



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.

P2971: R. L. Sherry-McKenna, *et al.* Monoamine oxidase inhibitors: effects on tryptophan concentrations in the rat brain. *J. Neural Transm* 1994;41(155-163)

ALZET Comments: Phenelzine; Tranylcypromine, 4-methoxy-; Acetylphenelzine, N2-; Tranylcypromine, 4-fluoro-; Tranylcypromine; Deprenyl; SC; IP; Rat; 28 days; antidepressant; controls received mp with vehicle; comparison of TCP and PLZ ip injections vs. mp.

P2709: J. G. de Yebenes, *et al.* Continuous intracerebroventricular infusion of dopamine and dopamine agonists through a totally implanted drug delivery system in animal models of Parkinson's disease. *Movement Disorders* 1987;2(3):143-158

ALZET Comments: Dopamine; Pargyline; Deprenyl; Lisuride; Pergolide; HCl; Sodium metabisulfate; CSF/CNS; Rat; 2001; 6,7 days; controls received mp with vehicles; replacement therapy (lesion in dopamine pathway); stability verified for 1 week by measuring dopamine concentrations and its metabolites at varying time intervals with HPLC; concomitant dopamine infusion w/ pargyline and w/ deprenyl; antihypertensive; neurodegenerative (Parkinson's disease).

P2496: P. R. Paetsch, *et al.* Down-regulation of b-adrenergic and dopaminergic receptors induced by 2-phenylethylamine. *Cell. Molec. Neuro* 1993;13(3):203-215

ALZET Comments: Phenylethylamine HCl, 2-; Deprenyl HCl; SC; Rat; 2002; 2ML2; 28 days; Pumps replaced after 14 days; multiple pumps per animal (2); antidepressant.

P2407: P. R. Paetsch, *et al.* Induction of functional down-regulation of beta-adrenoceptors in rats by 2-phenylethylamine. *J. Pharm. Pharmacol* 1993;82(1):22-24

ALZET Comments: Phenelzine sulfate; Phenylethylamine HCl, 2-; Deprenyl HCl; Saline; SC; Rat; 2002; 2ML2; 21, 22 days; Antidepressant; controls received mp w/ vehicle; multiple pumps per animal (2).

P1313: J. G. de Yebenes, *et al.* Continuous intracerebroventricular infusion of dopamine and dopamine agonists through a totally implanted drug delivery system in animal models of Parkinson's disease. *J. Neural Transm* 1988;27(141-160)

ALZET Comments: Deprenyl; Dopamine; Lisuride; Pargyline; Pergolide; HCl; Sodium metabisulfite; Water; CSF/CNS; Rat; 2001; 6, 7 days; mp connected to cannula; stability of DA verified in several vehicles, p 146; concomitant DA infusion with pargyline; DA infusion with deprenyl; replacement therapy (dopamine deficiency); stability verified in vitro; antihypertensive; neurodegenerative (Parkinson's disease).

P1096: D. O'Regan, *et al.* A behavioural and neurochemical analysis of chronic and selective monoamine oxidase inhibition. *Psychopharmacology* 1987;92(42-47)

ALZET Comments: Deprenyl HCl; Clonidine HCl; Clorgyline HCl; Saline; SC; Rat; 2002; 13 days; controls received mp w/vehicle; hypothalamic electrodes implanted for self-stimulation to further access agents effects; antihypertensive.

P0211: R. M. Cohen, *et al.* Cardiovascular changes in response to selective monoamine oxidase inhibition in the rat. *Eur. J. Pharmacol* 1982;80(155-160)

ALZET Comments: Deprenyl, 1-; Clorgyline; Saline; SC; Rat; 21-24 days; mp model not stated; comparison of ip injection vs. infusion.

3. Levetiracetam

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



ALZET Comments: Levetiracetam; Saline; SC; Rat; 2ML4; 28 days; 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

ALZET Comments: Levetiracetam; Saline; SC; Rat; 2ML2; 2 weeks; 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

ALZET Comments: Levetiracetam; SB202190; BQ788; SC; Rat; 1003D; 3 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 7 days); pumps replaced between trials;.

Q4439: A. M. Hall, *et al.* Tau-Dependent Kv4.2 Depletion and Dendritic Hyperexcitability in a Mouse Model of Alzheimer's Disease. JOURNAL OF NEUROSCIENCE 2015;35(6221-6230

ALZET Comments: Levetiracetam; Saline; SC; Mice; 2004; 28 days; Controls received mp w/ vehicle; animal info (hAPPJ20 on C57BL6J background); neurodegenerative (Alzheimer's disease); pumps primed at 37C for 24 hours;.

