

ALZET Comments: Valproic acid; PBS; CSF/CNS (intrathecal); Rat; 1003D; 3 days; Dose (1.5 μg VPA); Controls received mp w/ vehicle; animal info (Female adult Sprague-Dawley rats (n =41; 250 +/-30 g)); post op. care (sodium ampicillin); behavioral testing (locomotor function); enzyme inhibitor (histone deacetylase (HDAC) inhibitor); ALZET brain infusion kit 3 used; spinal cord injury;

8. Vigabatrin

Q6994: D. C. Walters, *et al.* Preclinical tissue distribution and metabolic correlations of vigabatrin, an antiepileptic drug associated with potential use-limiting visual field defects. *Pharmacol Res Perspect* 2019;7(1):e00456

ALZET Comments: Vigabatrin; PBS; SC; Mice; 2002; 12 days; Dose (35, 70, and 140 mg/kg/d); Controls received mp w/ vehicle; animal info (Male C57BL/6J mice, 8-10 weeks old, 20.8-26.1 g); post op. care (Carprofen); dependence;

Q5697: K. R. Vogel, *et al.* mTOR Inhibition Mitigates Molecular and Biochemical Alterations of Vigabatrin-Induced Visual Field Toxicity in Mice. *Pediatr Neurol* 2017;66(44-52 e1)

ALZET Comments: Vigabatrin; PBS; SC; Mice; 2002; 14 days; Controls received mp w/ vehicle; animal info (C57BL6, 8 weeks old);



R0242: W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. *Epilepsia* 2007;48(7):1245-1258

ALZET Comments: Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4,2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments); half-life (p. 1247) table 1 (18 compounds); animal info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.

R0177: A. Pitkanen. Efficacy of current antiepileptics neurodegeneration in epilepsy to prevent models. *Epilepsy Research* 2002;50(1-2):141-160

ALZET Comments: Vigabatrin; Tiagabine; SC; Rat; 2 months; Neuroprotection; pump use mentioned on p. 147 and 155; long-term study.

P4904: T. Halonen, *et al.* Chronic elevation of brain GABA levels beginning two days after status epilepticus does not prevent epileptogenesis in rats. *Neuropharmacology* 2001;40(536-550)

ALZET Comments: Vigabatrin; Saline; SC; Rat; 2ML2; 10 weeks; controls received mp w/ vehicle; long-term study, pumps replaced every 2 weeks for 10 weeks; epilepsy; seizures.