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Short communication

Prevention of tissue necrosis due to accidental extravasation of cytostatic drugs by a conservative approach

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Summary. The purpose of the present study was to evaluate comparatively the effectiveness of a conservative approach to treatment, using two therapeutic schedules (with and without sodium thiosulfate (ST), so as to minimize necrosis due to drug extravasation and to avoid the need for reconstructive surgery. The 63 patients entered into this study were seperated into two groups; these in group A were treated with hydrocortisone and dexamethasone, and these in group B received the combination plus ST. In both groups, the drugs that had extravasated included doxorubicin, epirubicin, vinblastine, mitomycin C. The healing time varied with the different drugs used and was proportional to the extent of extravasation and to the time at which therapy was begun. The mean healing time for group B, which received ST was about half that for group A, which did not. We conclude that the application of conservative measures during chemotherapy may prevent tissue necrosis due to drug extravasation and the subsequent need for reconstructive surgery. The administration of ST can help in the achievement of this goal.

Introduction

Chemotherapeutic agents for cancer treatment can cause both local and generalized side effects. One of the most troublesome local side effects associated with a high morbidity rate is tissue necrosis due to extravasation of certain chemotherapeutic drugs. Although this is not a very common event, it can further aggravate the poor quality of life of cancer patients [1, 4, 6, 12, 21].

There are different ways to approach this problem, including infiltration of the damaged tissue with hydrocortisone, hyalouronidase, or certain antidotes and early plastic surgical intervention with parallel incisions throughout the involved area [2, 3, 7, 11, 16, 18, 19]. In the presence of severe and extensive necrosis or in the case in which conservative measures have failed, plastic reconstruction of the necrotic area using skin grafts is indicated [9, 10, 13]. In a previous study [18], we found that the application of conservative measures in extravasated areas during chemotherapy may prevent tissue necrosis and subsequent reconstructive surgery.

The purpose of the present study was to apply a conservative approach and evaluate its effectiveness. On the other hand, we used two different therapeutic schedules to examine the effectiveness of an antidote (sodium thiosulfate) preventing tissue necrosis and sloughing so as to avoid the need for any kind of surgery. Substances such as dimethylsulfoxide, alpha tocopherol [14], vasopressors [15], heparin, hyalouronidase, sodium thiosulfate and bicarbonates among others [20], are well known for their applicability in the conservative management of extravasation injury.

Patients and methods

Over the last 5 years, 63 patients were enrolled in the study, including 37 men and 25 women aged 17–70 years. The eligibility criteria dictated that the extravasation be recent (0–15 min after the event) and that the area involved measure <1800 mm^2.

Patients were separated into two groups; group A (30 subjects) was treated according to therapeutic schedule A, and group B (32 subjects) underwent treatment according to schedule B. The cytostatic drugs that had extravasated were doxorubicin (ADM), epirubicin (EPR), vinblastine (VLB), and mitomycin C (MMC) (Table 1). These drugs had been infused over 5–10 min through a butterfly needle connected to a running intravenous line following their dilution according to the suppliers instructions. The site of infusion was on the dorsal surface of the hand. Patients were entered into the study as soon as extravasation had been noted by medical personnel at the clinic.

According to the protocol, prior to the initiation of treatment, the surface area of the skin injury was estimated by mapping the circumference and noting the characteristics of the injury; the lesions were then photographed. This measurement was repeated every 2–4 days until the injury had completely healed. Estimation of the surface area was performed using millimeter squaring paper (Table 2).

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Table 1. Treatment group A and B according to the extravasated drug and to the age and sex of the patients

Drug	Patients (*n*)		Age (years)		Men (*n*)		Women (*n*)	
	A	B	A	B	A	B	A	B
ADM	10	10	41	43	6	6	4	4
EPR	12	11	51	55	7	7	5	4
VLB	5	8	61	58	4	1	0	2
MMC	4	3	62	64	3	3	1	0

Table 2. Extravasation surface values measured in treatment groups A and B

Drug	Cases (*n*)		Mean extravasation surface (mm^2)		"*P*" value
	A	B	Group A	Group B	
ADM	10	10	1180.0 (942–1842)	956.5 (428–1372)	0.173
EPR	12	11	659.9 (220–1850)	1001.4 (378–1619)	0.109
VLB	5	8	612.0 (223–1085)	1016.0 (596–1881)	0.058
MMC	4	3	1146.0 (655–1860)	1229.0 (984–1602)	0.542

The treatment phases were carried out as follows. In group A, the area of extravasation was infiltrated with a hydrocortisone solution (500 mg diluted in 10 ml 0.9% normal saline. Infiltration was accomplished through a thin needle (the type used for insulin injection) that was insarted subcutaneously (or deeper in certain cases) at intervals of 1 cm, beginning at the periphery of the damaged area and ending in the center. Next betamethazone ointment containing Garamycin (Schering, Kenilworth, NJ) was applied to the lesion along with a tight elastic bandage. The ointment was replaced every 12 h for the first 2 days and then every 24 h until the injury had completely healed.

