UNIVERSITY OF HELSINKI

ECVAA Training Day

4.3.2009

Helsinki, Finland

THEME: Evidence based use of opioids, alpha-2 agonists in anaesthesia

The Association of Veterinary Anaesthetists

info@ava09.fi ■ www.ava09.fi

ECVAA Training Day Program

Theme: Evidence based use of opioids, alpha-2 agonists in anaesthesia

Wednesday 4.3.2009
LECTURE HALL 1

Chair Dr. Johanna Kaartinen, University of Montreal and University of Helsinki

08.00 – 09.00 Registration

09.00 – 10.00 **1. Dexmedetomidine in Human Anaesthesia and Intensive Care Medicine. ...3**
Dr. Riku Aantaa, MD, DMedSci, Department of Anesrhesia, Intensive Care, Emergency Medicine and pain Therapy, Turku University Hospital, Turku, Finland

10.00 – 11.00 **2. Recent Advances in Use of Opioids in Balanced Anaesthesia – Special Attention to Drug Interactions. 7**
Dr. Reino Pöyhiä, MD, PhD, Helsinki University Central Hospital

11.00 – 11.30 Coffee, Lobby

11.30 – 12.30 **3. Use of Opioids and Alpha-2s in Geriatric Patients. 9**
Professor Peter J. Pascoe, Davis, USA

12.30 – 13.30 Lunch, Cafeteria 2nd floor

13.30 – 14.30 **4. Drug-induced Adverse Effects: When Certain Drugs Should Not be Used....16**
Professor Peter J. Pascoe, Davis, USA

14.30 – 15.30 **5. Preemptive Aanalgesia: Controversy Over the Evidence. 20**
Alicia Z Karas, MS, DVM, Dipl ACVA, Tufts Cummings School of Veterinary Medicine, North Grafton, MA, USA

15.30 – 16.00 Coffee

16.00 – 17.00 **6. Somewhat Less Than Local: Efficacy and Safety of Intravenous and Intra-wound Infusion of Local Anesthetics for Postoperative analgesia. 24**
Alicia Z Karas, MS, DVM, Dipl ACVA, Tufts Cummings School of Veterinary Medicine, North Grafton, MA, USA

18.30-19.30 Get together Party / Helsinki City Reception
Old Court House, Aleksanterinkatu 20, Helsinki.

1. Dexmedetomidine in human anesthesia and intensive care medicine

Dr. Riku Aantaa, MD, DMedSci
Department of Anesrhesia, Intensive Care, Emergency Medicine and pain Therapy, Turku University Hospital, Turku, Finland

Alpha$_2$-agonists such as xylazine, detomidine, medetomidine and most recently dexmedetomidine are widely used for sedation, hypnosis and immobilisation of animals for a variety of surgical procedures (1). There are two alpha2-agonists available for human use: clonidine for treatment of arterial hypertension and dexmedetomidine for sedation of patients in the intensive care unit (ICU) and perioperatively.

Basic pharmacology
The physiologic effects of alpha2-agonists are mediated via stimulation of post-synaptic alpha2-adrenergic receptors that activate a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein) resulting in decreased activity of adenylyl cyclase (2). The consequent reduction of intracellular cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase activity result in a dephosphorylation of ion channels. The latter in turn modifies ion translocation and membrane conductance resulting in decreased neuronal activation in the locus coeruleus in the brainstem and consequently in sedation and anxiolysis. Activation of alpha$_2$-adrenergic receptors both in the brain and the spinal cord induces analgesia whereas activation of alpha$_2$-adrenergic receptors in the medullary vasomotor center, reduces norepinephrine release and decreases central sympathetic outflow, which in turn results in decreased heart rate and blood pressure (2).

Dexmedetomidine – clinical features
Dexmedetomidine is highly selective and specific alpha2-agonists. Qualities of dexmedetomidine relevant to its use as an adjunct to human anaesthesia include its sympatholytic and hemodynamic effects, plus its ability to reduce anaesthetic requirements and to confer sedation and moderate analgesia on patients in often highly stressful circumstances. The dosing in humans is distinctively smaller than in animals: clinical effects can be obtained already at 0.2 µg/kg/h after 0 - 1 µg/kg loading (3). Doses over 3.0 µg/kg/h are not commonly used due to increased risk of hemodynamic adverse effects (4).

Sympatholysis
Probably the most prominent effect of alpha2-adrenoceptor activation is the inhibition of release of several neurotransmitters, noradrenaline in particular. Most importantly, this decrease in sympathetic nervous system activity is accompanied by attenuation of the responses to various noxious stimuli such as endotracheal intubation and surgery. Increased sympathoadrenal stability is considered beneficial as it contributes to decreased oxygen consumption and increased hemodynamic stability (5).

Cardiovascular effects
Dexmedetomidine induces a moderate decrease in blood pressure and heart rate in clinically relevant doses. Perioperatively, increased adrenergic and hemodynamic stability mitigates imbalances between myocardial oxygen supply and demand. Particularly in the case of patients with overt or underlying cardiac disease the actions of dexmedetomidine can be expected to reduce the risk of procedure-related cardiac events. This expectation has been corroborated in clinical trials and meta-analyses on dexmedetomidine, clonidine and mivazerol, another experimental alpha2-agonist (6, 7).

Sedation
The value of effective sedation for patients in the stressful environment of an ICU is acknowledged and is not necessarily limited to patients who require ventilator assistance or weaning from ventilator sup-

port. For ICU patients in general, appropriate sedation can avert delirium, which has a highly adverse impact on later prognosis (8). Dexmedetomidine is the only alpha2-adrenoceptor agonist approved for use in the ICU in several countries. Dexmedetomidine is distinguished by the quality of sedation it confers: patients sedated with dexmedetomidine are characteristically easy to rouse but lapse into a tranquil, sleep-like state with no respiratory depression when left undisturbed (9). It has been hypothesized that the sedation achieved with dexmedetomidine may arise from the exploitation of innate sleep-promoting circuits operating through disinhibition of gammaaminobutyric acid-ergic neurons in the ventrolateral preoptic nucleus (10). Perioperatively, alpha2-agonists can be used to significantly reduce the dos dose requirements of general anaesthetics and analgesics (11).

Respiration
Dexmedetomidine-induced sedation is lack of an effect on respiratory drive (12).
Indeed, when patients treated in the ICU are weaned from the ventilator, the dosing of dexmedetomidine used for sedation doesn't need to be altered which provides improved sedative, analgesic and hemodynamic control of the patients throughout their stay in the ICU (13).

Analgesia
Dexmedetomidine shows moderate analgesic effects in doses recommended for human use (14). However, it has a significant synergistic interaction with opioids. In clinical setting, both perioperatively and in the ICU, the dosing of opioids can be significantly (by 20-50%) reduced thus decreasing the potentially deleterious effects of opioids on respiration and gastrointestinal motility (15).

Adverse effects
Although most often considered beneficial, the cardiovascular effects of dexmedetomidine also constitute its most serious adverse effects, of which hypotension and bradycardia are the two most often reported. Bradycardia, sometimes extensive, is seen particularly in healthy young patients with high vagal tone (16). As alpha2-agonists do not block the adrenoceptors nor do they inhibit the synthesis of the neurotransmitters, the receptors remain to be activated competatively by other ligands. Indeed, bradycardia and hypotension can be readily treated. Rapid administration of dexmedetomidine results in high peripheral drug concentrations. This activates peripheral alpha2B-receptors on smooth muscle cells in the vascular bed and results in vasoconstriction and consequently increased blood pressure, sometimes hypertension. This phenomenon is rapidly (in minutes) overcome as the drug penetrates the blood brain barrier and reaches brain and induces sympatholysis and decreased blood pressure (17).

Selected reading

Tranquilli WJ, Maze M. Clinical pharmacology and use of a2-adrenergic agonists in veterinary anaesthesia. *Anaesth Pharmacol* Rev. 1993; 1, 297-309.

Aantaa R, Marjamäki A, Scheinin M. Molecular pharmacology of alpha2-adrenoceptor subtypes. *Ann Med* 1995; 27: 439–449.

Precedex. Patient information leaflet. Hospira, Inc., Lake Forest, IL 60045 USA

Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000; 93: 382–394.

Taittonen MT, Kirvela OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; 78: 400–406.

Aantaa R, Jalonen J. Perioperative use of α2-adrenoceptor agonists and the cardiac patient. *European Journal of Anaesthesiology* 2006; 23: 361–372

Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 2003; 114: 742–752.

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007, 298: 2644-53

Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidinebased vs. propofol-based sedation regimens. *J Cardiothorac Vasc Anesth* 2003; 17: 576–584.

Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003; 98: 428–436.

Aantaa R, Jaakola ML, Kallio A, Kanto J. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. *Anesthesiology* 1997; 86: 1055–1060.

