Practical fluid therapy in companion animals – part 1

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Fluid therapy is a common, and usually essential, part of a treatment plan for most veterinary patients, including management of medical conditions or supporting fluid balance during surgical procedures.

Panel 1. Indications for administration of parenteral fluids (Mensack, 2008)

- Hypovolaemia.
- Hypotension.
- Dehydration.
- Electrolyte disorders.
- Metabolic and acid-based disorders.
- Prevention or treatment of decreased oxygen delivery.
- Replace ongoing losses, such as from burns, diarrhoea and vomiting.
- Fluid diuresis.

Panel 1. Indications for administration of parenteral fluids (Mensack, 2008).

Conditions parenteral fluids are indicated for are listed in **Panel 1**.

Fundamentally, fluid therapy refers to the provision of water, electrolytes and other substances. Additionally, it may include the provision of blood component therapy, but the discussion surrounding transfusions is beyond the scope of this article. It is vital to realise fluid therapy is a pharmacological intervention and should be treated and monitored as such.

It is also important to appreciate many fluid types do not have a specific veterinary licence.

Fluid dynamics

Water in the body is distributed over three compartments in intracellular and extracellular spaces, which are separated by semipermeable membranes (**Figure 1**).

Precise distribution and movement of the fluid in these compartments occurs through osmosis, according to relative concentrations of solutes present (**Table 1**). This is determined by the ability of each molecule to pass through the respective membranes by diffusion or passive transport and the presence of specific active transport mechanisms – most importantly, the sodium-potassium pump.

A basic understanding of solute concentrations in each compartment can be useful when choosing fluids to either prevent or treat electrolyte disturbances.

Types of fluid

Many different types of parenteral fluids are available, with some having very specific indications. Grouping these fluids into a number of broad categories is possible depending on type and use (**Panel 2**).

Figure 1. Fluid compartments and dynamics occurring in a typical adult mammal. Fluid distribution is different in neonatal mammals, with an overall greater percentage of total body water and relatively more extravascular fluid compared to intravascular fluid.

Table 2 illustrates distinguishing properties associated with specific fluids. Knowledge of such properties aids with understanding the indications for, and effects of, particular fluids.

Crystalloids

Crystalloid fluids contain small solutes, primarily electrolytes and occasionally molecules, such as glucose or lactate. These solutes will either readily cross semipermeable membranes or will be metabolised. This means administered fluid is rapidly (20 to 30 minutes) redistributed from the IV to

interstitial and intracellular compartments depending on the relative concentrations of solutes administered to plasma.

A common way to classify crystalloid solutions is based on their tonicity relative to plasma (280mOsm/L to 320mOsm/L), which also determines how the fluid is redistributed.

All veterinary practitioners will be familiar with using isotonic crystalloid solutions. Hypotonic or hypertonic solutions are less frequently used, and practitioners may be less aware of safety considerations around their use. Given the potentially severe consequences should these alternative solutions be administered inadvertently, it is recommended they be labelled clearly and kept separately from the isotonic solutions.

Isotonic solutions

Isotonic solutions include some of the most commonly administered fluids, with the primary indication being to replace lost extracellular fluid. As osmolarity is similar to extracellular fluid, redistribution will occur within the extracellular compartments in a ratio of 3:1 (**Figure 1**), with only 25% of administered fluid remaining in the intravascular compartment after approximately 30 minutes.

Table 1. Approximate concentration of ions in mEq/L in the various body fluid compartments (Chohan and Davidow, 2015)

Ion (mEq/L)		Extracellular space		Intracellular space
		Intravascular space	Interstitial space	
Cations	Na^+	142	145	12
	K^+	5	4	140
	Ca^{2+}	2	2	4
	Mg^{2+}	2	2	34
Anions	Cl^-	104	112	4
	HCO_3^-	24	27	12
	HPO_4^{2-} and H_2PO_4	2	2	40
	Proteins	14	1	50

Ca^{2+} = calcium ion, Cl^- = chloride ion, H_2PO_4 = dihydrogen phosphate, HCO_3^- = bicarbonate anion, HPO_4^{2-} = hydrogen phosphate, K^+ = potassium ion, Mg^{2+} = magnesium ion, Na+ = sodium ion

Table 1. Approximate concentration of ions in mEq/L in the various body fluid compartments (Chohan and Davidow, 2015).

