



References on the Administration of Nonsteroidal Anti-Inflammatory Drugs Using ALZET® Osmotic Pumps

1. Acetylsalicylic Acid

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

ALZET Comments: CI-988; chlordiazepoxide; Acetylsalicylic acid; DMSO; saline; SC; CSF/CNS (intrathecal); Rat; 2ML1; 2001; 2002; 14 days; 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).

P8555: A. Adamek, *et al.* High dose aspirin and left ventricular remodeling after myocardial infarction. *Basic Research In Cardiology* 2007;102(4):334-340

ALZET Comments: Acetylsalicylic acid, lysine; Saline; SC; Mice; 2002; 4 weeks; Controls received mp w/ placebo; functionality of mp verified by serum salicylate concentrations; pumps replaced after 2 weeks; cardiovascular; ischemia (cardiac); animal info (female, C57BL/6, 8-12 weeks old, 20-25 grams); MI induced by coronary artery ligation.

P4829: M. Yuan, *et al.* Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of *Ikkb*. *Science* 2001;293(1673-1677

ALZET Comments: Acetylsalicylic acid; salicylate, sodium; SC; Rat; mice; 2002; 2ML2; 3-4 weeks; Controls received mp w/ vehicle; 2ML2 used in rats, 2002 used in mice; acetylsalicylic acid also called aspirin: dose was 120 mg/kg/day; diabetes (type II).

P0455: T. Oshima, *et al.* Pharmacological manipulation of canine cyclooxygenase and thromboxane synthetase in vivo: differential renal and platelet recovery rates. *J. Pharmacol. Exp. Ther* 1984;229(2):598-602

ALZET Comments: Acetylsalicylic acid; DMSO; Saline; IV (superficial cervical vein); dog; 2ML1; 3 days; pumps primed for 4 hrs. before implant; used prefilled catheter in vein; greater solubility of ASA in DMSO allowed greater concentration in smaller total volume.

2. Diclofenac

P5994: T. Murase, *et al.* Synergistic effects of nitric oxide and prostaglandins on renal escape from vasopressin-induced antidiuresis. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* 2003;284(2):R354-R362

ALZET Comments: Vasopressin, 1-desamino-8-D arginine; L-NAME; diclofenac; ranitidine; Saline; DMSO; SC; Rat; 2001; 2002; 5 days; Vasopressin, 1-desamino-8-D arginine was infused in the 2002 pump; L-NAME was dissolved in saline and diclofenac was dissolved in 50% DMSO; both were infused from a 2001 pump.

P3383: O. Risto, *et al.* The effect of low dose diclofenac sodium administered locally on heterotopic bone formation in rats. *Int. Orthopaedics (SICOT)* 1995;19(392-395

ALZET Comments: Diclofenac; NaCl; bone; Rat; 2001; < or = 2 weeks; controls received mp w/saline; tissue perfusion (demineralized bone implant); functionality of mp verified by residual volume; diclofenac is an NSAID.

3. Flurbiprofen

Q0222: C. Campanella, *et al.* Influence of prolonged exposure of a short half life non-steroidal anti-inflammatory drugs on gastrointestinal safety. *INFLAMMOPHARMACOLOGY* 2009;17(4):205-210

ALZET Comments: Flurbiprofen; PEG 400; IP; Rat; 2002; 7 days; Comparison of IP injections vs. mp; stability verified in vitro test for 14 days; animal info (male, Sprague Dawley, adult, 300-350 g.); "There was no significant difference between the two i.p. groups in the post-mortem plasma R or S-flurbiprofen concentration or in the percent of the dose excreted as glucuronidated flurbiprofen in urine on days 1 and 7" pg 207.



P7625: I. Peretto, *et al.* Synthesis and biological activity of flurbiprofen analogues as selective inhibitors beta-amyloid (1-42) secretion. *Journal of Medicinal Chemistry* 2005;48(18):5705-5720

ALZET Comments: Flurbiprofen analogues; flurbiprofen; SC; Rat; 2001; 4-7 days; Dose-response; neurodegenerative (Alzheimer's disease); cassette dosing technology; 2-6 different analog compounds administered simultaneously to one animal.

