An update on extravasation: basic knowledge for clinical pharmacists

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SUMMARY

Extravasation is the leakage of intravenously administered solution into surrounding tissues, which can cause serious damage to the patient. The impact of extravasation is mostly determined by the localisation and volume of extravasation, but the physicochemical properties of the drugs are also important. In this paper a stepwise approach to managing an extravasation is described, with recommendations on the role of the pharmacist. Information on osmolality, pH, pKa and the buffering capacity of drugs is given in relation to extravasation, which is summarised in a practical crash card that can be used in clinical practice.

INTRODUCTION

A patient with ventricular tachycardia was admitted to the cardiology ward. Due to the need for a quick response and multiple risk factors (time, procedure, triple anticoagulation) amiodarone was intravenously administered into a vein in the patient's foot. The amiodarone extravasated subcutaneously, which resulted in serious pain and discomfort. The pain continued after admission, resulting in permanent psychological and physical damage (eg, the need for a walker for several months). No specific action was taken towards the extravasations due to the fact that a clinical hospital-wide protocol for extravasation with non-chemotherapy medication was missing.

An extravasation is defined as leakage of an intravenous administered solution into surrounding tissues.[1] Others distinguish infiltrations of non-vesicant solutions from extravasations with vesicant solutions.[1] For the scope of this article no distinction is made. Causes of extravasation are mechanical (unstable catheter, poor securing of the needle, patient activity) and physiological (clot formation above the cannula). Most extravasations resolve spontaneously; however, serious consequences such as tissue damage, formation of scar issue or even functional damage can occur. The degree of damage depends, among others, on physicochemical factors, such as pH, osmolality and fluid volume.[1]

The amiodarone extravasation prompted the urgent development of a hospital-wide protocol. This protocol includes information about non-chemotherapeutic drugs and treatment recommendations. The structure is comparable with a Dutch nationwide crash card for chemotherapeutic drugs. We included the most recent information about this topic in the protocol (May 2019) and in this paper we provide hands-on information about how to act when an extravasation occurs, drug specific information, and information that should be interpreted by clinical pharmacists.

CLINICAL QUESTION

What is the role of a clinical pharmacist in managing an extravasation? Follow a stepwise approach, using the physicochemical properties of a drug to determine the intervention.

RECOMMENDATIONS

When an extravasation occurs, it is important to follow the steps in the flowchart shown in online supplementary figure S1. These recommendations are based on the literature.[1–5]

Non-pharmacological intervention

The first intervention is always elevation of the affected body part (for a period of up to 48 hours). This helps in preventing and decreasing the swelling as the hydrostatic pressure in the capillaries is lowered.[4] Second, the use of both hot and cold compresses are described in literature. These compresses should be used repeatedly over several hours (up to 24 hours). It is important that 'dry' packs are used to prevent any further damage (eg, skin maceration) to the skin.

Hot packs are recommended when the strategy is to dilute and disperse the drug to a larger area; cold packs are recommended when the goal is to maintain a drug at the place of infusion. Cold packs cause vasoconstriction, resulting in decreased blood flow and increased local re-absorption of the extravasated drug.[1] When it is unknown whether a warm or cold pack is the preferred option, both methods can be used, depending on the preference of the patient, in combination with further treatment strategies.

Pharmacological interventions

Pharmacological interventions can be divided in two categories: (1) dispersion and dilution; (2) neutralising the drug with an antidote.

1. Hyaluronidase is an enzyme that hydrolyses hyaluronic acid. Hyaluronic acid is an important part of the skin and tissue, and by breaking it down the extravasated drug can disperse and dilute more easily. As antidote its purpose is to increase the area available for diffusion and absorption of the extravasated drug. Hyaluronidase should be used in combination with warm compresses as fast as possible when indicated (within 60 min).[1 4 5]
2. Phentolamine is an antagonist of α-adrenergic receptors and is therefore used to counteract the

Table 1 Pharmacological and physicochemical properties of drugs and solvents that can be used for the interpretation of extravasations

Physicochemical property	Crash card definition	Therapy	Comments	For example
Osmolarity	High ≥500 mOsm/L Low ≤200 mOsm/L 200–500 mOsm/L physiological (290 mOsm/L)[2]	Warm compresses; possibly hyaluronidase Physiological: cold compresses when dispersion/dilution is not indicated	High osmolarity is defined in the crash card as ≥500 mOsm/L which is rather low when reviewing the literature. However, as there is no formal evidence this boundary is used in the crash card[2] Higher osmolarity increases the risk of damage	▶ Total parenteral nutrition (TPN) ▶ Infusion fluids such as glucose 5%, 10%, mannitol 10%, and dextrose 50%, etc ▶ Contrast fluids ▶ Electrolyte solutions
Cationic solutions	N/A	Warm compresses; possibly hyaluronidase	Be aware of delayed reactions	▶ Calcium solutions ▶ Potassium solutions ▶ TPN
pH	Physiological (7.4) Low ≤5.0 High ≥9.0 Range considered 'physiological': 5.0–9.0[1 2]	Warm compresses; possibly hyaluronidase Physiological: cold compresses when dispersion/dilution is not indicated	Extreme pH <2 and >11 are thought to cause most damage Closer to 7.4 means lesser damage Alkaline solutions are more likely to cause damage than acidic solutions	**Alkaline** ▶ Phenytoin ▶ Co-trimoxazole ▶ Dantrolene ▶ Thiopental ▶ Trometamol ▶ Aciclovir ▶ Phenobarbital ▶ Epoprostenol **Acidic** ▶ Vancomycin ▶ Amiodarone ▶ Doxycycline ▶ Esmolol ▶ Promethazine
Vasopressors	N/A	Warm compresses; phentolamine	Do not use cold compresses because of additional vasoconstriction	▶ Terlipressin ▶ Desmopressin ▶ Dobutamine ▶ Dopamine ▶ Phenylephrine Norepinephrine

