Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 4 Number 1 January 1998

Treatment of Intravenous Extravasations

Marcia L. Buck, Pharm.D.

Use of the intravenous (IV) route for administration of fluids and medications always carries with it the risk of tissue damage following catheter malfunction. Extravasation, or infiltration, occurs when fluids or medications penetrate into the tissues surrounding an IV site following damage to the vessel endothelium.[1,2]

The incidence of extravasations varies in the literature, but is believed to range from 10 to 30%.[1-3] Most extravasations have relatively minor sequelae, but severe tissue injuries requiring surgical debridement, tissue grafting, or amputation have been reported. This brief review will focus on those fluids and medications known to cause significant tissue damage and the most commonly used approaches to patient management.

Risk Factors

There is little information available on methods for identifying patients at risk for extravasations. Age is considered to be the most significant risk factor. Infants and young children are known to have more extravasations, possibly due to their need for smaller catheters and their inability to communicate pain at the IV site as an early warning sign. The elderly are also at risk. Other factors associated with extravasations include: increasing cannula gauge (smaller size), use of steel needles, darker skin which makes assessment difficult, and infusion of substances known to cause direct cell damage.[2,4]

Extravasation Hazards

All intravenous medications and fluids can cause tissue injury following extravasation. However, certain substances are associated with a greater risk of tissue necrosis. Hyperosmolar substances, such as parenteral nutrition solutions, cause tissue damage by altering osmotic pressure.[5] Nearly all cancer chemotherapeutic agents have been reported to cause local tissue injury after extravasation. These agents cause direct cellular toxicity in the tissues they penetrate. Among this class, there are several agents (Table 1) which are considered to have a greater potential for causing substantial tissue necrosis.[6-10]

Table 1. Chemotherapeutic agents with a high potential for local tissue injury

Actinomycin D
Amsacrine
Dactinomycin
Daunorubicin
Doxorubicin
Epirubicin
Idarubicin
Mithramycin
Mitomycin
Vinblastine
Vincristine
Vindesine
Vinorelbine

Table 2 lists other medications associated with significant tissue injury.[3,11-13] The mechanisms involved vary. Acyclovir, phenytoin, and sodium thiopental are highly alkaline. Phenytoin and other medications such as diazepam have propylene glycol or ethyl alcohol diluents which can precipitate in local tissue, resulting in necrosis. Vasoconstrictive agents can cause local ischemia.

Table 2. Examples of other IV medications associated with significant tissue damage

Acyclovir

Aminophylline
Calcium
Chlordiazepoxide
Diazepam
Digoxin
Dobutamine
Dopamine
Epinephrine
Mannitol
Nafcillin
Norepinephrine
Penicillin
Phenytoin
Potassium
Sodium thiopental
Vancomycin

Initial Management

Early intervention following extravasation can lessen the severity of tissue injury. The first steps after discovery of an infiltrated IV line are to discontinue the infusion and thoroughly examine the site. If the catheter appears to be lodged in the tissues, an attempt to aspirate any fluid remaining in the catheter can be made to lessen the amount of drug at the site.[1-3,14]

Patient management often includes measures such as elevation of the site and the application of warm (dry) or cold compresses.[1,2,14] Despite their wide-spread use, documenting the efficacy of these methods has been difficult. Early studies clearly demonstrated their beneficial effect on patient comfort. In addition, several studies documented that cold compresses applied soon after extravasation reduced the ultimate size and duration of skin ulcerations.

More recent research, however, has provided controversial results. In 1993, Hastings-Tolsma and coworkers[15] studied healthy volunteers given intentional extravasations of normal or hypertonic saline and found no benefit from warm or cold compresses on pain intensity or surface area of induration. The only positive response noted was the effect of warm compresses in decreasing the volume of the hypertonic saline infiltrate, when measured by MRI. Continuing with this project in 1994, Yucha and colleagues[16] evaluated the benefit of limb elevation in volunteers. The authors found no significant difference in pain, surface area, or volume of the infiltrate between patients with elevated limbs and controls.