P1533: S. Offenbacher, *et al.* Changes in cyclooxygenase metabolites in experimental periodontitis in macaca mulatta. *J. Periodontal Res* 1989;24(63-74)

ALZET Comments: Flurbiprofen; SC; monkey; 2ML2; 2ML4; 6, 12 months; controls received no drugs or sham pumps; multiple pumps per animal (2) (simultaneously); pumps replaced every 2 weeks or monthly; long-term study; one animal removed from study due to a 'secondary infection caused by a cage-pressure abrasion at the site of the s.c.

P1208: S. Offenbacher, *et al.* Effects of flurbiprofen on the progression of periodontitis in macaca mulatta. *J. Periodontal Res* 1987;22(6):473-481

ALZET Comments: Flurbiprofen; Tris buffer; SC; monkey; 2ML2; 2ML4; 6 months; controls received mp w/ tris buffer; dose-response (table); 2 doses of agent infused; high dosage group received 2 pumps (2ML2); pumps replaced every 4 weeks for 2ML4, 2 weeks for 2ML2; long-term study.

4. Ibuprofen

R0376: R. G. Kenny, *et al.* Toward Multi-Targeted Platinum and Ruthenium Drugs-A New Paradigm in Cancer Drug Treatment Regimens? *Chemical Reviews* 2019;

Agents: Chloridotetrakis (ibuprofenato)diruthenium-(II,III) **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: cancer (glioma);

Q7850: M. L. D. Rayner, *et al.* Developing an In Vitro Model to Screen Drugs for Nerve Regeneration. *Anat Rec (Hoboken)* 2018;301(10):1628-1637

Agents: ibuprofen **Vehicle:** Saline; **Route:** CSF/CNS (sciatic nerve); **Species:** Rat; **Pump:** 1004; **Duration:** 21 days; **ALZET Comments:** Dose (7 µg/day); Controls received mp w/ vehicle; animal info (male, Wistar, 220-250g); pump was implanted locally parallel to re-connected nerve (p.1631);

Q5442: F. Streijger, *et al.* Combinatorial treatment of acute spinal cord injury with ghrelin, ibuprofen, C16, and ketogenic diet does not result in improved histologic or functional outcome. *J Neurosci Res* 2014;92(7):870-83

Agents: Ibuprofen **Vehicle:** PBS; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated; **ALZET Comments:** Controls received mp w/ vehicle; animal info (male Sprague-Dawley rats, 278-315 g); spinal cord injury; behavioral testing (grooming test, cylinder rearing test, Montoya staircase test, horizontal ladder test); Healing/recovery after spinal cord injury study; Dose (2.5 mL/hour);

Q3526: D. Jurk, *et al.* Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nature Communications* 2014;5(U235-U248)

Agents: Ibuprofen **Vehicle:** PEG; DMSO; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 8 weeks; **ALZET Comments:** Animal info (male, nfk1b1 -/-, 24 weeks old); pumps replaced every 28 days; 50% DMSO used; 50% PEG used; behavioral testing (tightrope test); used 7mm wound clips;

Q4703: M. Benadiba, *et al.* Growth inhibitory effects of the Diruthenium-Ibuprofen compound, [Ru(2)Cl(Ibp)(4)], in human glioma cells in vitro and in the rat C6 orthotopic glioma in vivo 1993. *JOURNAL OF BIOLOGICAL INORGANIC CHEMISTRY* 2014;19(1025-1035)

Agents: Diruthenium-ibuprofen **Vehicle:** Ethanol; CSF, artificial; **Route:** CSF/CNS (intratumoral); **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;



ALZET Comments: Animal info (female, Wistar, 250-350g); ALZET brain infusion kit used; 15% ethanol used; comparison of injection vs mp; cancer (glioma); tissue perfusion (intratumoral, glioma); "Using the orthotopic C6 model the effects of either chronic 14-day treatment by intra-peritoneal injection of chronic 14-day intra-tumour infusion by an Alzet osmotic pump attached to a brain infusion cannula were tested. Tumour growth was reduced by both routes of administration with the osmotic pump appearing to be the less harmful route in terms of haematological responses." pg 1033; Diruthenium-Ibuprofen aka Rulbp;

