



2007

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David J. Reeves

Butler University, [dreeves@butler.edu](mailto:dreeves@butler.edu)

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### Recommended Citation

Reeves, David J., "Management of Anthracycline Extravasation Injuries" (2007). *Scholarship and Professional Work – COPHS*. 203.

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# Management of Anthracycline Extravasation Injuries

David Reeves

## Abstract

**OBJECTIVE:** To review the evidence for the management of anthracycline extravasation and determine the optimal treatment of such injuries.

**DATA SOURCES:** A search of MEDLINE (1966–February 2007) and *International Pharmaceutical Abstracts* (1970–February 2007) was performed using the search terms anthracyclines and extravasation.

**DATA SYNTHESIS:** Extravasation of anthracyclines can have devastating effects. After infiltration of these drugs into the interstitial tissue, damage may range from mild erythema and pain to severe tissue necrosis. Many agents have been studied in the management of these injuries; however, few have demonstrated efficacy and treatment remains controversial. Nonpharmacologic modalities shown to limit extravasation injuries include local tissue cooling and elevation of the affected area. Corticosteroids, sodium bicarbonate, hyaluronidase, hyperbaric oxygen, heparin fractions,  $\alpha$ -tocopherol, N-acetylcysteine, and granulocyte macrophage-colony stimulating factor have all either been shown to be ineffective or have limited data supporting their use. Topical dimethyl sulfoxide (DMSO) has been shown in prospective studies to limit the course of extravasation injuries. Dexrazoxane has been shown in animal models and case reports to be useful in the management of anthracycline extravasation. Two recent prospective clinical trials examining intravenous dexrazoxane 1000 mg/m<sup>2</sup> within 6 hours of extravasation, 1000 mg/m<sup>2</sup> 24 hours after extravasation, and 500 mg/m<sup>2</sup> 48 hours after extravasation injuries add to the data supporting the use of this agent in such injuries. Of the 54 patients enrolled, surgery-requiring necrosis was avoided in 98.2%.

**CONCLUSIONS:** The optimal treatment of anthracycline extravasation includes local tissue cooling, elevation of the afflicted extremity, dexrazoxane administration, and possibly topical DMSO. Many other drugs have been investigated; however, due to a lack of data, they cannot be recommended for the management of anthracycline extravasation.

## **Request**

What is the optimal treatment for anthracycline extravasation?

## **Response**

### **BACKGROUND**

Extravasation is a devastating complication that can develop when a drug infiltrates the interstitial tissue surrounding the blood vessel. It can occur with any intravenously administered drug; however, damage caused by some chemotherapeutic agents is particularly serious. Injury due to extravasation has been reported to be responsible for 0.5–6% of adverse effects related to chemotherapy administration.<sup>1</sup> Those particularly harmful when extravasated include the anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), and treatment of such a complication due to these agents remains controversial.

The severity of tissue damage due to anthracycline extravasation is proportional to the amount and concentration of drug that has infiltrated the interstitial tissue.<sup>2,3</sup> The extent of damage can range from mild erythema, edema, and pain to severe tissue necrosis and ulceration involving underlying structures such as the extensor tendons of the hand. Ulceration may not present for weeks, which is consistent with the mechanism of tissue injury caused by anthracyclines. Once these agents infiltrate the tissue, they complex with DNA as an extension of their antitumor mechanism of action and cause cell death. After the dying cells lyse, the anthracyclines are released and are able to interact with additional cells, leading to a vicious cycle of tissue damage.<sup>1–3</sup> Doxorubicin has been shown to be present in the area of extravasation for up to 5 months after the incident.<sup>4</sup> This prolonged retention leads to continuing damage and prolongs healing time.

Use of an antidote for such injuries would be ideal; however, evidence supporting any one method of managing anthracycline extravasation is limited. This lack of evidence is due partly to the rarity of occurrences, as well as the complicated, urgent nature of the injury, which makes it difficult to investigate in large, prospective, randomized studies. Unlike anthracycline-induced cardiomyopathy, literature addressing anthracycline extravasation management is limited to animal studies, case reports, and small human studies. Some of the therapeutic modalities investigated for the management of anthracycline extravasation include tissue cooling and elevation of the affected area, surgical debridement and reconstruction, injected and topical cortico-steroids, sodium bicarbonate, hyaluronidase, hyperbaric oxygen, heparin fractions,  $\alpha$ -tocopherol, N-acetylcysteine, granulocyte macrophage-colony stimulating factor (GM-CSF), dimethyl sulfoxide (DMSO), and dexrazoxane. The majority of human data in anthracycline extravasation includes the use of DMSO and dexrazoxane (Table 1).<sup>5–13</sup>

### **LITERATURE REVIEW**

A search of MEDLINE (1966–February 2007) and *International Pharmaceutical Abstracts* (1970–February 2007) was performed using the search terms anthracyclines and extravasation. Review articles, clinical trials, animal studies, and case reports were identified, and references of

these articles were reviewed for additional reports. Articles most pertinent to the treatment of anthracycline extravasation are reviewed here.

