EXTRAVASATION INJURIES

Sohrab N. Tomaraei
R.K. Marwaha

Children receiving intravenous (IV) chemotherapy are particularly prone to fluid escape, because of the thin, fragile, and mobile nature of their veins often necessitating multiple punctures(1). Small peripheral veins with low blood flow result in higher drug concentrations than do large veins with rapid flow. In patients receiving IV chemotherapy, 2 to 5% of all adverse reactions consist of local tissue irritation(2). Brown *et al.*(3) in a study of IV infusions in a large children's hospital found that extravasation occurred in one of nine patients receiving IV therapy. Larson(4) showed that 1 in 1000 cancer patients receiving doxorubicin or vincristine suffered an extravasation injury.

Therapeutic agents causing extravasation injuries can be divided into two broad categories: (*a*) those that do not bind to deoxyribonucleic acid (DNA), and (*b*) those that bind to DNA. *Table I* lists some of the common drugs categorized in this manner. The agents that do not bind to DNA cause immediate tissue damage but are quickly metabolized or inactivated. This type of injury is similar to a burn, in which the damage is instant, and is followed by repair by the normal healing mechanisms(5). In contrast, binding substances not only cause immediate injury but also lodge in the tissues attached to the DNA, thus inducing tissue necrosis over a prolonged period.

Extravasation of nonbinding agents (*e.g.*, hyperalimentation solutions containing concentrated glucose or calcium salts) frequently cause skin ulceration in children(6). Fat emulsion, used for provision of calories, also leads to subcutaneous fat necrosis. Brown *et al.*(3) treated extravasation of hypertonic glucose and calcium salts conservatively. They found no difference between topical applications of silver sulfadiazine, povidone iodine or saline soaks. Elevation of the extremity immediately after extravasation and avoiding warm soaks, which might increase skin maceration, produced good results. Yadav(7) has successfully treated superficial extravasation injuries with the help of ultraviolet light (personal communication). Children receiving hyperalimentation via the scalp or foot may develop small areas of skin slough, which should be treated conservatively(1). Larger wounds, or those in which healing process may lead to contracture require debridement and split thickness skin grafting(5). The subcutaneous extravasation of sodium bicarbonate may cause tissue necrosis, which initially appears as a skin blister but may progress to extensive necrosis. Such necrosis often requires skin grafting(8).

Extravasation of Chemotherapeutic Agents

Chemotherapeutic agents such as vinblastine and vincristine cause local

From the Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Reprint requests: Dr. R.K. Marwaha, Additional Professor of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Received for publication: May 5, 1993;
Accepted: June 29, 1993

TABLE I–*Therapeutic Agents Causing Extravasation Injuries*

Nonbinding agents	Binding agents
1. Hypertonic glucose solutions	1. Chemotherapeutic agents
2. Calcium salts	(*a*) Doxorubicin
3. Fat emulsions	(*b*) Dactinomycin
4. Sodium bicarbonate	(*c*) Mitomycin-C
5. Norepinephrine	(*d*) Mithramycin
6. Chemotherapeutic agents	(*e*) Daunorubicin
(*a*) Vinblastine	
(*b*) Vincristine	
(*c*) Alkylating agents (*e.g.*, nitrogen mustard)	
(*d*) Carmustine (BCNU)	
(*e*) Antimetabolites (*e.g.*, 5-fluorouracil)	

ulceration if they leak into the soft tissues. These drugs do not bind to DNA but inhibit mitosis. Ulcerations from these drugs are less severe than those caused by doxorubicin. Hyaluronidase (15 units diluted in 1 ml of saline, with 0.2 ml in each of 5 sites around and into extravasation) with steroids and local heat or local cold are recommended therapeutic measures(2).

Nitrogen mustard, an alkylating agent, rapidly fixes to tissues and causes immediate injury. Injection of sodium thiosulfate (26 mg/ml) locally is recommended. It inactivates the drug by allowing alkylation to itself rather than to surrounding tissues. Other alkylating agents, such as carmustine (BCNU) and antimetabolites such as 5-fluorouracil, rarely cause ulceration(2).

The most destructive extravasation injuries are those caused by doxorubicin, dactinomycin, mitomycin-C, mithramycin, and daunorubicin(9). These agents bind to nucleic acids leading to prolonged contact and a potential for sustained tissue injury and necrosis. Most of the experience has accrued from the use of doxorubicin but similar tissue injuries occur with any of these agents(10,11).

