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Current Thoughts on Extravasation Injuries

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Modern nonsurgical therapeutics revolves around the administration of bioactive agents, commonly using the intravenous route. It is not surprising then that extravasation, or leakage, of these agents out of the vein into the adjacent tissues is a fairly frequent occurrence. The exact incidence of extravasation has been varyingly reported in ranges from 0.01 to 6 per cent[7, 13, 16, 18] in patients receiving chemotherapeutic agents, whereas 11 per cent of children receiving intravenous infusions in a children's center were noted to suffer extravasations at some point in their management.[4] This wide range in incidence is undoubtedly related to differences in patient populations; variations in techniques for placement, maintenance, and monitoring of intravenous infusions; and subjectivity in reporting of extravasation occurrences. Suffice to say that extravasations are quite frequent although serious sequelae from such incidents are not. Nevertheless, skin and soft tissue ulceration resulting from intravenous extravasation is seen with increasing frequency in plastic surgery referral practices.

Rudolph and Larson[20] have suggested a useful general classification of types of extravasation injury based on a division of the extravasated substance into agents that bind to tissue nucleic acids and those that do not. The former fix to tissues and tend to have a prolonged noxious effect, whereas the latter generally have a more brief, although possibly profound, effect and are then metabolized or removed from the immediate area and excreted. The term *vesicant* is commonly applied to those agents that bind to nucleic acids and result in ulceration, but vesicant in its strictest sense applies to any agent that can cause blistering and therefore can be used with both the aforementioned general categories. The deoxyribonucleic acid (DNA) binding agents are, as a group, those with antineoplastic characteristics and these will be discussed separately.

EXTRAVASATION OF NONANTINEOPLASTIC AGENTS

Almost any chemotherapeutic agent given intravenously can, in susceptible patients or specific anatomic situations, cause local irritation and even lead to frank ulceration. The degree of injury is often concentration dependent, and the fact that the overwhelming majority of such extravasations do not lead to ulceration may be a clue to the fact that the active agents given intravenously are usually in quite dilute form. The mechanism of cellular injury with extravasation of these substances is most likely related to some of their physicochemical characteristics such as osmolarity, pH, pKa, and molecular weight.

Hyperalimentation solutions, fat emulsions, and 10 per cent glucose have been seen to cause skin necrosis when extravasated[9, 11, 32] as have radiographic contrast materials,[21] urea, and sodium bicarbonate.[10] Potassium chloride[7, 12] and calcium salts, particularly calcium chloride, have long been known to be prone to causing skin ulceration when extravasated,[14, 17] but calcium gluconate and calcium gluceptate can also cause similar problems, particularly in infants. The difference in skin and soft tissue toxicity between the various calcium salts seems to parallel their different degrees of dissociability (pKa)[14] with the toxic effect directly tied to the amount of free calcium ion present.

Vasoactive drugs such as norepinephrine have also long been recognized as having potential for causing severe injury when extravasated into soft tissues. Phentolamine has been recommended for local elysis to reverse the acute vasoconstrictive effects of extravasated norepinephrine,[31] and has also seemed effective in local treatment of dopamine extravasations. Various antibiotics including chloramphenicol, cephalothin, gentamycin, oxacillin, and nafcillin have also been implicated.[1, 33]

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Clinical Findings and Course

The clinical presentations of almost all extravasations are quite similar: Patients complain of pain at the intravenous site, usually burning and stinging in character. This pain may be modest but often is quite severe. Examination reveals localized swelling, redness, and tenderness. Local induration may or may not be present, but when induration persists for more than 24 hours, it has been, in my experience, the most reliable sign of eventual ulceration.

Ulceration, when it does occur, is usually not evident until 1 or 2 weeks after injury and presents with a dry, black eschar initially. This, in due time, sloughs to reveal the underlying ulcer cavity.

