7

Training Objectives:

- ✓ Knowledge of the different fluid spaces in the body and their respective interactions.
- ✓ Comprehension of the decisive influence of the sodium concentration on the distribution of the infusion solutions to the fluid spaces
- ✓ Knowledge of the most important infusion solutions and their areas of application
- ✓ Knowledge of the standard infusion filters

THE INFUSION SOLUTIONS

All substances which are supplied externally that shall have an effect **inside** the body (i. e. not on the body's surfaces) need to enter the blood circulation. Distribution from there to other fluid spaces or absorption by body cells mainly depends on the purpose the substance has got for the body. So, for example, oxygen enters blood circulation via the membranes of the lung tissue and is distributed from there into the body cells. Nutrients enter the blood circulation via the membranes of the intestine and in most cases they are distributed from there into the cells. There are, however, a few exceptions, such as the electrolyte ions sodium and chloride that are hardly absorbed by the cells and therefore remain in the fluid outside the cells, the so-called extracellular space.

Drugs that shall have an effect inside the body also need to enter the blood circulation first. They enter the blood circulation via the membranes of the lung, the intestine or possibly the mucous membrane. The way drugs enter the blood circulation are not the same for all drugs.

Generally speaking, for intake of nutrients as well as of drugs, entrance into the blood circulation takes place via the intestine. There are situations, however, where the intestine does not function (e. g. after major surgery of the intestine) or may not be used (e. g. preparation for surgery of the gastro-intestinal tract). Finally, there are substances such as insulin, for example, where the blood circulation is generally not entered via the intestine. In those cases the substance needs to be dissolved in water or a fat emulsion and is supplied by injection into then skin (subcutaneously), into the muscles (intramuscularly) or into the veins (intravenously). All methods of administration circumvent the intestine and are therefore termed **„parenteral“** (Greek: for by-passing the intestine).

With regard to preparation it is to be distinguished between solutions/emulsions for injection and solutions/emulsions for infusion. The amount to be administered is the decisive criteria for classification

- Solutions/emulsions for injection: $\leq$ 100 ml
- Solutions/emulsions for infusion $\geq$ 100 ml

The criteria of distinction for 100 ml containers is the configuration of the piercing spike of an infusion set which does not fit for an injection container (see chapter 9.1).

Usually injection is done by help of an injection needle or a syringe into the muscular tissue, sometimes injection is done into the skin or into a vein. The duration of application is relatively short (between a few seconds and several minutes).

In infusions administration is always done via a vein. Apart from acute situations an infusion lasts for a period of hours. Certain cases may require patients to be infused for days and even weeks. Containers that have run empty will then be replaced by new ones. Thus, the purpose of an infusion is to supply substances and fluids in large quantities and usually for a longer period of time.

This chapter deals with the most important types of infusion solutions/emulsions including their areas of application. It provides the physiological principles (physical and chemical processes) necessary to comprehend the composition of infusion solutions.

Important

Infusion solutions are large-quantity preparations of substances which are dissolved in water or lipid emulsions being supplied via the veins.

7.1 Fundamental Physiology of the Fluid Spaces

7.1.1 THE FLUID SPACES

Inside the body the cells are separated by membranes. The fluid space inside these cells is called **intracellular space**. This space is characterised by an electrolyte profile being rich in potassium, magnesium and phosphate while sodium, calcium and chloride are hardly present.

All cells are surrounded by a fluid, the fluid space being called **interstitial space**. The circulatory system is a further fluid space, called **intravascular space** partly being in contact with the interstitial space via membranes. With regard to their electrolyte profile the interstitial and the intravascular space are almost identical (see tab. 6). Compared with the intravascular space the fluids in these two spaces are relatively rich in sodium, calcium and chloride while the content of potassium, magnesium and phosphate is relatively low. The total of interstitial and intravascular space is termed **extracellular space**.

