



References on the Administration of Benzodiazepines Using ALZET® Osmotic Pumps

1. Adinazolam

P0433: A. Turmel, *et al.* Sensitization of rat forebrain neurons to serotonin by adinazolam, an antidepressant triazolobenzodiazepine. *Eur. J. Pharmacol* 1984;99(241-244)

ALZET Comments: Adinazolam; Diazepam; Benzyl alcohol; Ethanol; Propylene glycol; Sodium benzoate; Water; IP; Rat; 2002; 5 and 14 days; comparison of adinazolam. iv injec vs. mp infusion; comparison of agents effects; adinazolam. used with water vehicle, Diaz. with combination vehicle.

2. Alprazolam

Q5063: N. Ito, *et al.* Contribution of protein binding, lipid partitioning, and asymmetrical transport to drug transfer into milk in mouse versus human. *Pharm Res* 2013;30(9):2410-22

Agents: acetaminophen, cephalothin sodium salt, clindamycin hydrochloride, disopyramide phosphate salt, labetalol hydrochloride, nitrofurantoin +-propranolol hydrochloride, terbutaline hemisulfate salt, verapamil hydrochloride, Acyclovir, alprazolam, atenolol, anhydrous caffeine, cefotaxime sodium salt, cephapirin sodium salt, diltiazem hydrochloride, metronidazole, nitrazepam, prednisolone, 6-propyl-2-thiouracil, trazadone hydrochloride, chloramphenicol, cimetidine, theophylline, fluconazole, metoprolol, mirtazapine, praziquantel, quetiapine fumarate, triprolidine hydrochloride, metformin, moclobemide. **Vehicle:** DMSO; water; **Route:** IP; **Species:** mice; **Pump:** 1003D; **Duration:** Not Stated; **ALZET Comments:** animal info: lactating mice, postnatal age of 14 days; functionality of mp verified by measurement of drug concentration in milk and plasma; mp were used to infuse study lactational drug transfer.

P3498: V. A.-M. I. Tanay, *et al.* Chronic administration of antipanic drugs alters rat brainstem GABA-A receptor subunit mRNA levels. *Neuropharmacology* 1996;35(9/10):1475-1482

Agents: Phenelzine; alprazolam; imipramine; buspirone **Vehicle:** Water, sterile; DMSO; propylene glycol; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 21 days; **ALZET Comments:** Antidepressant; controls received mp w/ vehicle; pumps were turned in subcutaneous pocket to avoid fibrous tissue outgrowth

P3673: J. J. Byrnes, *et al.* Chronic benzodiazepine administration. *Psychopharmacology* 1993;111(91-95)

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** 2001; 2002; **Duration:** 7, 8, or 14 days; **ALZET Comments:** controls received vehicle; tolerance

P2332: G. B. Kaplan, *et al.* Effects of benzodiazepine administration on A1 adenosine receptor binding in-vivo and ex-vivo. *J. Pharm. Pharmacol* 1992;44(700-703)

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** IP; **Species:** mice; **Pump:** 2001; **Duration:** 6 days; **ALZET Comments:** controls received mp w/ vehicle

P3033: J.-L. Moreau, *et al.* Physical dependence induced in DBA/2J mice by benzodiazepine receptor full agonists, but not by the partial agonist Ro 16-6028. *European Journal of Pharmacology* 1990;190(269-273)

Agents: Triazolam; Alprazolam; Diazepam **Vehicle:** Propylene glycol; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days; **ALZET Comments:** controls received mp with vehicle; functionality of mp verified by receptor binding study; comparison of oral alprozolam vs. mp; ". . .the use of implantable minipumps. . .permitted. . .development of behavioral tolerance associated with downregulation of benzodiazepine receptor binding and GABA receptor function. . ."; dependence



3. Chlordiazepoxide

Q5755: C. Brouillard, *et al.* Long-lasting bradypnea induced by repeated social defeat. *American Journal of Physiology Regulatory, Integrative, and Comparable Physiology* 2016;311(2):R352-64

Agents: Chlordiazepoxide **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 5 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (weight: 290-310g); behavioral testing (Social defeat); chlordiazepoxide is a benzodiazepine receptor agonist; Days infused (D5 – D+10) (Housing: individual cages post. Op.); Therapeutic indication (Anxiety); Dose (10 mg/kg*day);

Q2541: C. Sevoz-Couche, *et al.* Involvement of the dorsomedial hypothalamus and the nucleus tractus solitarii in chronic cardiovascular changes associated with anxiety in rats. *JOURNAL OF PHYSIOLOGY-LONDON* 2013;591(7):1871-1887

Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 6 days;

ALZET Comments: Control animals received mp w/ vehicle; animal info (Sprague Dawley, male, 250-300 g)

R0297: A. de Mooij-van Malsen, *et al.* Cross-species behavioural genetics: A starting point for unravelling the neurobiology of human psychiatric disorders. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2011;35(6):1383-1390

Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1 week;

ALZET Comments: Animal info (C57BL/6J)