Treatment

With the possible exception of local infiltration of phentolamine as antidotal therapy for agents with alpha vasoconstricting properties, treatment of nononcoplastic agent extravasations has mostly been nonspecific. The intravenous line should be immediately discontinued, and the injured extremity should be splinted and elevated. Topical thermal packs or cold packs have not been shown to significantly alter the clinical course, although local warmth with subsequent local vasodilation may hasten the resolution of the acute phase of swelling and pain. If local blistering occurs, indicative of at least a partial-thickness skin injury, we recommend application of silver sulfadiazine with gentle local cleansing to prevent infectious superimposition. Similar topical management is used for frank full-thickness necrosis with eschar. Smaller lesions will slough and heal spontaneously through wound contraction and epithelialization. Larger ulcers will require excision and grafting. There is some suggestion that ulcers caused by calcium salt extravasation do better if débridement is carried out first and grafting accomplished as a delayed primary type closure with a several-day-interval in between.[14]

EXTRAVASATION OF ANTINEOPLASTIC AGENTS

Recent excellent reviews with extensive bibliographies of this topic have been presented by several authors.[7, 33, 35, 36] Readers interested in pursuing the subject and references in depth will do well to direct themselves to these works. I will try to present a more brief and somewhat personally biased view of the subject.

A number of commonly used cytotoxic agents have been listed as having potential for local injury with extravasation, but doxorubicin is the agent most commonly reported to result in tissue necrosis.[8, 13, 16] Table 1 lists common cytotoxic agents according to their anticipated effects when extravasated.[7] It is fair to say that some of the allegedly more benign drugs in the first two categories in Table 1 may have also caused ulceration in isolated instances, which have not been reported, and even the most locally active drugs in group III do not always cause irreversible damage. The extent of damage seems related, as would be expected, to total dose delivered, concentration of drug per gram of tissue exposed, and resistance of the particular local tissues and host in general.

Table 1. *Cytotoxic Agents and Their Extravasation Effects**

I.	Cytotoxic agents that do not usually cause local problems after extravasation
	Asparaginase
	Bleomycin sulfate
	Cytarabine
	Etoposide
	Methotrexate
	Thioguanine
II.	Cytotoxic agents that cause local irritation after extravasation
	Carmustine
	Cyclophosphamide
	Dacarbazine (DTIC)
	Streptozocin
	Teniposide
	Thiotepa
III.	Cytotoxic drugs likely to cause ulceration after extravasation
	Actinomycin D
	Cisplatin
	Daunorubicin hydrochloride
	Doxorubicin hydrochloride
	Fluorouracil
	Mithramycin
	Mitomycin C
	Mitoxantrone hydrochloride
	Mustine hydrochloride
	Nitrogen mustard
	Vinblastine sulfate
	Vincristine sulfate
	Vindesine sulfate

*Adapted from Cox K, Stuart Harris R, Abdini G, et al: The management of toxic drug extravasation: Guidelines drawn up for the Clinical Oncology Society of Australia. Med J Aust 148:185, 1988; with permission.

Clinical Findings and Course

Symptoms and signs in the area of extravasation usually occur immediately and most notably include pain, swelling, and erythema. Confusion can occur with the so-called flare phenomenon, which occurs in about 3 per cent of cases[30, 31] and has been documented in patients receiving infusions of doxorubicin, daunorubicin, and mechlorethamine.[15] Flare consists of an erythematous streak along the course of the peripheral vein receiving the infusion and does not imply extravasation or any of its dire sequelae. It can have associated local urticaria or pruritus and is transient, usually disappearing within 30 minutes.

Depending upon the extent of extravasation tissue damage, the local swelling and erythema may subside

within 24 hours. The onset of blistering, firm induration, and persistent pain usually indicates a more severe extravasation injury. Early, firm induration, with or without tenderness, has, in my experience, been the most reliable parameter in predicting the probability of eventual ulceration.