Q3146: E. Suberbielle, *et al.* Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-beta. Nature Neuroscience 2013;16(5):613-U140

ALZET Comments: Levetiracetam; Saline; SC; Mice; 28 days; Controls received mp w/ saline; animal info (4-5 months, heterozygous hAPP transgenic and wild-type, C57NI/6J);.

Q6777: A. M. Spiegel, *et al.* Hilar interneuron vulnerability distinguishes aged rats with memory impairment. J Comp Neurol 2013;521(15):3508-23

ALZET Comments: Levetiracetam; Saline; SC; Rat; 4 weeks; Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Aged, male Long-Evans rats at 8–9 months of age);.

Q2454: P. E. Sanchez, *et al.* Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 2012;109(42):E2895-E2903

ALZET Comments: Levetiracetam; Saline, sterile; SC; Mice; 2004; 28 days; Control animals received mp w/ vehicle; animal info (hAPPJ20, 4-6 mo old); neurodegenerative (Alzheimer's disease).

Q1474: S. Sugata, *et al.* Neuroprotective effect of levetiracetam on hippocampal sclerosis-like change in spontaneously epileptic rats. Brain Research Bulletin 2011;86(1-2):36-41

ALZET Comments: Levetiracetam; Saline, physiological; SC; Rat; 2ML4; 4 weeks; Controls received mp w/ vehicle; animal info (spontaneously epileptic (SER), 4 wks old); functionality of mp verified by serum levetiracetam levels.

Q0813: Y. Sugaya, *et al.* Levetiracetam suppresses development of spontaneous EEG seizures and aberrant neurogenesis following kainate-induced status epilepticus. Brain Research 2010;1352(:):187-199

ALZET Comments: Levetiracetam; Saline; CSF/CNS; Rat; 2004; 28 days; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 8 wks old); 15 ul saline allowed for 3-day delayed delivery followed by 25-day levetiracetam delivery; "A preliminary study in which a mini-pump was filled with bromophenol blue instead of levetiracetam, confirmed that the pumped drug solution was constantly separated from the predrug saline for 3 days at 37 °C." pg 196; delayed delivery;.

Q1259: L. Paulson, *et al.* Effect of levetiracetam on hippocampal protein expression and cell proliferation in rats. Epilepsy Research 2010;90(1-2):110-120

ALZET Comments: Levetiracetam; SC; Rat; 2ML1; 7 days; Controls received mp w/ saline; animal info (female, Sprague Dawley, 200-225 g).



P9736: E. A. Elzayat, *et al.* Effect of Antiepileptic Agent, Levetiracetam, on Urodynamic Parameters and Neurogenic Bladder Overactivity in Chronically Paraplegic Rats. *UROLOGY* 2009;73(4):922-927

ALZET Comments: Levetiracetam; Saline, normal; SC; Rat; 2ML1; 2ML2; 1, 2 weeks; Controls received no spinal cord transection; dose-response (Fig 2A); animal info (female, Sprague Dawley, 225-275 g, spinal cord transection).

P9181: E. A. Van Vliet, *et al.* Development of tolerance to levetiracetam in rats with chronic epilepsy. *Epilepsia* 2008;49(7):1151-1159

ALZET Comments: Levetiracetam; Water, distilled; SC; Rat; 2ML1; 2 weeks; Functionality of mp verified; pumps replaced after 1 week; tolerance; animal info (male, Sprague Dawley, adult, 500-700 g.); "flow rate of each pump was verified after removal and corresponded to the range given by the manufacturer indicating that all minipumps functioned properly." pg. 1156.

P8935: D. G. Margineanu, *et al.* Effects of chronic treatment with levetiracetam on hippocampal field responses after pilocarpine-induced status epilepticus in rats. *Brain Research Bulletin* 2008;77(5):282-285

ALZET Comments: Levetiracetam; SC; Rat; 3 weeks; 21 days; Controls received mp w/ vehicle; functionality of mp verified by drug plasma levels; dose-response (table 1, pg. 283); animal info (male, Sprague Dawley, 220-250 g.); epilepsy; "chronic treatment with levetiracetam completely inhibits the development of hippocampal hyperexcitability following pilocarpine-induced (status epilepticus)".

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.

R0168: W. Löscher. Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. *Epilepsy Research* 2002;50(1-2):105-123

ALZET Comments: Levetiracetam; Rat; 2 weeks; ALZET pumps mentioned on pg. 113.