Reference	Design	Pts. (N)	Drug	Treatment	Results
Olver (1988) <sup>5</sup>	prospective	20	doxorubicin (n = 18) daunorubicin (n = 2)	topical DMSO 99% every 6 h for 14 days	no pt. developed ulcerations or required surgery
Bertelli (1995) <sup>6</sup>	prospective	144	doxorubicin, epirubicin, mitomycin (n = 68) <sup>a</sup>	topical DMSO 99% every 8 h for 1 wk and local cooling for 60 min every 8 h for 3 days	58.8% had complete resolution of symptoms at 1 wk 29.3% of pts. continued DMSO up to 6 wk until resolution of pain and erythema
Ludwig (1987) <sup>7</sup>	prospective	8	anthracycline (n = 7) mitomycin (n = 1)	topical DMSO 90% and 10% $\alpha$ -tocopherol every 12 h for 48 h	no pt. developed ulceration
Bos (2001) <sup>8</sup>	case report	1	epirubicin	dexrazoxane 1000 mg iv 12 h after extravasation, topical DMSO for 20 min, ice for 12 h, hydrocortisone for 3 wk	all functions of pt.'s wrists completely restored
Jensen (2003) <sup>9</sup>	case report	1	epirubicin	dexrazoxane 1000 mg/m <sup>2</sup> iv 2 h after extravasation, 1000 mg/m <sup>2</sup> on day 2, 500 mg/m <sup>2</sup> on day 3; application of ice	pain and erythema subsided at 24 h after extravasation
El-Saghir (2004) <sup>10</sup>	case report	1	doxorubicin	dexrazoxane 1500 mg iv 1 h after extravasation, 1500 mg at 5 h, 750 mg at 24 h; DMSO every 6 h for 3 doses	pain relieved after first dose; 3 mo later, the pt. developed an ulcer at the site and required surgical debridement
Langer (2000) <sup>11</sup>	case report	2	epirubicin (n = 1) doxorubicin (n = 1)	dexrazoxane 1000 mg/m <sup>2</sup> iv within 5 h of extravasation, 1000 mg/m <sup>2</sup> on day 2, 500 mg/m <sup>2</sup> on day 3	neither pt. had sequelae at 3 mo
Frost (2006) <sup>12</sup>	case report	2	doxorubicin	dexrazoxane 1500 mg iv on days 1 and 2, 750 mg on day 3; DMSO for 5 days	no necrosis occurred in either pt.
Mouridsen (2007) <sup>13</sup>	prospective	53	epirubicin doxorubicin daunorubicin	dexrazoxane 1000 mg/m <sup>2</sup> iv within 6 h of extravasation, 1000 mg/m <sup>2</sup> 24 h after extravasation, 500 mg/m <sup>2</sup> 48 h after extravasation	1 pt. (1.8%) required surgical debridement; 71% continued scheduled chemotherapy

DMSO = dimethyl sulfoxide.  
<sup>a</sup>The remaining 76 subjects received mitoxantrone, cisplatin, carboplatin, ifosfamide, or fluorouracil.

To prevent anthracycline extravasation, drug administration through a central line, when possible, and ensuring good blood return prior to administration are of utmost importance. Moreover, the use of liposomal doxorubicin has been shown to cause only mild extravasation reactions. In a report of 8 extravasations of liposomal doxorubicin, patients developed transient, mild irritation at the infusion site that resolved after removal of the catheter, elevation of the extremity, and application of ice.<sup>14</sup> Nevertheless, the anthracycline infusion should be stopped at the first sign of extravasation. Cooling the site has been studied and is advocated in the product labeling of idarubicin<sup>15</sup> and doxorubicin.<sup>16</sup> In a series of 50 patients treated with intermittent ice for 3 days after extravasation of an antitumor agent, only 12 (24%) required surgical intervention.<sup>17</sup> Additionally, product labeling recommends elevation of the involved extremity.