In group B therapy started with infiltration of the area of extravasation area with 2% sodium thiosulfate, followed by a 3 to 5 min massage, after which the steps of schedule A were carried out. Prior to the injection of sodium thiosulfate or hydrocortisone solution, the injured area was cleaned with betadine and alcohol. The solution was injected at the periphery of the damaged area at 5 min intervals. Thereafter injections were continued toward the center of the damaged area and bellow it. These injections were done subcutaneously in such a way as to raise the skin overlying the injured area.

Results

We observed 63 cases of tissue damage due to extravasation of cytotoxic drugs in 25 women and 37 men. We found no significant difference in sex, age, or the mean extravasation surface area between the two groups of patients according to the extravasated drug (Tables 1, 2). Only the mean area of extravasation for VLB was greater in group B.

For DOX the mean extravasation surface was 1180 mm^2 ranges 942–1842 mm^2, in group A and 956.5 mm^2 ranges 428–1372 mm^2 in group B. There was a significant difference in the mean time to recovery as based on the extravasation surface, 21 days for group A vs

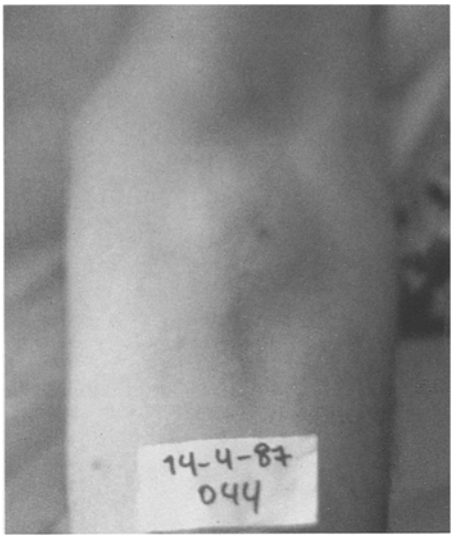

Fig. 1. A patient with DOX extravasation, before treatment

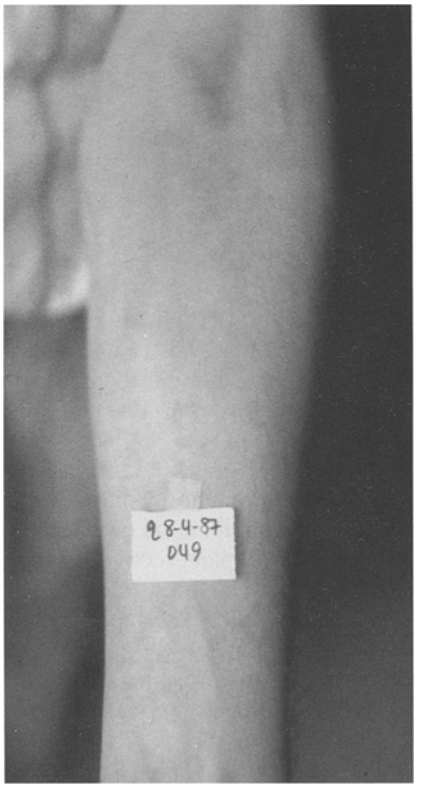

Fig. 2. The same patient with DOX extravasation, after treatment with ST

5 days for group B (P <0.006, Table 3, Figs. 1, 2, 3 A, 3 B). The mean surface of extravasation for EPR was 659.9 mm^2 range, 220–1850 mm^2 in group A and 1001.4 mm^2 range, 378–1619 mm^2 in group B. The mean time to recovery was 16 days for group A and 9 days for group B (P <0.013, Table 3). The mean surface of extravasation for VLB was 612 mm^2 range, 223–1085 mm^2 in group A and 1016 mm^2 range, 596–1881 mm^2 in group B. The mean time to recovery was 8 days for group A and 4 days for group B (P <0.040, Table 3). The mean surface of ex-