Isotonic crystalloids (such as Hartmann’s solution) have an electrolyte composition similar to

plasma, and sometimes are described as “balanced” (for example, as compared to 0.9% normal saline; NaCl).

Additionally, as administration of solutions, such as 0.9% NaCl, can be acidifying – causing a metabolic acidosis – balanced solutions contain buffers (such as lactate) to produce an alkalising effect. However, balanced crystalloids are still not a perfect replacement for plasma (**Table 2**). In clinical practice, isotonic replacement solutions (**Panel 2**) are often used as short-term maintenance solutions.

Although in most situations, a patient’s kidneys will correct the electrolyte disturbances resulting from such fluids, their use in this way is not ideal. Hypernatraemia, hypokalaemia and a hyperchloraemic metabolic acidosis can develop, particularly if concurrent renal disease is present.

Hypotonic solutions

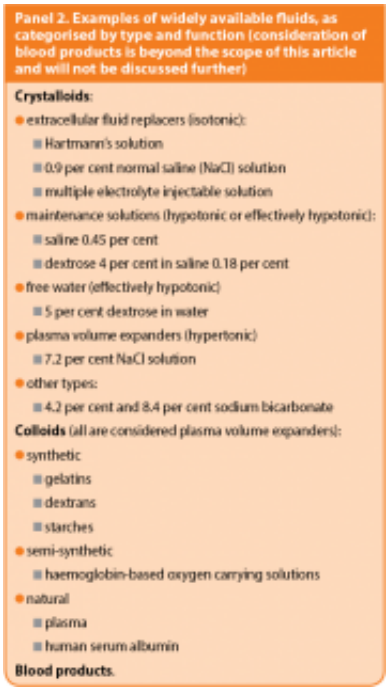
Hypotonic solutions contain lower sodium ions (Na+)and chloride ions (Cl-) and thus osmolarity, compared to plasma. This results in redistribution occurring throughout all fluid compartments, with the majority redistributing into the intracellular space. This allows for replenishment of free water deficits while accounting for maintenance requirements.

Hypotonic solutions are not suitable for bolus therapy as they are ineffective in expanding intravascular volume and may cause cerebral oedema from intracellular fluid shifting.

Direct administration of a hypotonic solution into the blood causes haemolysis due to water movement into erythrocytes. Therefore, many hypotonic solutions contain dextrose, so the initial administration is of an isotonic solution. The dextrose is rapidly metabolised and a hypotonic solution remains. Although these fluids are free to provide intracellular water, they are often still inappropriate regarding maintenance electrolyte requirements; sodium and chloride often provided in excess with an inadequate concentration of potassium.

It is usually more appropriate to provide a patient’s maintenance fluid requirements through food and water, where possible, rather than using hypotonic solutions.

Hypertonic solutions



Panel 2. Examples of widely available fluids, as categorised by type and function (consideration of blood products is beyond the scope of this article and will not be discussed further)

Crystalloids:
- extracellular fluid replacers (isotonic):
  - Hartmann's solution
  - 0.9 per cent normal saline (NaCl) solution
  - multiple electrolyte injectable solution
- maintenance solutions (hypotonic or effectively hypotonic):
  - saline 0.45 per cent
  - dextrose 4 per cent in saline 0.18 per cent
- free water (effectively hypotonic)
  - 5 per cent dextrose in water
- plasma volume expanders (hypertonic)
  - 7.2 per cent NaCl solution
- other types:
  - 4.2 per cent and 8.4 per cent sodium bicarbonate

Colloids (all are considered plasma volume expanders):
- synthetic
  - gelatins
  - dextrans
  - starches
- semi-synthetic
  - haemoglobin-based oxygen carrying solutions
- natural
  - plasma
  - human serum albumin

Blood products.

Panel 2. Examples of widely available fluids, as categorised by type and function (consideration of blood products is beyond the scope of this article and will not be discussed further).