5. Indomethacin

Q7826: L. Hao, *et al.* Indomethacin Enhances Brown Fat Activity. *J Pharmacol Exp Ther* 2018;365(3):467-475
Agents: indomethacin **Vehicle:** saline, Kolliphor HS15 buffered; **Route:** SC; **Species:** Mice; **Pump:** 2006; **Duration:** 4 weeks;
ALZET Comments: Dose (10 mg/ml at 0.15 ml/h); saline with 18.75% Kolliphor HS15 used; Controls received mp w/ vehicle; animal info (6 weeks, male, C57BL/6J); good methods ("We connected a piece of silicon tubing at the end of each pump, and sutured the tubing on the mouse back muscle to ensure that the opening of the tubing was on the iBAT of the mouse during pump implantation." p.469); controls split into three groups (saline, Kolliphor HS15, saline + Kolliphor HS15); Therapeutic indication (expression of genes involved in thermogenesis in iBAT (interscapular brown adipose tissue) and improved hyperglycemia found in DIO (diet-induced obesity) mice along with promoting mouse brown adipocyte differentiation,);

Q4542: Y. R. Na, *et al.* Consistent Inhibition of Cyclooxygenase Drives Macrophages towards the Inflammatory Phenotype. *PLoS One* 2015;10(U1730-U1742)

Agents: NA-398; SC-560; indomethacin **Vehicle:** DMSO; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 30 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (female, BALB/c); immunology;

Q7687: S. D. Hursting, *et al.* Diet and cancer prevention studies in p53-deficient mice. *J Nutr* 2001;131(11 Suppl):3092s-4s
Agents: fenretinide; indomethacin **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Mice; **Pump:** Not Stated; **Duration:** 24 weeks;

ALZET Comments: animal info (6 weeks, male, p53+/-); comparison of caloric restriction vs mp; long-term study; fenretinide is a synthetic retinoid. indomethacin is a nonsteroidal anti-inflammatory drug; cancer (bladder); citation for study listed as (Hursting, S.D. and Perkins, S.N., unpublished observations, 2001);

P4819: M. C. Babin, *et al.* Systemic administration of candidate antivesicants to protect against topically applied suitor mustard in the mouse ear vesicant model (MEVM). *Journal of Applied Toxicology* 2000;20(S141-S144)

Agents: Hydrocortisone; indomethacin; olvanil **Vehicle:** PEG 200; **Route:** SC; **Species:** mice; **Pump:** Not Stated; **Duration:** 2 days;

ALZET Comments: Controls received mp w/ vehicle; toxicology

P4475: M. G. Zlatnik, *et al.* The effect of indomethacin and prostacyclin agonists on blood pressure in a rat model of preeclampsia. *American Journal of Obstetrics & Gynecology* 1999;180(5):1191-1195

Agents: Iloprost; Cicaprost; L-NAME; Indomethacin **Vehicle:** Saline;; **Route:** SC;; **Species:** Rat (pregnant);; **Pump:** 2ML2;; **Duration:** 2 weeks;;

ALZET Comments: controls received mp w/vehicle; comparison of SC injections vs. mp; cardiovascular; L-NAME is a synthase inhibitor;

6. Ketorolac

P8822: J. M. Scarlett, *et al.* Regulation of central melanocortin signaling by interleukin-1beta. *Endocrinology* 2007;148(9):4217-4225

ALZET Comments: Ketorolac; Saline, sterile; SC; Mice; 1007D; 2 days; Controls received mp w/ vehicle; animal info (male, C57BL/6J, 4-5 wks old).



P5091: M. D. Southall, *et al.* Twenty-four hour exposure to prostaglandin downregulates prostanoid receptor binding but does not alter PGE(2)-mediated sensitization of rat sensory neurons. *Pain* 2002;96(285-296)

ALZET Comments: Ketorolac tromethamine; Saline; CSF/CNS (intrathecal); Rat; 2001; 48 hours; controls received mp w/ vehicle; ketorolac is an NSAID sold as Toradol; cannula patency verified by saline injection.