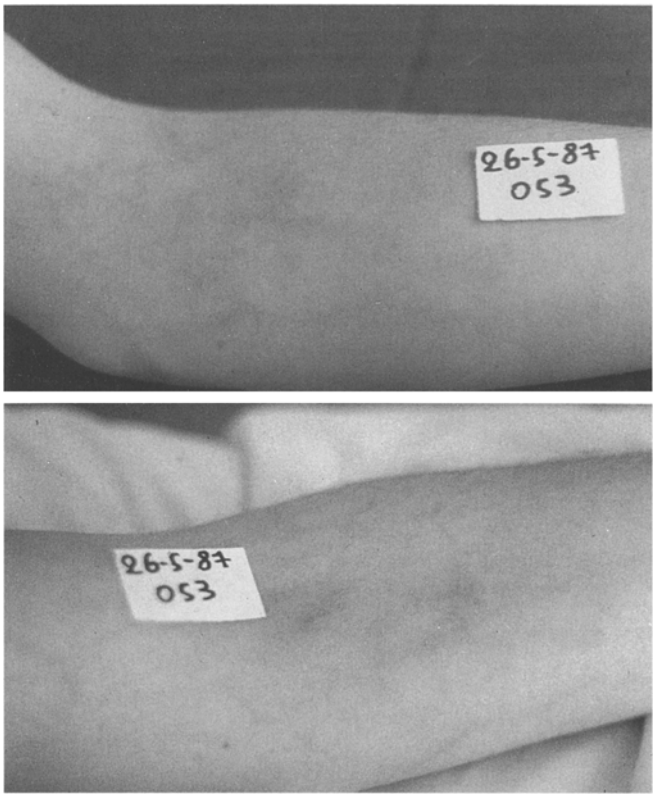

Fig. 3 A, B. After complete healing, the same patient with DOX extravasation and treatment with ST

travasation for MMC was 1146 mm^2 range, 655–1860 mm^2 in group A and 1229.3 mm^2 range, 984–1602 mm^2 in group B. The mean time to recovery was 11 days for group A and 4 days for group B ($P < 0.045$, Table 3).

Extravasation injuries produced by DOX and EPR took the longest to heal, with hyperpigmentation of the skin bring the only lasting effect. Two patients showing areas measuring >1600 mm^2 following complete recovery experienced constant sensitivity and muscle pain in the area of extravasation for 4–6 months. Surgery was performed only on one patient in whom DOX and etoposide had extravasated over an area of >2200 mm^2; in this case, surgery was done only to assist the healing process.

Discussion

Although extravasation of cytostatic drugs is not very common, it can cause tremendous distress to cancer patients and interfere with the quality of their lives. The tissue damage can range from mild to severe painful localized inflammation to widespread necrosis extending to the periosteum. In instances of the former, immediate conservative measures may prevent necrosis.

In a previous study [18] we found that in cases in which large amounts of drug extravasation conservative measures fail and reconstructive surgical introviation with a skin graft is inevitable. We established a simple and effective method that could be applied on an outpatient basis regardless of the time elapsing between the diagnosis of extravasation and the initiation of therapy. Therefore we separated cases of extravasation according to the time of the event into two groups new (<30 min after extravasation) and old (>60 min) injuries and used a different therapy for each group.

Table 3. Mean extravasation surface values and time to complete recovery determined for treatment groups A and B

Drug	Mean extravasation time to complete						*"P"* value
	Cases *(n)*		Surface (mm2)		Recovery (days)		
	A	B	A	B	A	B	
ADM	10	10	1180	956.5	21	5	0.006
EPR	12	11	659.9	1001.4	16	9	0.013
VLB	5	8	612	1016	8	4	0.040
MMC	4	3	1146	1229.3	11	4	0.045

Two factors are most important in the treatment of tissue damage due to extravasation of vesicant cytostatic drugs: first that the injury be diagnosed as soon as possible, and second, that the area involved be as small as possible. Under these conditions, such damage can be treated using conservative methods. In an effort to improve our method of treating the new extravasations, we used a reductive substance (sodium thiosulfate) to neutralize the cytostatic drug. Sodium thiosulfate has previously been used by some investigators to treat cytostatic drug extravasations [5]. Therefore we established two groups of patients so as to evaluate its effectiveness comparatively. We obtained better results, especially in the duration of recovery which was approximately halved in subjects who received sodium thiosulfate. We believe that it is essential that the cytostatic drug be neutralized as this decreases its local toxicity.

In the present study all lesions healed and no surgical intervention was necessary. The rate of healing varied with the different drugs used and was proportional to the size of the lesion and to the time at which therapy was begun. The longest healing time was required for DOX and EPR induced injuries. The size and depth of the lesions in this study were not large.