Hypertonic solutions, however, contain higher Na+ and Cl- compared to plasma. This results in osmotic fluid shifts into the intravascular space, leading to significant intravascular fluid expansion. Hypertonic solutions are used for treating hypovolaemia and reducing raised intracranial pressure.

The plasma volume expansion effect is only transient, lasting approximately 30 minutes, as, after this time, the electrolytes redistribute throughout the extracellular space. Administration of hypertonic fluids should be followed by an isotonic (or effectively hypotonic) solution to replace the “borrowed” fluid and ensure a longer-term increase in intravascular volume.

Hypertonic solutions require careful administration, as large volumes can be fatal. When using a 7.2% solution of hypertonic saline, suggested doses are 2ml/kg to 4ml/kg in cats and 4ml/kg to 7ml/kg in dogs (Auckburally, 2016).

Sodium bicarbonate

Sodium bicarbonate is a specific type of hyperosmolar crystalloid solution used for the treatment of severe metabolic acidosis. Few indications and many adverse effects are associated with its use. Therefore, careful consideration should be taken prior to its administration.

Colloids

Colloidal solutions contain large molecules that increase intravascular colloid osmotic pressure (COP). Such particles are unable to pass through capillary pores, so remain in the intravascular space longer than crystalloid solutions. Indications include plasma volume expansion and hypoproteinaemia.

It should be noted that interpretations of total solid measurements via a refractometer are not reliable following colloid administration. Total solid values given following administration of dextran 70, hetastarch and pentastarch are 45g/L, 45g/L and 70g/L respectively (Auckburally, 2016).

The initial plasma volume expansion achieved depends on the number, rather than the size, of the colloidal molecules. However, the duration of action depends on molecular size, as larger molecules (more than 50kDa to 60kDa) require hydrolysis before renal filtration and excretion, while smaller molecules are freely filtered at the glomerulus.

Colloids can be classified as:

- Monodisperse – molecules of a single molecular weight.
- Polydisperse – molecules of a range of sizes and weights.

The only monodisperse colloid solution available in the UK is human serum albumin, although canine-specific albumin is available in the US (Craft and Powell, 2012). Molecular weight of colloids can be described either as:

- Number average molecular weight (MWn) – the arithmetic mean of all molecular weights.
- Weighted average molecular weight (MWw) – total sums of individual molecular weights multiplied by the proportion each molecule makes up of the total weight of all molecules (Goggs et al, 2008).

The MWw is influenced more by the larger molecules and so gives a larger value compared to the MWn. The ratio MWw/MWn gives an indication of the polydispersity (Westphal et al, 2009).

Adverse effects

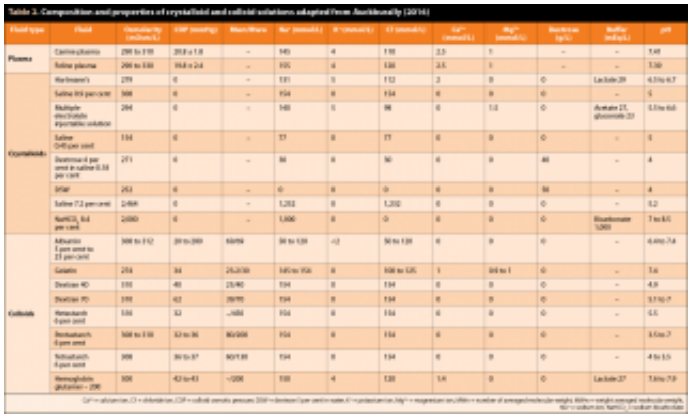


Table 2. Composition and properties of crystalloid and colloid solutions adapted from Auckburally (2016).

Use of colloids, specifically starches, has come under scrutiny in the medical field. As with any therapeutic intervention, the use of colloids carries some risk of adverse effects (**Table 3**).

Human clinical trials suggest starches may increase the incidence of renal failure in septic patients (Brunkhorst et al, 2008; Myburgh et al, 2012; Perner et al, 2012). Meta-analyses have not shown a benefit of colloids over crystalloids in medical practice (Gattas et al, 2013; Perel et al, 2013; Zarychanski et al, 2013) and, although the veterinary evidence is limited, reviews have called for the re-evaluation of colloid use (Adamik et al, 2015; Cazzolli and Prittie, 2015).

