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Corticosteroid and Antihistamine Modification of Bleomycin-Induced Fever (40603)[1]

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Fever is a frequent complication following the administration of bleomycin to cancer patients (1–7). Various antipyretic agents have been advocated for the prevention or treatment of this toxicity (1, 2, 5) but their effectiveness appears to be erratic. Furthermore, no controlled studies of their efficacy in humans or animals have been published. The rabbit provides an acceptable model for human bleomycin-induced fever, developing a dose-related fever after a latent period of 1 to 2 hr following bleomycin injection (8). Bleomycin stimulation of endogenous pyrogen production by host leukocytes appears to be a mechanism of fever induction in this system.

Because corticosteroids prevent fever in a variety of clinical settings and because they have been demonstrated to reduce the amount of endogenous pyrogen released from stimulated human monocytes *in vitro* (9), we studied the effectiveness of single dose corticosteroid treatment in preventing or reducing bleomycin fever in rabbits. Antihistamine therapy with diphenhydramine has been stated to be effective (1) and possibly superior to other agents (4) in preventing bleomycin-induced fever. Therefore, this study also evaluates the effectiveness of diphenhydramine in preventing rabbit bleomycin-induced fever.

Materials and methods. Eighty female New Zealand albino rabbits weighing 2–3 kg each were used. No animals had received previous bleomycin, antihistamine, or corticosteroid injections. The rabbits were trained in wooden stocks prior to the day of testing. Rectal temperatures were continuously monitored with thermistor probes connected to a thermometer (YSI Telethermometer, Yellow Springs, Ohio) which was in turn connected to a recording device. Only rabbits with a baseline temperature varying less than 0.2° during the 1-hr preinjection period were used.

Bleomycin (Blenoxane) was generously provided by Bristol Laboratories in 15-unit ampules. Bleomycin preparations was tested for endotoxin contamination with the limulus amebocyte lysate test (Associates of Cape Cod, Inc., Woods Hole, Mass.). Fifteen units were diluted in 5 ml of pyrogen-free 0.9% saline immediately prior to injection. All rabbits received bleomycin 1 unit/kg injected intravenously through the lateral ear vein. Forty-one received no other medication (Group I). In 18 rabbits the bleomycin was preceded by an injection of hydrocortisone 5 mg/kg IV given 60 min earlier (Group II). Another group of 21 rabbits received 5 mg/kg hydrocortisone 1 hr after the bleomycin injection (Group III). Group IV is comprised of 14 rabbits who received diphenhydramine 1 mg/kg IV 15 min prior to bleomycin. Fevers are expressed as ΔT (change of temperature in °C from baseline). A febrile response is defined as $\Delta T \geq 0.3°$.

Results. The effects of hydrocortisone and of diphenhydramine on bleomycin-induced fever are presented in Table I. The 90% of Group I rabbits developed fever with a mean peak ΔT of 0.80°. In contrast, only 44% of rabbits pretreated with hydrocortisone developed fever ($P < 0.005$). The mean peak ΔT in this group was 0.39°, significantly lower than that in Group I ($P < 0.0025$). Postbleomycin hydrocortisone did not significantly decrease the incidence of fever from bleomycin but did lower the mean peak ΔT to 0.50° ($P < 0.005$). Thirteen of forty-one rabbits (32%) who received bleomycin alone developed fevers >1.0° compared to 3/39 rabbits (8%) who received hydrocortisone. For those animals who developed bleomycin-induced fever, the latent period preceding the onset of progressive temperature rise and the latent period preceding the attainment of ΔT

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TABLE I. EFFECT OF HYDROCORTISONE AND DIPHENHYDRAMINE TREATMENT ON BLEOMYCIN-INDUCED FEVER[a]