P5035: M. Glien, *et al.* Effects of the novel antiepileptic drug levetiracetam on spontaneous recurrent seizures in the rat pilocarpine model of temporal lobe epilepsy. *Epilepsia* 2002;43(4):350-357

ALZET Comments: Levetiracetam; Water, distilled; SC; Rat; 2ML1; 6 weeks; anticonvulsant; controls received mp w/ vehicle; functionality of mp verified by residual aspiration, plasma levels; pumps replaced every week; good methods (priming, filling p. 352-53); rats received 2-week saline infusion (pre-drug control period) then 2 week levetiracetam infusion then another 2-week saline infusion.

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.

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. Kuhnz, *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.

P0036: B. Tabakoff, *et al.* The effect of selective lesions of brain noradrenergic systems on the development of barbiturate tolerance in rats. Brain Research 1979;176(327-336

ALZET Comments: Phenobarbital, sodium; Propylene glycol; Water; CSF/CNS; Rat; 3 days; some groups given 6-OHDA or vehicle of ascorbic acid in Artificial CSF prior to 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/ μ l); 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 μ g 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;

Q3024: R. C. Bates, *et al.* Chronic central administration of valproic acid: increased pro-survival phospho-proteins and growth cone associated proteins with no behavioral pathology. *Pharmacology Biochemistry and Behavior* 2012;103(237-244

ALZET Comments: Valproic Acid; SC; Rat; 2004; 28 days; Controls received mp w/ saline; animal info (Sprague-Dawley, adult male, 250-280g); ALZET brain infusion kit (1) used; behavioral testing (elevated plus maze, and open field maze).

P9619: K. Kitazoe, *et al.* Valproic acid exerts anti-tumor as well as anti-angiogenic effects on myeloma. *International Journal of Hematology* 2009;89(1):45-57



ALZET Comments: Valproic acid; PBS; SC; Mice (SCID); 2002; 14 days; Controls received mp w/vehicle; cancer (myeloma); animal info (8-10 wks old, female).

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.

P9073: Q. Shu, *et al.* Valproic Acid prolongs survival time of severe combined immunodeficient mice bearing intracerebellar orthotopic medulloblastoma xenografts. *Clin. Cancer Res* 2006;12(15):4687-4694

ALZET Comments: Valproic acid; Sodium chloride; SC; Mice (SCID); 2001; 14 days; Controls received no treatment; pumps replaced after 7 days; animal info (6-10 wks old, Rag 2).

P8386: A. Serralta, *et al.* Effect of intracerebroventricular continuous infusion of valproic acid versus single i.p. and i.c.v. injections in the amygdala kindling epilepsy model. *Epilepsy Research* 2006;70(1):15-26

ALZET Comments: Valproic acid; Saline; CSF/CNS; Rat; 2001; 2002; 7 days; Controls received no treatment; dose-response (fig. 1); comparison of icv, IP injections vs. mp; no stress (see pg. 22); toxicology; multiple pumps per animal (2); animal info (male, Wistar, amygdala-kindled epilepsy, 380-420g.); mp primed 1 hr. in 37.5 celsius saline; evans blue dye used to confirm cannula placement, "chronic i.c.v. VPA infusion affords protection against kindled seizures accompanied by less ataxia and sedation" (pg. 24).

P3616: S. Ohdo, *et al.* Influence of feeding schedule on the chronopharmacological aspects of sodium valproate in mice. *J. Pharmacol. Exp. Ther* 1996;278(1):74-81

ALZET Comments: Valproic acid; Saline, sterile physiological; SC; mice; 2001; no duration posted; functionality of mp verified by plasma levels; half-life of less than 1 hour (p. 76); 2 mps implanted concomitantly.

P2820: J.-G. Song. Chronopharmacokinetics of valproic acid in mice following constant-rate administration by osmotic minipump. *Chinese Pharmacological Bulletin* 1995;11(2):135-136

ALZET Comments: Valproic acid; SC; mice; no duration posted; comparison of iv injections vs. mp; article in Chinese w/ abstract in English.

P1335: R. Paulson, *et al.* Effects of sodium valproate and oxygen on the CD-1 mouse fetus. *J. Craniofac. Genet. Dev. Biol* 1988;8(35-42)

ALZET Comments: Valproic acid; Sodium carbonate; Water; SC; mice (pregnant); 2001; 7 days; dose-response (text, graph); half-life; 2 pumps implanted simultaneously; functionality of mp verified by plasma levels; no stress; toxicology/teratology.

