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Topical dimethylsulfoxide may prevent tissue damage from anthracycline extravasation

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Summary. The optimal management of anthracycline extravasation remains unclear. Traditional topical measures to reduce local tissue damage, including corticosteroids, sodium bicarbonate, and ice applications, have not consistently demonstrated beneficial effects. This report describes our experience with four adult patients who suffered anthracycline extravasation and were treated with a regimen of ice, local glucocorticoid injection, and dimethylsulfoxide (DMSO) 55%–99% applied topically every 2–4 h after extravasation for a minimum of 3 days. In all four cases, pain and erythema resolved within 2 days; in no case did tissue necrosis or skin ulceration occur. Topical DMSO is a safe, inexpensive agent that appears to reduce the risk of anthracycline-induced tissue damage. Further studies are needed to determine the optimal dose and schedule of DMSO application and to assess its efficacy in extravasation injuries from other vesicants.

Introduction

The anthracyclines, doxorubicin (Adriamycin, Adria Laboratories) in particular, have perhaps the widest spectrum of antineoplastic activity of any class of cancer chemotherapeutic agents [10]. However, both doxorubicin and daunorubicin can cause severe tissue necrosis and nonhealing skin ulteration when extravasated in even small amounts. The optimal treatment for accidental anthracycline extravasations remains to be defined. A variety of topical measures, including the injection of corticosteroids, sodium bicarbonate, and the application of ice, have been used immediately after extravasation in attempts to minimize tissue damage, but there is no clear-cut evidence that any of these interventions provide significant benefit [3, 9]. Because of our previous observation of a possible beneficial effect of topically applied DMSO in a patient suffering a major doxorubicin extravasation [5], we began to treat prospectively all anthracycline extravasation with a regimen including frequent topical applications of DMSO. We report that in four consecutive cases, including our initial case, skin ulceration and tissue necrosis have uniformly been prevented by a local treatment regimen including topical DMSO.

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Materials and methods

Patients. The clinical data for each of the four patients in this report are outlined in Table 1. Patient 1, who has previously been described [5], was treated with daunorubicin at Oregon Health Sciences University, whereas the other three were patients of the Martinez Veterans Administration Medical Center and received doxorubicin. In all cases, the concentration of anthracycline given was 2 mg/ml.

Case reports. Patient 2 was a 68-year-old man with metastatic prostate cancer receiving 20 mg/m^2 doxorubicin by weekly i.v. injection. During one treatment, he suffered an extravasation of approximately 2 mg doxorubicin into the volar aspect of the medial region of his forearm, producing a dime-sized area of erythema and induration that spread proximally to the antecubital space and distally to the carpal region within 10 min despite the immediate application of ice packs. He was given an i.d. injection of 8 mg dexamethasone into the extravasation site and 15 cc 99% DMSO solution was rubbed on the area. The patient was sent home with an ice bag on his forearm and instructed to apply the DMSO every 2–4 h for the next 24 h. A day later, the patient reported by telephone that the extravasation site had only a slightly pink tinge. He continued to apply DMSO every 4 h during waking hours for 2 days. On subsequent clinic follow-ups, typical examination revealed no skin ulceration or subcutaneous scarring and the patient had nor furthr local reactions to subsequent doxorubicin injection.

Patient 3 was a 62-year-old man receiving 5-fluorouracil, doxorubicin, and mitomycin-C (FAM) chemotherapy for metastatic adenocarcinoma of the stomach. An extravasation of approximately 10 mg doxorubicin occurred into the lateral aspect of his right arm proximal to the antecubital fossa. The patient complained of burning at the injection site and developed a quarter-sized lump in the area. After the withdrawal of 1 cc fluid from the i.v. line, the i.v. needle was removed; 8 mg dexamethasone was injected i.d. into the affected tissue and an ice pack was applied, and 15 cc DMSO as a 50% solution was rubbed on the site. The patient was given instructions similar to those given patient 1 when he was sent home from the clinic. The next day, repeat examination revealed slight erythema and ecchymosis. The site appeared normal 1 week later, and on subsequent clinic visits there was no evidence of ulceration or scarring.