P9959: C. H. Vinkers, *et al.* The rapid hydrolysis of chlordiazepoxide to demoxepam may affect the outcome of chronic osmotic minipump studies. *Psychopharmacology* 2010;208(4):555-562

Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** In vitro; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: "When the cumulative CDP concentration over time was corrected for its hydrolysis, drug release from the minipumps followed the theoretical release profile over time (white symbols), suggesting that CDP hydrolysis completely accounted for the declined CDP release over time." pg 558; "In general, the use of osmotic minipumps presents a valid and attractive alternative to the labor-intensive daily injections. However, the issue of drug stability and release should always be carefully investigated before initiating chronic minipump experiments." pg 562

Q0421: C. Rivat, *et al.* Chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. *Pain* 2010;150(2):358-368

Agents: CI-988; chlordiazepoxide; Acetylsalicylic acid **Vehicle:** DMSO; saline; **Route:** SC; CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2ML1; 2001; 2002; **Duration:** 14 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (Male, Sprague-Dawley, 300-325 g, 8 wks old; ALZET intrathecal catheter used (0007740); behavioral testing (elevated plus-maze)

4. Clonazepam

P3556: M. I. Arnot, *et al.* Dimethyl sulfoxide/propylene glycol is a suitable solvent for the delivery of diazepam from osmotic minipumps. *J. Pharm. & Tox. Meth* 1996;36(29-31

ALZET Comments: Diazepam; Clonazepam; flumazenil; DMSO; Propylene glycol; Tetraglycol; ³H tracer; Radio-isotopes; in vitro (egg); 2ML4; no duration posted; no comment posted.

P3305: L. Lima, *et al.* Serotonin turnover rate, [3H] paroxetine binding sites, and 5-HT1A receptors in the hippocampus of rats subchronically treated with clonazepam. *Neuropharmacology* 1995;34(10):1327-1333

ALZET Comments: Clonazepam; PEG; CSF/CNS (dorsal raphe nucleus); Rat; 10 days; comparison of IP injections vs. mp.

P2654: K. Brodin, *et al.* Clomipramine and clonazepam increase cholecystokinin levels in rat ventral tegmental area and limbic regions. *Eur. J. Pharmacol* 1994;263(175-180



ALZET Comments: Nortriptyline; Amitriptyline; Clomipramine; Alaproclate; Clonazepam; Alcohol; Saline; SC; Rat; 2ML2; 14 days; antidepressant; controls received mp w/ vehicle; functionality of mp verified by plasma levels; dose-response (Table 1; pg. 177); enzyme inhibitor; clonazepam is a benzodiazepene; the others are monoamine uptake inhibitors.

P1650: L. G. Miller, *et al.* Chronic benzodiazepine administration. VI. a partial agonist produces behavioral effects without tolerance or receptor alterations. *J. Pharmacol. Exp. Ther* 1990;254(1):33-36

ALZET Comments: Clonazepam; RO-16-6028; PEG 400; SC; mice; 14 days; functionality of mp verified by tissue levels; dose-response (graph); tolerance/dependence.

5. Diazepam

Q7673: L. E. Villasana, *et al.* Diazepam Inhibits Post-Traumatic Neurogenesis and Blocks Aberrant Dendritic Development. *J Neurotrauma* 2019;36(16):2454-2467

Agents: Diazepam **Vehicle:** DMSO, Propylene Glycol; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Dose (15 mg/kg/day); 1:1 DMSO:Propylene glycol used; Controls received mp w/ vehicle; animal info (Male and female C57Bl/6J wild-type mice); Therapeutic indication (traumatic brain injury);

Q7777: M. C. D. Bridi, *et al.* Two distinct mechanisms for experience-dependent homeostasis. *Nat Neurosci* 2018;21(6):843-850

Agents: Diazepam; Ro 25-6981 **Vehicle:** Saline; Propylene Glycol; DMSO; **Route:** CSF/CNS (left lateral ventricle); SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (2 mg/mL Diazepam; 30mg/kg/day Ro 25-6981); 50% Propylene glycol, 50% saline used for Diazepam and 20% DMSO, 80% Saline for Ro 25-6981; Controls received mp w/ vehicle; animal info (C57BL/6, Pv-cre); post op. care (Meloxicam); enzyme inhibitor (Ro 25-6981 is a GluN2B-specific antagonist); Dental cement used; dependence;

Q2140: C. H. Vinkers, *et al.* GABA-A Receptor alpha Subunits Differentially Contribute to Diazepam Tolerance after Chronic Treatment. *PLoS One* 2012;7(8):U614-U624

Agents: Diazepam; zolpidem; TPA023; bretazenil **Vehicle:** PEG 400; alcohol; water, distilled; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (129 Sv/Ev Tac, 10-12 wks old); 95% PEG 400 used; 2.5% alcohol used; stress/adverse effects "severe hypothermia likely explains the death of seven animal's postsurgically..." pg 9; TPA023 is an alpha 2/3 selective GABAa receptor positive allosteric modulator

