ALZET Research Application

Chronic Delivery

Chronic administration of several months or longer may be necessary to evaluate the long-term effects of test compounds *in vivo*, or to establish a stable animal model of disease. In these cases, it is essential to maintain steady-state levels of the test substance in tissues or plasma during the duration of the study to ensure reliable results. Injections are commonly used in research, but repeated injections over prolonged periods are inadequate for some compounds (i.e., those with short half-lives), stressful to the animals, and inconvenient for the researcher.

For studies requiring chronic dosing, ALZET® Osmotic Pumps offer a reliable and convenient alternative to injections and other repetitive dosing methods. With ALZET pumps, drug administration continues, around the clock, for up to 6 weeks with a single pump, and the duration can be extended for multiple months through serial implantation. For instance, Ravindranath *et al.* used ALZET pumps for chronic administration of buserelin acetate to bonnet macaque monkeys for a period of 3 years, with pumps replaced every 3 weeks and up to 52 serial implantations. (Table 4 contains a list of the longest ALZET pump studies by species.)

Listed below is a summary of recent research publications describing the use of ALZET pumps in chronic duration studies. Additional references are available from ALZET Technical Services at 800.692.2990 or alzet@durect.com.

Table 1. Selected animal models induced by chronic administration with ALZET pumps

Animal Model	Infused Agent/Drug
Alzheimer's	β-Amyloid protein
Alzheimer's	Okadaic acid
Amnesia	Scopolamine
Breast cancer	Estrogens
Cardiac injury	Isoproterenol
Hormone replacement	Testosterone, estrogen, others
Hypertension	Angiotensin II
Immune suppression	Immunosuppressants
In vivo cell labeling	BrdU
Osteoporosis	Desmopressin
Parkinson's	MPTP
Parkinson's	Rotenone
Psychosis	Amphetamines
Renal fibrosis	Angiotensin II
Sepsis	LPS (endotoxin)
Smoke inhalation	Nicotine

Table 2. Selected list of diseases requiring chronic dosing

- Alzheimer's disease
- Cancer
- Cardiomyopathy
- Depression
- Diabetes
- Drug abuse and addition
- Dysrhythmia (irregular heartbeat)
- Epilepsy
- Hemophilia
- Hyperlipidemia (high cholesterol)
- Hypertension (high blood pressure)
- Hypothyroidism
- Obesity
- Pain management
- Parkinson's disease
- Rheumatoid arthritis

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Table 3. Recent research describing the use of ALZET pumps in chronic duration studies

Duration	Pump	ALZET Pump Use (Citation)
16 weeks	Model 2006 (replaced after 8 weeks)	Chronic administration of various doses of INFα and/or INFλ to evaluate the effect of interferon-accelerated disease in a mouse model of systemic lupus erythematosus. *Yuan et al. Molecular Immunology 2012;52(2):61-70*
4 months	Model 2004 (replaced every month)	ALZET pumps were used to supply a continuous dose of NPY to investigate the peptide's long-term effect on baroreflex sensitivity in Wistar rats. *Xie et al. Cellular Physiology and Biochemistry 2012;29(1-2):111-120*
4 months	28-day pump (replaced monthly)	ALZET pumps were used to establish elevated, steady-state plasma concentrations of epoxyeicosatrienoic acid (EET) to evaluate the signaling molecule's long-term effect in various mouse cancer models. *Panigrahy et al. J Clin Invest. 2012;122(1): 178-191*
12 weeks	Model 1004 (replaced every 3 weeks)	ALZET pumps were used to provide steady-state delivery of Ex-4 to SOD1 mice to investigate neuroprotective activity in amyotropic lateral sclerosis (ALS). *Li et al. PLoS One 2012;7(2):U436-U448*
3 months	Model 2ML4 (replaced every 28 days)	ALZET pumps used for long-term, low-dose angiotensin II infusion to induce hypertension and study activation of renal sympathetic nerve activity (RSNA) in rabbits. *Moretti et al. J Hypertension 2012;30(3):551-560*
10 weeks	Models 1002 and 1004 (replaced at 4 and 8 weeks)	Continuous administration of aliskiren to evaluate the renoprotective effect of supplemental aliskiren therapy on valsartan-treated diabetic mice. *Lei et al. Journal of Pharmacological Sciences 2012;119(2):131-138*
9 weeks	N/A	Continuous administration of supraphysiological leptin doses to female rats to evaluate long term skeletal effects. *Stunes et al. Endocrinology 2012:153(5): 2245-2253*
8 weeks	Model 2004 (replaced after 28 days)	Chronic administration of testosterone and/or nandrolone in a rat model of spinal cord injury to evaluate their impact on muscular atrophy. *Wu et al. J. Neurotrauma 2012;29(8):1663-1675*
8 weeks	Model 2ML4	Haloperidol administration to rats to evaluate the effect of chronic antipsychotic treatment on brain morphology. ALZET pumps were used to avoid multiple daily injections and to maintain clinically relevant drug levels throughout the treatment period. *Vernon et al. Biological Psychiatry 2012;71(10):855-863*

Table 4. Longest ALZET pump duration studies by species

Species	Duration	Pump Model	Replacement	Publication
Cattle (bull)	9 weeks	2ML4	After 28 days	*Contri et al. Vet Quarterly 2012;32(1):51-54*
Dog	18 months	2002; 2ML4	Every 2-4 weeks	*McRae et al. J Reprod Fertil 1985;74(2):389-397*
Guinea-pig	8 weeks	2002	Every 13 days	*Tang et al. International Tinnitus Journal 2001;7(1):4-12*
Monkey	3 years	2002	Every 3 weeks	*Ravindranath et al. Fertil Steril 1992;57(3):671-676*
Mouse	7 months	2004	Every 4 weeks	*Banach-Petrosky et al. Cancer Res. 2007;67(19):9089-9096*
Rabbit	36 weeks	2004	Every 4 weeks	*Ma et al. Bone 2007;41(3):386-392*
Rat	1 year	N/A	N/A	*Murphy et al. J Urol 1986;135(4):840-844*

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