R0077: N. Ray, *et al.* Implantable osmotically powered drug delivery systems. In 'Drug Delivery Systems: Fundamentals and Techniques,' P. Johnson and J. G. Lloyd-Jones (eds.), Ellis Horwood Ltd. , Chichester, England and VCH Verlagsgesellschaft mbH, Weinheim, Federal Republic of Germany 1987;Ch. 7):120-138

ALZET Comments: Antipyrine; bleomycin; dopamine HCl; melatonin; methotrexate, sodium; nicotine; prednisolone; radio-isotopes; valproic acid; ¹⁴C tracer; ³H tracer; IA; IP; SC; Mice, rabbit, Rat; no duration posted; ALZA-authored; synoptic review of mp; post op. care (antibiotic); comparison of sc injections vs. mp infusion; pulsed delivery.

P0848: H. Nau. Valproic acid teratogenicity in mice after various administration and phenobarbital-pretreatment regimens: the parent drug and not one of the metabolites assayed is implicated as teratogen. *Fundam. Appl. Toxicol* 1986;6(4):662-668

ALZET Comments: Valproic acid; Water; SC; mice; 1 day; teratology; states pump rate at 8 ul/hr; 2 doses of vpa infused; comparison of SC or IP injections or oral dose vs. mp infusion.



P0886: W. Loscher. Development of tolerance to the anticonvulsant effect of GABA-mimetic drugs in genetically epilepsy-prone gerbils. *Pharmacol. Biochem. Behav* 1986;24(1007-1013)

ALZET Comments: Aminobutyric acid, γ -acetylenic γ -; Aminooxyacetic acid; Diazepam; THIP; Valproic acid; Saline; SC; Rat; 2ML2; 2 weeks; controls received mp w/saline; diazepam too unstable to be used in mp; epilepsy; functionality of mp verified after 14 day exper. period - all 50 mps worked accurately; stability of VPA, THIP, GAG and AOAA.

R0079: H. Nau, *et al.* Controlled-rate drug administration in testing for toxicity, in particular teratogenicity toward interspecies bioequivalence. In 'Topics in Pharmaceutical Sciences,' D. D. Breimer and P. Speiser (eds.), Elsevier Science Publishers B. V. , 1985 1985;143-157

ALZET Comments: Cyclophosphamide; Valproic acid; SC; mice; no duration posted; pump model not stated; review; dose-response (graph); half-life; comparison of injections vs. mp infusion; teratology.

R0061: H. Nau. Improvement of testing for teratogenicity by pharmacokinetics. *Concepts Toxicol* 1985;3(130-137)

ALZET Comments: Valproic acid; no duration posted; teratology; injection-infusion comparison protocol w/ VPA discussed.

P0366: W. Loscher, *et al.* Distribution of valproic acid and its metabolites in various brain areas of dogs and rats after acute and prolonged treatment. *J. Pharmacol. Exp. Ther* 1983;226(3):845-854

ALZET Comments: Valproic acid; SC; Rat; 2ML2; 1, 3, or 14 days; no comment posted.

P0274: H. Nau, *et al.* Pharmacokinetics of valproic acid and metabolites in mouse plasma and brain following constant-rate application of the drug and its unsaturated metabolite with an osmotic delivery system. *Biopharm. Drug Disp* 1982;3(317-328)

ALZET Comments: Valproic acid; Sodium bicarbonate; Water; SC; mice; 2001; 2002; 1 week; intermittent sc. injec. vs. mp infusion; 1 or 2 pumps/animal; comparison of human vs. animal pharmacokinetics.

P0175: H. Nau, *et al.* A new model for embryotoxicity testing: teratogenicity and pharmacokinetics of valproic acid following constant-rate administration in the mouse using human therapeutic drug and metabolite concentrations. *Life Sci* 1981;29(26):2803-2813

ALZET Comments: Valproic acid; Water; SC; mice; 2001; 7 days; 1 or 2 pumps/mouse; comparison of injection vs. infusion and human vs. animal pharmacokinetics.

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. Loeschner. 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.

P4343: A. Pitkanen, *et al.* Effects of vigabatrin treatment on status epilepticus-induced neuronal damage and mossy fiber sprouting in the rat hippocampus. *Epilepsy Research* 1999;33(67-85)

ALZET Comments: Vigabatrin;; Saline;; SC;; Rat;; 2ML1;; 2 months;; controls received mp with vehicle; functionality of mp verified by plasma levels and residual volume; long-term study, pumps replaced every 2 weeks; enzyme inhibitor;.

P4249: D. A. Golombek, *et al.* Inhibition of GABA transaminase enhances light-induced circadian phase delays but not advances. *J. Biol. Rhythms* 1994;9(3-4):251-261

ALZET Comments: Vigabatrin; Saline; IP; hamster; 2002; 14 days; controls received mp w/saline or no treatment; comparison of injections vs. mp; GABA transaminase inhibitor.