THE **ALZET** OSMOTIC PUMP NEWSLETTER – **WINTER 2008**

Special Delivery

▸ *Pharmacology Focus*

The primary objective of a pharmacology study is to optimize the conditions of drug administration in order to achieve maximum therapeutic efficacy with the least burden of adverse effects. Key parameters of drug action that are commonly investigated are the level and duration of drug exposure, as well as the spatial distribution of the drug. Rate-controlled drug delivery by ALZET® Osmotic Pumps allows researchers to set drug concentration at a desired level and maintain it for a chosen duration. ALZET pumps also allow direct delivery of drugs into target tissues, thus enabling careful analysis of local versus systemic effects. By manipulating these variables, drug effects can be explored and optimized early in preclinical development, increasing the odds that a drug program graduates to the clinical phase.

Since the mid-1970's, ALZET pumps have been used as a powerful experimental tool to facilitate pharmacology research. ALZET pumps are commonly used in the pharmaceutical industry to optimize delivery of novel drugs and ignite product development. They are also used in academic institutions to educate the next generation of young scientists on the basic principles of pharmacology research. Described below are select applications of ALZET pumps in pharmacology research, drawn from more than 10,000 published ALZET studies. Please contact us if you would like references on any of the applications described below, or a custom reference list relevant to your research area.

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Pharmacokinetics of target-organ directed drug delivery

–by Dr. H.A.J. Struijker-Boudier, Dept. of Pharmacology, University of Maastricht

Ideal drug delivery limits drug distribution to its target site, thus avoiding systemic effects. Several drug delivery systems have been developed to facilitate target-organ directed drug delivery, including liposomes, antibodies, magnetic nanoparticles[1], and organ-specific pro-drugs. The most direct way of target-organ directed drug delivery is intra-arterial administration via infusion into the feeding artery. In experimental animals this approach is often used by means of osmotic minipumps. The aim of this review is to describe, from a pharmacokinetic perspective, some of the applications of target-organ directed drug administration. We focus on intra-arterial infusion as a method for target-organ directed drug delivery in view of the abundant application of this technique.

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Pharmacokinetic theory

The pharmacokinetic principles underlying the analysis of the benefits of intra-arterial drug administration have been reviewed by Dedrick *et al.* and Daemen *et al.*[2,3] In short, the systemic advantage, i.e. the reduction in the systemic drug concentration during intra-arterial versus systemic drug administration, is expressed by the ratio of:

$$C_{s,ia}/C_{s,iv}$$

Where $C_{s,ia}$ is the systemic concentration during intra-arterial and $C_{s,iv}$ the systemic concentration during systemic drug infusion. This ratio can be expressed by the formula:

$$1 - E_t$$

in which E_t is the extraction ratio of the drug in the organ. It indicates that the reduction of the systemic concentration during intra-arterial, compared to systemic administration, is high if a drug is infused into the artery of a target organ which extracts the drug extensively.

A second purpose of target-organ directed drug administration is to increase selectively the drug concentration in the target organ. Enhancement of the drug concentration in the artery supplying the target organ is expressed by the ratio:

$$C_{t,ia}/C_{t,iv}$$

Where $C_{t,ia}$ equals the steady-state concentration in the artery supplying the target organ during intra-arterial administration, and $C_{t,iv}$ that during systemic administration of the same dose. On the basis of equi-effective drug concentrations at the target site, this ratio also indicates the reduction in the intra-arterially infused dose, and thus the reduction in systemic effects. At steady-state conditions, this co-called regional advantage can be expressed by the formula:

$$1 + Cl_s/Q_t$$

This formula indicates that a regional gain is achieved when a drug with a relatively high systemic clearance (Cl_s) is infused into a target organ with a relatively low blood flow (Q_t). Therefore, organs with a relatively high blood flow, like the liver and the kidney, only allow a limited regional advantage unless the flow is reduced, for instance, by the simultaneous administration of vasoconstrictor agents or degradable starch microspheres. The second conclusion from this relationship is that a high systemic clearance is a favorable property for a drug candidate for intra-arterial infusion.

Intra-arterial drug administration using osmotic minipumps

Osmotic minipumps have been used for target-organ directed drug administration to define sites of drug action or to alter selectively the function of an organ or tissue. The introduction of the osmotic minipump has greatly facilitated the experimental possibilities for local drug administration. There is now a vast body of literature dealing with local administration of drugs to the kidneys, brain, myocardium, liver, and other organs of different animal species. A wide variety of drugs with different pharmacokinetic properties has been used in these experiments. The pharmacokinetic principles discussed above can also be applied to analyze the potential benefits of these methods of drug administration. Again, surprisingly little attention has been given to them.