Hsu Y-W, Cortinez LI, Robertson KM et al. Dexmedetomidine pharmacodynamics: Part I. Crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. *Anesthesiology* 2004; 101: 1066–1076.

Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care*. 2000; 4: 302-308.

Angst MS, Ramaswamy B, Davies MF, Maze M. Comparative analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and alfentanil in humans. *Anesthesiology* 2004; 101: 744–752.

Lin T-F, Yeh Y-C, Lin F-S, Wang Y-P, Lin C-J, Sun W-Z, Fan S-Z. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; 102: 117-22.

Hammer GB, Drover DR, Cao H, Jackson E, Williams G, Ramamoorthy C, Van Hare G, Niksch A, Dubin A. The effects of dexmedetomidine on cardiac electrophysiology in children. *Anesth Analg* 2008; 106: 79-83

Talke PO, Maze M. Expecting the unexpected. *Anesth Analg* 2008; 106: 1605-6

2. Recent advances in use of opioids in balanced anaesthesia – special attention to drug interactions.

Dr. Reino Pöyhiä, MD, PhD
Helsinki University Central Hospital

Opioids are commonly used for both perioperative analgesia during balanced anaesthesia and postoperative pain in man and in other species. Older water-soluble opioids (morphine, pethidine) are substituted by newer lipid soluble fast-acting piperidine analogues (fentanyl, alfentanil, remifentanil), many of which can be administered not only intravenously, subcutaneously and intramuscularly but also epidurally and intrathecally. Also, a more and more popular practice in human medicine is, in a pre-empitve manner, to give slow-release, long-acting opioid agonist orally prior to surgery for postoperative pain. However, the severe untoward effects of opioids need to be addressed. They can be reduced to some extent using concomitantly other medications with positive and desired interaction with opioids.

Interaction is the modification of the effect of one drug (the object drug) by the prior concomitant administration of another (precipitant drug). The interactions between the drugs may be chemical or physical, pharmacokinetic or pharmacodynamic. The outcomes of interactions are commonly seen as 1) increases (addition, potentiation, synergism) in pharmacological activity, 2) loss of therapeutic effect, 3) toxicity. The benefit of interaction would be the possibility to reduce the dose-related untoward effects of one drug by combining it with another one with a additive or synergistic action.

Opioids possess their pharmacodymic effects by acting on opioid μ-, κ- and δ-opioid receptors located in the sensory nerves both in peripheral and central nervous system. The distribution of opioid receptors is affected by gender (Table 3, from REF 1) and species of individual biotype.

TABLE 3. *Incidence (percentage of cases) of sex differences in μ opioid analgesia in various species (based on cases listed in Tables 1 and 2)*

Species	M > F	M = F	F > M
Rat*	35 (66%)	16 (30%)	2 (4%)
Mouse	7 (33%)	13 (62%)	1 (5%)
Rhesus Monkey	0 (0%)	1 (100%)	0 (0%)
Human	0 (0%)	4 (29%)	10 (71%)

*Approximately 60% of sample is the Sprague-Dawley strain; 57% of sample is from two laboratories.

An example of interaction at the receptor level is that between opioids and alpha-2-adrenergic agonists (2).

In this lecture the interactions between opioids and propofol, ketamine, volatile anaesthetics and dexmedetomidine are discussed. Special attention will be paid on the novel methods to distinguish the interactions using anaesthetic depth monitoring devices and computer simulations (Fig 5, from REF 3).

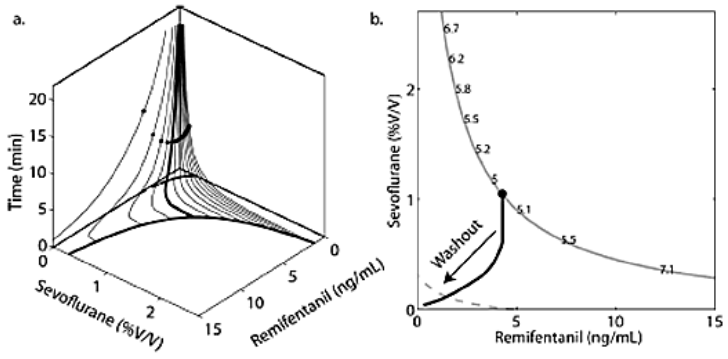

Fig. 5. Results of computer simulations designed to identify optimal target concentration pairs of remifentanil and sevoflurane that minimize the time to responsiveness. *A* shows the predicted decline in effect site and alveolar concentrations for remifentanil and sevoflurane after stopping drug administration regimens targeted to reach the EC_{95} isobole for tetanic stimulation for 1 h. The EC_{95} isobole is on the "floor" of the cube; the vertical axis represents time elapsed since stopping the administration of the drugs. The isobole representing an 80% probability of the return of responsiveness (Observer's Assessment of Alertness/Sedation score ≥ 4) is shown by a *dotted line* that is superimposed on the concentration decay curves. The *highlighted curve* is the sevoflurane and remifentanil target concentration pair that resulted in the fastest return of responsiveness. *B* shows the time in minutes to the return of responsiveness after a 1-h procedure in which sevoflurane and remifentanil were administered to target concentration pairs on the EC_{95} isobole for tetanic stimulation. The *highlighted trace* on the panel on the left is shown topographically. The minimum time to regain responsiveness represents the target concentration pairs for a 1-h procedure.

References:

R.Craft: Sex differences in opioid analgesia: from mouse to man. Clin J Pain 2003; 19: 175-186
Tan et al. J Biol Chem 2009 (Epub), 3) Sandeep et al. Anesthesiology 2006; 105: 267-78.

3. Use of opioids and alpha-2 agonists in geriatric patients

Professor Peter J. Pascoe, *Davis, USA*

A definition of geriatric is an animal that has reached the last 25-20% of their expected life span. In a survey of veterinarians the following values were generated as ages at which dogs and cats "started having diseases associated with aging" (Goldston 1989):

Small dogs	(0-10 kg)	11 ± 2 yrs
Medium dogs(	11-23 kg)	10 ± 2 yrs
Large dogs	(24-40 kg)	9 ± 1 yrs
Giant dogs	(>41 kg)	7 ± 1 yrs
Cats		12 ± 2 yrs

Data gathered from pet cemetery records suggests that a dog would have reached the last 20% of its life by 13-14 years and a cat by 7-8 years (Hayashidani et al. 1988; Hayashidani et al. 1989). There may be great variation in rates of senescence among individual animals and even within an individual, where some organs or systems may deteriorate faster than others. While normal ageing tends to induce changes in organ function, intercurrent diseases may cause far more significant changes in one or more systems and many pathological conditions are more common in the older animal. Clinicians must therefore try to evaluate the individual patient carefully with respect to the signs of ageing and presence of disease in order to plan an appropriate approach for optimal management.

Behaviour
As with ageing people, older cats and dogs tend to become fixed in their behaviours and become more distressed if their environment is altered (Chapman & Voith 1990). Older dogs and cats are less likely to eat and drink normally when hospitalized which may affect their response to drugs that are administered.

Neurons begin to die off with age and the brain of an older dog or cat weighs less than in its youth. Within the brain there is not only a loss of neuronal numbers but there is a progressive decline in the numbers of connections between neurons. This also means that the senses are dulled and motor functions are decreased. This progressive diminution of sensory perception leads to some of the behaviours associated with old age and may contribute to the altered responses to drugs. The peripheral nervous system is also affected and there seems to be a decrease in nociceptive transmission by A-delta fibres (Chakour et al. 1996). Alpha-2 agonists may enhance some cognitive functions in older animals but it is difficult to know the clinical relevance of this in practice (Rama et al. 1996). Opioids, with the exception of meperidine (pethidine), did not increase the postoperative incidence of confusion or cognitive impairment in old human patients (Fong et al. 2006).

Geriatric physiology
Oxygen delivery

1. Cardiovascular function

In 10.5 year-old Beagles versus 2.4-year-old dogs at rest there were no differences in cardiovascular parameters (Yin et al. 1981). However, the older dogs could not tolerate severe exercise and some of them collapsed. They had a reduced stroke volume so cardiac output could not increase to the same extent. Systemic vascular resistance decreased initially but did not decrease further with increasing exercise. This study also showed that aortic impedance increased in older dogs during exercise but barely changed in their younger counterparts. In healthy old people the response to exercise is somewhat different in that heart rate is not increased as much and so they compensate for this by increasing stroke volume.