P4204: J. V. Shufflebarger, *et al.* The effect of ketorolac on microvascular thrombosis in an experimental rabbit model. *Plast. Reconstr. Surg* 1996;98(140-145)

ALZET Comments: Ketorolac; IV (jugular); rabbit; 2ML1; 7 days; controls received mp w/saline; functionality of mp verified by residual volume; comparison of i.m. injections vs. mp; ketorolac also called Toradol; NSAID.

7. Meclofenamate

P1305: E. L. Sargent, *et al.* Intraluteal infusion of a prostaglandin synthesis inhibitor, sodium meclufenamate, causes premature luteolysis in rhesus monkeys. *Endocrinology* 1988;123(5):2261-2269

ALZET Comments: Meclofenamate, sodium; Saline; Water; intraovarian (corpus luteum); IV (jugular); monkey; 2ML1; 7 days; stress/adverse reaction (cortisol and progesterone levels); tissue perfusion.

8. Naproxen

Q3710: A. C. Rosa, *et al.* Prevention of Bleomycin-Induced Lung Inflammation and Fibrosis in Mice by Naproxen and JNJ7777120 Treatment. *Journal of Pharmacology and Experimental Therapeutics* 2014;351(308-316)

ALZET Comments: JNJ7777120; naproxen; SC; Mice; 1004; Control animals received mp w/ vehicle; animal info (male, C57BL/6, ~2 mo old, 25-30 g); infusion rate listed as 0.11 ul/hr; JNJ7777120 also known as (1-[(5-chloro-1H-indol-2-yl)carbonyl]-4-methylpiperazine), is a selective H4R antagonist; one group received combination of JNJ7777120 and naproxen.

P8571: C. Baj-Rossi, *et al.* Continuous monitoring of Naproxen by a cytochrome P450-based electrochemical sensor. *Biosens Bioelectron* 2014;53(283-7)

ALZET Comments: Naproxen; PBS; In vitro; 1002; Naproxen is a non-steroidal anti-inflammatory agent; This paper reports the characterization of an electrochemical biosensor for the continuous monitoring of Naproxen delivered by alzet pumps.

Q4700: C. Baj-Rossi, *et al.* Continuous monitoring of Naproxen by a cytochrome P450-based electrochemical sensor. *BIOSENSORS & BIOELECTRONICS* 2014;53(;):283-287

ALZET Comments: Naproxen; Methanol; In Vitro; 1002; 16 hours; Functionality of mp verified by naproxen levels measured with sensors;

P9697: X. X. Wang, *et al.* Ibuprofen Enhances Recovery from Spinal Cord Injury by Limiting Tissue Loss and Stimulating Axonal Growth. *Journal of Neurotrauma* 2009;26(1):81-95

ALZET Comments: Ibuprofen; naproxen; PBS; SC; Rat; mice; 2004; 2ML4; 4 weeks; Controls received mp w/ vehicle; animal info (female, Sprague Dawley, 11-12 wks old, 250-270 g., female, C57BL/6, 8-9 wks old, 20 g.); spinal cord injury; behavioral testing (BBB locomotor scale, Basso mouse scale).

P1504: W. Y. Chan, *et al.* Effects of inhibition of prostaglandin synthesis on uterine oxytocin receptor concentration and myometrial gap junction density in parturient rats. *Biol. Reprod* 1988;39(1117-1128)

ALZET Comments: Naproxen, sodium; Saline; SC; Rat (pregnant); 2001; 3 days; no comment posted.

9. Superoxide Dismutase-PEG



P3263: E. H. Karran, *et al.* A simple in vivo model of collagen degradation using collagen-gelled cotton buds: the effects of collagenase inhibitors and other agents. *Inflamm. Res* 1995;44(36-46

ALZET Comments: Collagenase inhibitor A; Collagenase inhibitor B; Collagenase inhibitor C; tempol; Superoxide dismutase-PEG; Cytochalasin B; Pepstatin; APMSF; TLCK; SBTI; Leupeptin; E-64; Methylamine; SC; Rat; 2001; 2ML1; 7 days; controls received mp w/vehicle; no stress (see pg. 39); immunology; pumps connected with catheter tubing to 14C-collagen-gelled cotton buds.