Table 6: Concentration of selected electrolytes in different fluid spaces

	Intracellular space	Extracellular space	
		Intersitial space	Intravascular space
Sodium	10 mmol/l	143 mmol/l	141 mmol/l
Potassium	155 mmol/l	4 mmol/l	4 mmol/l
Calcium	< 0.001 mmol/l	1.3 mmol/l	2.5 mmol/l
Magnesium	15 mmol/l	0.7 mmol/l	1 mmol/l
Chloride	8 mmol/l	115 mmol/l	103 mmol/l
Phosphate	65 mmol/l	1 mmol/l	1 mmol/l

Important **Sodium is the predominant cation in the extracellular fluid**

7.1.2 EXCHANGE PROCESSES BETWEEN THE FLUID SPACES

There is a constant process of exchange between the above fluid spaces. This entails surmounting of barriers since the degree of the membranes‘ permeability is not the same for all substances. Processes of exchange have to take place through the membranes and there exists a large number of different possibilities.

The easiest method of exchange is the substances passing the pores of the membrane without being hindered. The pores‘ diameter is much larger than the diameter of the substances they shall let pass. The pores of the membranes surrounding the intravascular and the interstitial space are so large, that substances such as electrolytes, amino acids and glucose may easily pass while large molecules (so-called macro-molecules) such as plasma proteins hardly pass. Since plasma proteins retain water, exchange of the above products may take place between the interstitial and the intravascular space without the level of fluid in the intravascular space being reduced.

Sometimes exchange processes take place via special channels that allow transportation of only certain substances or even one substance only. A special mechanism is able to recognise the substance(s) in question and ensures transport through the membrane by activating energy. This kind of transport is responsible to ensure, for example, that sodium that has entered the intracellular space be pumped out. This entails passive flow of water at a quantity that the sodium concentration in the extracellular space remains normal. In view to distribution of an infusion solution to the intra and the extracellular space the sodium concentration is therefore the decisive parameter. In case a solution has got a sodium concentration that corresponds to the one in the extracellular space the fluid that has been administered cannot reach the intracellular space and is therefore distributed into the intravascular and the interstitial space according to their relative sizes.

Solutions, that shall make water available to the cells as well (intracellular) need to have a sodium concentration that is considerably lower than the one of the extracellular space.

Important

The sodium concentration of an infusion solution is the decisive factor with regard to distribution of the fluid between the intra- and the extracellular space.

Solutions that shall remain in the intravascular space (see below plasma volume substitutes) need to have the same sodium concentration as it is the case in plasma as well as a macro-molecular substance, that ensures that the fluid is kept in the intravascular space.

Important

If an infusion solution shall remain in the intravascular space its sodium concentration needs to be the same as in plasma. Further more, a macro-molecular substance must be contained.

7.2 Administration of Water, Sodium and Chloride

7.2.1 CRYSTALLOID SOLUTIONS

Surgery may entail severe losses of extracellular fluid (interstitial fluid and blood). The loss of interstitial fluid may be compensated by solutions that have a similar concentration of sodium and chloride as extracellular fluids. Blood losses may also be compensated by these solutions provided the quantity of the loss is not too critical.

Solutions used for this purpose in clinical work are called **crystalloid solutions**. Along with the right concentration of sodium and chloride their concentration of potassium and calcium is the same as in extracellular fluids. Since extracellular fluid does also contain bicarbonate which produces quite some problems when preparing an infusion solution, admixture of this substance is dispensed with in any case. Instead, some crystalloid solutions do contain acetate and lactate, which the body may easily transform into bicarbonate.

Crystalloid solutions are rapidly excreted by the kidney and appear virtually unchanged. Furthermore these solutions are suitable to be used for dissolution and parenteral administration of drugs. Upon supply these solutions are rapidly eliminated. They have therefore proven to be the solutions of choice for administration of drugs. Table 7 summaries typical crystalloid solutions.

Tab. 7: Some typical examples of full electrolyte solutions

	Electrolyte concentration in mmol/l				
Solution	Sodium	Potassium	Calcium	Chloride	Lactate
Ringer’s solution	147	4	2.3	155.5	0
Lactated Ringer’s	131	5	2.0	112	28
Normal saline solution	154	0	0	154	0

Important

The electrolyte profile of crystalloid solutions is very similar to the one of plasma. They act as substitutes for losses of extracellular fluid caused by surgical interventions or trauma and as carrier solution for drugs.