Despite these recent studies, elevation and the use of compresses should not be ruled out as an adjunct to the management of extravasations. While they may not reduce the amount of drug penetration, these therapies may significantly improve patient comfort. In most cases, the choice of treatment should be tailored to the individual patient.

An exception should be made for extravasations of chemotherapeutic agents. Heat may actually facilitate further tissue damage from most agents. In fact, some authors have suggested local cooling to minimize injury by reducing cellular drug uptake. Larson and colleagues[17] conservatively treated 119 patients with mild chemotherapeutic agent extravasations. In this study, the affected limb was elevated and ice packs were applied for 15 minute periods 4 times daily for 3 days. The majority of the patients (89%) required no further treatment.

Although the authors had considerable success with this method, it should be noted that extravasations of vinca alkaloids may be worsened with cooling therapy. Management of patients with extravasations caused with agents from this class should include the application of warm compresses.

In addition to these steps, administration of medications to relieve tissue damage may be considered. Hyaluronidase and phentolamine are useful in the management of many types of extravasations. Topical dimethylsulfoxide (DMSO) and sodium thiosulfate are useful in the management of chemotherapy extravasations but have not been widely used in children.

Hyaluronidase

For substances which cause increasing tissue damage with increasing concentrations, hyaluronidase may significantly reduce tissue injury. This agent has been shown to reduce the extent of tissue damage following extravasation of parenteral nutrition solutions, electrolyte infusions, antibiotics, aminophylline, mannitol, and chemotherapeutic agents, including the vinca alkaloids.[18]

Hyaluronidase is a highly purified enzyme derived from bovine protein sources. It acts by modifying permeability via hydrolysis of hyaluronic acid, a polysaccharide found in the intracellular ground substance of connective tissue. Hyaluronidase temporarily decreases the viscosity of the ground substance and promotes diffusion of fluids through tissues. The increased permeability caused by hyaluronidase is transient. Restoration of normal tissue structures occurs within 24 to 48 hours after administration.[19]

Hyaluronidase is available as lyophilized powder requiring reconstitution and a stabilized solution (Wydase®; manufactured by Wyeth-Ayerst). Both products result in a final concentration of 150 units/ml.[20] Administration techniques differ, but most sources recommend making a ten-fold dilution of hyaluronidase to provide a concentration of 15 units/ml, then injecting 1 ml of the solution through the catheter, if still in place, or subcutaneously around the site.[1,3,18]

Banta[18] recommends dividing the dose into 0.2 ml subcutaneous injections given with a tuberculin syringe and a 25 gauge needle in four sites equally spaced around the edges of the extravasation site. Flemmer and Chan[14] describe a similar technique and provide a detailed protocol for the overall management of extravasations.

Hyaluronidase is most effective if administered within the first two hours after an extravasation, however, it may still be beneficial when given up to 12 hours after the event. Hyaluronidase is generally well tolerated. There have been rare reports, however, of allergic reactions, ranging from urticaria to anaphylaxis following its use. Hyaluronidase should not be injected into an infected or cancerous site.[18,20]

Stabilized hyaluronidase solution and solutions made from the reconstituted powder require refrigeration. Solutions that are discolored or have a precipitate should not be used. Unused reconstituted solution should be discarded within 24 hours.[20]

Phentolamine

Extravasation of a vasoconstrictive agent, such as dopamine, dobutamine, epinephrine, or norepinephrine, may result in significant tissue injury. Local administration of a vasodilator may prevent ischemia in the tissues surrounding the infiltration. Phentolamine is a nonspecific alpha-adrenergic blocking agent which serves as a competitive antagonist of alpha-adrenergic agonists. It acts at both arterial and venous sites, inhibiting vasoconstriction and allowing improved blood circulation through the affected area.[1]