A few examples may illustrate how the formulae can be used. The first is intrarenal administration of hippuric acid. This drug is strongly extracted by renal tissue and thus, a systemic advantage may be expected. On the other hand, in view of the high renal blood flow no major regional advantage may be expected. Experimental evidence obtained in rats shows that the actual values upon intrarenal infusion of hippuric acid show a systemic advantage ($C_{s,ia}/C_{s,iv}$) of 0.2 and a regional advantage ($C_{t,ia}/C_{t,iv}$) of close to 1.0.[3] The second example pertains to a low flow tissue. It is the chronic infusion of propranolol into the cerebrospinal fluid of rats.[4] The flow of blood through the lateral ventricles of the rat brain is extremely low when compared to cardiac output. The regional advantage in this situation is 100-300.[4]

Conclusion

Direct infusion of a drug into the artery supplying a target organ is an important method for drug application. It is used both in clinical practice and in experimental research. In some circumstances, it can be an effective means of reducing drug dosage and systemic side-effects. These circumstances can be defined on the basis of a relatively simple physiological pharmacokinetic model. Recent experiments confirm the validity of this model. However, application of intra-arterial drug infusions has in some instances not led to significant advantages. This lack of effect can partly be explained by the fact that investigators did not critically analyze the physiological and pharmacokinetic principles underlying target-organ directed drug administration. Future design of experimental and clinical applications of target-organ directed drug administration should take these principles into account.

[1] *Alexiou et al. Anticancer Res 2007;27(4A):2019-2022*
[2] *Dedrick RL. J Pharmacol Sci 1986;75:1047-1052*
[3] *Daemen et al. Trends Pharmacol Sci 1988;9:138-142*
[4] *Smits et al. J Pharmacol Exp Ther 1979;209:317-322*

Benefits of ALZET Pumps in Pharmacology Research

- Improved bioavailability of drugs with short half-lives
- Continuous and controlled delivery of experimental agents
- Convenient & cost-effective for chronic dosing of lab animals
- Ensures reproducible, consistent results
- Reduced toxicity and drug side effects
- Reduced drug waste (often with significant cost savings)
- The only implantable pump available for use in mice and young rats
- Automatic nighttime and weekend dosing
- Less stressful to the animal
- Ideal for studies involving behavioral testing - no animal handling required during infusion period
- Easily attached to a catheter for targeted delivery into vessels or other tissues
- Over 30 years of published research (well-established dosing method)

Why Pharmacologists Use ALZET Pumps in Their Research

"We used constant infusion of a low dose of drug to achieve sustained occupancy of only high-affinity receptors."

(p. 2109) Simard et al. Journal of Clinical Investigation 2007;117(8):2105-2113

"This dosing regimen also takes into consideration the reported 4-6 times shorter half-life of antipsychotic drugs in rodents than humans and highlights the advantage of using minipumps in the present study for continuous drug administration to achieve receptor occupancies comparable to clinical use in humans."

(p. 1131) Lin et al. Neuropharmacology 2006;51(7-8):1129-1136

"Due to its short half-life, amylin was administered via subcutaneous infusion as a proof of concept for its potential use as an antiobesity agent."

(p. R1861) Mack et al. Am J Physiol Integr Comp Physiol 2007;293:R1855-R1863

"Osmotic mini-pumps provided consistent and dose-dependent delivery of AEOL 10150…a continuous availability of antioxidant via osmotic infusion pumps throughout the study."

(p. 575) Rabbani et al. Int J Radiation Oncology Biol Phys 2007;67(2):573-580

""This mode of delivery [ALZET pumps] maintains consistent plasma levels of SM16 over the course of the study."

(p. 2356) Suzuki et al. Cancer Res 2007;67(5):2351-2359

"The advantage of kallikrein protein infusion via osmotic minipumps is to provide a stable supply of the therapeutic protein or peptide without potential side effects."

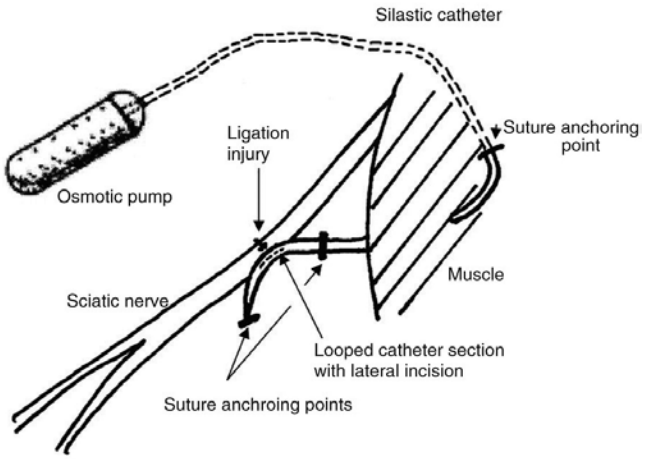
(p. 18) Yao et al. Regulatory Peptides 2007;140(1-2):12-20

Effective Therapeutic Cannabinoid Analgesia Requires Targeted Delivery

–by Laura Whitman

Neuropathic pain is often difficult to manage clinically, thus the development of novel treatments is an important area of investigation. Advancement of cannabinoids into useful analgesic drugs has been hampered by their narrow therapeutic index and association with psychosis risk when delivered systemically. Lever *et al.* demonstrated that delivery of systemically ineffective doses of the aminoalkylindole cannabinoid compound WIN 55,212-2, when administered directly to the site of nerve injury via ALZET Osmotic Pumps, can effectively induce a peripheral antihyperalgesic effect.