In people there is a decrease in the response of the heart to autonomic control. In general older human beings have higher circulating concentrations of catecholamines than young adults and yet the chronotropic response of the heart to a beta-adrenergic agonist is decreased (Bertel et al. 1980; Buhler et al. 1980). This decreased response has also been demonstrated in older dogs. Older dogs (8-12 yr old) increased their heart rates from 147 to 249 beats per min. vs 148 to 286 in younger dogs (1-4 yr old) when given isoproterenol (Yin et al. 1979). These animals were electrically paced under anaesthesia and there was no difference in maximum heart rate achieved with pacing. The mechanism for this decreased response to catecholamines could be a decrease in the number or sensitivity of the receptors and there is some evidence for both mechanisms. In older human patients, the dose of phenylephrine required to increase mean arterial pressure by 20 mm Hg was almost twice that required in younger patients (Elliott et al. 1982; Reid et al. 1985) but this was not the case in older Beagles (Yin 1988). In rats it required 10 times the dose of xylazine to increase the diastolic pressure by 45 mmHg in older animals vs the younger ones (Docherty & Hyland 1986). In humans there is an increased basal sympathetic nerve activity in muscle vasculature but this is accompanied by a decrease in response to norepinephrine release. In experiments in the forearm and in the leg in elderly people there was no difference in the response to alpha-2 stimulation in the forearm compared with younger individuals but the response was blunted in the leg (Dinenno et al. 2002; Smith et al. 2007).

Parasympathetic control of heart rate is also affected as elderly people have a decreased response to atropine. Heart rate, in people over 60, increased by 23 beats per minute in response to atropine (0.014 mg/kg IV) vs 38 beats per minute in patients 20-40 years old in one study whereas in another study heart rate only increased by about 4 beats per minute in patients 65-75 year old vs 36 beats per minute in those between the ages of 16-41 (atropine at 0.02 mg/kg IV).

Older dogs are also known to have a higher incidence of heart disease. The most common condition seen is acquired valvular heart disease, with a prevalence of >35% in dogs ≥12 years old with greater predisposition for the disease in some breeds (e.g. Cavalier King Charles Spaniels, Chihuahuas and Miniature Poodles). The mitral valve is most commonly affected. Alpha-2 agonists would tend to worsen any regurgitation due to the increase in systemic vascular resistance. Although dogs do not suffer from coronary arterial disease to the extent seen in the human population, arteriosclerosis is a frequent necropsy finding in older dogs. In one study there was a strong correlation between arteriosclerotic lesions and microscopic intramural myocardial infarction (MIMI) suggesting that an anaesthetic technique which leads to a significant increase in myocardial oxygen demand (e.g. alpha-2 agonists ± anticholinergics) may cause MIMIs due to restricted flow to some regions of the heart.

In people blood pressure appears to rise with age. Blood pressure in normal geriatric dogs and cats is similar to that in younger animals (Meurs et al. 2000) but many older animals also suffer from renal failure and they tend to be more obese than younger animals, both of these latter factors tend to predispose the animal to hypertension. Although this is usually not of great clinical importance to the animal during its daily activities it may be important under anaesthesia because a hypertensive animal may not tolerate the decreased blood pressures found to be acceptable in a younger patient.

2. Pulmonary function

The relationship between PaO2 related to age in people can be described by the equation:

$$PaO2 = 100 - (0.32 \times \text{age in yrs}) \text{ mmHg}$$

One study examined 24 healthy pet dogs from 8 to 14 years old and found a mean PaO2 of 103 ± 8 mmHg which is similar to the reference range for normal dogs (King et al. 1992). Another study reported an increased P(A-a)O2 in dogs >10 years old (2.5 vs 1.4 kPa in 2-4 yr old dogs) (Aguilera-Tejero et al. 1997). In older people there is a greater decrease in PaO2 post-anaesthesia, caused by a greater increase in the low ventilation/perfusion (V/Q) areas of the lung. Opioids may contribute to an exacerbation of this effect.

Older dogs and cats are also more likely to have chronic bronchial disease which may be seen as chronic coughing, wheezing and gagging (Robinson & Gillespie 1973; Hyde et al. 1977). As the disease progresses there may be acute bouts of paroxysmal coughing with accompanying respiratory distress. This is particularly evident in small and toy breed dogs where there is a predisposition to tracheal collapse (e.g. Yorkshire Terriers) and in cats where there may be an allergic component to the bronchial disease (feline asthma). Chronic bronchitis tends to cause an intrathoracic airway collapse and this is particularly serious for the anaesthetist as it can be very difficult to recover these animals without getting a potentially fatal hypoxemia. Preoperative treatment with corticosteroids, especially careful intubation technique and a quiet recovery using opioids for their antitussive properties and oxygen supplementation are all helpful in minimizing the potential for disaster with these cases.

Metabolism and excretion
Basal metabolic rate and the ability to thermoregulate decline with age. In humans, elderly patients are more likely to become hypothermic because they have less subcutaneous fat, a decreased heat production, deficient thermostatic control and a decreased vasoconstrictor response to hypothermia (Kurz et al. 1993). Both opioids and alpha-2 agonists tend to blunt the response to hypothermia thus making animals more prone to this.

The size of the liver decreases with age and consequently hepatic blood flow also decreases. This becomes important in the clearance of drugs undergoing extensive first pass metabolism. Other changes in hepatic function are somewhat controversial. In one study in Beagles there was an increase in both cholesterol and alkaline phosphatase in older dogs but the increased values were still well within the normal range. In humans there is an impaired excretion of bromsulphthalein after age 50 but there was no change in this measure of hepatic function in ageing Beagles. Age related decreases in hepatic microsomal mixed function oxidase enzymes have been reported in rats but there are no data available for the dog and cat. The cytochrome P450 enzymes are responsible for the metabolism of most opioids and alpha-2 agonists. Medetomidine has been shown to inhibit microsomal enzymes so it may alter the elimination of other drugs, such as opioids (Pelkonen et al. 1991).

Renal function is often impaired in geriatric dogs and cats due to the natural process of ageing and the prevalence of diseases which affect the kidneys. In humans and rats there is up to a 20% decline in the weight and volume of the kidneys with age. The changes associated with age impair the ability of the kidney to concentrate urine and it would be expected that fluid balance would be more fragile in an older patient. The response of the kidney to injury is also compromised compared with a younger animal and this may further contribute to decreased renal excretion of solutes in geriatric dogs and cats. Despite these documented changes older animals can still function at near normal levels. Ageing Beagles showed no significant increase in blood urea nitrogen (BUN) and there was no change in the excretion of phenolsulphthalein (Sheffy et al. 1985). In a longitudinal study of 155 Beagles, 128 dogs demonstrated no alteration in BUN with age, 8 dogs developed renal failure resulting in death and 19 dogs died of other causes but developed some azotemia in the course of their disease. Nephrosclerosis was the most common renal lesion found at post mortem (Cowgill & Spangler 1981).

A number of endocrine changes have been documented in geriatric dogs. Hypothyroidism is a common condition in dogs and although the peak incidence of the disease is in younger animals it can still be seen in older animals. The signs of hypothyroidism relate principally to the decreased metabolic function caused by a lack of thyroid hormone but these signs may be very diverse and include all systems. It is important to recognize this condition and treat it before anaesthesia because these animals may become profoundly hypotensive and respond poorly to pressors and positive inotropes. Cats are more likely to become hyperthyroid in old age. In one report of 126 cats with hyperthyroidism the age at diagnosis was 13 years (Thoday & Mooney 1992). Again it is important to treat these animals prior to anaesthesia because the hypertrophic cardiomyopathy associated with hyperthyroidism significantly increases the risk of death under anaesthesia. In one report of 85 cats operated on for hyperthyroidism 8 cats died and 6 of these had not been rendered euthyroid before surgery (Peterson et al. 1984).

Alpha-2 agonists may be of use in these patients as they may help to control some of the symptoms associated with hyperthyroidism. In a study in cats with hypertrophic cardiomyopathy medetomidine at 20 µg/kg maintained or decreased heart rate and decreased the degree of systolic anterior motion (SAM) thus improving forward flow (Lamont et al. 2002). Opioids may have minimal effects on the cardiovascular system but will not improve SAM.

The response of older dogs to a glucose load is impaired. In elderly humans the insulin response to a glucose load is slower than normal but most of the decreased response to a glucose load is attributed to an increased peripheral resistance to insulin. In aged Beagles given an oral glucose load the peak glucose concentrations were similar between the young and old dogs but the plasma concentrations of glucose took longer to return to normal in the older animals. Alpha-2 agonists are known to increase blood glucose concentrations and this effect may be more prolonged in older animals.