7.2.2 HALF-STRENGTH ELECTROLYTE SOLUTIONS

An infusion solution that contains half the sodium concentration contained in plasma is termed „half-strength electrolyte solution“. A part of the solution administered acts to supply the cells with water. These solutions serve to ensure the patient to be moderately supplied with the most important nutrients such as water and sodium in case an oral intake is not possible or allowed for a short period of time (some few days). A certain amount of potassium is frequently added to these solutions.

The electrolyte profile is exactly half the one being typical for full electrolyte solutions and is therefore termed „half-strength“ (half-strength Ringer’s solution, half-strenmgth lactated Ringer’s solution and half-strength normal saline solution).

Important

Half-strength electrolyte solutions primarily serve to supply the body with water and sodium. They may act as simple basic solution if the necessary amount of potassium is being added.

7.2.3 REHYDRATION SOLUTIONS

Solutions that do only contain a quarter of the sodium concentration compared to full electrolyte solutions are termed „quarter electrolyte solutions“ or „rehydration solutions“ since they make a large amount of water available to the cells. These solutions do neither contain potassium or calcium nor acetate or lactate.

The solutions are used in patients suffering from a fluid deficiency and unknown renal function. If the patient‘s kidneys work properly infusion of a sufficient quantity of those solutions leads to the formation of urine. In case of improper renal function production of urine is disturbed and the patient would not be able to tolerate large quantities of sodium particularly well. The same is true for the administration of potassium and calcium which might also entail severe problems for the patient.

Important

Rehydration solutions serve to supply large quantities of water to patients with unknown renal function.

7.2.3.1 GLUCOSE 5 %

Pure water may make the red blood cells burst. So, if water shall be supplied parenterally without sodium being added, a 5 % glucose solution should be given. The addition of glucose prevents the undesired side effects of pure water.

Actually, the administration of water without adding sodium is an exception which does only make sense in patients suffering from a renal impairment. In those patients the quantity of sodium supplied cannot be compensated by excretion in urine thus leading to an increase of sodium in blood with a great deal of problems involved.

Glucose 5 % is therefore often used together with other solutions, e.g. in order to complete parenteral nutrition with regard to the total demand of water, or as carrier solution for drugs.

Important

Glucose 5 % is used for the administration of water. It further serves as carrier solution for drugs in injections or infusions

7.3 Administration of Further Electrolytes

A lack of external supply will soon result in a deficiency of water and sodium as well as of potassium, magnesium, calcium and phosphate. If a patient is not supplied with electrolytes for a period of a few days even life-threatening deficits my develop within a very short period of time. Electrolyte concentrates are designed to be administered in quantities covering the daily demand. They are added to other solutions and are mainly used in parenteral nutrition.

Electrolyte concentrates, for example, are sodium chloride 5.85 % (1 molar), potassium chloride 14.9 % (2 molar), potassium phosphate acc. to USP (United States Pharmacopeia), magnesium sulphate 50 % (2 molar) and calcium gluconate 10 % (0.225 molar).

Important

Electrolyte concentrates serve to add electrolytes to infusion solutions to be administered.

7.4 Partial and Total Parenteral Nutrition

To get through a short-term nutrient deficiency adult patients with good nutritional status and normal metabolic activity do require the administration of water and electrolytes in quantities that meet the daily demand as well as of about 100 – 150 g of glucose per day. This quantity does not cover the daily demand, it suffices, however, to reduce the degree of protein catabolism considerably (see chapter 5.1).

Among the typical solutions for partial parenteral nutrition are Sterofundin® BG-5 and Normofundin® (see table 8). These solutions are also termed basic solutions, 2.5 – 3 l of them covering the basic needs. Since the combination of calcium and phosphate entails the precipitation of calcium phosphate the two substances must not be contained in one and the same solution.

Tab. 8 Constituents of typical basic solutions (Sterofundin® BG-5 and Normofundin® G-5)

	Sterofundin® BG-5	Normofundin® G-5
Sodium (mmol/l)	53,7	100,0
Potassium (mmol/l)	24,2	18,0
Calcium (mmol/l)	0,0	2,0
Magnesium (mmol/l)	2,5	3,0
Chloride (mmol/l)	53,5	90,0
Phosphate (mmol/l)	7,3	0,0
Acetate (mmol/l)	0,0	38,0
Lactate (mmol/l)	25,0	0,0
Glucose (g/l)	50,0	50,0

Important

Basic solutions serve to supply sufficient quantities of water and electrolytes as well as a minimal quantity of glucose in case a short-term nutrient deficiency shall be got through.