Experimental results indicated that continuous perineural delivery of WIN 55,212-2 to the injury site significantly reduced hypersensitivity to mechanical and cooling stimuli, compared to vehicle or sham-ligation controls. The analgesic effects of WIN 55,212-2 were reversed by the CB1 receptor antagonist SR141716a, co-delivered via the same pump. Furthermore, co-delivery of the CB2 receptor antagonist SR144528 reversed only the early analgesic effects of peripheral WIN 55,212-2 treatment. Additional testing showed that the effect of continuous delivery of WIN 55,212-2 on mechanical paw withdrawal responses was dose related. Furthermore, delivery to the contralateral side of nerve injury showed no significant effect on reflex behaviors, thus ruling out the possibility of any cannabinoid systemic activity.



(Figure 1) *Schematic of the system for continuous delivery of WIN 55,212 2 to the sciatic nerve injury site. The diagram shows the positions of the ALZET pump, the perineural catheter, and the site of partial ligation injury. [Reprinted by permission from Macmillan Publishers Ltd: Level et al British Journal of Pharmacology 2007;151:292-302]*

In a study published in the British Journal of Pharmacology, Lever *et al.* presented a novel method to achieve localized analgesic effects with a cannabinoid using a perineural catheter-osmotic pump delivery system. ALZET osmotic pumps (Model 2001) containing WIN 55,212-2 were implanted subcutaneously in Wistar rats, which had received a partial ligation injury to the sciatic nerve. A catheter attached to the pump was tunneled subcutaneously and positioned with a loop directly over the nerve injury site. An incision was made in the loop of the catheter to allow drug delivery directly to the injury site (See Figure 1 for schematic). WIN 55,212 2 was delivered continuously for 7 days, and its analgesic effects were assessed by measuring the animals' hypersensitivity to sensory stimuli.

Continuous cannabinoid delivery using ALZET Osmotic Pumps allowed researchers to achieve therapeutic efficacy at doses below those reported to be effective for analgesia when given by bolus injection. These results indicate that cannabinoids can effectively prevent aspects of neuropathic pain when delivered continuously at relatively low doses. Moreover, localized delivery of WIN 55,212 2 can eliminate the psychoactive side effects normally associated with systemic cannabinoid delivery.

Lever et al. British Journal of Pharmacology 2007;151:292-302.

Dosing Methods for Antiepileptic Drugs

–by Jose Gadea

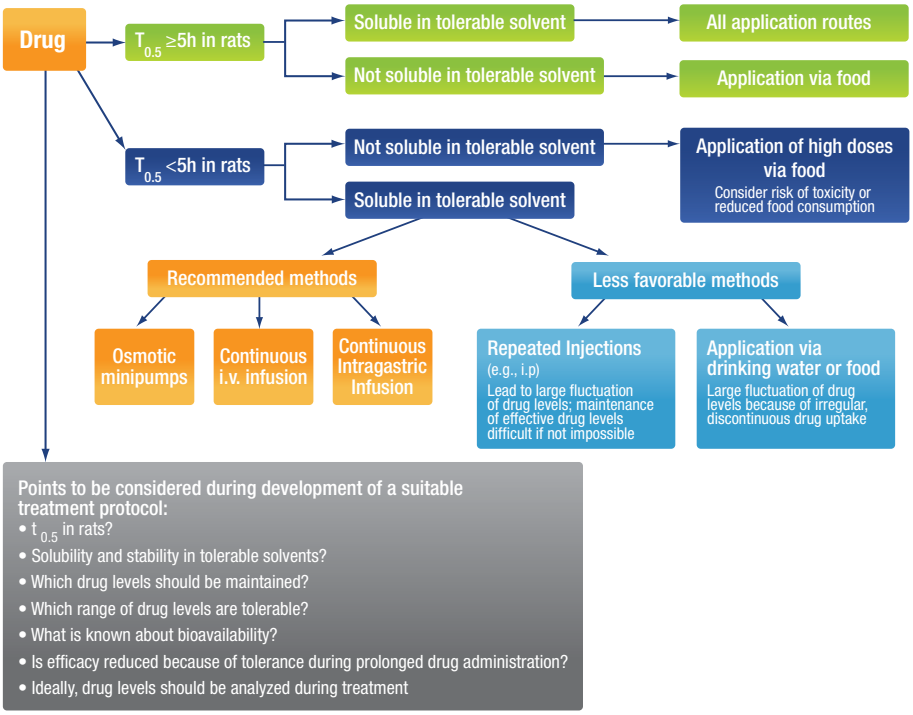
Antiepileptic drugs (AEDs) are important therapeutics for controlling seizures in epilepsy patients. Successful therapy is highly dependent on achieving and maintaining effective steady-state AED plasma concentrations for prolonged periods. When evaluating the efficacy of new AEDs in rodent models of chronic epilepsy, researchers face the critical task of selecting the most appropriate dosing method for their study: one that is both convenient and effective at maintaining prolonged AED exposure at therapeutic levels.