Geriatric pharmacology
It is well established in human medicine that geriatric patients, in general, require less drug for a given effect but this is not well documented in dogs and cats. There is considerable uncertainty about the reasons for altered drug requirement but some of the contributing factors are listed here:

1. The decrease in neuronal and synaptic density in the central nervous system leads to a decrease in cerebral metabolism and this would suggest that less drug would be needed to achieve a particular effect.
2. Alterations in receptor populations and receptor activation. Older animals and people seem to be more sensitive to some of the effects of opioids and this may be a receptor mediated phenomenon. Studies in rats and mice have shown decreased mu receptor densities with ageing (Hess et al. 1981; Ueno et al. 1988). In a detailed study comparing the pharmacodynamics of fentanyl and alfentanil in older and younger human patients they found minor differences in pharmacokinetics but the older patients were affected more rapidly and required a lower dose to achieve the same effect on the EEG (Scott & Stanski 1987). Similar results were found with remifentanil (Minto et al. 1997).
3. Decreased hepatic size and blood flow leading to decreased clearance of drugs which normally have high extraction in the liver. This would apply to a drug like fentanyl. Phase I (oxidation, reduction, and hydrolysis) reactions in the liver are affected more than Phase II reactions with ageing and this may also decrease the clearance of drugs which are metabolized by this route. Most opioids and alpha-2 agonists would fall into this category.
4. Decreased renal excretion may reduce the elimination of some compounds. In humans decreased renal function has lead to accumulation of all opioids or their active metabolites except buprenorphine (Pergolizzi et al. 2008). Opioids (mu agonists) have been shown to decrease urine output, although the mechanism for this has not been elucidated (Castiglia et al. 1997; Robertson et al. 2001). Alpha-2 agonists significantly increase urine output but there are few data on their effect in dehydrated or elderly animals.
5. Alterations in the composition of the body. In general there is an increase in body fat content and a concomitant decrease in total body water. There is generally a loss of muscle mass which is an important site for the redistribution of drugs which are only slowly metabolized. These changes suggest that highly lipid soluble drugs will tend to have a greater volume of distribution and hydrophilic drugs a smaller volume. In people concentrations of fentanyl after application of a fentanyl patch were almost twice those of their younger counterparts and this was ascribed to a more rapid uptake through the thinner skin of the elderly (Holdsworth et al. 1994).
6. Changes in plasma protein binding. The relative fractions of albumin and a-1 acid glycoprotein tend to change with age (decreased albumin, increased a-1 acid glycoprotein) and their binding capacities for some drugs also change. If a highly protein bound drug is given to an older patient with decreased binding capacity then more of the free drug is available and so the effect of the drug becomes more pronounced. Buprenorphine is bound to the globulin fraction rather than albumin so it is less likely to be affected by this.

References:

Aguilera-Tejero E, Fernandez H, Estepa JC et al. (1997) Arterial blood gases and acid-base balance in geriatric dogs. Res Vet Sci 63, 253-256.

Bertel O, Buhler FR, Kiowski W et al. (1980) Decreased Beta-adrenoreceptor responsiveness as related to age, blood pressure, and plasma catecholamines in patients with essential hypertension. Hypertension 2, 130-138.

Buhler FR, Kiowski W, van Brummelen P et al. (1980) Plasma catecholamines and cardiac, renal and peripheral vascular adrenoceptor-mediated responses in different age groups of normal and hypertensive subjects. Clin Exp Hypertens 2, 409-426.

Castiglia YM, Braz JR, Vianna PT et al. (1997) Effect of high-dose fentanyl on renal function in dogs. Rev Paul Med 115, 1433-1439.

Chakour MC, Gibson SJ, Bradbeer M et al. (1996) The effect of age on A delta- and C-fibre thermal pain perception. Pain 64, 143-152.

Chapman BL, Voith VL (1990) Behavioral problems in old dogs: 26 cases (1984-1987). J Am Vet Med Assoc 196, 944-946.

Cowgill LD, Spangler WL (1981) Renal insufficiency in geriatric dogs. Vet Clin North Am Small Anim Pract 11, 727-748.

Dinenno FA, Dietz NM, Joyner MJ (2002) Aging and forearm postjunctional alpha-adrenergic vasoconstriction in healthy men. Circulation 106, 1349-1354.

Docherty JR, Hyland L (1986) Alpha-adrenoceptor responsiveness in the aged rat. Eur J Pharmacol 126, 75-80.

Elliott HL, Sumner DJ, McLean K et al. (1982) Effect of age on the responsiveness of vascular alpha-adrenoceptors in man. J Cardiovasc Pharmacol 4, 388-392.

Fong HK, Sands LP, Leung JM (2006) The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 102, 1255-1266.

Goldston RT (1989) Preface. Veterinary Clin North Am: Small Anim Pract 19, ix-x.

Hayashidani H, Omi Y, Ogawa M et al. (1988) Epidemiological studies on the expectation of life for dogs computed from animal cemetery records. 50, 1003-1008.

Hayashidani H, Omi Y, Ogawa M et al. (1989) Epidemiological studies on the expectation of life for cats computed from animal cemetery records. 51, 905-908.

Hess GD, Joseph JA, Roth GS (1981) Effect of age on sensitivity to pain and brain opiate receptors. Neurobiol Aging 2, 49-55.

Holdsworth MT, Forman WB, Killilea TA et al. (1994) Transdermal fentanyl disposition in elderly subjects. Gerontology 40, 32-37.

Hyde DM, Robinson NE, Gillespie JR et al. (1977) Morphometry of the distal air spaces in lungs of aging dogs. J Appl Physiol 43, 86-91.

King LG, Anderson JG, Rhodes WH et al. (1992) Arterial blood gas tensions in healthy aged dogs. Am J Vet Res 53, 1744-1748.

Kurz A, Plattner O, Sessler DI et al. (1993) The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. Anesthesiology 79, 465-469.

Lamont LA, Bulmer BJ, Sisson DD et al. (2002) Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats. J Am Vet Med Assoc 221, 1276-1281.

Meurs KM, Miller MW, Slater MR et al. (2000) Arterial blood pressure measurement in a population of healthy geriatric dogs. J Am Anim Hosp Assoc 36, 497-500.

Minto CF, Schnider TW, Egan TD et al. (1997) Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86, 10-23.

Pelkonen O, Puurunen J, Arvela P et al. (1991) Comparative effects of medetomidine enantiomers on in vitro and in vivo microsomal drug metabolism. Pharmacol Toxicol 69, 189-194.

Pergolizzi J, Boger RH, Budd K et al. (2008) Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 8, 287-313.

Peterson ME, Birchard SJ, Mehlhaff CJ (1984) Anesthetic and surgical management of endocrine disorders. Vet Clin North Am Small Anim Pract 14, 911-925.

Rama P, Linnankoski I, Tanila H et al. (1996) Medetomidine, atipamezole, and guanfacine in delayed response performance of aged monkeys. Pharmacol Biochem Behav 55, 415-422.

Reid JL, Pasanisi F, Meredith PA et al. (1985) Clinical pharmacological studies on the interaction between alpha-adrenoceptors and calcium antagonists. J Cardiovasc Pharmacol 7 Suppl 6, S206-209.

Robertson SA, Hauptman JG, Nachreiner RF et al. (2001) Effects of acetylpromazine or morphine on urine production in halothane-anesthetized dogs. Am J Vet Res 62, 1922-1927.

Robinson NE, Gillespie JR (1973) Morphologic features of the lungs of aging beagle dogs. Am Rev Respir Dis 108, 1192-1199.

Scott JC, Stanski DR (1987) Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 240, 159-166.

Sheffy BE, Williams AJ, Zimmer JF et al. (1985) Nutrition and metabolism of the geriatric dog. Cornell Veterinarian 75, 324-347.

Smith EG, Voyles WF, Kirby BS et al. (2007) Ageing and leg postjunctional alpha-adrenergic vasoconstrictor responsiveness in healthy men. J Physiol 582, 63-71.

Thoday KL, Mooney CT (1992) Historical, clinical and laboratory features of 126 hyperthyroid cats. Vet Rec 131, 257-264.

Ueno E, Liu DD, Ho IK et al. (1988) Opiate receptor characteristics in brains from young, mature and aged mice. Neurobiol Aging 9, 279-283.

Yin FC (1988) Aging and aortic impedance in beagle dogs. Mechanisms of ageing and development 42, 49-62.

Yin FC, Spurgeon HA, Greene HL et al. (1979) Age-associated decrease in heart rate response to isoproterenol in dogs. Mechanisms of ageing and development 10, 17-25.

Yin FC, Weisfeldt ML, Milnor WR (1981) Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs. J Clin Invest 68, 28-38.

Antisedan® vet 5 mg/ml solution for injection
Active ingredient: Atipamezole hydrochloride. Target species: Dog, cat. Indications: Elimination of sedative and other effects of medetomidine or dexmedetomidine. Contraindications: None known. Adverse reactions: Transient decrease in blood pressure has been observed in dogs within the fist 10 minutes after injection. Vomiting, panting, tachycardia, hyperactivity, faecal and urinary incontinence and muscle tremor have been reported in connection with recovery. Pregnancy and lactation: The use of the drug is not recommended for pregnant animals. Dosing: im, sc. Dog: Antisedan dose calculated in ml is the same as that of medetomidine or dexmedetomidine. Cat: Antisedan dose in ml is half of the dose of medetomidine or dexmedetomidine. For more information see Pharmaca Fennica Veterinaria. Package: 10 ml.