In adult patients with bad nutritional status and/or strongly increased metabolic rate parenteral nutrition should be started as early as possible. In this case all nutritive substances should be contained in quantities that do cover the respective requirements. This kind of parenteral nutrition is called total parenteral nutrition (TPN). Among the nutritive substances used are amino acids (e, g. Aminoplasmal®), highly concentrated glucose solutions ($\geq$ 20 %), fat emulsions such as Lipofundin® MCT/LCT, and electrolytes, vitamins and trace elements (Tracutil®) in the form of concentrates. The criteria that are decisive for the composition of the parenteral nutrition regimen are subject of a one-week training course and are therefore not treated in more detail now.

7.5 Plasma Substitutes (Plasma Volume Replacement Fluids)

A major deficiency of fluid in the circulation (so-called plasma volume) is hardly tolerated and leads to shock and – if not compensated - finally to organ failure and death. Possible reasons for such a fluid deficiency in the circulation are blood looses or an enlargement of the blood vessels (vasodilation). While in former times whole blood had been supplied as substitute, nowadays much more caution is exercised in view to the risks involved, particularly the risk of life-threatening infections that might be transmitted. If blood losses amount to 30 – 40 % of the total blood volume it is often sufficient to substitute the volume which has been lost intravascularly. The solutions used for this purpose are formulated as full electrolyte solutions with a macro-molecular substance. These solutions are termed plasma volume substitutes or plasma volume replacement fluids, typical examples being Gelafundin® 4 % (abroad: Gelofusine®) and Hemohes® 6 % or 10 %. Plasma volume substitutes are often supplied together with blood components or blood.

Important

Plasma volume substitutes serve to compensate for a loss of plasma volume or to fill the additional plasma space in case of a vasodilation

Trend

Due to the considerable risks involved in homologous blood transfusion the concept of **autologous blood transfusion** (transfusion of the patient's own stored blood) is playing an increasingly important role. In advance of planned operations the patient's own blood is taken which is then being re-transfused during surgery.

In surgery blood may also be drawn and replaced with a plasma volume substitute within certain limits. The patients blood is re-transfused during the operation.

7.6 Osmotic Diuretics

The kidney produces urine by filtering plasma water (blood without cells and plasma proteins) off the functional units (nephrons). Along with the nutritive substances dissolved in the plasma water this „primary urine" contains susbtances originating from the metabolic process which the body needs to eliminate. Filtering of plasma water is followed by a process where water and nutritive substances are taken back almost completely from the primary into the blood. Finally, the actual urine, the so-called „secondary urine“ reaches the bladder.

In case, the primary urine contains a substance which is filtered off but cannot be returned into the blood, this substance carries some of the water into the secondary urine which results in an increase of the urinary volume. This is the case for mannitol, for example. Upon infusion of mannitol solutions (e. g. Osmofundin® 15 %) the volume of urine is increased thus flooding out water and keeping the kidney functioning.

Areas of application for mannitol solutions:

- Reduction of the intra-ocular and cerebral pressure (dehydration of the tissues is the decisive aspect).
- Prevention of an acute renal insufficiency provided failure is only about to develop and a certain critical stage has not yet been exceeded (keeping the kidney functioning is the decisive aspect).

A further field of application is the „forced diuresis“ (forced increase of urine excrection) combining infusions of a mannitol solution with the administration of a crystalloid solution. Since crystalloid solutions are excreted as urine rapidly and in almost unchanged form, the urine volume may be significantly increased which helps to flood water-soluble and glomerularly filtrated poisons out of the body.

Important

Mannitol solutions serve to flood out water. In combination with crystalloid solutions they help to eliminate glomerularly filtrated poisons.

7.7 Solutions Regulating the Acid-base Balance

The body produces large quantities of carbon dioxide. Acids and bases are supplied by nutrient intake. While carbon dioxide is eliminated via the lungs the other acids and bases are excreted via the kidneys ensuring that the pH of the extracellular fluid is kept within limited bounds (7.35 – 7.45). Shifts of the pH outside these bounds are life-threatening and need to be treated with regard to their cause. In case of lung and respiration being the cause, correction is made by ventilation, for example. If metabolism is concerned the primary disease is to be treated. In the latter case an acute shift of the pH is to be regulated by additional supply of either an acid or a base.