For AEDs with relatively long half-lives (>5 hours), conventional methods of drug administration, such as daily injections or oral dosing, are viable options for maintaining effective drug levels. However, most AEDs have short elimination half-lives in rodents (<5 hours), making these methods inadequate for effective dosing. Furthermore, these methods are labor intensive and often lead to higher drug toxicity and stress during chronic treatment. Administration via drinking water or food is not a viable alternative either given that rodents drink or eat mostly at night, thus drug levels fluctuate widely according to the animal's feeding and drinking behavior. Further, administration via drinking water is not an option for water insoluble AEDs, or for those that alter the palatability of the water.

For AEDs that are rapidly eliminated, effective levels can be sustained by continuous administration. Tethered infusion systems consisting of external pumps and chronically implanted intravenous catheters can be used for continuous administration of AEDs. However, these methods are costly and carry increased risk of catheter clotting, infection, and animal stress, thus jeopardizing experimental results. On the other hand, ALZET® osmotic pumps have successfully been used as a convenient method for chronic AED dosing in laboratory animals. Importantly, ALZET pumps are specifically designed to deliver a continuous and automatic dose for up to six weeks, thus ensuring constant exposure of short half-life AEDs over the course of the study.

AEDs administered via ALZET pumps

- Carbamazepine
- Clonazepam
- Diazepam
- Gabapentin
- Levetiracetam
- Phenobarbital
- Phenytoin
- Tiagabin
- Valproic acid
- Vigabatrin



(Figure 2) Decision flow chart for researchers planning studies with prolonged AED administration in rats. [Reproduced by permission of Blackwell Publishing Ltd. Wolfgang Loscher. Epilepsia 2007;48(7):1245-1258]

Valproic acid (VPA) is an example of an AED with too short of a half-life (0.8 hr in mice; 1-5 hr in rats, depending on the dose) for prolonged dosing by conventional methods.[1] ALZET pumps have been used successfully for continuous administration of VPA in preclinical models of epilepsy.[2,3] Stout *et al.* studied the effects of continuous VPA administration on corticotrophin-releasing factor (CRF) levels in the rat brain. Subcutaneous VPA treatment for 7 days using ALZET pumps resulted in decreased CRF concentrations in various brain regions. Serralta *et al.* studied the schedule-dependent effects of VPA on anticonvulsant efficacy in the kindled epilepsy model. The study demonstrated that, compared to acute injections, continuous intracerebroventricular administration by ALZET pumps was more effective at controlling seizure intensity and duration. More importantly, the continuous administration method effectively reduced ataxia and sedation in the absence of systemic toxicity.

The various dosing methods available for AED administration are summarized in a review by Wolfgang Loscher, and a set of experimental recommendations for chronic AED administration in rats is summarized on Figure 2.

Contact ALZET Technical Services at 800.692.2990 or alzet@durect.com for references on AEDs that have been administered via ALZET pumps.

[1] *Loscher, W. Epilepsia 2007; 48(7):1245-1258.*
[2] *Stoutet al. Neuropsycopharmacology 2001;24(6):624-631*
[3] *Serralta et al. Epilepsy Research 2006;70(1):15-26*

Pharmacoeconomics of Continuous Drug Administration Using ALZET Pumps

–by Dr. Jaymin Shah

New compounds in early stages of preclinical investigation are very expensive to synthesize and are only available in minimal quantities for evaluation in animal models. Many of these compounds have very rapid elimination rates and low volume of distribution, thus requiring frequent dosing to maintain a certain threshold concentration in the body for therapeutic efficacy. In such cases, continuous drug administration using ALZET® Osmotic Pumps may offer significant cost savings in terms of total amount of drug required for *in vivo* activity.