Ulceration, when it occurs, is typified by a necrotic, yellowish, fibrotic base with a surrounding rim of persistent erythema. There is a conspicuous lack of granulation tissue formation and a paucity of the peripheral epithelial ingrowth that characterizes normal wound healing.[36] This particular pattern is most clearly outlined for doxorubicin ulcers but is also seen, to varying degrees and with modest variations, in ulcers caused by the other vesicants. Ulceration persists and may even be progressive for many months. Over prolonged periods of time smaller ulcers may gradually heal, but larger ulcers inevitably require surgical intervention to obtain a closed wound.

Pathogenesis

The pathogenesis of antineoplastic agent–induced extravasation ulcers is best understood for doxorubicin ulcers and this, therefore, serves as a model for our current insights.

Histologic studies of doxorubicin-induced ulcers in rabbits[22] showed a necrotizing lesion with a lack of inflammatory response, and a primary vascular or vasospastic mechanism was suggested. Studies of similar experimental skin lesions in a rat model showed normal myofibroblast ultrastructure, suggesting that the observed lack of wound contraction might be owing to cellular dysfunction from nuclear function alterations related to DNA base binding.[28] Prolonged tissue retention of doxorubicin is also well known, with retention of drug within tissues demonstrated at 5 months postinjury.[9] Silvestrini[28] showed that doxorubicin complexes with intracellular DNA, and it is postulated that a major reason for chronicity in doxorubicin ulcers is the liberation of these doxorubicin-DNA complexes from dead cells. These complexes are then taken up by viable cells (endocytosis), thereby recycling the necrosing process.[28] This process may also explain the frequent observation of doxorubicin ulcers slowly, progressively enlarging over long periods of time.

Treatment

Management of extravasation injuries may be conveniently divided into subtopics of treatment of acute extravasations and accomplished ulceration, with subdivisions of the proposed medical (pharmacologic) and surgical approaches for each.

Acute Extravasation Injuries

A wide variety of pharmacologic measures to alleviate acute symptomatology and prevent eventual ulceration have been proposed. These have been nicely reviewed by Montrose[29] and are summarized in Table 2.

Suffice it to say that with the possible exception of the use of sodium thiosulfate in nitrogen mustard extravasations, no convincing evidence, experimental or clinical, has been brought forth to allow one to strongly advocate the use of any of these agents. Clinical reports have been anecdotal or have involved small series at best. Animal experiments, particularly those involving doxorubicin, have been plagued with difficulties in developing a truly representative experimental model. Subcutaneous injections of doxorubicin were found to yield wide variability in resulting ulcers, so that the majority of worthwhile experimental evidence has been derived from the Rudolph intradermal injection model.[37] This model produced a doxorubicin-induced ulcer of reproducible size that was also dose-related, allowing accurate characterization of ultrastructural and wound healing characteristics as well as cellular characterization. Unfortunately, the extravasation injury seen clinically occurs primarily in the subcutaneous space with secondary effects both on overlying structures (skin) and deeper structures (fascia, tendons, nerves), which has limited the clinical applicability of pharmacologic or antidotal measures studied in this particular model. It would seem fair to state that at this time, despite valuable contributions by a large number of investigators, no scientifically valid, truly reproducible, clinically useful extravasation antidote for vesicant extravasation injury has been found.

Thermal manipulation in the form of local cooling has been shown to reduce ulceration caused by intradermal doxorubicin in the mouse.[9] Larson[17] applied local cooling in a large clinical series and claimed salutary results. Unfortunately, the hypothermia applied was, in my opinion, poorly controlled and standardized in terms of exact degrees of thermal cooling and the lack of any evaluation of subcutaneous temperatures achieved. This study, like most others, therefore remains somewhat anecdotal albeit slightly more convincing owing to the large numbers of patients involved.

In actuality, any currently conceivable study of extravasation antidotes in humans will remain less than scientifically ideal because of the impossibility of establishing adequate controls. What is needed is a large number of "volunteers" who would permit creation of control lesions by subcutaneous injection of standardized doses of selected vesicants. This is, of course, impossible in any humane society and we are, therefore, faced with studies involving the use of proposed antidotal or ameliorative measures without prior knowledge of exact amounts of drug accidentally extravasated. In the overwhelming majority of clinical situations, this can at best be only roughly estimated. It is quite possible, therefore, that many purported "successful" antidotal treatments may have occurred in individuals who had received too small an extravasation dose to cause skin ulceration in the first place.