Q1966: M. Spolidoro, *et al.* Food restriction enhances visual cortex plasticity in adulthood. *Nature Communications* 2011;2(;):U210-U217

Agents: Diazepam; mercaptopropionic acid **Vehicle:** Propylene glycol; **Route:** CSF/CNS (visual cortex); **Species:** Rat; **Pump:** 2002; **Duration:** Not Stated;

ALZET Comments: Animal info (Long Evans hooded, P60-P90, male, female); 50% propylene glycol used

P9449: E. A. Stone, *et al.* Evaluation of the repeated open-space swim model of depression in the mouse. *Pharmacology Biochemistry and Behavior* 2008;91(1):190-195

Agents: Imipramine HCl, desmethyl; diazepam; fluoxetine; haloperidol **Vehicle:** Saline; DMSO; water; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Controls received mp w/either saline, 25, 50% or 100% DMSO; half-life (p. 191); animal info (male, Swiss Webster, 8-10 wks old); behavioral testing (swimming behavior, tail-suspension test, sucrose suspension test); "since drugs have relatively short half-lives in mice, to more closely mimic the human condition in which blood levels are maintained for prolonged periods, all agents were administered by osmotic minipump." (p. 191); all mice were housed singly for the duration of the experiment (3 weeks). Dose: desmethylimipramine in saline (10–11.5 mg/kg/d) in a 35–40 g mouse, fluoxetine dissolved at the same concentration in 50% DMSO; haloperidol dissolved in 25%DMSO at 0.3–0.34 mg/kg/day (2 mg/ml) and diazepam in 100% DMSO at 1–1.1 mg/kg/day (6.66 mg/ml).



6. Lorazepam

P8188: J. M. Fahey, *et al.* The effect of chronic lorazepam administration in aging mice. *Brain Research* 2006;1118(13-24)

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1, 14 days;
ALZET Comments: Controls received mp w/ vehicle; functionality of mp verified by lorazepam plasma concentrations; tolerance; animal info (male, CD-1, 2-3 months old, 10-12 months old, 22-24 months old)

P4914: J. M. Fahey, *et al.* Pharmacodynamic and receptor binding changes during chronic lorazepam administration. *Pharmacology Biochemistry and Behavior* 2001;69(1-8)

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** Not Stated; **Duration:** 1 or 14 days;
ALZET Comments: controls received mp w/ vehicle; plasma lorazepam levels; brains examined postmortem for membrane binding; lorazepam is a benzodiazepine with anxiolytic and anti-insomnia properties;

P4593: M. H. J. Tehrani, *et al.* Sequestration of g-Aminobutyric acid_A receptors on clathrin-coated vesicles during chronic benzodiazepine administration in vivo;. *The Journal of Pharmacology and Experimental Therapeutics* 1997;283(1):384-390

Agents: Lorazepam; **Vehicle:** PEG 400;; **Route:** SC;; **Species:** mice;; **Pump:** 2001;; **Duration:** 7 days;;
ALZET Comments: controls received mp w/vehicle; tolerance;

P3328: M. Mortensen, *et al.* The effect of lorazepam tolerance and withdrawal on metabotropic glutamate receptor function. *J. Pharmacol. Exp. Ther* 1995;274(1):155-163

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: tolerance

P3673: J. J. Byrnes, *et al.* Chronic benzodiazepine administration. *Psychopharmacology* 1993;111(91-95)

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** 2001; 2002; **Duration:** 7, 8, or 14 days;
ALZET Comments: controls received vehicle; tolerance

7. Triazolam

P2656: C. Cohen, *et al.* Tolerance, cross-tolerance and dependence measured by operant responding in rats treated with triazolam via osmotic pumps. *Psychopharmacology* 1994;115(86-94)

ALZET Comments: Triazolam; Propylene glycol; SC; Rat; 2ML2; 14 days; controls received mp w/ vehicle; tolerance; dependence.

P2115: L.-W. Zhou, *et al.* Triazolam blocks the initial rotational effects of quinpirole but permits the later developing reduction of dopamine D2-mediated rotational behavior and dopamine D2 receptors. *Eur. J. Pharmacol* 1992;218(219-227)

ALZET Comments: Quinpirole HCl; Sulpiride; Triazolam; Ascorbic acid; DMSO; SC; mice; 2001; 6 days; Quinpirole is a dopamine agonist; antidepressant; stability verified in vitro for 7 days.

P3033: J.-L. Moreau, *et al.* Physical dependence induced in DBA/2J mice by benzodiazepine receptor full agonists, but not by the partial agonist Ro 16-6028. *Eur. J. Pharmacol* 1990;190(269-273)

ALZET Comments: Triazolam; Alprazolam; Diazepam; Propylene glycol; SC; mice; 2001; 7 days; controls received mp with vehicle; functionality of mp verified by receptor binding study; comparison of oral alprazolam vs. mp; ". . .the use of implantable minipumps. . .permitted. . .development of behavioral tolerance associated with downregulation of benzodiazepine receptor binding and GABA receptor function. . ."; dependence.