ALZET pumps are small infusion devices for implantation in laboratory animals as small as mice. ALZET pumps allow researchers to effectively control the level of drug exposure as well as the duration of administration. Relative to bolus dosing, some of the obvious advantages of using ALZET pumps in animal studies are:

- Increased drug efficacy
- Fewer side effects
- Constant blood levels
- Reduced animal stress
- Reduced requirement of drug for experiment
- Cost effective experimental approach

The drug savings advantages of continuous administration are evident when evaluating the pharmacokinetic profiles of drugs with short half lives, such as risperidone, glucagon-like peptide-1 (GLP-1), and relaxin. To demonstrate this pharmacologic benefit, we performed compartmental pharmacokinetic simulations using nonlinear regression analysis with a WinNonlin software package (Pharsight, Mountain View, California).

Risperidone Pharmacokinetics

Risperidone is a short-acting, atypical antipsychotic drug commonly used for the treatment of schizophrenia. Risperidone shows potent *in vivo* blocking activity against serotonin (5-HT_2) and dopamine (D_2) receptors. A pharmacokinetic profile for risperidone comparing repeated bolus to continuous administration can be used to extrapolate the potential amount of drug savings. Following a 0.5 mg/kg bolus dose in rats, risperidone exhibits an elimination half-life of 1 hour and a volume of distribution of about 1 L/kg (in-house data). If the same dose is administered intravenously (IV) to a 300 gram rat every 4 hours during two days, the resultant plasma profile is as depicted in Figure 3 (blue line). Alternatively, if risperidone is infused for 48 hours using ALZET pumps (to maintain D_2 receptor occupancy levels at 100 or 150 ng/mL), the plasma profile is as shown in Figure 3 (green and orange lines, respectively). As observed in Figure 3, continuous administration not only ensures that steady-state levels of risperidone are maintained at 100 or 150 ng/mL over the dosing period, but also a significant drug savings of 48% or 22%, respectively, can be realized.

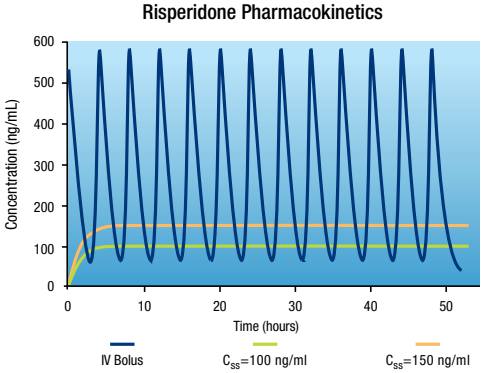


Figure 3: Pharmacokinetic profile of risperidone in rats: comparison of IV bolus dosing (0.5 mg/kg) to continuous administration via ALZET pumps.

GLP-1 Pharmacokinetics

Similar analysis can be performed using some of the pharmacokinetic parameters exhibited by GLP-1, a gut-derived incretin hormone with potential therapeutic effects for diabetes mellitus.[1] GLP-1 stimulates the production of glucose-responsive β cells and increases the amount of insulin secreted by each β cell in response to glucose. Maintaining adequate levels of GLP-1 may be required in some pharmacology animal studies, and it can be effectively achieved by continuous infusion using ALZET pumps. The expected pharmacokinetic profile for GLP-1 in dogs (~10 kg animal weight) following repeated IV bolus administration compared to continuous infusion via ALZET pumps is shown in Figure 4. This analysis assumes a 50 µg/kg IV bolus dose given every 6 hours for 3 days, as well as a continuous dose resulting in maintenance concentrations of 10 and 15 ng/mL. As can be elucidated from the graph, steady-state concentrations (C_{SS}) of GLP-1 at 10 and 15 ng/mL can lead to a total drug savings of 48% and 21.5%, respectively, compared to repeated bolus dosing.

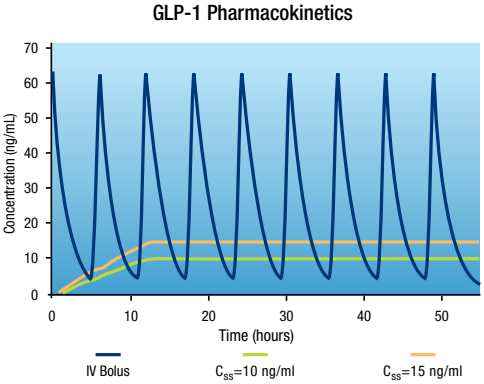


Figure 4: Pharmacokinetic profile of GLP-1 in dogs: comparison of IV bolus dosing (50 ug/kg) to continuous administration via ALZET pumps.