Table 2. *Proposed Local Antidotes for Extravasation of Chemotherapeutic Agents*

ANTIDOTE*	PROPOSED MECHANISM	CHEMOTHERAPEUTIC AGENT	COMMENTS
Cimetidine	H_2 antihistamine	Doxorubicin	Negative result in mouse model
Corticosteroid	Anti-inflammatory	Doxorubicin and others	No inflammatory activity histologically present in extravasation
			Positive result for doxorubin in low doses only in mouse model. Positive anecdotal reports.
			Tissue toxic in large doses. Ulceration increased in Vinca extravasation mouse model
Diphenhydramine	H_1 antihistamine	Doxorubicin	Negative result in mouse model
Dimethyl sulfoxide	Free radical scavenger	Doxorubicin	Positive anecdotal reports. Positive result in rat and pig models. Negative result in mouse model
Heparin	Binding with doxorubicin	Doxorubicin	Negative result in mouse model
Hyaluronidase	Promotion of dispersion and absorption	Vinca alkaloids	Positive result in mouse model. Nontissue toxic
Lidocaine	Cell membrane stabilizer	Doxorubicin	Negative result in mouse model
Isoproterenol	Beta adrenergic agent	Doxorubicin	Early results positive in mouse model
N-Acetylcysteine	Free radical scavenger	Doxorubicin	Increased ulceration in mouse model
Propranolol	Beta adrenergic agent	Doxorubicin	Early results positive in mouse model
Sodium bicarbonate	Chemical inactivation	Doxorubicin	Inherently tissue toxic. Positive result in rat model.
			Negative result in mouse model.
			Increased ulceration in mouse model.
Sodium thiosulfate	Alternate substrate	Nitrogen mustard	Systemically anecdotal. Positive anecdotal report

*Extensive references to each proposed antidote may be found in the original article.[24]
From Montrose PA: Extravasation management. Semin Oncol Nurs 3:128, 1987; with permission.

Larson[17] indicates that 11 per cent of 119 patients in his hospital with clinical signs and symptoms of extravasation progressed on to ulceration, whereas 89 per cent resolved (without ulceration) with conservative management. If these figures could be taken to be a reasonably reliable ulceration incidence figure, then antidotal therapy in a similarly large series might be reasonably evaluated using this as an external, literature control.

Local Clysis with Saline/Hyaluronidase

In the early 1970s, my colleagues and I became interested in extravasation injuries caused by solutions containing calcium salts.[18] This led to a series of laboratory experiments in which a standardized control lesion was developed, and the interesting observation was made that the occurrence or nonoccurrence of skin ulceration with extravasation was dependent on the concentration of free calcium ion (Ca^{++}) in the extravasate rather than on total Ca^{++} delivered. Simply put, more dilute solutions did less damage.

Since pre extravasation dilution was beneficial, we then wondered if dilution of the injurious agent *after* extravasation might also be beneficial. A number of agents were tried, using subcutaneous clysis of each. Included among these was a mixture of normal saline and hyaluronidase. This mixture was selected as one of the trial therapeutic agents based upon a Russian language report indicating its efficiency in a single clinical case.[24] This particular agent turned out to be the most successful one in preventing skin necrosis from $CaCl_2$ extravasation experimentally.

Soon afterward, we were asked to see a patient who had suffered an acute doxorubicin extravasation. For lack of availability of any clearly defined effective antidote, we empirically clysed the area of extravasation with a saline/hyaluronidase solution and were gratified to observe that no skin necrosis occurred. Encouraged by this first case, we began encouraging our oncologic colleagues to notify me immediately regarding any patient with clinical symptoms and signs of extravasation of any agent known to have the potential for causing skin ulceration.*

At the same time, my colleagues and I began a series of experiments with vesicants to try and duplicate our previous successful laboratory demonstration of the efficacy of this treatment, using an experimental model and routine similar to the one that we had used in calcium injuries.

