References on the Administration of Benzodiazepines Using ALZET® Osmotic Pumps

1. Adinazolam


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


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, 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.


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


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


Agents: Alprazolam; Lorazepam Vehicle: PEG 400; Route: IP; Species: mice; Pump: 2001; Duration: 6 days;

ALZET Comments: controls received mp w/ vehicle


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

**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);

**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)

**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

**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

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

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

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.

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

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);

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); post op. care (Meloxicam); enzyme inhibitor (Ro 25-6981 is a GluN2B-specific antagonist); Dental cement used; dependence;

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

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

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


**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;


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

**ALZET Comments**: controls received mp w/ vehicle; tolerance;


**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 mp with 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.


**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 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.