While a **metabolic acidosis** (metabolism-induced reduction of the pH-level to < 7.35) is treated by the administration of the base **sodium bicarbonate** a **metabolic alkalosis** (metabolism-induced increase of the pH-level to > 7.45) is regulated by supplying **hydrochloric acid.**

Important

Sodium bicarbonate serves to treat a metabolic acidosis while hydrochloric acid is supplied in case of a metabolic alkalosis.

7.8 Infusion Solutions and Filters

Infusion solutions and preparations may contain particles and germs. In order to reduce any resulting risks involved for the patient two different types of infusion filters are used:

- **Particle filters**

are often made of a synthetic wire-cloth screen with pores usually having a size of 5 µm (µm = micrometer = 1 (/1000 millimetre). This size corresponds to the diameter of the smallest capillaries in the blood stream. Larger particles of firm components such as glass, for example, would occlude these capillaries thus causing a micro embolism. Filtration of infusion solutions using 5 µm particle filters helps to prevent this kind of complication, some bacteria, however, still being small enough to pass these filters.

- **Bacterial filters**

Due to the smallness of bacteria it is required to use a 0.2 µm filter to ensure their proper retention. They are too large to pass it, however, after some time bacteria tend to grow through such a filter. This is the reason why nowadays membrane filters are usually used. Instead of a wire-cloth screen they have got a porous membrane, the size of their largest pores corresponding to the nominal size. Since this membrane is relatively thick, growth of bacteria takes place only very slowly. The membrane is able to filter much smaller particles. The size of the pores is too small to be measured and is therefore validated, this means they are compared with calibrated sizes. To do so, air is pressed through these pores. The moment of passage is called „bubble point“. By comparing this value with standardised filters the largest pore size can be determined. Since those pressures exceed by far the pressures that are usually exerted these filters do also ensure reliable air venting.

Viruses cannot be retained by filters since they are even smaller and enter the body using further pathways.

A further aspect to consider is the kind of fluid which is to be infused. Lipids or Lipid-containing drugs cannot be supplied via bacteriatight filters, since lipid emulsions contain small lipid droplets in a carrier solution. These droplets would immediately obstruct 0.2 µm. filters. It is therefore recommended to use so-called lipid filters which have a pore size of 1.2 µm.

A further problem are the so-called endotoxins which are fractions of the coat of a certain type of bacteria, that develop as the bacterium is deactivated. These endotoxins may cause reactions such as fever and even shock and therefore need to be retained. Since their size is not exactly known retention cannot be done mechanically but by way of an **electrically charged filter membrane** which attracts these endotoxins and keeps them. Along with a pore size of 0.2 µm these charged filters ensure both, **retention of bacteria and endotoxins**.

Due to the absolutely different profile of blood a different type of filter is used for transfusions.

For the administration of blood usually filters with a pore size of 200 µm, i. e. 0.2 millimetres are being used. Such a pore size is adequate to retain major blood clots which would obstruct the catheter or needle thus causing an interruption of transfusion. Use of these filters does ensure prevention of microembolisms.

For more effectiveness **micro filters** with a pore size of 40, 20 and even 10 µm may be used. These filters are designed to retain significantly more and particularly smaller clots, and even some of the larger blood cells. Since erythrocytes having a diameter of about 7 µm are by far the most important component in transfusion of whole blood the smallest available filter has got a pore size of 10 µm.

These very small pores tend to obstruct rather quickly, however, this means the capacity of a filter (quantity of filtered blood) and its flow rate are considerably reduced.

A **blood filter** with an adequate pore size is to be used, depending on the area of application, the quantity of blood to be transfused as well as the patient's state of health.

Important

Due to their very small pore size infusion filters are absolutely unsuitable for the administration of blood.

7.9 Summary

Infusions serve the intravenous administration of large quantities of substances or fluids, usually for a longer period of time. Basic physiological interrelations need to be observed such as the concentration of electrolytes in the different fluid spaces of the body or the interchange between these fluid spaces. Sodium plays a particular role with regard to distribution of the fluid supplied between the intracellular- and extracellular space.