As a number of investigators have noted since, this was not a simple task. Doxorubicin, when injected subcutaneously in rats, produced skin ulcera-

*The author is grateful to his oncologic colleagues at Kessler USAF Hospital, University of Mississippi Medical Center, and Allegheny General Hospital for generously allowing him to participate in the care of their patients with extravasation injuries.

tions of widely varying sizes and severity, such that no statistical reproducibility was possible. Similar problems in establishing a control lesion were encountered with mice, pigs, guinea pigs, dogs, and rabbits. After several years of trying, we finally settled upon a model in which doxorubicin was injected subcutaneously in the distal extremity of rabbits rather than under the loose skin of the trunk. This at last gave a lesion of reasonable reproducibility against which various elysis agents could be tested.

Test agents included saline, hyaluronidase alone, steroids, and saline/hyaluronidase (150 units per 1000 cc saline). The latter was clearly the most effective and gave significant improvement in terms of lessening skin necrosis up to 60 minutes after the extravasation.

Over the past 12 years, we have continued to utilize this elysis approach with any patient referred to us with clinical signs and symptoms of vesicant extravasation. We have stayed with a protocol in which patients are only treated if seen within 1 hour of the *acute* extravasation, and patients who were known to have been receiving agents with a strong propensity for causing skin ulceration.

We have now treated 148 patients with this approach. Approximately 80 per cent of these suffered doxorubicin extravasation, with the remainder being injured with a variety of other antineoplastic agents. Clysis volume varied with the anatomic area involved, with clysis being carried out over a wide area until the overlying skin was tense, but not so tight that blanching occurred. Volumes ranged from 12 to 38 cc. The extremity (all injuries were in the upper extremity) was then elevated on pillows and observed. No other treatment modalities were applied. All patients were followed personally by the author.

None of the patients suffered full-thickness skin loss or permanent loss of motion of any joint. Many had subcutaneous induration persisting many weeks, some had transient blistering. None required débridement or skin grafting.

It is difficult to firmly claim this series of patients as an unqualified success since, as stated earlier, it is hard to know if any of them would have suffered skin ulceration in the first place, as accurate quantification of the extravasated dose is impossible. It is probable, however, based on Larson's incidence statistics,[17] that approximately 16 patients might have been expected to ulcerate. Since none did, we feel that this approach appears to have merit, and is worthy of further trial in additional centers. Parenthetically, no complications attributable to the saline/hyaluronidase clysis itself were seen.

Surgical Management of Extravasation

Immediate excision of extravasation sites was advocated by some in the past.[4] The hypothesis was that the extravasation injury could be analogous to a snake envenomation, in which it has been suggested that one can "cut out the venom," thereby minimizing soft tissue damage. As already noted, however, the majority of patients with clinical pictures consistent with acute extravasation do not progress to frank skin necrosis. The immediate excision approach has not, therefore, been widely accepted, since undoubtedly many patients would undergo unnecessary surgery.

The most widely accepted current indications for surgical management would seem to be clearcut full-thickness skin necrosis with or without frank ulceration, or intractable pain.[17]

If surgical excision is embarked upon, it should include *all* residual doxorubicin as well as the ulcerated and damaged tissue. In practicality, this means the ulcer and the ever-present surrounding rim of erythema and induration. The real problem is the underlying tissues, since these often are the extensor tendons when the injury is on the dorsum of the hand.

