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Original Articles

Use of Sodium Bicarbonate as a Means of Ameliorating Doxorubicin-induced Dermal Necrosis in Rats

Linda Bartkowski-Dodds and J. R. Daniels

Division of Medical Oncology, Oncology Day Care Center, Room C005, Stanford University School of Medicine, Stanford, California 94305, USA

Summary. *To test whether $NaHCO_3$ infiltration provides protection against doxorubicin-induced dermal necrosis, we infiltrated rat dermis with doxorubicin immediately followed by $NaHCO_3$ (experimental) or saline (control) and measured the subsequent evolution of necrosis, erythema, and induration. Experimental groups were substantially protected, having a reduction of the maximum area of the lesion and more rapid healing.*

Introduction

Doxorubicin is an anthracycline glycoside that has been demonstrated to be an effective chemotherapeutic agent against a variety of malignancies. Inadvertant extravasation of doxorubicin into dermis and subcutaneous tissue during IV administration results in local tissue injury [1, 5]. These doxorubicin-induced injuries are distinctive, and the local pathologic processes often progress over an extended period. The progressive lesion may assume invasive characteristics extending to deep structures such as the underlying tendon and joint [1, 5, 6]. Early excision appears to prevent this progression [5]. Suggested interventions for reducing tissue injury at the time of extravasation have included local infiltration with a corticosteroid, saline, or $NaHCO_3$, and application of ice for the first 24 h. Recently, Zweig and Kabakow reported a single case with no ulceration after inadvertent extravasation of 40 mg doxorubicin into the subcutaneous tissue, which was then followed by deliberate infiltration of $NaHCO_3$, into the same area [9].

Rudolph and Suzuki have developed an animal model of doxorubicin ulceration after ID injections. The extent and duration of ulceration are a function of dose and of concentration [7]. In our study we used their model to test the potential usefulness of immediate injections of $NaHCO_3$ into the site of ID instillation of doxorubicin.

Reprint requests should be addressed to: L. Bartkowski-Dodds

Methods

Wistar rats (100–120 g) were anesthesized with IP sodium pentobarbital (0.015 cm^3 at 60 mg/ml) and shaved at the time of injection. Injections into the posterior right and left flanks were given through a 27-gauge butterfly needle, with change of syringes to maintain needle placement.

Each injection consisted of 0.3 ml doxorubicin at 2 mg/ml. At control sites these injections were immediately followed by 0.3 ml normal saline, and at experimental sites they were followed by 0.3 ml $NaHCO_3$ (8.4%). Care was taken to deliver the solutions ID. At weekly intervals, serial measurements of lesion areas (derived from diameter measures) were recorded for ulceration, erythema and induration. Three experiments were performed, each in five animals with paired injections.

Results

Results were similar for all evaluated parameters and are presented in Figs. 1–3, each of which represents one of

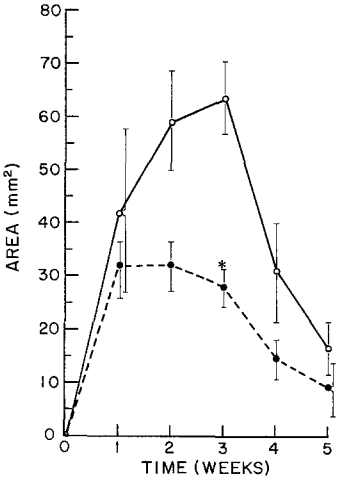

Fig. 1. Average area of ulceration at weekly intervals after doxorubicin injections. At control sites injections were immediately followed by instillation of normal saline (○——○) and at experimental sites they were followed by $NaHCO_3$ (●– – –●). Each point represents mean of five lesion areas (± SE). * Significantly different from control, $P < 0.002$

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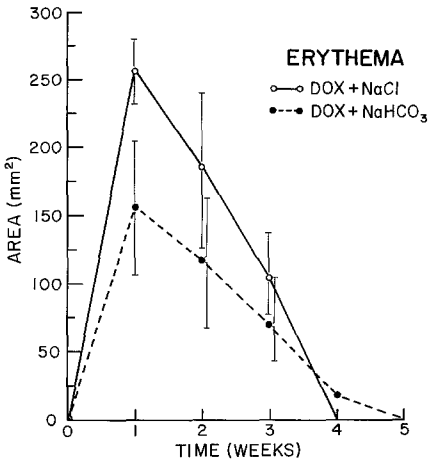