P3114: D. Truelove, *et al.* Neuronal protection with superoxide dismutase in repetitive forebrain ischemia in gerbils. *Free Rad. Biol. Med* 1994;17(5):445-450

ALZET Comments: Superoxide dismutase-PEG; Saline; CSF/CNS; gerbil; 1007D; 6 days; controls received mp with vehicle; ischemia (cerebral).

10. Tempol or Superoxide Dismutase

Q8077: T. Li, *et al.* Elevated Oxidative Stress and Inflammation in Hypothalamic Paraventricular Nucleus Are Associated With Sympathetic Excitation and Hypertension in Rats Exposed to Chronic Intermittent Hypoxia. *Front Physiol* 2018;9(840

Agents: Tempol **Vehicle:** Not stated; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 7 days;

ALZET Comments: Dose (5 ug/min); Controls received mp w/ vehicle; animal info (Male, Sprague Dawley, 10 weeks old, 300-325 g); Tempol aka superoxide scavenger ; bilateral cannula used; cardiovascular;

Q7198: O. Le, *et al.* INK4a/ARF Expression Impairs Neurogenesis in the Brain of Irradiated Mice. *Stem Cell Reports* 2018;10(6):1721-1733

Agents: Porphyrin-based superoxide dismutase mimetic (MnHex) **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 8 weeks;

ALZET Comments: Dose (450 ug/kg/day); pumps replaced every 4 weeks; Porphyrin-based potent superoxide dismutase mimetic aka (Mn(III) meso-tetrakis-(n-hexylpyridinium-2-yl) porphyrin (MnTnHex-2-PyP5+); neurodegenerative (Ionizing radiation);

Q7118: J. M. Cline, *et al.* Post-Irradiation Treatment with a Superoxide Dismutase Mimic, MnTnHex-2-PyP(5+), Mitigates Radiation Injury in the Lungs of Non-Human Primates after Whole-Thorax Exposure to Ionizing Radiation. *Antioxidants (Basel)* 2018;7(3):

Agents: mitochondrial superoxide dismutase mimetic (Hexyl) **Vehicle:** Saline; **Route:** SC; **Species:** Monkey; **Pump:** Not Stated; **Duration:** 6 weeks;

ALZET Comments: Dose (0.1 mg/kg/day); Controls received mp w/ vehicle; animal info (Rhesus monkeys); MnTnHex-2-PyP5+ aka hexyl; cardiovascular;

Q6941: W. Cao, *et al.* A renal-cerebral-peripheral sympathetic reflex mediates insulin resistance in chronic kidney disease. *EBioMedicine* 2018;37(281-293

Agents: Losartan; Tempol; Clonidine **Vehicle:** CSF, artificial; **Route:** CSF/CNS (lateral ventricle); **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: Dose (1 mg/kg/day losartan; 4.5 ug/kg/day tempol; 5.76 ug/kg/day clonidine); Controls received mp w/ vehicle; animal info (Five-week-old male Sprague-Dawley rats); Therapeutic indication (5/6 nephrectomy);

Q6541: K. L. Wu, *et al.* Effects of high fructose intake on the development of hypertension in the spontaneously hypertensive rats: the role of AT1R/gp91(PHOX) signaling in the rostral ventrolateral medulla. *J Nutr Biochem* 2017;41(73-83

Agents: Tempol **Vehicle:** Saline; **Route:** CSF/CNS (cisterna magna); **Species:** Rat; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Dose (10 mM); Controls received mp w/ vehicle; animal info (Male, adult spontaneously hypertensive rats and Wistar-Kyoto rats); ALZET brain infusion kit 2 used;



11. Tolmetin

P2007: K. E. Rodgers, *et al.* Effect of tolmetin sodium dihydrate on adhesion formation by intraperitoneal administration of antineoplastic agents. *Cancer Chemother. Pharmacol* 1992;29(248-251

ALZET Comments: Doxorubicin HCl; Mitoxantrone; Tolmetin sodium; Bleomycin; Cisplatin; Methotrexate; PBS; IP; Rat; 2ML1; 7 days; Antibiotic; cancer; no stress (see p249).