Since the extravasation occurs into the subcutaneous tissues, it is reasonable to assume that not only is the overlying skin secondarily involved, but also underlying contiguous structures such as fascia, tendon, nerve, and muscle. Hesitancy to débride questionable but functionally important structures in the ulcer bed may have led to some of the lack of success with immediate skin grafting noted in several centers. Use of the fluorescent characteristics of doxorubicin intraoperatively[6] has been suggested as an aid to positive identification of doxorubicin-containing tissues requiring excision. We have preferred Larson's approach using clinical appearance as a guide to excision, but delaying skin grafting to assure the adequacy of the remaining graft recipient bed.[17]

More complex coverage techniques, such as groin or trunk flaps and free flaps would seem unnecessarily complex, particularly in this patient population, many of whom are quite ill and who have limited prognoses. It has been my observation that even when such complex modalities are employed with the idea that eventual hand function will be improved, this is not the case. Patients suffering extravasation ulcers on the dorsum of the hand or distal forearm seem to end up with extension contractures regardless of how wound closure is achieved. The limitation of motion seems generally to be in achieving metacarpophalangeal flexion, with proximal interphalangeal and distal interphalangeal joint motion relatively preserved.

In our animal experiments utilizing experimental extravasations over distal extremities in rabbits, my colleagues and I consistently noted that not only the overlying skin but also the underlying tendons showed evidence of injury and fibrosis from this "subcutaneous burn." It may not, therefore, be surprising that patients with extravasation injuries severe enough to cause skin ulceration also seem to incur permanent decreases in extensor motion regardless of coverage techniques used (this is much less marked in volar and proximal forearm injuries). For these reasons, débridement and delayed skin grafting remain our preference.

Nonsurgical Management of Ulcerated Lesions

A number of years ago, we began a trial of treating patients with accomplished full-thickness skin ulceration following extravasation *without* resorting to surgical intervention. Rather, these patients were all managed as outpatients with twice daily applications of silver sulfadiazine to the injured areas, with a soft gauze wrap over. Careful cleansing of skin and ulcer was performed at each dressing change. Wound care was usually done by the patient with occasional assistance from family members.

We were pleased with the overall comfort and well-being of the patients so tested, but were also mindful of the experiences of others who generally found such wounds to be intolerably painful and prone to complications in their patient populations. We, therefore, initiated a study of 84 patients, the first 40 of whom were evaluated by personal interview or retrospective chart evaluation (for those who had died). The remaining 44 patients were followed prospectively and some are still being followed. Minimum follow-up for those included is 8 months.

Since the major reasons for espousing the need for wound coverage have been pain and potential complications in these debilitated and frequently immunocompromised patients, we thought the best evaluation might be to seek the answers to several questions:

1. Did the patient require analgesia owing to pain from the extravasation ulcer other than during the early acute phase (that is, 1 week)?
2. Did the necessity for dressing changes every 12 hours cause difficulties for the patient?
3. Did the presence of the open wound cause any major alteration in the patient's normal activities of daily living? (Note that many of these patients were limited in their activities anyway by the severity of their underlying disease.)
4. Did the patient ever suffer invasive sepsis as a result of this particular wound?
5. Did any planned adjuvant treatments such as chemotherapy, immunotherapy, or radiotherapy have to be curtailed because of the persistent ulcer?

All of the listed situations might be considered reasonable indications for surgical closure of the extravasation wound. Interestingly, *none* of the 84 patients incurred any of the potential problems enumerated. Balanced against these potential problems (which were not found in this patient population) must be the additional hospitalization time, possible morbidities and complications, and pain and separation from family and loved ones, which this population with already limited prognoses must bear if surgery is embarked upon.

We do not feel that this conservative approach is necessarily the right one for all patients with extravasation ulcers. Rather, our success with this nonsurgical treatment in a large group of patients means that the physician caring for these unfortunate people has one additional potential regimen to factor into the final decision as to what approach to use in managing extravasation injuries. This nonsurgical regimen would, however, seem to be quite reasonable for selected situations.

CONCLUSIONS

Extravasation injuries will continue to be a problem despite excellent suggestions for minimizing their occurrence.[1,23,25] A number of acute "antidotal" approaches have been suggested. The saline/hyaluronidase regimen suggested herein seems at least as effective, if not more so, than any previous agent and is recommended.

Accomplished ulcers are best managed by the technique of thorough excision and delayed skin grafting. Few indications exist for complex closure with distant flaps. Selected patients will do quite well with nonsurgical management.

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