Dexdomitor® vet 0,5 mg/ml solution for injection
Active ingredient: Dexmedetomidine hydrochloride. Target species: Dog, cat. Indications: Non-invasive, mildly to moderately painful procedures and examinations which require restraint, sedation and analgesia in dogs and cats. Premedication in cats before induction and maintenance of general anaesthesia with ketamine. Deep sedation and analgesia in dogs in concomitant use with butorphanol. For medical and minor surgical procedures. Premadication in dogs before induction and maintenance of general anaesthesia. Contraindications: Puppies below 6 months of age or in kittens below 5 months of age. Animals with cardiovascular disorders. Animals with severe systemic disease or in animals that are moribund. Animals which have known hypersensitivity to the active substance or to any of the excipients. Adverse reactions: Decrease in heart rate and body temperature. Blood pressure will increase initially and then return to normal or below normal. Decrease in respiratory rate, pale mucous membranes, vomiting, muscle tremors. In rare cases pulmonary oedema. Pregnancy and lactation: The use of the drug is not recommended for pregnant or lactating animals. Dosing: Dogs: im, iv. Cats: im. The dosage is dependent on the degree of sedation and analgesia required. For more information see Pharmaca Fennica Veterinaria. Package: 10 ml, 10 x 10 ml.

Domitor® vet 1 mg/ml solution for injection
Active ingredient: Medetomidine hydrochloride. Target species: Dog, cat. Indications: Veterinary sedation and analgesia for the duration of examination and treatment procedures, and in any situations where administration of the product makes handling the animal more convenient. Pre-medication before anaesthesia. Contraindications: Seriously ill animals with heart failure, respiratory disease or impaired liver or kidney function. Adverse reactions: Because of the mechanism of medetomidine, the animal's pulse decreases and its respiratory rate slows down. Dogs, and especially cats, may vomit a few minutes after injection. Some animals may experience muscle tremors and may be sensitive to loud noises. Rare cases of pulmonary oedema have been reported. Pregnancy and lactation: The use of the drug is not recommended for pregnant animals. Dosing: im, iv, sc. The dosage is dependent on the degree of sedation and analgesia required. For more information see Pharmaca Fennica Veterinaria. Package: 10 ml.

Domosedan® vet 10 mg/ml solution for injection
Active ingredient: Detomidine hydrochloride. Target species: Horses, cattle. Indications: Sedation and analgesia in animals during various examinations and treatments as well as in other situations where the handling of animals is facilitated by administration of the drug. Contraindications: Seriously ill animals with heart failure, respiratory disease or impaired liver or kidney function. Concurrent use of potentiated sulphonamides Adverse reactions: Decreased heart rate due to the mechanism of action of detomidine, conduction blocks, changes in respiratory rate, sweating in horses and mild bloating in cows. Pregnancy and lactation: The use of the drug is not recommended during the last trimester of pregnancy. Dosing: im, iv. The dosage is dependent on the degree of sedation and analgesia required. For more information see Pharmaca Fennica Veterinaria. Package: 5 ml, 20 ml.

4. Drug-induced adverse effects: when certain drugs should not be used.

Professor Peter J. Pascoe, *Davis, USA*

In the practice of anaesthesia there are very few absolute contraindications to any specific drug. In the hands of the skilled practitioner a drug that would appear to be contraindicated may be used without adverse consequences because the clinician is so attuned to the nuances of change in the patient. However, a person specializing in anaesthesia should have a good understanding of the pharmacology of the agents he/she is using and minimize risk by using the best technique under the circumstances.

Acepromazine and other phenothiazine tranqullisers
These drugs are potent alpha-1 antagonists and will cause hypotension if the animal is not capable of mounting a response to the induced vasodilation. This effect with acepromazine (ACE) occurs at very low doses (e.g. 1 µg/kg) and so it is not something one can avoid by using 'low' dose ACE because any sedative dose is likely to exceed this amount. Patients that are volume depleted (e.g. trauma victims) or lack an adequate sympathetic response (geriatric patients) are examples of animals that may become hypotensive with acepromazine. However, cardiac output may increase following acepromazine so if flow is better to tissues is this hypotension detrimental? Early work with chlorpromazine showed that it prolonged survival times (Inglis et al. 1959) and that it improved renal blood flow and urine output (Murphy et al. 1966) in the face of hemorrhagic shock. More recent work with chlorpromazine has shown that it downregulates tumour necrosis factor (Bertini et al. 1993; Jansen et al. 1998; Clancy et al. 2000) and alters the effect of endotoxin on nitric oxide synthetase production (Palacios et al. 1993) so ACE may have unmeasured protective effects that counter the effect that we measure (blood pressure).

ACE is contraindicated in Boxer dogs due to circulatory effects. Unfortunately the specific effect has never been documented and it is unlikely that all Boxers are at risk. The effect may be a profound hypovolemia associated with the above effect but is more likely an increase in vagal tone which may be reversed with the use of anticholinergics.

ACE is contraindicated in dogs with epilepsy. This is one of those statements that is widespread in the literature but has no basis. The original work was supposed to have been done with chlorpromazine but I have not been able to find it. A recent clinical study calls this notion into question as none of the patients with epilepsy had seizures following ACE and some even had reduced seizure activity (Tobias et al. 2006).

Alpha-2 agonists
According to the data sheets of several alpha-2 agonists they are contraindicated in cardiac patients. The data sheet for Domitor in the USA used to state that "Domitor should not be used in dogs with…. cardiac disease" and "Users (meaning people) with cardiovascular disease (e.g., hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product." Such statements were in contrast to the extensive published use of dexmedetomidine in human cardiac patients. Knowing the specific and dose-related effects of alpha-2 agonists allows one to put this contradiction into perspective. The human use of the drug is to limit tachycardia (reduced likelihood of repeat heart attack), and to increase diastolic pressure to improve coronary perfusion. These aims have proven to be effective in cats with hypertrophic cardiomyopathy (Lamont et al. 2002) but may cause serious concern in a dog with mitral insufficiency and a high regurgitant fraction.

These drugs significantly increase blood glucose and so should not be used when testing an animal for diabetes. They also induce a significant diuresis which may alter the results of a urinalysis. In most species the increase in urine output is dramatic and so could exacerbate dehydration but it is not clear whether the effect persists under these conditions.

Thiopental
Recovery from a single dose of thiopental has taken 24 hours or more in some Greyhounds. This effect has been broadened to include all 'sight-hounds' and the list of these breeds seems to expand yearly. Modern genetic analysis would suggest that some of the breeds that had been thought to be closely related, are not. For example the Afghan Hound and the Saluki are closely related but they are not very close to the Greyhound and Borzoi (Parker et al. 2004). The early work with thiopental in Greyhounds suggested that it was strictly due to their large muscle mass and lack of fat (Bogan 1970) but later work has implied that hepatic metabolism may also be different in Greyhounds (Sams et al. 1985; Court et al. 1999). Although it is likely that thiopental may delay recovery time in sight-hounds the relevance of this to breeds other than Greyhounds should be re-examined.

Thiopental should not be used in animals with cardiomyopathy, the resulting increase in heart rate and increased negative inotropic effect in the diseased myocardium can lead to cardiac arrest. I have witnessed two dogs killed in this way.

Ketamine and Tiletamine
Ketamine is known to be metabolized to norketamine in cats and this metabolite has about 35% of the activity of the parent compound. In cats with renal insufficiency this may mean a prolonged recovery. The metabolic pathway for tiletamine in cats has not been elucidated and although it may not have the same issues we have avoided using it in cats with renal insufficiency.

Ketamine will increase cerebral metabolic rate and this was thought to increase intracranial pressure (ICP) in animals with limited intracranial compliance. This has recently been questioned and ketamine has now been used in human patients with raised ICP and under the conditions of controlled ventilation and concomitant administration of a GABA antagonist (e.g benzodiazepine, propofol) there has been no increase in ICP (Bourgoin et al. 2003; Schmidt et al. 2008). Ketamine, via its effects as an NMDA antagonist may have nueroprotective effects but these have not been shown in clinical patients (Himmelseher & Durieux 2005).

As with thiopental ketamine is probably a poor choice for the induction of anaesthesia in patients with cardiomyopathy. In cats with hyperthryroidism ketamine was associated with a high mortality (Peterson et al. 1984).

Propofol
In its current formulation in egg lecithin and soybean oil there has been concern that animals with allergic reactions to either of these in their food may react to injectable propofol. It is not certain that a food allergy translates to a systemic allergy although this was implied in one human case (Hofer et al. 2003).

Propofol is a phenol and the usual metabolic pathway with phenolic compounds is to glucuronidated the molecule. In cats this may mean delayed elimination and we have shown that a prolonged infusion with propofol in cats leads to a delayed recovery (Pascoe et al. 2006). Others have also documented problems with repeated administration of propofol with delayed recoveries, increased Heinz body formation and malaise (Andress et al. 1995; Wetmore et al. 1997). More recently cats that were anaesthetized 12 times over 19 days for radiation therapy showed no change in recovery times or increase in Heinz bodies and it is not clear what the difference was between the studies (Bley et al. 2007).