Pharmacologic approaches to treatment of extravasation have demonstrated varying response rates; many have fallen out of favor. Sodium bicarbonate administered locally to increase tissue pH and therefore decrease pH-dependent interactions of anthracyclines with cell components has been shown to be of no benefit. In fact, local administration of sodium bicarbonate itself is associated with tissue damage.<sup>1,2</sup> Likewise, the use of glucocorticoids have fallen out of favor due to the relative absence of inflammatory mediators in the afflicted area.<sup>1-3</sup>

Additional agents have been studied; however, many have limited data supporting their use. Hyaluronidase breaks down hyaluronic acid, allowing increased absorption of anthracyclines.<sup>18</sup>

Moreover, heparin fractions are believed to have beneficial effects in anthracycline extravasation by binding anthracycline, inhibiting coagulation, and promoting the formation of new vasculature.<sup>19</sup> In rat models, those receiving both subcutaneous hyaluronidase and heparin fractions had significantly smaller ulcers compared with controls.<sup>18,19</sup> Hyperbaric oxygen has also been studied in the management of anthracycline extravasation. Conflicting results from 2 animal studies (1 showing potentiation of cytotoxicity; 1 showing beneficial effects) limit the use of this treatment modality.<sup>4</sup> N-acetylcysteine has been shown to be of no benefit in treating anthracycline extravasations.<sup>1</sup> GM-CSF has been shown to accelerate wound healing, promote cellular adhesion, and cause fibroblasts to have a more differentiated state. However, few cases describing the successful use of GM-CSF have been reported.<sup>10</sup> Due to a lack of clinical trial data, use of these agents cannot be recommended.

Successful outcomes have been noted with the use of topical DMSO. Case reports and prospective studies demonstrate that this agent can limit the course of the tissue injury caused by anthracycline extravasation.<sup>5-7,20-22</sup> In these reports, use of a 90–99% topical DMSO solution was described. For the treatment of anthracycline extravasation, DMSO is believed to work by acting as a free radical scavenger and by increasing systemic absorption of the extravasated drug.<sup>1</sup> In an early animal study (mouse model) evaluating the combination of DMSO and vitamin E (tocopheryl salts) for the treatment of doxorubicin extravasation, investigators found that DMSO plus vitamin E did not reduce ulceration.<sup>21</sup> Reports<sup>23,24</sup> in other animals have been favorable; it is not understood why there was a lack of response in this mouse model.<sup>21</sup>

A prospective study was conducted in patients with either doxorubicin or daunorubicin extravasation.<sup>5</sup> DMSO was applied topically and allowed to air dry. Median time to DMSO application after extravasation was 25 minutes, and none of the patients developed ulcerations or required surgery. Severe blistering did occur in one patient who had DMSO applied under a bandage. In a similar prospective study of 144 patients who experienced extravasation with doxorubicin, epirubicin, mitomycin, mitoxantrone, cisplatin, carboplatin, ifosfamide, or fluorouracil, the effect of DMSO was investigated.<sup>6</sup> Forty of the 68 patients who received doxorubicin, epirubicin, or mitomycin had complete resolution of symptoms by the end of one week. Mild local burning was associated with DMSO application in this study. In another prospective study, the effects of DMSO in combination with  $\alpha$ -tocopherol were investigated for the treatment of extravasation after administration of an anthracycline or mitomycin.<sup>7</sup> None of the patients developed ulceration, and the only adverse effects noted were local skin irritation and blisters in 2 patients. Based on the results of these studies, some clinicians recommend the use of DMSO in conjunction with immediate cessation of anthracycline infusion and application of ice.<sup>1,2,4</sup>

Dexrazoxane has a Food and Drug Administration (FDA)—approved indication for use in reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration to women with metastatic breast cancer. In addition, recent data support its potential role in the treatment of anthracycline extravasation. After intravenous administration, dexrazoxane is metabolized intracellularly to ADR-925, which binds free iron and removes iron from the iron—doxorubicin complex, thereby preventing formation of free radicals.<sup>25</sup> Interactions between

anthracyclines and topoisomerase are also inhibited by dexrazoxane preventing the DNA-cleaving activity of these agents.<sup>25</sup> Three animal studies have examined the use of dexrazoxane in mice.<sup>26–28</sup> In all 3 studies, injuries caused by subcutaneous anthracycline administration were reduced by intraperitoneal or intravenous dexrazoxane.