Relaxin Pharmacokinetics

Relaxin, a hormone from the insulin growth factor family that promotes collagen remodeling, is another example of a drug that can benefit from continuous administration. Cossum *et al.* studied the pharmacokinetics of relaxin after IV bolus administration in pregnant and nonpregnants rats.[2] Furthermore, the use of ALZET pumps has been successfully demonstrated by Garber *et al.* in studies the effects of continuous relaxin administration on renal disease.[3] Figure 5 describes a hypothetical pharmacokinetic profile for relaxin in rats when an IV bolus dose of 90 µg/kg is given every 6 hours, or when delivered continuously for 54 hours by ALZET pumps in order to maintain steady-state concentrations of 50 and 100 ng/mL. Again, a substantial drug savings can be reached with continuous administration.

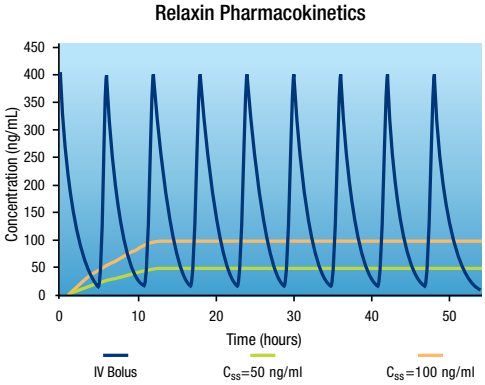


Figure 5: Pharmacokinetic profile of relaxin in rats: comparison of IV bolus dosing (90 ug/kg) to continuous administration via ALZET osmotic pumps.

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The amount of drug savings can be estimated by using the target steady-state concentration as multiples of the minimum drug concentration (C_{min}) obtained following bolus administration. Following an IV bolus dose, the minimum relaxin concentration observed prior to the next dose is ~9.7 ng/mL. If relaxin is administered by continuous infusion using ALZET pumps to achieve concentrations at a certain multiple of C_{min}, the percent drug savings is shown in Figure 6. For example, if the desired steady-state concentration is targeted to be at six times the C_{min} (6 x 9.7 = 58.2 ng/mL), the percent drug savings would be approximately 42%. Figure 6 clearly shows that the total drug savings advantage diminishes as the requirement for a higher C_{ss} increases.

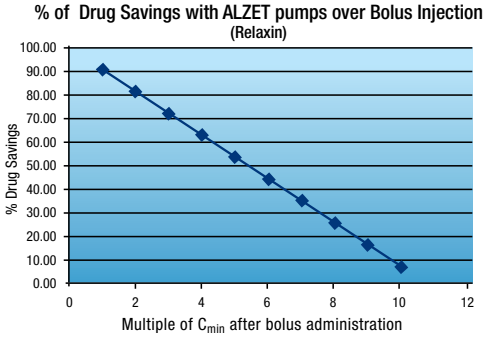

Figure 6: Percent drug savings for relaxin when delivered continuously by ALZET pumps at various multiples of C_{min}.

The greatest potential benefit of continuous administration is realized with drugs that exhibit fast clearance rates *in vivo*, thus requiring frequent dosing to maintain effective steady-state concentrations. As demonstrated by the pharmacokinetic simulations for risperidone, GLP-1 and relaxin, the use of ALZET pumps for continuous administration offers significant drug savings advantages over frequent dosing methods. Depending on the drug's C_{ss} required for therapeutic efficacy, continuous administration can afford up to a 48% savings in the amount of drug needed for a study. ALZET pumps should be considered as a valuable dosing method when evaluating novel compounds *in vivo* as these pumps can help ensure maximum therapeutic benefit with the least amount of drug, thus maximizing research success and lowering overall study cost.

[1] *Pridal et al. European Journal of Drug Metabolism and Pharmacokinetics 1996;21:51-59.*
[2] *Cossum P. et al. Pharm. Res. 1992;9:419-424.*
[3] *Garber S. et al. Kidney International 2001;59:876-882.*

Steady-state concentrations needed for *in vivo* activity of VEGFR inhibitors

– by Kurt Kemling

The development of novel anticancer therapeutics for clinical use requires the complex analysis of pharmacokinetic-pharmacodynamic relationships in preclinical animal models. With this in mind, researchers at GlaxoSmithKline studied the pharmacokinetics, and *in vivo* effects of GW771806 (a VEGFR inhibitor with similar enzymatic and cellular activity as pazopanib) on antitumor and antiangiogenesis activity following two different routes of administration. In turn, they hoped to determine whether $C_{steady\text{-}state}$ or C_{max} was the primary determinant of activity and ultimately ascertain the optimal *in vivo* concentration required for their clinical anticancer compound, GW786034 (a.k.a. pazopanib).