Phentolamine is available 5 mg (per 1 ml) vials (Regitine®; manufactured by Ciba-Novartis Pharmaceuticals).[21] For treatment of an extravasation, the contents of the vial should be diluted to 5-10 ml. A dose of 0.1 to 0.2 mg/kg (up to a maximum of 10 mg) should then be injected through the catheter or subcutaneously around the site. As with hyaluronidase, phentolamine should be administered as soon as the extravasation is detected, but may be given up to 12 hours later. Unused diluted solution should be discarded.[1,14,21]

The use of phentolamine in children has not been well documented. At this time, some sources recommend that it not be given to premature infants due to the potential for excessive vasodilation.[1] All patients given phentolamine should be closely monitored for hypotension or tachycardia.[21]

Clinicians wishing to use this therapy should be aware that Regitine® continues to be in short supply. During this period, the manufacturer will provide small quantities of drug to hospitals for specific patients at no charge. For more information on current availability, contact Ciba-Novartis at 1-800-526-0175.

Summary

Extravasations are an inherent risk of intravenous therapy. The primary methods for reducing tissue injury following extravasation are discontinuation of the infusion and the administration of hyaluronidase or phentolamine, when appropriate. Other measures, such as elevation or the application of hot or cold compresses, may not affect ultimate outcome, but may increase patient comfort.

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Pharmacology Literature Review

Are Gentamicin Levels Necessary?

Peak and trough serum gentamicin concentrations were followed in 150 children between the ages of 3 months and 15 years. Using conventional dosing regimens (typically 2.5 mg/kg every 8 hours), 96% of the children achieved the desired peak concentration (4 mcg/ml) and all children had trough concentrations less than 2 mcg/ml. Based on these data, the authors conclude that routine monitoring of serum concentrations in children > 3 months of age with normal renal function does not appear warranted. Substantial cost savings (nearly $50,000 for the levels drawn in this study), along with a reduction in blood sampling and personnel time could result from this change in practice. Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. **Ann Pharmacother 1997;31:1514-8** (accompanying editorial **Ann Pharmacother 1997;31:1539**).

Mycophenolate Review

Mycophenolate mofetil was approved by the FDA in 1995 for prevention of renal allograft rejection when used in combination with other immunosuppressives. This article provides a thorough review of the mechanism of action and pharmacokinetics of mycophenolate, in addition to a synopsis of the published clinical trials describing its efficacy. Studies conducted in pediatric renal transplant patients are included. Sievers TM, Rossi SJ, Ghobrial RM, et al. Mycophenolate mofetil. **Pharmacotherapy 1997;17:1178-97.**

Oral Ampicillin in Neonates

Twelve neonates $\geq$ 34 weeks gestational age were studied to determine the degree of absorption of ampicillin. All patients initially received ampicillin 100 mg/kg intravenously and were then converted to oral doses of 200 to 300 mg/kg/day divided every 6 to 12 hours. Serum ampicillin concentrations were measured after both parenteral and oral doses. Overall, serum peak concentrations were lower with oral dosing (40 to 70 mcg/ml versus 241 mcg/ml with IV dosing). Trough concentrations averaged 14 to 42 mcg/ml, well above typical MIC values for group B streptococcus. The authors conclude that oral dosing may be a useful alternative route for term neonates requiring antibiotic prophylaxis. Avent M, Ransom JL, Gal P, et al. Serum ampicillin concentrations following conversion from parenteral to oral ampicillin in neonates: A pilot study. **J Pediatr Pharm Pract 1997;2:344-8.**

Zidovudine Drug Interactions

This brief article offers an overview of drug interactions involving zidovudine. The authors focus on newer agents, particularly medications used in combination with zidovudine for the treatment of HIV infection. Two concise tables and an extensive reference list will make this review a useful addition to the files of clinicians caring for patients taking zidovudine. Robertson-Dallas S, Read SE, Bendayan R. New drug interactions with zidovudine. **Pharmacotherapy 1997;17:1198-1209.**

Formulary Update

The results of the December meeting of the Pharmacy and Therapeutics Committee were provided in the December issue. The next meeting will be on 1/23/98.

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If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.