In addition to the aforementioned animal studies, dexrazoxane use for the treatment of extravasation was described in 7 patients (Table 1).<sup>8–12</sup> Three patients had extravasation with epirubicin and 4 with doxorubicin. Dosage schedules and other supportive therapies varied among the cases. Overall, injury due to extravasation was limited by administration of dexrazoxane. Three patients did not experience necrosis and 6 patients were able to avoid surgery.<sup>8,9,11,12</sup> Adverse reactions reported included pain during dexrazoxane infusion, transient increases in results of liver function tests, and leukopenia.<sup>9,11</sup>

Most recently, the results of 2 international studies were reported.<sup>13</sup> Both were European multicenter, open-label, single-arm trials. Patients (N = 17 and N = 36) were included if they had developed anthracycline (ie, epirubicin, doxorubicin, or daunorubicin) extravasation proven by fluorescence-positive tissue biopsy. The majority of patients were female, and the mean age was 55 years. Participants in both studies were allowed to receive localized cooling; topical treatment with DMSO or steroids was not allowed. All patients received intravenous dexrazoxane 1000 mg/m<sup>2</sup> within 6 hours after extravasation, 1000 mg/m<sup>2</sup> 24 hours after extravasation, and 500 mg/m<sup>2</sup> 48 hours after extravasation. The primary endpoint of both studies was prevention of surgery-requiring necrosis.

All of the patients in the first study avoided surgery; one patient in the second study required surgery. Additionally, 71% of the patients continued their scheduled chemotherapy regimen without postponement. Overall, patients experienced only mild sequelae including sensory disturbances, skin atrophy, pain, disfigurement, and limitation of movement. Toxicities with the administration of dexrazoxane were mild. In the first study, 60.8% experienced injection site reactions; after unspecified buffer changes in the second study, injection site reactions were reduced to 14%. Wound infections, nausea, and vomiting occurred in 10.0%, 18.8%, and 7.5% of the participants, respectively. Hematologic toxicities were demonstrated in this study; however, it was unclear whether these were caused by the study drug or chemotherapy. Although these studies were small, their results significantly add to existing data supporting the use of dexrazoxane in anthracycline extravasation.<sup>13</sup>

Based on animal studies, case reports, and 2 prospective Phase II/III trials, dexrazoxane is a promising agent for the treatment of anthracycline extravasation. Currently, dexrazoxane is available in the US in 250- and 500-mg vials and is approved for prophylaxis of anthracycline-induced cardiomyopathy. TopoTarget (Denmark) is seeking licensure of dexrazoxane for the treatment of anthracycline extravasation and was granted orphan drug status by the FDA in 2004. Doses used in the studies of dexrazoxane in anthracycline extravasation differ from those used in the prevention of cardiomyopathy. For the prevention of cardiomyopathy, the drug is dosed in a 10:1 ratio (eg, dexrazoxane 500 mg/m<sup>2</sup>: doxorubicin 50 mg/m<sup>2</sup>). All doses reported in humans for the treatment of anthracycline extravasation were fixed, ranging from 500 mg/m<sup>2</sup> to 1500 mg/m<sup>2</sup>.

Adverse effects associated with the use of dexrazoxane in anthracycline extravasation were mild in the 2 recently reported clinical trials and included injection site reactions, wound infections, nausea, and vomiting.<sup>13</sup> However, tissue necrosis was attributed to the use of dexrazoxane in one case report in which the patient was receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in addition to dexrazoxane for the treatment of non-Hodgkin's lymphoma.<sup>29</sup> During the dexrazoxane infusion, the patient experienced pain at the infusion site without evidence of extravasation and subsequently developed tissue necrosis necessitating recurrent skin grafts.

## Summary

Many agents have been investigated for use in anthracycline extravasation, yet results have not shown effectiveness. Tissue cooling has been shown to be moderately effective and is recommended in the product labeling of doxorubicin and idarubicin. Until recently, DMSO has shown the most promising results in anthracycline extravasation. The latest agent to be investigated, dexrazoxane, has shown efficacy in animal studies, case reports, and prospective studies. Despite the limited nature of these reports, dexrazoxane appears to be a promising agent for the treatment of anthracycline extravasation. Based on available literature, the optimal treatment of anthracycline extravasation includes a combination of ice application, elevation of the extremity, dexrazoxane administration, and possibly DMSO. Lack of evidence supporting use of the additional agents discussed here limits their use.

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