Etomidate
This drug has the least effect on cardiovascular function of any of the anaesthetics and so it has become popular for emergency induction in people. It has been known for a long time that it inhibits the release of cortisol and it has now become a controversial issue as to whether it should be used in patients who might have an adrenocortical insufficiency (Morris & McAllister 2005; Cotton et al. 2008). It is probably not used widely enough to gather good evidence for this in veterinary medicine so we will probably need to extrapolate from the human literature.

Inhaled anaesthetics
These drugs alter cerebral vascular autoregulation such that the blood flow to the brain becomes pressure dependent and they also diminish the response of the cerebral vasculature to carbon dioxide. Some of us therefore avoid the use of these drugs in patients with raised intracranial pressure if possible. However, this effect is dose related and it seems to be minimal at about 0.5MAC. This means that inhalants can be used in these patients if another anaesthetic is added that also does not alter cerebrovascular reactivity (e.g. propofol, fentanyl). In human medicine there is minimal support for an injectable over an inhalant technique for people undergoing surgery for brain tumours (Magni et al. 2005).

Malignant hyperthermia (MH) is a defect in the ryanodine receptor that is triggered by inhaled anaesthetics. There has been a perception that it was only halothane that triggered this condition but all of the halide anaesthetics have been shown to be involved. A patient with known or suspected MH should be anaesthetized using a technique that excludes the inhalants (e.g propofol CRI) and should be connected to new circuit and a clean anaesthetic machine so that it is not exposed to any of the inhalant (succinylcholine must not be given either). The vaporizers should be taped over or removed so that they cannot be turned on accidentally during the procedure.

Mask induction is a commonly used technique but it is a concern with brachycephalic breeds. Because the animal will relax as the inhalant takes effect it may obstruct its airway and yet it may not be relaxed enough to intubate. Using an injectable technique is much safer in these animals.

Conspicuous in their absence from the above discussion are the anticholinergics, benzodiazepines, opioids and neuromuscular blocking (NMB) drugs because there are few absolute contraindications to the use of these drugs that are not immediately obvious (e.g high dose opioids and the NMBs cause respiratory depression/arrest and one needs the ability to ventilate the patient).

References:

Andress JL, Day TK, Day D (1995) The effects of consecutive day propofol anesthesia on feline red blood cells. Vet Surg 24, 277-282.

Bertini R, Garattini S, Delgado R et al. (1993) Pharmacological activities of chlorpromazine involved in the inhibition of tumour necrosis factor production in vivo in mice. Immunology 79, 217-219.

Bley CR, Roos M, Price J et al. (2007) Clinical assessment of repeated propofol-associated anesthesia in cats. J Am Vet Med Assoc 231, 1347-1353.

Bogan J (1970) Factors affecting duration of thiopentone anaesthesia in dogs, with particular reference to greyhounds. 18-24.

Bourgoin A, Albanese J, Wereszczynski N et al. (2003) Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. Crit Care Med 31, 711-717.

Clancy KD, Lorenz K, Dries D et al. (2000) Chlorpromazine modulates cytokine expression in the liver and lung after burn injury and endotoxemia. J Trauma 48, 215-222; discussion 222-213.

Cotton BA, Guillamondegui OD, Fleming SB et al. (2008) Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. Arch Surg 143, 62-67; discussion 67.

Court MH, Hay-Kraus BL, Hill DW et al. (1999) Propofol hydroxylation by dog liver microsomes: assay development and dog breed differences. Drug Metab Dispos 27, 1293-1299.

Himmelseher S, Durieux ME (2005) Revising a dogma: ketamine for patients with neurological injury? Anesth Analg 101, 524-534, table of contents.

Hofer KN, McCarthy MW, Buck ML et al. (2003) Possible anaphylaxis after propofol in a child with food allergy. Ann Pharmacother 37, 398-401.

Inglis FG, Hampson LG, Gurd FN (1959) Effect of chlorpromazine on survival time and mesenteric blood flow in experimental shock. Ann Surg 149, 43-52.

Jansen MJ, Hendriks T, Knapen MF et al. (1998) Chlorpromazine down-regulates tumor necrosis factor-alpha and attenuates experimental multiple organ dysfunction syndrome in mice. Crit Care Med 26, 1244-1250.

Lamont LA, Bulmer BJ, Sisson DD et al. (2002) Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats. J Am Vet Med Assoc 221, 1276-1281.

Magni G, Baisi F, La Rosa I et al. (2005) No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanil in patients undergoing craniotomy for supratentorial intracranial surgery. J Neurosurg Anesthesiol 17, 134-138.

Morris C, McAllister C (2005) Etomidate for emergency anaesthesia; mad, bad and dangerous to know? Anaesthesia 60, 737-740.

Murphy GP, Benson DW, Schirmer KA (1966) Renal response to chlorpromazine in hemorrhagic hypotension: hemodynamic and metabolic changes and adrenolytic effect in dogs. Ann Surg 164, 867-876.

Palacios M, Padron J, Glaria L et al. (1993) Chlorpromazine inhibits both the constitutive nitric oxide synthase and the induction of nitric oxide synthase after LPS challenge. Biochem Biophys Res Commun 196, 280-286.

Parker HG, Kim LV, Sutter NB et al. (2004) Genetic structure of the purebred domestic dog. Science 304, 1160-1164.

Pascoe PJ, Ilkiw JE, Frischmeyer KJ (2006) The effect of the duration of propofol administration on recovery from anesthesia in cats. Vet Anaesth Analg 33, 2-7.

Peterson ME, Birchard SJ, Mehlhaff CJ (1984) Anesthetic and surgical management of endocrine disorders. Vet Clin North Am Small Anim Pract 14, 911-925.

Sams RA, Muir WW, Detra RL et al. (1985) Comparative pharmacokinetics and anesthetic effects of methohexital, pentobarbital, thiamylal, and thiopental in Greyhound dogs and non- Greyhound, mixed-breed dogs. Am J Vet Res 46, 1677-1683.

Schmidt A, Oye I, Akeson J (2008) Racemic, S(+)- and R(-)-ketamine do not increase elevated intracranial pressure. Acta Anaesthesiol Scand 52, 1124-1130.

Tobias KM, Marioni-Henry K, Wagner R (2006) A retrospective study on the use of acepromazine maleate in dogs with seizures. J Am Anim Hosp Assoc 42, 283-289.

Wetmore LA, Glowaski MM, Schlesinger S et al. (1997) Observations on the clinical use of propofol in cats receiving repeated doses for radiation therapy. Vet Surg 26, 164.

5. Preemptive Analgesia: Controversy Over the Evidence

Alicia Z Karas, MS, DVM, Dipl ACVA
Tufts Cummings School of Veterinary Medicine, North Grafton, MA, USA

Many of us added the term "preemptive analgesia" to our teaching lexicon in the 1990s. For many years now, experts have been telling us that the concept of pre-emptive analgesia is not well enough supported by the published studies and that a new approach to timing and prospective therapies is needed. Should we be removing the term from our veterinary manuscripts, chapters and teaching?

In its original conception, the term preemptive analgesia meant simply that an opioid or a local anesthetic, if given prior to incision, would reduce the intensity of postoperative pain. (McCartney et al. 2004). Refining the experimental approach, a number of clinical studies were aimed at testing whether a drug or technique reduced pain more effectively when given prior to, compared with after the occurrence of incision or tissue injury. This theory was so attractive that for many, the idea that preemptive timing of onset of analgesia mattered, even without qualifying the type, dose or duration of drug; and it became entrenched as a critical feature of optimal perioperative analgesia. Many of us preached preemption, a theory that would basically require that analgesia be given before the patient awakened and writhed or thrashed (and in the case of horses, injured themselves) with pain. The result seemed to be worthwhile, in that we began to see more animal patients recover peacefully when we did our local anesthetic injections before incision, our opioid, lidocaine, ketamine and alpha 2 agonist infusions pre and intraoperatively, our epidurals before animals left the prep room for surgery. While it is true that sufficient veterinary clinical trial data in support of specific techniques is lacking, we are more confident in our ability to ensure comfortable awakening and less total pain than ever before. Is this apparent benefit of energetically loading our patients with analgesia due to pre-emption, or is it something else?