Treatment	Group I bleomycin alone	Group II bleomycin after hydrocortisone pretreatment	Group III bleomycin followed by hydrocortisone	Group IV bleomycin after diphenhydramine pretreatment
Number of rabbits injected	41	18	21	14
Fever incidence number (%)	37 (90%)	8 (44%)	15 (71%)	14 (100%)
		$P < 0.005$	NS	NS
Latent period, hours to onset of fever	2.14 ± 0.12	3.25 ± 0.55	2.22 ± 0.13	1.46 ± 0.20
		$P < 0.0025$	NS	$P < 0.01$
Latent period[b] hours to $\Delta T = 0.3°$	2.79 ± 0.15	3.81 ± 0.55	2.88 ± 0.28	1.91 ± 0.15
		$P < 0.01$	NS	$P < 0.005$
Time to peak[b] ΔT (hours)	4.61 ± 0.17	5.19 ± 0.52	4.87 ± 0.25	4.45 ± 0.25
		NS	NS	NS
Mean peak ΔT (°C)	0.80 ± 0.08	0.39 ± 0.09	0.50 ± 0.06	1.21 ± 0.15
		$P < 0.0025$	$P < 0.005$	$P < 0.05$
ΔT at: 3 hr	0.46 ± 0.06	0.06 ± 0.06	0.26 ± 0.05	0.86 ± 0.12
4 hr	0.63 ± 0.07	0.19 ± 0.07	0.36 ± 0.05	1.04 ± 0.13
5 hr	0.71 ± 0.07	0.21 ± 0.08	0.42 ± 0.07	1.16 ± 0.13

[a] *P* values represent *t* test comparison of groups II,III, and IV, respectively, with group I. Bleomycin dose 1.0 unit/kg IV for all groups. Hydrocortisone dose 1 mg/kg IV 60 min before (group II) or 45 min after bleomycin (group III). Diphenhydramine dose 1 mg/kg IV 15 min before bleomycin (group IV).

[b] Latent period and time to peak data represent only those animals developing $\Delta T \geq 0.3°$.

$\geq 0.3°$ were measured. Pretreatment with hydrocortisone prolonged this latency by approximately 1 hr. Significant prolongation of the latent period was not seen when the hydrocortisone was administered 1 hr after the bleomycin.

Pretreatment with diphenhydramine (Benadryl) was ineffective in reducing bleomycin fever in rabbits. In fact, it caused significant enhancement of fever and accelerated its development (Table I). Fever exceeded 1° in 64% of rabbits receiving diphenhydramine before bleomycin. Diphenhydramine given alone to five rabbits caused no significant temperature change (mean $\Delta T = 0.12°$).

Bleomycin preparations were tested by limulus amebocyte lysate and were found to have no detectable endotoxin. When 0.01 μg/ml endotoxin (*Escherichia coli* 127:B8, Difco) was added to 2 units/ml of bleomycin, the limulus test was positive, demonstrating that bleomycin does not inhibit the limulus test under the conditions utilized and confirming that the bleomycin preparation itself was endotoxin-free.

Discussion. Bleomycin-induced fever has been observed in 20–57% of patients receiving this drug (1–7). In lymphoma patients the incidence is greater than 50% (1, 2, 5, 6). The febrile reaction usually starts 2 to 6 hr after bleomycin administration, lasts to 8–18 hr after drug administration and is frequently associated with chills, rarely with hypotension (1, 5). Rabbits develop fever after receiving bleomycin in amounts of 0.8 mg/kg or more (8). This response is dose related and not associated with endotoxin contamination. Previous studies of rabbit bleomycin-induced fever have demonstrated that bleomycin stimulates secretion of endogenous pyrogen from host cells as its mechanism of fever induction.

Control of bleomycin-induced fever has not been formally studied. There is anecdotal evidence that antihistamines and antipyretics may ameliorate bleomycin fever in some patients (1, 4, 5). One review based on clinical evaluation of bleomycin in 160 patients stated that intramuscular diphenhydramine appeared to minimize fever while antipyretics and corticosteroids were ineffective (5). Published data are not available, however, to permit evaluation of the effectiveness of these measures (1, 5). Because of the sporadic incidence of bleomycin-induced fever in patients and because bleomycin is now generally used in combination with other chemotherapeutic agents, controlled studies on human bleomycin fever are rarely feasible. We have observed that some lymphoma patients have apparent amelioration of bleomycin-induced fever when pretreated with corticosteroids. Corticosteroids have been shown to diminish endogenous pyrogen secretion from stimulated human monocytes (9), a mechanism that could be important in bleomycin-

induced fever. Therefore, we studied the ability of pretreatment with a single dose of corticosteroids to prevent or lessen the fever occurring after bleomycin administration to rabbits. The results demonstrate that single-dose corticosteroid pretreatment decreases the incidence, severity, and rapidity of onset of bleomycin fever in rabbits. Later administration of hydrocortisone also diminished the magnitude of temperature increase after bleomycin but had no effect on the incidence or on the duration of the latent period. These findings are compatible with the endogenous pyrogen mechanism proposed for bleomycin-induced fever, administration of corticosteroids during the activation of endogenous pyrogen synthesis by host cells, hence, the essentially unaltered latency and incidence of fever. Since prolonged endogenous pyrogen secretion is required to sustain fever for several hours and since the peak bleomycin fever occurs 5 hr after its administration, late corticosteroid treatment is effective in diminishing the peak ΔT in some instances.

