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European Veterinary Conference Voorjaarsdagen

Amsterdam, Netherlands
24 - 26 April, 2008



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HEART FAILURE MANAGEMENT; THE USE OF DIURETICS VASODILATORS AND INOTROPES

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Heart failure is a complex syndrome initiated by an inability of the heart to maintain a normal cardiac output at normal filling pressures. Clinical signs of heart failure are often a consequence of either excessive retention of fluid in the venous circulation leading to signs of congestion, inadequate delivery

of blood to the arterial circulation leading to signs of underperfusion and hypotension or a combination of the two. Patients have sometimes been divided into those that are wet i.e. congested or dry i.e. not congested and those that are cold i.e. have poor perfusion and those that are warm i.e. those that have adequate perfusion.

Treatment can be targeted at either relieving signs of congestion by reducing the overfilling of the venous circulation or improving signs of poor perfusion by improving output from the heart. Which type of treatment is most effective will vary according to which sort of clinical sign predominates. In animals with predominantly signs of congestion (those that are "wet") then treatment will be targeted to a greater extent at reduction of circulating fluid volume by preload reduction; in animals with predominantly signs of poor perfusion (those that are "cold") then treatment will be predominantly targeted at the improvement of output from the heart. In patients showing both signs of poor perfusion and signs of congestion therapy will need to balance the sometimes conflicting requirement of improving output and reducing venous filling.

Diuretic therapy

All diuretic drugs used in the treatment of heart failure share a common mechanism of action. They increase the fractional excretion of sodium i.e. they increase the proportion of sodium filtered at the glomerulus that eventually ends up being excreted in the urine. Increasing the total sodium loss in the urine results in a net loss of sodium. Extracellular fluid volume is intrinsically linked to the total amount of sodium in the body and therefore sodium loss results in a reduction in extracellular fluid volume; tending to relieve signs of congestion. Different classes of diuretic vary according to the mechanism by which they block renal sodium reabsorption and the extent to which they can increase the fractional excretion of sodium

Loop diuretics

Furosemide is, for good reason, the most widely used diuretic in the treatment of congestive heart failure in both dogs and cats. It works by blocking the reuptake of sodium, potassium and chloride in the ascending limb of the loop of Henle. It has the ability to dramatically increase the fractional excretion of sodium and therefore can have a profound diuretic effect. It can be administered orally and by injection via various routes. It has a wide margin of safety and can be given in widely varying doses according to the severity of the patient's clinical signs. For this reason it tends to be the first choice agent for administration to patients with acute onset signs of congestive heart failure.

Other classes of diuretic

Other diuretics that are used include thiazide diuretics and "potassium-sparing" diuretics. There is increasing evidence that the latter group, particularly the aldosterone receptor antagonist spironolactone, have benefits over and above their simple diuretic effect. Other diuretics tend to be given in conjunction with Furosemide as their differing mechanisms of action tend to result in a potentiating effect when they are administered together. The utilisation of this beneficial effect is sometimes referred to as "sequential nephron blockade".

Any given dose of diuretic when administered to a patient will disturb their equilibrium sufficiently to result in a net loss of sodium over a period of a few days. This net loss of sodium will result in the stimulation of sodium retaining mechanisms which will eventually be sufficient to establish a new state of equilibrium in which the patient will have a lower total amount of sodium in their body, and therefore a lower circulating fluid volume but the rate of intake will again match the rate of loss. This new equilibrium tends to be established within a period of a few days and it is during this time that any adverse consequences of diuresis may become apparent. Adverse effects of diuretics include electrolyte disturbances, including hypokalaemia, and the development of prerenal azotaemia. It is worth routinely checking these parameters after the introduction of diuretic therapy and any modification to the treatment regime. Usually I would check these 7-10 days after any change.

Spironolactone has its effect through antagonism of the aldosterone receptor. It thus blocks sodium uptake within the kidney and prevents other potentially harmful

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Heart failure management; the use of diuretics vasodilators and inotropes Adrian Boswood, MA, VetMB, DVC, DipECVIM-CA (Cardiology), MRCVS, The Royal Veterinary College, London, UK, aboswood@rvc.ac.uk

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1 Scientific Proceedings: Companion Animals Programme

effects of elevated aldosterone concentrations; these include myocardial fibrosis leading to progression of myocardial dysfunction.

Venodilators

As well as the volume of blood in the circulation the other determinant of the pressure within the venous circulation is the venous tone. Drugs that dilate veins have a similar effect to diuretics in that they tend to relieve signs of venous congestion and therefore relieve signs of congestive heart failure. Many balanced vasodilators have a venodilating effect. Some drugs have a predominant venodilating effect and these include nitrate agents such as glyceryl trinitrate. Venodilating drugs are particularly useful in the setting of emergency management of acute congestive heart failure e.g. fulminant congestive failure secondary to dilated cardiomyopathy or mitral insufficiency in dogs.

Vasodilators

Agents that cause blood vessels to dilate are termed vasodilators. Those which dilate predominantly arteries are called arteriodilators and those which dilate predominantly veins are termed venodilators. Ones which act on both arteries and veins are referred to as balanced vasodilators. The effect of venodilation has already been considered above. There are a great many mechanisms whereby drugs can act on blood vessels and result in their dilation. The main classes of vasodilator used in veterinary medicine include angiotensin converting enzyme inhibitors (ACEI), phosphodiesterase inhibitors (e.g. Pimobendan), calcium channel blockers (e.g. amlodipine), balanced nitrate vasodilators (e.g. nitroprusside) and "direct-acting" arteriodilators such as Hydralazine.