We obtained better results using the sodium thiosulfate solution. A possible explanation for the protective action of sodium thiosulfate in damaged tissue might be the following: as a slightly reductive molecule (see Eq 1), thiosulfate ion could neutralize the oxidative action of the semiquinone free radical as well as that of oxygen radicals, thus protecting the cellular membrane from oxygen-radical-mediated toxicity [8, 17].

$$2\,S_2O_3^{2-} \dashrightarrow S_4O_6^{2-} + 2e^- \quad E^o = -0.08\ V \quad (1)$$

In conclusion, conservative nonsurgical measures are very effective in treating small and medium-sized tissue necroses and skin ulcerations caused by extravasation of chemotherapeutic drugs. The present results indicate that the current methods might be improved by the use of sodium thiosulfate.

References

1. Barr PD, Benton SG, Belbeck LW (1981) Soft tissue necrosis induced by extravasated cancer chemotherapeutic agents. J Natl Cancer Inst 68: 1129–1136
2. Bartkowski-Dodds L, Daniels JR (1980) Use of sodium bicarbonate as a means of ameliorating doxorubicin induced dermal necrosis in rats. Cancer Chemother Pharmacol 4: 179–181
3. Desai MH, Teres D (1982) Prevention of doxorubicin induced skin ulcers in the rat and pig with dimethyl sulfoxide (DMSO). Cancer Treat Rep 66: 1371–1374
4. Dufresne RG (1987) Skin necrosis from intravenously infused materials. Cutis 39: 197–198
5. Harwood KV, Aisner J (1984) Treatment of chemotherapy extravasation: current status. Cancer Treat Rep 68: 1939–1945
6. Henneman HH, Kihm U, Voigtlander V (1984) Necrosis after extravasation of cytostatic drugs. Med Klin 79: 506–508
7. Ignoffo RJ, Friedman MA (1980) Therapy of local toxicities caused by extravasation of cancer chemotherapeutic drugs. Cancer Treat Rev 7: 17–27
8. Katakis D (1976) Inorganic chemistry, vol 2, University of Athens Press, Athens, pp 95–96
9. Kosmidis P, Zambakos J, Viglas J (1981) Immediate reconstruction by plastic surgery of necrotic tissue from Adriamycin extravasation. (abstract 07–0443) Proceeding UICC Congress Clinical Oncology, Lausanne
10. Larson DL (1982) Treatment of tissue extravasation by antitumor agents. Cancer 49: 1796–1799
11. Larson DL (1985) What is the appropriate management of tissue extravasation by antitumor agents? Plastic Reconstr Surg 75: 397–402
12. Lokich JJ, Moore C (1986) Drug extravasation in cancer chemotherapy. Ann Intern Med 104: 124
13. Loth TS (1986) Minimal surgical debridement for the treatment of chemotherapeutic agent induced skin extravasations. Cancer Treat Rep 70: 401–404
14. Ludwing CU, Stoll HR, Obrist R, Obrecht JP (1987). Prevention of cytostatic drug induced skin ulcers with dimethyl sulfoxide (DMSO) and alpha tocopherol. Eur J Cancer Clin Oncol 23: 327–329
15. Lynch DJ, Key JC, White RR (1979) Management and prevention of infiltration and extravasation injury. Surg Clin North Am 59: 939–949
16. Reilly JJ, Neifeld JR, Rosenberg SA (1977) Clinical course and management of accidental Adriamycin extravasation. Cancer 40: 2053–2056
17. Salmon SE, Sartorelli AC (1987) Cancer chemotherapy. In: Katzung BG (ed) Basic and clinical pharmacology, 3rd ed, Norwalk, Appleton and Lange, pp 665–701
18. Schuind F, Gangji D, Zorman D (1987) Surgical treatment of skin ulcers due to chemotherapy. Ann Chir Main 6: 38–42
19. Tsavaris NB, Karagiaouris P, Tzannou I, Komitsopoulou P, Bacojannis C, Karabellis A, Papanikolaou V, Mylonakis N, Karvounis N, Zoannou A, Kosmidis P (1990) Conservative approach to the treatment of chemotherapy induced extravasation. J Dermatol Surg Oncol 16: 519–522
20. Villani C, Doninelli M, Giobbi L, et al (1985) Extravasation after use of antitumor drugs: clinical experience, procedures of prevention and therapy. Patol Clin Obstet Ginecol 13: 267–272
21. Wang JJ, Cortes E, Sink LF, Holland JF (1971) Therapeutic effect and toxicity of Adriamycin in patients with neoplastic disease. Cancer 28: 837–843