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Prevention of Cytotoxic Drug Induced Skin Ulcers with Dimethyl Sulfoxide (DMSO) and α-Tocopherole

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Abstract—*Accidental subcutaneous extravasation of several antineoplastic agents may provoke skin ulcerations for which there has been no simple and effective treatment. Since January* 1983 *we have treated all patients in our institution sustaining extravasation by a cytotoxic drug with a combination of DMSO and α-Tocopherole. During the first* 48 hr *after extravasation a mixture of* 10% *α-Tocopherole acetate and* 90% *DMSO was topically applied. The bandage was changed every* 12 hr. *So far eight patients with extravasation of an anthracycline or Mitomycin were treated on this protocol. No skin ulceration, functional or neurovascular impairment occured in any of these patients. The only toxic effect observed by this treatment was a minor skin irritation. The combination of DMSO and α-Tocopherole seems to prevent skin ulceration induced by anthracyclines and Mitomycin.*

INTRODUCTION

With the increasing importance of chemotherapy in the treatment of cancer, there is a greater awareness of the major systemic and local complications which may arise. The incidence of chemotherapy extravasation is difficult to discern from the literature and can only be estimated from the data reported for the most frequently used vesicant Doxorubicin. Based on the number of patients treated, Barlock [1] and Laughlin [2] reported an incidence of between 0.45 and 6.5% for Doxorubicin extravasation. Analysing the number of injections applied, an incidence of between 0.1 and 2% has been reported [3, 4]. In the period of our study we have observed at our institution five extravasations in 383 Doxorubicin injections performed, which is approx. 1%. Based on a report published by Svingen *et al.* [5] demonstrating the effectiveness of the combination of DMSO and α-Tocopherole in the prevention of Doxorubicin induced skin ulceration in an animal model, a clinical pilot study using the same combination was started.

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PATIENTS AND METHODS

From January 1983 all patients presenting at our clinic with an extravasation of Doxorubicin or Mitomycin were entered into the study. The following criteria for the evidence of drug extravasation were applied: local swelling, pain, lack of blood return and local induration. At least three of the four mentioned criteria had to be present in each patient for eligibility. An estimate of the volume of paravenously injected drug solution was made by the treating nurse. After extravasation had occurred, dressings of 90% DMSO and 10% α-Tocopherole acetate (Vitamin E) were applied to the area. Dressings were changed every 12 hr for a total treatment duration of 48 hr. The following parameters were analysed in our study: local swelling, redness, induration and ulceration. The area of extravasation was checked before treatment, after 12, 24 and 48 hr, 1 and 2 weeks and thereafter 1–2 weeks until resolution of all signs of inflammation.

RESULTS

During the study period from January 1983 to June 1985, extravasation of an anthracycline or Mitomycin had occurred in eight patients. Table 1 shows the estimated amount of extravasated drug, the drug concentration injected, localization of injection and treatment results. In all patients a local induration at the place of extravasation

Table 1. Patients with extravasation of Anthracyclines or Mitomycin

Patient No.	Drug	Amount	Concentration	Localization	Induration	Ulceration
1	Mitomycin	2 ml	0,16 mg/ml	Forearm	Yes	No
2	Doxorubicin	2–3 ml	2,0 mg/ml	Cubital	Yes	No
3	4-Deoxydoxo-rubicin	1–2 ml	0,45 mg/ml	Forearm	Yes	No
4	"	~3 ml	0,45 mg/ml	Forearm	Yes	No
5	Doxorubicin	~1 ml	2,0 mg/ml	Cubital	Yes	No
6	Doxorubicin	~1 ml	2,0 mg/ml	Forearm	Yes	No
7	Doxorubicin	1–2 ml	2,0 mg/ml	Dorsum of hand	Yes	No
8	Doxorubicin	3–5 ml	0,46 mg/ml	Forearm	Yes	No

formed, which is indirect evidence that drug extravasation had occurred, but in no patient did skin ulceration occur. There was no neuromuscular, vascular or functional impairment in any patient. The only side-effect observed was a local transient skin irritation by DMSO, consisting of erythema and rarely blisters (two patients), strictly restricted to the area covered by the dressing. The erythema always disappeared completely within 24 hr after terminating the DMSO-dressings.

DISCUSSION

The natural course of extravasation of vesicant cytotoxic drugs is difficult to discern. However, Larson [3] found that of 50 patients with extravasation of Doxorubicin (and/or Vincristine) treated with ice and elevation of the arm, 12 required surgical intervention for pain or skin necrosis. In the present pilot study eight patients with extravasation of an anthracycline or Mitomycin were treated with dressings of DMSO and α-Tocopherole. No skin ulceration occurred in any of these patients. In the preceding year from January 1982 to January 1983 three skin ulcerations due to extravasation of cytotoxic drugs (2 times Doxorubicin and once Vincristine) had occurred at our clinic.

Several antidotes mainly for Doxorubicin extravasation had been tested in animal models [6]. Svingen *et al.* [5] tested the effect of DMSO with or without α-Tocopherole on Doxorubicin induced ulcerations in rats. DMSO, but even better the combination of DMSO and 10%-Tocopherole significantly reduced the size of skin ulcers in this animal model. The activity of topically applied DMSO to reduce Doxorubicin skin ulcers has also been shown by Desai *et al.* [7] and Okano *et al.* [8] using pigs and piglets. On the other hand, Dorr and Alberts using mice found no protective role for α-Tocopherole [9]. This discrepancy of results in animals studies may partially be related to the animal model used: positive results have been obtained in pigs, piglets and rats [5, 7, 8], negative ones in mice [9].

Since we have started our study, two clinical case reports have been published demonstrating the usefulness of DMSO in preventing skin ulceration induced by Doxorubicin extravasation [10, 11].

The mechanism of Doxorubicin and Mitomycin cytotoxity is not completely understood. In both drugs reductive metabolic activation to reactive intermediates including the semiquinone free radicals seem to occur [12]. In the presence of oxygen, the semiquinone free radical undergoes oxydation–reduction cycling to form superoxide free radicals. At the same time hydrogen peroxide is formed, which may react with the semiquinone free radical to form hydroxyl radicals [13]. In the prevention of Doxorubicin or Mitomycin induced skin necrosis, α-Tocopherole may be useful as a free radical scavenging agent and DMSO as a hydroxyl radical scavenger. DMSO has the additional advantage of acting as a vehicle for α-Tocopherole and enhancing its penetration into the skin [5]. Recently, butylated hydroxy toluene (BHT), another potential free radical scavenger, has also been shown in animal models to reduce Doxorubicin induced skin ulcers [14].

Our preliminary data support the hypothesis that the combination of DMSO and α-Tocopherole can prevent skin ulcerations induced by anthracyclines and Mitomycin. Only a prospectively randomized comparison between the treatment and other conservative methods, for example application of ice [15], will allow determination of the exact activity of any specific intervention.

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