Table 1. Patient characteristics

Patient number	Age/sex	Primary malignancy	Anthracycline given[a]	Estimated amount extravasated	Additional topical measures
1	42/M	Acute non-lymphocytic leukemia	Dauno	10 mg	Dex[b], sodium bicarbonate, ice
2	68/M	Prostatic cancer	Dox	2 mg	Dex, ice
3	62/M	Gastric cancer	Dox	10 mg	Dex, ice
4	71/M	Small-cell lung carcinoma	Dox	8 mg	Solu-Cortef, ice

[a] Anthracycline given: Dauno, daunorubicin; Dox, doxorubicin
[b] Dex, dexamethasone by local injection

Patient 4 was a 71-year-old man with small-cell carcinoma who was treated with cyclophosphamide, doxorubicin, and etoposide (CAVP). During an injection of doxorubicin, he developed acute burning and induration at the i.v. site on his forearm. Immediate local measures included the injection of Solu-Cortef, application of ice packs, and topical application of 75% DMSO. The patient was instructed to apply DMSO to the extravasation site every 4 h for at least 3 days. On subsequent clinic visits, no tissue necrosis or scarring was noted.

Results

All four patients experienced extravasation of 2–10 mg anthracycline and developed immediate signs and symptoms of erythema, induration, and burning. All patients underwent the topical application of DMSO as 50%–99% solutions every 2–4 h for a minimum of 3 days, in addition to immediate measures including the i.d. injection of dexamethasone and application of ice packs. In all cases, pain and erythema had resolved within 48 h, and in no case did skin ulceration or subcutaneous scarring develop.

Parenthetically, a fifth patient (described in our previous abstract [6]) was treated with topical DMSO for a suspected doxorubicin extravasation with no subsequent local tissue damage. On retreatment with doxorubicin, she developed recurrent episodes of transient erythematous streaking along the vein proximal to the injection sites, which resolved spontaneously. Her initial episode was therefore determined retrospectively to represent a localized hypersensitivity reaction to the drug and not a true extravasation.

Discussion

Recent reviews of the management of extravasation injuries due to cancer chemotherapy agents have stressed the lack of evidence that the local injection of agents such as sodium bicarbonate or corticosteroids reduces the incidence of tissue necrosis [3, 9]. Larson [4] has reported that the immediate application of ice packs resulted in skin ulceration in only 11% of 115 documented extravasations, suggesting that the use of cold may be beneficial in these situations. In cases where necrosis and ulceration occur despite immediate local measures, early surgical debridement should be considered [9].

Our data suggest that the addition of topical DMSO to other traditional local measures used in the treatment of anthracycline extravasation may change the natural history of these chemically induced injuries. The rationale for this approach arose from the experimental observations of Desai and Teres [2], who reported the prevention of doxorubicin-induced skin ulceration in the skin of rats and pigs by topical application of DMSO. The mechanism for this protective effect is unknown but may be related to anti-inflammatory properties of DMSO or to its ability to penetrate skin and soft tissues and serve as a carrier for many agents [7].

Our fifth patient exemplifies the phenomenon of a local hypersensitivity reaction to doxorubicin, which was initially constructed as an extravasation. A hypersensitivity reaction may be difficult to discriminate from a true extravasation but typically has distinguishing features that include an erythematous streaking of the skin overlying the vein proximal to the injection site and pruritus, both of which usually resolve spontaneously in 30 min or less [1].

During the preparation of this manuscript, a recent abstract by Olver et al. [8] reported a multi-institutional prospective trial of topical DMSO in the treatment of anthracycline extravasation. These authors report that 21 consecutive patients were treated with frequent applications of a 99% solution of DMSO for periods of up to 2 weeks; they noted no ulceration in any case. Toxicities of treatment were limited to transient burning sensations at the sites of application and a bad breath odor characteristic of DMSO. These observations support our data that DMSO has a beneficial effect in reducing anthracycline-induced soft tissue damage. In view of its low cost, ease of administration, and lack of major side effects, we feel that DMSO should be part of the immediate local treatment of accidental anthracycline extravasations. The optimal schedule and duration of DMSO applications is unclear but should probably be at least every 6 h for a minimum of 3 days. The use of DMSO in the treatment of extravasations due to other classes of cancer chemotherapeutic agents remains to be explored.

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