effect of an extravasated vasoconstrictor. Extravasations with vasoconstrictors (eg, norepinephrine, dopamine) can lead to extreme local vasoconstriction, potentially causing ischaemia and necrosis. This can be resolved with phentolamine (in combination with warm heat). It can be administered up to 12 hours after the event. Also topical nitroglycerine (glyceryl trinitrate) (2%) is mentioned in the literature to relieve ischaemia.[1 4 5]

Physicochemical properties of drugs

To determine the intervention, the physicochemical properties of the drug are important (table 1). It must be noted that most of these recommendations are based on theoretical concepts.[1–5]

Osmolality and pH

Osmosis is the transport of water over a semipermeable membrane caused by a difference in the concentration of the solutes. Hypertonic drugs move water out of cells, causing shrinkage, and hypotonic solutions move water into cells, causing rupture or haemolysis of the cells. Both of these mechanisms might result in damage to surrounding tissues in the case of an extravasation. Hypertonic fluids in particular seem to have a negative impact on tissue damage. For example, total parenteral nutrition (TPN) solutions can have an osmolality of up to 1500 mOsml/L and are known to cause phlebitis when administered peripherally. A retrospective study showed that 40% of paediatric patients receiving TPN >1000 mOsm/L had signs of phlebitis compared with only 7% in patients with TPN <1000 mOsm/L.[6] Grazitua *et al* showed that the highest risk on phlebitis was found with administered solutions of >600 mOsm/L.[7] Unfortunately, these limits are not evidence based and different upper limits are mentioned in the literature. Also the duration and rate of infusion are of importance. We can state that a high osmolality is a risk factor for damage when an extravasation occurs.[2]

Hypertonic cation-containing solutions (such as potassium and chloride solutions) both have high osmolality and contain high numbers of cations.[8] These cations can precipitate with proteins causing additional damage.

pH, pKa and buffering capacity

Acidity and alkalinity are expressed as pH. The human blood has a pH of ~7.4 and has a good buffer mechanism—the acid-bicarbonate system. A buffer contains both a weak acid and a conjugate base, making a solution resistant to pH changes when acidic or basic drugs are infused. The pH of a drug or parenteral fluid is thought to be important with extravasations, as extreme pH can cause severe damage to cells.[2] However, the influence of pH on cell damage is not well studied in humans. In particular, alkaline solutions are thought to cause more severe damage than acidic solutions due to deeper tissue penetration.[3] Furthermore, the type of tissue exposed to the pH and the duration of exposure are of influence; for example, phenytoin does not cause any issues when applied topically, but causes toxicity when infused.[2]

Also the pKa is important as it indicates whether a solution is a weak or strong acid/base. Strong acids (low pKa) have a larger influence on the pH of the blood than weaker acids (high pKa), as more buffer capacity is needed with stronger acids. The same is true when drugs are diluted. For example, sodium chloride 0.9% does not have any buffering capacity, so the pH of the admixture is determined by the drug and not by the solvent.

OUTCOME AND DISCUSSION

Extravasations with non-chemotherapeutic drugs not only cause discomfort to the patient, they can also be harmful and lead to permanent damage as described with our patient. In this article we aimed to summarise how to manage an extravasation and to discuss the most important treatment strategies (online supplementary figure S1; online supplementary table S1).

In online supplementary table S1 we have compiled information available on the parenteral drugs most commonly used in our hospital. However, this list is not exhaustive and some treatments advised are based on local experience. Also, information about pH and osmolality is added, which is mostly adapted from the drug label stating the pH and osmolality of undiluted drugs. Depending on the physicochemical properties of the drugs and the dilute used, the pH of the admixture can be altered, but that is not necessarily always the case (for example, for strong acids). In our opinion, as pharmacists, it is important to interpret the data and give drug-specific information to the care taker. When consulting on an extravasation event it is always important to ask the nurse or treating physician about the condition of the patient, as this can affect the outcome of the event. Neonatal veins, for example, which are small and fragile, and damaged fragile veins of elderly patients, present a risk for extravasation. Also in patients on the intensive care unit the categorisation should be done carefully, as most patients cannot tell that they are in pain and therefore large amounts of fluids might extravasate without being noticed.

Pharmacists can provide information on how to manage extravasation, based on physicochemical properties; they can assess the potential risks and have a role in the organisation of a hospital-wide protocol. However, in our opinion, clinical symptoms (degree of injury) and nursing interventions are the most important factors for determining the outcome. When there is doubt, the physician should always contact the plastic surgeon to determine whether surgery is needed.

In conclusion, a multidisciplinary approach is needed to improve the treatment of an extravasation event, involving the patient, nurses, pharmacists and physicians. By implementing a hospital-wide protocol on extravasation of chemotherapeutic and non-chemotherapeutic drugs, the management and prevention of complications can be improved.

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