Clinically, the first sign of doxorubicin extravasation may be a local burning sensation. The local discomfort can be quite severe, lasting minutes to hours and on rare occasions even days, but it eventually subsides. The tissues at the extravasation site become red and firm. At this stage, the skin overlying the area of extravasation may still blanch when pressure is applied, suggesting infection or local irritation. If the amount of the extravasation is quite small, the redness will gradually diminish over the ensuing weeks. Necrosis may become obvious within a few days of a large extravasation(1). Larson(9) noted that of 115 documented extravasations treated immediately with ice and elevation of the affected part, ulceration occurred in only 11%. Doxorubicin "flare", an immediate redness and swelling, can occur without extravasation and usually disappears within 1-2 hours, rarely lasting longer than 12 to 24 hours.

Ulcers secondary to doxorubicin may have an insidious beginning but could prog-

ress to a much deeper extent than would be expected from their initial appearance. Deep structures, such as tendon or bone, may become exposed. The ulcers are indolent and do not develop a granulation tissue response or epithelialization, as might be expected from their early appearance. Injections of doxorubicin into veins on the dorsum of the hand or foot should be avoided when possible, since tendons in these regions have little skin cover. Moreover, grafting with local tissues, in case of skin loss is difficult.

Whilst prevention is important, early surgical intervention in case of extravasation is recommended to prevent progressive deep involvement. If the extravasation has been significant, a small necrotic area will appear in the centre of the reddened, painful skin. Once this painful necrosis appears, surgical debridement is indicated. Wide excision of all inflamed tissue is the treatment of choice, with split-thickness skin grafting or flap coverage(12). If debridement is not performed, the process can progress resulting in a thick, leathery eschar surrounded by a 2 to 3 cm rim of red painful skin. The eschar does not usually slough spontaneously. When this eschar is removed, deep subcutaneous necrosis is found(1,13,14,15). Clinically, these ulcerations resemble ulcers following therapeutic radiation, having raised, red, painful edges and shaggy necrotic centres with little spontaneous tendency towards healing. Under ultraviolet light, tissues in the ulcer bed containing doxorubicin may glow with a dull red color, and may aid identifying injured tissues(16,17). Extravasated doxorubicin can be found locally up to five months after the initial injury(18). An additional possible doxorubicin effect is the "radiation-recall" effect (areas that have received radiation in the past could undergo tissue damage and even ulceration when the patient receives systemic doxorubucin). However, this reaction was not observed in the series of extravasation injuries described by Larson(9).

Therapeutic Principles

The essential principles of management of extravasation injuries are summarized in *Table II*. The most critical area of management is in preventing extravasation. Unfortunately, the veins in patients who need chemotherapy are often fragile and mobile. Multiple injections lead to thrombosis and limit the availability of injection sites. The most reasonable location to give IV chemotherapy is in the proximal forearm over the muscle bulk of the flexor or extensor muscles, although such veins are often not available(9). A flexible catheter should be used rather than a stiff metal needle, which could be easily dislodged. Generally, it is recommended that doxorubicin be given through a freely flowing IV line over 2-5 min(12,19). The longer the time of infusion, the more likely the possibility of needle dislodgement and subsequent extravasation(17). A recent approach to the prevention of extravasation is the placement of a large indwelling venous catheter(20). Since intermittent injections in small peripheral veins is so fraught with dangers of extravasation and thrombosis, patients who require frequent and large doses of chemotherapy may best be served by a long line catheter placed via the antecubital fossa or subclavian vein into the vena cava. Greater use of central line catheters should greatly reduce extravasation injury and is highly recommended(1).

If infiltration is suspected, the infusion must be stopped immediately, aspiration performed, and the needle removed. Based on histologic studies, there does not seem to be any justification for local injection or topical use of steroid(1). Injection of

TABLE II–*Principles of Management of Extravasation Injuries*

(*a*)	Prevent extravasation by careful infusion technique; Choose appropriate venous access site; Use flexible catheters.
(*b*)	Stop infusion at the first complaint of burning or stinging.
(*c*)	In the event of an extravasation, elevate and rest the extremity for the first 24 to 48 hours.
(*d*)	Avoid warm soaks; cold packs are helpful.
(*e*)	After 48 h, encourage use of extremity and physiotherapy.
(*f*)	Injection of substances at the site of extravasation are of doubtful benefit.
(*g*)	Early consultation with surgeon mandatory when blistering and ulceration are first seen.

sodium bicarbonate to alter the PH of the normally acidic solutions or injection of substances such as sodium thiosulfate are more theoretical than practical in inactivating the effect of the drug on cells(2). Larson(9) used immediate ice and elevation, but no drug injection. He stated that locally injected substances not only failed to accomplish their theoretic goals, but could make the problem worse.