The *in vivo* antitumor activity of GW771806 was evaluated in Swiss nude mice bearing HT29 human tumor xenografts. GW771806 was administered either by oral gavage at dosages of 3, 10, 30, or 100 mg/kg twice daily, or by continuous administration at dosages of 1, 3, or 10 mg/kg/day for 5 days using subcutaneously implanted ALZET Osmotic Pumps (Model 2001; 1 µl/hr release rate). Similar treatment regimen and GW771806 dosages were given to nude mice to investigate the antiangiogenic activity of the VEGFR inhibitor. Plasma samples were also collected on day 2 of continuous dosing, and further analysis indicated that continuous treatment at 0.3, 1, 3, and 10 mg/kg/d resulted in steady-state concentrations of 0.09, 0.23, 0.65, and 2.67 µmol/L, respectively.

While continuous infusion and bolus oral dosing of GW771806 both significantly inhibited tumor growth (57-96% and 58-101% respectively), the study results "clearly showed that C_{max} is not a good indicator of antitumor activity because 2.57 µmol/L constant plasma concentration of GW771806 with continuous infusion was more effective than >20 µmol/L C_{max} achieved with 10 and 30 mg/kg oral dosing" (p. 2019). Additionally, a $C_{steady\text{-}state}$ of >2.50 µmol/L showed 90% inhibition of angiogenesis, compared to a ten-fold higher concentration required with oral gavage. The data suggests that both tumor growth and angiogenesis are not driven by C_{max} of the VEFGR inhibitor, and that continuous delivery is the best administration method to maximize the therapeutic potential of GW771806.

Kumar *et al.* had attempted these studies with pazopanib; however, due to the large differences in C_{max} and C_{trough} observed after bolus administration, they investigated the continuous infusion of GW771806, a similar VEGFR inhibitor with better solubility characteristics for infusion studies. The use of ALZET pumps enabled steady-state concentrations of GW771806 to be maintained during the dosing period. By comparing the pharmacokinetics of GW771806 by two different routes of administration, Kumar *et al.* clearly demonstrated that the *in vivo* activity of the VEGFR inhibitor is dependent on steady-state concentrations above a threshold. These results underscore the value of pre-clinical models for clinical dose selection. Data obtained from these studies enabled the scientists to select an optimum pazopanib dose for use in a phase 1 clinical study.

Kumar et al. Molecular Cancer Therapeutics 2007;6(7):2012-2021.

Newest ALZET Pump Models

With infusion durations of 4 and 6 weeks, the ALZET Models 1004 and 2006 are ideal for chronic administration of agents to mice and other small laboratory animals. They also feature uniquely low release rates, which are ideal for targeted delivery to the cerebral ventricles or brain parenchyma.

	Model 1004	Model 2006
Reservoir Volume	100 µl	200 µl
Duration	4 weeks	6 weeks
Release Rate	0.11 µl/hr	0.15 µl/hr
Dimensions	1.5 cm x 0.6 cm	3.0 cm x 0.7 cm

Targeted Delivery with ALZET Catheters

A range of specialized catheters, customized for a specific target and animal species, are available from DURECT Corporation to enable direct delivery of agents to a vessel, spinal cord, or other sites. These catheters incorporate useful features, such as retention beads or suture patches to facilitate placement and stabilization in a vessel or tissue. For added convenience, they are available sterile and specifically designed to attach securely to any ALZET pump model.

CATHETER	TARGET SITE	SPECIES	CATHETER MATERIAL	CATHETER FEATURES‡	ORDER #
RJC	Jugular vein	Rat	Silicone	Dacron patch[1] Flexible material[2] Bevel tip[3]	0007710
RFC	Femoral vein	Rat	Polyurethane	Retention beads[1] Flexible material [2]	0007720
RFC-T	Femoral vein	Rat	Opaque Polyurethane	Retention beads[1] Tapered ID[4] Radio-opaque[5]	0007730
RIC	Intrathecal	Rat	Polyurethane	Occipital access Teflon coated stylet[6] Protected junctions[7]	0007740
RIC-S	Intrathecal	Rat	Polyurethane	Lumbar access Teflon coated stylet[6] Protected junctions[7]	0007741
MJC	Small vessels	Mouse	Polyurethane	Retention beads[1] 28G PU catheter tip[9] Markings on tip[8]	0007700
MJC-AL	Small vessels	Mouse	Polyurethane	Adjustable length[10] Retention beads[1] 28G PU catheter tip[9] Markings on tip[8]	0007701
MJC-LT	Jugular vein	Mouse	Polyurethane	Large tip[11] Adjustable length[10] Retention beads[1] Markings on tip[8]	0007702
Vinyl tubing	Various	Rat, mouse, other	Vinyl	Flexible material 10 per bag	0007760
PE tubing	Various	Rat, mouse, other	Polyethylene	Thermo formic 10 per bag	0007760