There has been some compelling evidence from pain research in animals that simple timing of analgesic administration does play an important role in the adequacy of pain relief. Ranging from neurophysiologic preparations to "whole animal" studies, studies may suggest that pre-emptive administration reduces the amount of drug needed, or the amount of pain perceived. In a mouse model, peripheral (IP) application of morphine inhibited measurable episodes of pain behaviors (writhing) in response to IP injection of an irritant substance (acetic acid). (Reichert et al, 2001). When morphine was given prior to acetic acid, the dose required to suppress 90% of writhing was 1/10 that needed when morphine was given after acetic acid. This pre-emptive low dose of morphine, when given intravenously prior to acetic acid, did not suppress writhing. The authors suggest that their results mean that morphine can preempt pain of the type caused by an irritant stimulus, but also that this effect of morphine was peripherally rather than centrally (spinal cord or brain) mediated. Using a common neuropathic pain model in the mouse (partial sciatic nerve ligation), Rashid and Ueda (2005) found that morphine pretreatment could prevent development of thermal and mechanical hyperalgesia, and prevented the increases in expression of spinal cord c-Fos and PKCgamma (two important markers of neuronal hyperactivity and thus pain), for at least 7 days. The route of administration of morphine impacted its effectiveness in reducing pain; intra-cerebroventrical (ICV) and subcutaneous injection provided significant benefit, intrathecal administration did not. The authors theorize that intrathecal morphine has acute effects in reducing pain transmission, but that the prevention of central sensitivity is optimal when morphine receptors in the brain are targeted (compared to spinal cord receptors). In addition, these authors also found that pre-injury intrathecal injection of a serotonin uptake inhibitor (fluoxetine) and an alpha-2 adrenergic agonist (clonidine) prevented hyperalgesia. Lascelles et al (1997) studied VAS scores and mechanical hyperalgesia in dogs having overiohysterectomy. They found that a single dose of pethidine

given pre-operatively resulted in significantly lower pain scores and less mechanical allodynia at several time periods for up to 20 h post-extubation compared to dogs given the same dose post-extubation.

In human clinical trials, evidence mounted on both sides of the issue of the "for/against" pre-emptive effect hypothesis, and several large systematic reviews or meta-analyses seemed to indicate a finding that was generally more often 'against' (Dahl and Moiniche, 2004, Moiniche et al, 2002). Along came two more reviews (Ong et al, 2005 and McCartney et al, 2004) and these seemed to indicate that there was at least some value to some preemptive techniques. Ong et al (2005) analyzed 5 categories of techniques (epidural analgesia, local anesthetic wound infiltration, systemic NMDA antagonists, systemic NSAIDS and systemic opioids) with respect to 3 outcomes (pain scores, supplemental analgesic consumption, and time to first rescue analgesia). The authors concluded that although only pre-incisional epidural analgesia improved all 3 outcomes, local anesthetic wound infiltration or NSAIDS improved some outcomes. McCartney et al (2004) reported that two NMDA receptor antagonists, ketamine and dextromethorphan, showed a benefit of reducing pain scores and analgesic consumption for a period of time lasting more than 5 half lives beyond the time of administration. Nevertheless, strong sentiment followed, indicating that many experts were willing to retire the concept of pre-emptive analgesia.

"Now, it is generally agreed that starting an analgesic treatment before surgery has minimal benefits compared with starting the treatment after surgery begins or even administering the treatment at the conclusion of surgery." (Brennan and Kehlet, 2005)

What also transpired was that, still sensing that something about timing was probably important even though the "magic bullet" concept had failed, experts began to examine the reasons for failure. For one thing, the nature of the beneficial outcome of a pre-emptive approach was not perceived to be the same by every party. Consider this ambitious set of objectives:

"Preemptive analgesia has three goals. First, to decrease acute pain after tissue injury, both intraoperatively and postoperatively. Second, to prevent pain-related pathologic modulation of the central nervous system ("pain memory"). Third, to inhibit the persistence of postoperative pain and the development of chronic pain" (Grape and Tramer, 2007).

It would be an impressive thing indeed if any single technique were found that could accomplish all three goals! And while the controversy simmered, the understanding of the pathophysiology of pain evolved. It began to occur to the experts that: 1. not all pain is alike in etiology, 2. perhaps the optimal strategy was not to give a "pulse" dose of an analgesic, but that a duration of drug in the biophase was needed, sufficient to prevent the afferent barrage of signals of sensitized nociceptors from establishing central sensitization and 3. perhaps there are other beneficial reasons for giving certain analgesics, starting prior to incision. The second realization above gave rise to a new concept, that of "preventive analgesia". (McCartney et al, 2004, Pogatzki-Zahn and Zahn, 2006). This newer theoretical approach to minimization of pain is still on the drafting table – it is entwined with other concepts such as multimodal analgesia, and of course pathophysiologic mechanism.

There is one more new theory of "timing" of analgesia, and that is "protective premedication". Bromley (2006) suggests that it is now possible to prevent pain in the postoperative patient at rest but that two important goals are to improve dynamic pain (pain upon movement) and to prevent acute pain from transitioning to a chronic pain state. The protective analgesic most studied at the present time is gabapentin, or perhaps pregabalin.

It has been suggested that one reason pre-emptive analgesia failed to translate from the animal to the human clinical arena is that humans and animals are different. (Grape and Tramer, 2007). We are not able to use some outcome measures for evaluating techniques in our patients, such as PCA morphine consumption, or self reported pain scores. We do not have a good idea of whether acute pain in our

patients commonly transitions to chronic pain, as it can in humans. We should however, consider the benefit of having our patients awaken from anesthesia with adequately low pain levels, because, one clear difference does exist between humans and animals; animals cannot know why they hurt or that it will get better. Even if having used a pre-emptive approach to experiencing pain does not confer much in the way of opioid sparing or reduction of chronic pain, we do have a reason to ensure that the analgesic effect is in place at the moment of return of consciousness from anesthesia in animals, and perhaps doubly so in animals used for research. Timing is critical, the sense is that not only initiation of analgesia but type and duration and combinations of drugs must also be considered. We may expect to see more of these two terms, preventive analgesia and protective premedication in the future, and they may soon replace the term "preemptive analgesia" in our scholarly teachings.

References:

Brennan TJ and Kehlet, H. (2005) Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain- not an easy path. Anesthesiology 103:681–3

Bromley, L. (2006) Pre-emptive analgesia and protective premedication. What is the difference? Biomedicine & Pharmacotherapy 60: 336–340

Dahl JB, and Moiniche S. (2004) Preemptive analgesia. Br Med Bull; 71:13–27.

Gonzalez M et al (2000) Ovariohysterectomy in the rat: a model of surgical pain for evaluation of pre-emptive analgesia? Pain 88:79-88

Grape, S. and Tramer, M.R. (2007) Do we need preemptive analgesia for the treatment of postoperative pain? Best Practice & Research Clinical Anaesthesiology 12(1): 51–63

Lascelles, BDX et al (1997) Post-operative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy Pain 73: 461–471

McCartney CJL et al. (2004) A Qualitative systematic review of the role of n-methyldaspartate receptor antagonists in preventive analgesia. Anesth Analg; 98:1385–400

Moiniche S, et al (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 96:725–741.

Ong CK, et al. (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 100:757–773.

Pogatzki-Zahn EM and Zahn PK. (2006) From preemptive to preventive analgesia. Curr Opin Anaesthesiol 19:551–555.

Rashid MH and Ueda H (2005) Pre-injury administration of morphine prevents development of neuropathic hyperalgesia through activation of descending monoaminergic mechanisms in the spinal cord in mice. Molecular Pain 1:19

Reichert, JA et al (2001) Peripheral and preemptive opioid antinociception in a mouse visceral pain model Pain 89: 221-227

Healthy Pets, Happy People

Intervet
Schering-Plough Animal Health

6. Somewhat Less Than Local: Efficacy and Safety of Intravenous and Intra-wound Infusion of Local Anesthetics for Postoperative Analgesia

Alicia Z Karas, MS, DVM, Dipl ACVA
Tufts Cummings School of Veterinary Medicine, North Grafton, MA, USA

Traditional local anesthetic administration techniques are valuable adjuncts to anesthesia and control of acute pain in animals. Several limitations exist however, in that technical expertise is needed and the duration of the drugs used is relatively short after a single administration. Two methods of achieving long duration analgesia using local anesthetics include intravenous infusion of lidocaine and the use of intra-wound infusion devices. The benefits of local anesthetics are seemingly not limited to simple inhibition of nerve function. They have been shown to have broad anti-inflammatory effects, including to inhibit leukocyte functions, to reduce production of eicosanoids, thromboxane, leukotriene, histamine, and inflammatory cytokines, and scavenge oxygen free radicals. These effects are proposed to explain the effect of local anesthetics to inhibit edema formation in various conditions, reduce acute lung injury and improve survival in sepsis models. Lastly, they have antimicrobial, antifungal and antiviral effects (Cassuto et al 2006). Vital though it is in the overall immune response, inflammation can be responsible for severe morbidity in patients, in addition to its impact on the generation and maintenance of pain. When used appropriately, the "less local" techniques of intravenous and intra-wound administration of local anesthetics may be regarded as having multiple beneficial effects on pain and as a bonus, perhaps even on survival.