It is recommended that the extremity be elevated for 48 hours following the suspected extravasation in conjunction with ice application for 15 min, 4 times a day(4,9). While some authors have used warm soak applications(2), this is fraught with the danger of enhanced metabolic rate and further damage of the tissues. After this period of elevation, rest and ice, the patient is encouraged to use the extremity normally. The healing process may be prolonged even if ulceration does not occur, and may involve stiffness, neuropathy, *etc.* Active use of the hand coupled with careful physiotherapy can reduce the patient's discomfort, and reduce ultimate stiffness from nonulcerating lesions. Persistent swelling, erythema, and pain are indications for surgical intervention even if ulceration is not yet apparent.

REFERENCES

1. Rudolph R, Larson DL. Etiology and treatment of chemotherapeutic agent extravasation injuries: A review. J Clin Oncol 1987, 5: 1116-1126.
2. Ignoffo RJ, Friedman MA. Therapy of local toxicities caused by extravasation of cancer chemotherapeutic drugs. Cancer Treat Rev 1980, 7: 17-27.
3. Brown AS, Hoelzer DJ, Piercy SA. Skin necrosis from extravasation of intravenous fluids in children. Plast Reconstr Surg 1979, 64: 1451-50.
4. Larson DL. Treatment of tissue extravasation by antitumor agents. Cancer 1982, 49: 1796-1799.
5. Rudolph R. Toxic drug ulcers. *In:* Chronic Problem Wound. Eds Rudolph R, Noe JM. Boston, Little Brown and Company, 1983, pp 95-102.
6. Yosowitz P, Ekland DA, Shaw RC, Parsons RW. Peripheral intravenous infiltration necrosis. Ann Surg 1975, 182: 553-556.
7. Yadav NS. Treatment of extravasation injuries using ultraviolet light (personal communication).
8. Gaze NR. Tissue necrosis caused by commonly used intravenous infusions. Lancet 1978, 2: 417-419.
9. Larson DL. What is the appropriate treatment of tissue extravasation by antitumor agents? Plast Reconstr Surg 1985, 75: 397-405.

10. Fuller B, Lind M, Bonami P. Mitomycin-C extravasation exacerbated by sunlight. Ann Int Med 1981, 94: 542.

11. Argenta LC, Manders EK. Mitomycin-C extravasation injuries. Cancer 1983, 51: 1080-1082.

12. Rudolph R, Stein RS, Pattillo R. Skin ulcers due to adriamycin. Cancer 1976, 38: 1087-1094.

13. Bowers DG Jr, Lynch JB. Adriamycin extravasation. Plast Reconstr Surg 1978, 61: 86-92.

14. Rudolph R. Ulcers of the hand and wrist caused by doxorubicin hydrochloride. Orthopedic Rev 1978, 7: 93-97.

15. Rudolph R. Inhibition of myofibroblasts by skin grafts. Plast Reconstr Surg 1979, 63: 473-480.

16. Cohen FJ, Manganaor J, Bezozo RC. Identification of involved tissue during surgical treatment of doxorubicin-induced extravasation necrosis. J Hand Surg 1983, 8: 43-45.

17. Petro JA, Garham WP, Miller SH, *et al.*. Experimental and clinical studies of ulcers indiced with adriamycin. Surg Forum 1979, 30: 535-537.

18. Garnick M, Israel M, Khetarpac V, *et al.* Persistence of anthracycline levels following dermal and subcutaneous Adriamycin extravasation. Proc Ann Mect Am Assoc Cancer Res 1981, 22: 173.

19. Reilly JJ, Niefeld JP, Rosenberg SA. Clinical course and management of accidental Adriamycin extravasation. Cancer 1977, 40: 2053-2056.

20. Raaf JH. Vascular access for chemotherapy. *In:* Angio Access. Eds Waltzer WC, Rapaport FT, Orlando FL, Grune and Stratten, 1984, pp 161-192.