‡CATHETER BENEFITS

[1] Facilitates accurate placement within vessel and improves catheter patency
[2] Reduced risk of vessel trauma
[3] Facilitates insertion into vessels
[4] Tapered internal diameter (ID) for improved long-term patency and reduced risk of kinking
[5] Improved catheter patency, and reduced clotting risk
[6] Teflon coated, stainless steel stylet to facilitate insertion during cannulation
[7] Leak free catheter junctions to ensure adequate flow and minimize kinking
[8] Markings at 9 and 11 mm from tip to simplify adaptation for smaller animals
[9] Optimum for cannulating small vessels (i.e., carotid, femoral, etc)
[10] Can be trimmed to achieve smaller lengths
[11] Optimum for jugular cannulation in mice

Pharmacology Publications

Therapeutic antibodies, enzyme inhibitors, antidepressants, anticonvulsants, growth factors, and nucleic acids are all examples of agents that have been successfully delivered via ALZET pumps. New publications for these and other experimental agents are constantly added to the ALZET bibliography. Contact us to request citations specific to your research interest.

Surgical Training Video

Learn how to use and implant ALZET pumps, or train your staff on these procedures, with the ALZET Surgical Implantation Techniques video available on CD. Request your copy today at www.alzet.com.

Teaching Pharmacology with ALZET pumps at UCSD

– by Dr. Masahiko Hoshijima, Assistant Adjunct Professor of Medicine, UCSD

In 2005, the National Institute of General Medical Sciences (NIGMS) selected the University of California at San Diego (UCSD) as one of four awardees of a new educational grant aimed to support the inception of short educational workshops in animal physiology and pharmacology. With these funds, the UCSD Department of Pharmacology developed an intensive 3-week summer course in Systems Pharmacology and Translational Biology with focus on the central nervous system (nociception; neuropsychiatric disease), the cardiovascular system (hypertrophic cardiac disease; heart failure), and new *in vivo* imaging techniques. With the generous support of ALZET, we also teach various mini-pump implantation techniques during the course. We clearly recognize the wide range of applications and unrivaled versatilities of the ALZET mini-pump technology to efficiently test small molecules *in vivo*. The pumps are used to generate a mouse model of drug-induced cardiac disease to enable chronic testing of various small molecules. The UCSD program, directed by Dr. Larry Brunton, has been training up to 20 scientists each year. The participants are graduate students, post-docs and scientists from the biotech and pharmaceutical industry, reflecting the rising need to train scientists in the use of animal subjects in different aspects of medical research. For most students, this program offers the first real opportunity to perform experimental procedures in mice. However, at the end of the 3-week course, participants acquire invaluable skills and experiences that they confidently take back to their institutions.

SPECIAL DELIVERY
Volume 25, No. 1
December 2008
DURECT Corporation
Jose R Gadea, Editor

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Recently Infused Agents

Continuous delivery is a popular form of drug administration in pharmacology studies since it allows constant levels to be maintained over time. The following list represents agents that have recently been delivered via ALZET pumps.

Agent	Descr./ Therapeutic Category	Ref.#
Flesinoxan	*Selective Serotonin$_{1A}$ Agonist*	P8647
Ro3303544	*GSK3β inhibitor; Indole maleimide*	P8645
BMS-200261	*Protease-activated receptor 1 antagonist*	P8644
TY-51469	*Chymase inhibitor*	P8639
Dutasteride	*5α-reductase type 1 and 2 inhibitor*	P8636
JSM5562	*Integrin antagonist*	P8750
AY9944	*3β-hydroxysterol-Δ^7-reductase inhibitor*	P8476
Darifenacin	*M3 receptor antagonist*	P8489
EMD472523	*$\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin antagonist*	P8366
FR901459	*Novel cyclosporin A derivative*	P8541
Fractalkine	*Chemokine; a.k.a. CXCL1*	P8487
GW771806	*Multikinase angiogenesis inhibitor*	P8520
JSM6427	*α5β1 integrin inhibitor*	P8610
JSM6424	*α5β1 and αvβ3 inhibitor*	P8610
Lipoxins	*Antiinflammatory lipid mediators*	P8433
LY-117018	*Raloxifene analog*	P8475
NSC23766	*Small molecule Rac activation inhibitor*	P8493
TAT (47-57, dV1-1)	*Protein kinase C inhibitor*	P8460
Temocaprilat	*ACE inhibitor*	P8612
Tuftsin	*ACE inhibitor*	P8509
(pro)renin receptor blocker	*Prorenin activation inhibitor*	P8642
Ro26-2198	*Vitamin D analogue*	P8637
NBI-31772	*IGF-1 aptamer*	P8486
17-DMAG	*Hsp90 inhibitor; a.k.a. NSC 707545*	P8635
GN8	*Anti-prion compound*	P8646
Repaglinide	*Sulfonylurea receptor 1 blocker*	P8643

References on these and other agents are available to you as a complementary service. Contact ALZET Technical Services at 800.692.2990, or via e-mail at alzet@durect.com to request a customized list of references in your area of interest.