Intravenous infusion:
IV lidocaine (IVL) has been shown to have anti-hyperalgesic effects in human and animal models of incisional, burn, visceral, thermal and mechanical stimulus. (Ness, 2000, Robertson et al, 2005). The mechanisms by which IVL produces its analgesic, anti-hyperalgesic, and anti-inflammatory effects include sodium channel blockade, and inhibition of both GPC receptors and NMDA receptors (Kaba et al, 2007).

Koppert et al (2004) found that an intraoperative infusion of lidocaine ending at 1 hour after surgery resulted in lower pain scores during movement and less morphine consumption for 72 hours. Kaba et al (2007) demonstrated multiple beneficial aspects of IVL in a study of human colectomy surgery patients; significant reductions in time to return of bowel function and length of hospital stay as well as pain, opioid consumption and fatigue scores occurred with use of a 24 hour infusion. In addition, IVL treated patients had a 35% reduction in inhalant anesthetic and reduced intraoperative opioid requirements. IVL may be a promising therapy for pain and minimization of tissue damage in burn patients (Mattssona et al, 2000). And in a recent meta-analysis involving 706 patients, IVL was able to cause short term alleviation of neuropathic pain of various origins. (Tremont-Lukats et al, 2005). However, a recent study of IVL during hip replacement surgery in humans did not show a benefit of lidocaine (Martin et al, 2008).

Despite the absence of studies to show benefit in veterinary patients, a rather compelling case can be made for the use of perioperative IVL for pain control in a variety of abdominal surgical procedures, with the added benefit of MAC reduction. Extrapolating from human data, it is less clear whether the same is true for orthopedic or other types of surgeries. However, because of the potential to reduce neuropathic and visceral pain, it may be possible that orthopedic, neurosurgical and acute disease states (e.g. pancreatitis) as well as trauma pain, could stand to benefit from the use of IVL. This is especially true if the technique could provide opioid sparing and other (e.g. antimicrobial, anti-inflammatory) effects. Caution is needed in avoiding toxicity, as the reduction in hepatic blood flow that occurs during

inhalant anesthesia may decrease clearance of lidocaine, leading to serum concentrations outside of the safe range. This has been shown to be the case in the cat but not in the dog (Thomasy et al, 2005). At our teaching hospital, we routinely use perioperative IVL in the dog for any surgery of moderate to severe painful nature; only in certain cases is it continued postoperatively. Although we recommend it as a safe and sparing adjunct to opioid and other analgesics for surgery, trauma, and pancreatitis at a dose of 50 mcg/kg/min, we have no actual data to support its benefit. Good quality studies are clearly needed. We have seen few complications in a several year long period of using it in upwards of 1000 canine cases. We do not use IVL in cats, due to a concern about toxicity (Robertson, 2005).

Intra-wound local anesthetic infusion:
Incisional, intraperitoneal, intrapleural, and intraarticular infiltration with local anesthetics for surgical pain management is widely reported to improve patient comfort, and techniques can usually be performed prior to incision. In recent years, the availability of wound infusion catheters has enabled repeated or continuous infusion of local anesthetics into the affected area. The devices used range from relatively costly FDA approved cathetersa, to modified red- rubber urinary catheters, but for veterinary use, at least two moderately priced types are commercially availableb,c. The basic form is a soft pliable catheter with tiny holes along the end that is implanted; functioning somewhat like a garden "soaker hose". The catheter is implanted in the wound bed during surgical closure. Infusion is maintained by either syringe pump or ambulatory infusion pumps. An elastomeric balloon pump is a modestly priced option for ambulatory patients.

From a recent meta-analysis of the use of wound incision catheters for surgery in humans, the overall conclusion was that: "Continuous wound catheters consistently demonstrated analgesic efficacy in terms of reduced pain scores or opioid use for all surgical subgroups, despite heterogeneity in type of surgical procedure, location of wound catheter, mode of delivery of local anesthetic, dose of local anesthetic, and analgesic mixture" (Liu et al, 2006). The review covered a period of more than a decade, and study sizes were small. Catheters were placed in a variety of locations (subcutaneous, suprafascial, subfascial, intraarticular, peripleural, and periosteal) and the local anesthetics most often used were bupivacaine and ropivacaine. In most cases, placement and infusion occurred at the end of surgery, and infusion duration was approximately 2 days. Beneficial outcomes included reduction of mean VAS scores at rest and with activity, reduction of daily consumption of opioids, and trends towards better patient satisfaction and length of hospital stay.

A small number of veterinary clinical studies have been reported involving the use of continuous wound infusion of local anesthetics. Most studies involve dogs, and the most studied surgical indication was total ear canal ablation (prospective studies), but use for extensive soft tissue resection in cats (retrospective, fibrosarcoma resection) is also reported.(Davis et al 2007a, 2007b, Radlinsky et al 2005, Woolfe et al, 2006). Collectively, the studies reported to date have used either bupivacaine or lidocaine infusion, and, as with human studies, pain was generally perceived to be adequately managed with the infusion, and complication rates low and not perceived to be problematic. The ability to detect improvements in pain scores with local infusion compared to parenteral opioid or other analgesics may not occur due to the use of active controls and other study design features, but ancillary benefits include reduction in the level of sedation or opioid side effects and reduced hospital stay (Davis et al 2007b, Wolfe et al, 2006). Abelson et al (2009, in press) performed a retrospective review of the use of 'wound soaker' catheters for limb amputation in 56 patients (52 dogs, 2 cats, 2 goats). Although this study did not analyze adequacy of pain relief, we have been using wound soaker catheters routinely since 2004 for infusion of lidocaine (dogs) and to a limited extent intermittent bupivacaine (cats, goats, camelids, 1 rabbit) after a variety of procedures, including limb amputation, ear canal ablation, intercostal and sternal thoracotomy, celiotomy, and soft tissue tumor excision. Qualitatively, we find that the pain relief afforded to patients is excellent, allowing ambulation and other movement far superior to standard opioid/adjunct pain relief, and that the amount of postoperative opioid use is diminished. In addition, the level of acceptance by the surgeons is higher than for many "new" techniques. Although we still use pre-and intraoperative multimodal analgesia, consisting of intravenous opioid, ketamine or

alpha 2 agonist infusion, and/or epidural analgesia, the postoperative analgesia resulting from wound soaker catheters is considered worth the cost and effort. The dose of lidocaine we use in dogs for limb amputation is approximately 50 mcg/kg/min, (lower rates or volumes for smaller wounds such as thoracotomy) and the duration of infusion is approximately 36 hours.

Clearly more studies are needed. One question involves the choice of local anesthetic type, since most human studies use bupivacaine or ropivacaine. Both the latter have been implicated in myotoxicity, although it appears that this has not been listed as a complication in most human studies. (Zink et al, 2005)

References:

Abelson, A (2009, in press) Characterization of the use of a wound soaker catheter to deliverperipheral local anesthetic: 56 cases. VetAnes Analg

Cassuto et al (2006) Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiol Scand 50: 265—282

Davis KM,et al (2007a) Feline fibrosarcoma: Perioperative management.Compend Contin Educ Vet 29:712-729.

Davis KM, et al (2007b) Correlation between perioperative factors and successful outcome in fibrosarcoma resection in cats. Vet Rec 161: 199-200,.

Kaba, A et al (2007) Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology 106:11–8

Koppert et al (2004) Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg 98:1050 –5)

Liu, SS et al (2006) Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg 203: 914-932.

Martin, F et al (2008) Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. Anesthesiol 109:118–23

Mattssona, U et al. (2000) Intravenous lidocaine infusion in the treatment of experimental human skin burns -digital colour image analysis of erythema development. Burns 26 710-715

Ness TJ. (2000)Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. Anesthesiol 92:1685–1691.

Radlinsky MG et al (2005) Use of continuous, local infusion of bupivacaine for post-operative analgesia in dogs undergoing total ear canal ablation. JAVMA 227: 414-419.

Robertson,SA. (2005)Assessment and management of acute pain in cats J Vet Emerg Crit Care 15(4) 261-272

Robertson, SA et al (2005) Effect of systemic lidocaine on visceral and somatic nociception in conscious horses. Equine vet. J. 37 (2) 122-127

Thomasy,SM et al (2005) Pharmacokinetics of lidocaine and its active metabolite, monoethylglycinexylidide, after intravenous administration of lidocaine to awake and isoflurane-anesthetized cats. AJVR 66:1162–1166

Tremont-Lukats IW et al (2005) Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. Anesth Analg 101:1738 –49

Wolfe TM, et al (2006). Evaluation of a local anesthetic delivery system for the postoperative analgesic management of total ear canal ablation- a randomized, controlled, double- blinded study. Vet Anaes Analg 33: 328-339.

Zink,W et al (2005)The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve block. Anesth Analg 101:548 –54

a http://www.iflo.com/products.php

b http://www.milaint.com/Epi.php

c http://www.recathco.com/staging/catheters/Post-Op.html

Markprint Oy, Lahti, 2009