Gelatins

Gelatin solutions are created by modifying bovine collagen by alkali treatment with urea cross-linking or via succinylation to increase molecular size (Ertmer et al, 2009). Of the three types of synthetic colloids, gelatins contain the smallest molecules with molecular weights, around 30kDa to 35kDa. This is below the glomerular filtration threshold of around 60kDa.

Therefore, gelatins are rapidly excreted, a process that starts within minutes of starting an infusion. Clinically, the plasma volume expansion effect lasts around two to three hours (Ertmer et al, 2009).

Dextrans

Dextrans are solutions of glucose polymers synthesised by bacteria from sucrose. These are often prepared in 0.9% NaCl, although a preparation with hypertonic saline is available (Ertmer et al, 2009). Commercially available products include dextran 40 (MWw 40kDa) and dextran 70 (MWw 70kDa).

Plasma volume expansion is significant – one to two times the volume infused. However, the small molecular weight of the glucose polymers allows them to be quickly excreted from the kidneys

(Goggs et al, 2008). As the MWw is greater in dextran 70 (so some molecular degradation is required before excretion), the duration of action is slightly longer – up to six hours (Auckburally, 2016). It is, however, quite difficult to obtain dextran solutions.

Dextrans reportedly alter blood viscosity, enhancing microvascular blood flow and providing effective thromboembolic prophylaxis. However, similar to many colloids, dextrans may have direct effects on coagulation factors, so the recommended maximum dose is 1.5g/kg/day in humans (Ertmer et al, 2009). No licensed veterinary products are available.

Starches

Hydroxyethyl starches (HES) are produced from the multi-branched polymer of glucose, amylopectin. Glucose monomers are substituted with hydroxyethyl groups at carbon positions C2, C3 and C6 to reduce intravascular hydrolysis. Substitution at the C2 position is most effective at reducing hydrolysis (Goggs et al, 2008). Many HES are presented in 0.9% saline, although some commercial HES are available as balanced electrolyte solutions.

Hydroxyethyl starches are identified by three numbers; for example, 6% HES 130/0.4. The first number indicates the concentration: 6% and 10% HES solutions are iso-oncotic and hyperoncotic, respectively. The second number indicates the mean molecular weight. Typically, HES are classified as high (more than 400kDa), medium (200kDa to 400kDa) or low (less than 200kDa) MW. The third number indicates the molar substitution (MS). This represents the average number of hydroxyethyl residues per subunit.

A greater degree of substitution (along with a high C2:C6 ratio) will prolong intravascular retention, but will confer a less favourable safety profile (Westphal et al, 2009). Clinical effects after a bolus are likely to last 24 to 48 hours for the high MW, high-substitution solutions and 4 to 6 hours for the lower MW solutions (Auckburally, 2016).

Commonly used names for HES are given based on the degree of substitution:

- hetastarch: MS = 0.7
- hexastarch: MS = 0.6
- pentastarch: MS = 0.5
- tetrastarch: MS = 0.4