The dilation of arteries has the effect of reducing the resistance to ejection from the ventricle. Flow through cylindrical vessels is proportional to the fourth power of the radius of the vessel thus a 25% increase in vessel diameter could in theory result in a 140% increase in flow through that vessel if all other variables remained constant. A lot of the work performed by the contracting myocardium is done overcoming the resistance to ejection from the ventricle. One of the main determinants of resistance to ejection from the left ventricle is the systemic vascular resistance, and one of the main determinants of this is arteriolar tone. Thus dilation of the arteries may reduce myocardial work load. One of the reasons for maintenance of fairly high arterial tone is that arterial tone is one of the main determinants of blood pressure. One risk therefore of arteriodilation is that blood pressure may fall. Thus the use of arteriodilators is a balancing act between improving output but not dropping blood pressure to

such an extent that patients show signs of hypotension.

As well as the effect that all vasodilators have on arterial tone many have additional class specific effects. Of most note the ACEI are thought to mediate a lot of their favourable effect on long term outcome in patients with heart failure by ameliorating the detrimental long term effects of chronically elevated angiotensin II concentrations. Phosphodiesterase inhibiting agents (depending slightly on which phosphodiesterases they inhibit) have effects on inotropy as well as vascular tone. Calcium channel blockers vary according to the channels on which they have their predominant effects. Some have greater electrophysiological effects and others have greater vascular effects.

In patients with primary or secondary mitral insufficiency an additional benefit of arteriodilation is the effect of preferentially favouring forward flow of blood out of the left ventricle, via the aorta, rather than regurgitant flow.

The ACEI have been shown to be associated with improved outcome in dogs with heart failure compared to placebo⁽¹⁾. More recently in dogs with heart failure secondary to dilated cardiomyopathy pimobendan was shown to improve outcome when added to standard therapy⁽²⁾. In patients with heart failure secondary to mitral insufficiency there is some evidence to suggest improved quality of life and possibly survival when pimobendan is used instead of, or in conjunction with ACEI^(3,4). Further evidence to inform this debate is expected in the near future with the results of the QUEST study.

Inotropes

Inotropic agents went out of vogue in the treatment of heart failure patients after increased mortality was observed in a number of clinical trials in which they were used⁽⁵⁾. Their continued development in the veterinary field was therefore met with some circumspection initially but the beneficial effects of some agents with inotropic effects in veterinary patients are increasingly becoming apparent as referred to above in the section on pimobendan. As already alluded to pimobendan has both vasodilating and inotropic effects. There are other inotropic drugs that are used in veterinary patients.

Digoxin

Prior to the advent of pimobendan, digoxin was the most widely used inotropic agent in small animal practice. Digoxin acts through antagonism of the Sodium/Potassium ATPase. This has the effect of increasing intracellular calcium concentrations. The calcium then binds to the contractile apparatus; resulting in an

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Inotropes Inotropic agents went out of vogue in the treatment of heart failure patients after increased mortality was observed in a number of clinical trials in which they were used(6). Their continued development in the veterinary field was therefore met with some circumspection initially but the beneficial effects of some agents with inotropic effects in veterinary patients are increasingly becoming apparent as referred to above in the section on pimobendan. As already alluded to pimobendan has both vasodilating and inotropic effects. There are other inotropic drugs that are used in veterinary patients.

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increased force of contraction. As well as the positive inotropic effect Digoxin has a negative chronotropic effect (slowing the heart rate). Extensive studies in human patients have demonstrated a neutral effect of digoxin on survival⁽⁹⁾. No similar studies have been conducted in veterinary patients.

Digoxin has a narrow therapeutic ratio, with the therapeutic dose being close to the toxic dose. This means it must be administered carefully and it is often dosed on a body surface area basis (0.22 mg/m²). Blood concentrations of digoxin can be measured to ensure a therapeutic, and non-toxic, concentration is reached.

Since the introduction of pimobendan the indications for administration of digoxin are reduced. I now use it primarily for the control of heart rate in patients with atrial fibrillation.

Dobutamine

Dobutamine is an intravenously administered catecholamine that is sometimes used for short term inotropic treatment of patients with severe signs of heart failure requiring hospitalisation. It can be very effective in helping control heart failure in patients with primarily systolic dysfunction but it has to be administered carefully and by constant rate infusion. Patients receiving dobutamine should be monitored at all times. Pro-arrhythmic effects are frequently observed at higher dose rates.

Summary

The success of therapy for heart failure relies in part on adequate targeting of the treatment at the problems observed. If a patient is mainly showing signs of congestion they will benefit most from the administration of diuretic and venodilating agents. If they are mainly showing signs of poor perfusion they may benefit most from inotropic agents or judicious use of vasodilators; although the use of the latter in patients that are

hypotensive should be avoided.

Ultimately successful treatment of the commonly encountered conditions in small animal practice involves a combination of agents and an understanding of the beneficial and potentially detrimental effects.

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Abstracts European Veterinary Conference Voorjaarsdagen 2008 | 47