The administration of water, sodium and chloride is of major importance in infusion therapy. A solution which has got an electrolyte composition similar to the one in plasma is termed crystalloid solution. It is indicated as substitute for the loss of extracellular fluid and as carrier solution for drugs. Half-strength electrolyte solutions do only contain 50 % of the sodium concentration contained in plasma. Above all they serve the administration of water and sodium. If water is to be made available to the cells (e. g. in patients suffering from a fluid deficiency and unknown renal function) rehydration solutions are to be used. They have got a quarter of the sodium concentration contained in plasma and do neither contain potassium nor calcium. If water shall be supplied parenterally without the simultaneous administration of sodium 5 % glucose is the solution of choice. While pure water can make the red blood cells burst this is prevented by the addition of glucose. In fact, glucose 5 % serves the administration of water and is also used as carrier solution for the injection of drugs. Along with the administration of water and sodium electrolyte concentrates need to be supplied in case of a several days lasting lack of external supply.

Short-term nutrient deficiency may be compensated by supplying water, electrolytes and glucose in quantities that cover the actual demand. This partial parenteral nutrition makes use of so-called basic solutions. If the patient is suffering from a bad nutritional state and/or a considerably increased metabolic rate a total parenteral nutrition (TPN) is required supplying all nutrients in quantities that cover the actual demand.

Volume substitutes represent a further group of infusion solution serving the compensation of a plasma deficiency. In case of blood losses amounting to 30 – 40% of the total blood volume solutions are given, their composition being the same as in crystalloid solutions with a macromolecular substance. In order to prevent the risk involved in homologous blood transfusion, autologous transfusion i. e. transfusion of the patient's own stored blood is more and more considered to be the method of choice.

For flooding out water mannitol solutions are supplied since they serve the increase of the quantity of urine and keep the kidney function. If supplied along with full electrolyte solutions the elimination of glomerularly filtrated poisons is achieved..

Shifts of the pH are regulated by treating the actual cause. It is supported by additional supply of an acid or a base. Metabolic acidosis, i. e. a metabolism-induced decrease of the pH is treated by supplying sodium bicarbonate while in case of a metabolic alkalosis, i. e. a metabolism-induced increase of the pH-value, hydrochloric acid is given.

When administering infusion solutions different types of filters are used which serve to prevent damage to the patient caused by particles and germs. There are two different types of filters, particle filters and bacterial filters. Furthermore, lipid filters are used for the filtration of lipids while invasion of endotoxins is prevented by using electrically charged filter membranes.

Due to their small pore size infusion filters are not suitable to be used for blood transfusion. There is a number of blood filters with different pore sizes available. Depending on the quantity of blood to be transfused and the patient's state of health pore sizes between 10 and 200 µm may be chosen.

7.10 Comprehension Questions

- What is the meaning of „parenteral“?
- What is the decisive difference between injection solution/emulsion and infusion solution/emulsion?
- Please define the term „infusion solution“!

- Intra cellular and extra cellular space are distinguished with regard to the concentration of electrolytes. Please give the main differences!
- What is the decisive parameter regarding distribution of an infusion solution between intracellular and extracellular space?
- What substances need to be contained in infusion solutions in order to provide water to the cells (intra cellular)?
- Please describe situations where the use of crystalloid solutions is indicated!
- Which fluid does the electrolyte composition of a crystalloid solution correspond to?
- Name some typical crystalloid solutions?
- What function do half-strength electrolyte solutions have?
- Describe the electrolyte concentration of rehydration solutions!
- Please name the fields of indication for the use of rehydration solutions!
- What purpose does „glucose 5 %“ serve?
- What function do electrolyte concentrates have?
- Please describe the indication for the infusion of basic solutions!
- Please name some typical plasma volume substitutes!
- What purpose do plasma volume substitutes serve?
- What is to be understood by autologous transfusion?
- Please describe the reaction triggered off by the infusion of mannitol solutions?
- Please name the areas of application for mannitol solutions!
- What substances are to be used for treating a metabolic acidosis and alkalosis?
- What diameter do the following filters have? Particle filter, bacterial filter, lipid filter, standard blood filter and microfilter?
- What is to be observed when using blood filters?