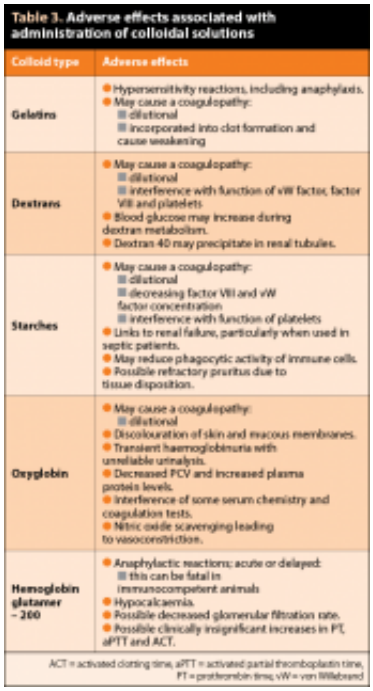


Table 3. Adverse effects associated with administration of colloidal solutions

Colloid type	Adverse effects
Gelatins	• Hypersensitivity reactions, including anaphylaxis. • May cause a coagulopathy: ▪ dilutional ▪ incorporated into clot formation and cause weakening
Dextrans	• May cause a coagulopathy: ▪ dilutional ▪ interference with function of vW factor, factor VIII and platelets • Blood glucose may increase during dextran metabolism. • Dextran 40 may precipitate in renal tubules.
Starches	• May cause a coagulopathy: ▪ dilutional ▪ decreasing factor VIII and vW factor concentration ▪ interference with function of platelets • Links to renal failure, particularly when used in septic patients. • May reduce phagocytic activity of immune cells. • Possible refractory pruritus due to tissue disposition.
Oxyglobin	• May cause a coagulopathy: ▪ dilutional • Discolouration of skin and mucous membranes. • Transient haemoglobinuria with unreliable urinalysis. • Decreased PCV and increased plasma protein levels. • Interference of some serum chemistry and coagulation tests. • Nitric oxide scavenging leading to vasoconstriction.
Hemoglobin glutamer – 200	• Anaphylactic reactions; acute or delayed: ▪ this can be fatal in immunocompetent animals • Hypocalcaemia. • Possible decreased glomerular filtration rate. • Possible clinically insignificant increases in PT, aPTT and ACT.

ACT = activated clotting time, aPTT = activated partial thromboplastin time, PT = prothrombin time, vW = von Willebrand

Table 3. Adverse effects associated with administration of colloidal solutions.

The lower MW and substitution solutions (such as tetrastarches) are more widely used in Europe while higher MW and substitution solutions are more typical in North America. Although no veterinary licensed product is available in the UK, one (6% HES 130/0.4) is available in the US.

In 2013, the UK medical community temporarily suspended all licences for HES products due to the suggested link with renal failure (Brunkhorst et al, 2008; Myburgh et al, 2012; Perner et al, 2012). One retrospective canine study with HES 10% 250/0.5 was associated with increased death or acute kidney injury (Hayes et al, 2016), while another showed no alterations in creatinine concentration after HES 6% 130/0.4 versus crystalloids up to 12 weeks after infusion (Yozova et al, 2016).

It is recommended HES can be used in acute blood loss in humans where crystalloids alone are insufficient, with contraindications in critically ill patients. A general recommendation is not to exceed 20ml/kg/day, although doses up to 70ml/kg/day have been reported with low MW and substitution solutions (Neff et al, 2003).

Albumin

Albumin is a vitally important plasma protein with many functions, including transport of molecules, normal platelet and coagulation function, free radical scavenging and maintenance of COP. It contributes to approximately 80% of plasma COP (Mazzaferro et al, 2002).

As COP regulates albumin synthesis via a negative feedback mechanism, iatrogenic alterations in COP (for example, administration of large volumes of any colloidal solution) may reduce albumin production.

Commercially available HSA is presented as a monodisperse solution (MWw 69kDa), either as a 4.5% (iso-oncotic) or 20% (hyperoncotic) solution. Indications for use include severe hypoalbuminaemia or hypovolaemia. Controversies over the use of HSA exist; a large-scale study in human medicine did not show any benefit in using HSA over 0.9% NaCl for fluid resuscitation (Finfer et al, 2004).

Although the use of 25% HSA in critically ill cats and dogs appears safe (Mathews and Barry, 2005), reports exist of severe acute and delayed reactions in healthy dogs, some of which were fatal (Cohn et al, 2007; Francis et al, 2007).

Plasma

Canine plasma is commercially available (fresh frozen or frozen). Although a colloidal solution, its indications are primarily for systemic inflammatory response syndrome and coagulopathies (Beer and Silverstein, 2015). Discussion of its use is beyond the scope of this article.

Conclusion

Numerous fluid preparation options exist for the veterinary practitioner. Fluid therapy is a complex topic and our understanding of the mechanisms of action and side effects of administration continues to increase.

A basic understanding of fluid dynamics and available products will allow a safe, appropriate plan to be devised for the patient. Advice regarding planning and monitoring fluid therapy will be covered in part two of this article.

- **Companion animal fluid therapy part 2: planning and monitoring**

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