The ineffectiveness of diphenhydramine in preventing rabbit bleomycin-induced fever contrasts with claims for its effectiveness in preventing human bleomycin fever (1, 4). Our observation, however, may reflect a species-specific effect of histamine which has been found to be a hypothermic agent when centrally administered to rabbits (10).

The present studies provide a rationale for testing corticosteroid pretreatment in the prevention of clinical bleomycin-induced fever. The rabbit model will facilitate studies to determine whether inhibitors of prostaglandin synthesis or inhibitors of protein synthesis, e.g., cycloheximide (11), will enhance the effectiveness of corticosteroid pretreatment in this system.

Summary. Fever is a common and frequently debilitating complication following the administration of bleomycin to patients. Bleomycin-induced fever has been demonstrated in rabbits where it is dose related and mediated through the release of endogenous pyrogen from phagocytes. Because corticosteroids are known to suppress fever in several clinical states and to reduce endogenous pyrogen release from stimulated human phagocytes *in vitro* the effect of hydrocortisone pretreatment on bleomycin-induced fever was studied. All rabbits studied received bleomycin 1 unit/kg i.v. One group received no other medication. A second group received hydrocortisone 5 mg/kg i.v. 1 hr before bleomycin, and a third group received the same dose of hydrocortisone administered as a single injection 1 hr after bleomycin. Hydrocortisone-pretreated rabbits, 44%, developed bleomycin-induced fever compared to 90% of the rabbits who received bleomycin alone. Hydrocortisone pretreatment diminished the mean peak fever (ΔT) from 0.80° to 0.39° and prolonged the latent period from 2.79 to 3.81 hr. Hydrocortisone administered 1 hr after bleomycin diminished the mean ΔT but had only slight effect on the incidence of fever and no effect on the latency. These studies provide rationale for clinical use of single-dose corticosteroid pretreatment in patients with bleomycin-induced fever. Antihistamine pretreatment with the H_1 receptor antagonist diphenhydramine was ineffective in protecting rabbits from bleomycin-induced fever; however, a species-specific effect might explain this result.

1. Blum, R. H., Carter, S. K., and Agre, K., Cancer, 903–914 (1973).
2. Rudders, R. A., Blood **40**, 317–332 (1972).
3. Halnan, K. E., Bleehen, N. M., Brewin, T. B., Deeley, T. J., Harrison, D. F. N., Howland, C., Kunkler, P. B., Ritchie, G. L., Wiltshaw, E., and Todd, D. H., Brit. Med. J. **4**, 635–638 (1972).
4. Yagoda, A., Mukherji, B., Young, C., Etcubanas, E., Lamonte, C., Smith, J. R., Tan, C. T. C., and Krakoff, I. H., Ann. Int. Med. **77**, 861–870 (1972).
5. Yagoda, A., and Krakoff, I. H., *in* "Fundamental and Clinical Studies of Bleomycin. Gann Monograph on Cancer Research" (S. K. Carter, T. Ichikawa, G. Mathe, and Umezawa, eds.), pp. 255–268. Univ. of Tokyo Press, Tokyo (1976).
6. Mosher, M. B., DeConti, R. C., and Bertino, J. R., Cancer **30**, 56–60 (1972).
7. Lokich, J. J., and Frei, E., Cancer Res. **34**, 2240–2242 (1974).
8. Dinarello, C. A., Ward, S. B., and Wolff, S. M., Cancer Chemother. Rep. **57**, 393–398 (1973).
9. Bondy, P. K., and Bodel, P., *in* "Pyrogens and Fever: A CIBA Foundation Symposium on Pyrogens and Fever" (G. E. W. Wolstenholme, and J. Birch, eds.), pp. 101–113. Churchill Livingston, London (1971).
10. Lomax, P., and Green, M. D., *in* "Temperature Regulation and Drug Action Proc. Symp.," pp. 85–94, Karger, Basel (1975).
11. Young, C. W., and Dowling, M. D., Cancer Res. **35**, 1218–1224 (1975).

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