Fig. 2. Average area of erythema at weekly intervals after doxorubicin injections. Each point represents mean of five lesion areas (± SE)

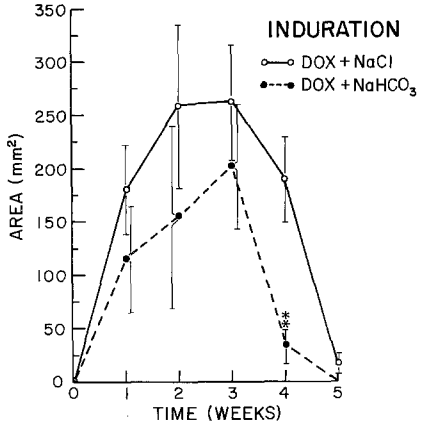

Fig. 3. Average area of induration at weekly intervals after doxorubicin injections. Each point represents mean of five lesion areas (± E). ** Significantly different from control; $P < 0.04$

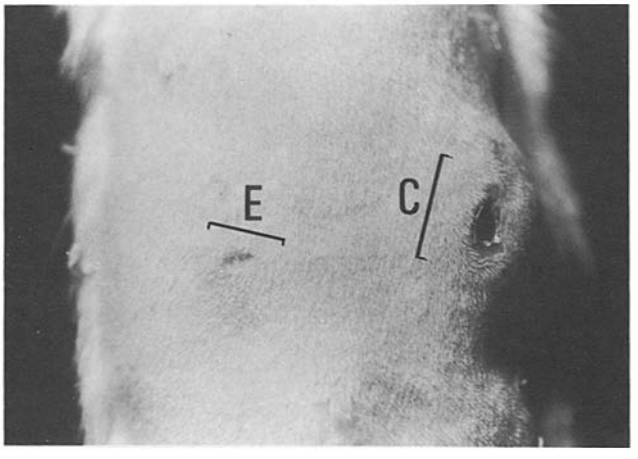

Fig. 4. Photograph of rat model at 4 weeks. Control lesion on right (C) received doxorubicin immediately followed by saline and measures 33 mm² for ulceration at 175 mm² for induration. Experimental lesion (E) is no longer indurated and has only a small residual defect

three experiments. Sodium bicarbonate lessened the severity and allowed earlier recovery compared with saline controls. A representative photograph (Fig. 4) illustrates this protection in week 4. For ulceration these differences achieved statistical significance (paired *t*-test evaluation at 2–3 weeks, $P < 0.002$); the difference in the area of induration was statistically significant at 4 weeks ($P < 0.04$); whereas, for erythema there was similar but not significant benefit according to the statistical test used.

Discussion

A known impact of $NaHCO_3$ in doxorubicin is to reduce solubility by shifting the duanosamine amine to the non-ionized form [8]. This effect could influence drug uptake or removal from the area and perhaps accounts for the apparent benefit of the presence of high, local concentrations of $NaHCO_3$.

Should we use $NaHCO_3$ in patients for doxorubicin extravasation? The encouraging results in this model suggest the use of *small* amounts following inadvertant infiltration of doxorubicin. It should be emphasized that only small amounts of $NaHCO_3$ can be tolerated by the subcutaneous tissue without tissue necrosis. Gaze [2] reports eight cases of tissue necrosis precipitated by $NaHCO_3$ extravasation. In four of these cases 200 ml was extravasated, while the amount was not specified in the remaining four cases. However, one might suspect that a large volume was used, considering the circumstances under which the extravasation occurred; i.e., cardiac arrest, ketoacidotic coma, hyperglycemic coma, and gastroenteritis.

Similarly, Jackson and Robinson [3] reported severe tissue damage following extravasation of $NaHCO_3$ in a patient who received this infusion during cardiac arrest. Again, a large volume was most probably used, since a considerable amount is required to correct the acidotic condition of a patient in cardiac arrest.

Our experience at Stanford University Hospital with 4 cm^3 $NaHCO_3$ after doxorubicin extravasation has produced excellent results in six different cases, with no tissue breakdown and only minor swelling and soreness lasting 4–6 days.

It wold be worthwhile to conduct further studies in this animal model, to determine how much and how often $NaHCO_3$ should be injected and whether or not corticosteroids or local temperature control have any additional benefit.

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