

TREATMENT OF ARTHRITIS IN THE RABBIT WITH INTRA-ARTICULAR DAUNORUBICIN LINKED TO PROTEIN

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Page Thomas & Phillips (1979) reported that intra-articular injection of free or liposome-entrapped daunorubicin (Dauno) suppressed an irritant-induced arthritis in rabbits. However, Dauno initially enhanced the inflammatory response, possibly due to the formation of free radicals and hydrogen peroxide which are thought to contribute to its toxicity (Davies et al, 1983). We have investigated the effect of linking Dauno to catalase, with the objective of preventing the damaging effects of hydrogen peroxide generated by both Dauno and phagocytosing cells.

An allergic bilateral arthritis was induced in the knee joints of Old English rabbits using the procedure described by Consden et al (1971). Inflammation was assessed by measuring changes in joint diameter and skin temperature over the joint. Dauno was linked to bovine serum albumin (BSA) or catalase with glutaraldehyde to form a Schiff's base with the amino group of Dauno and a free amino group of the protein (Williams et al, 1981). Intra-articular injection of Dauno (50µg) alone or linked to BSA, 1 week after induction of arthritis, caused an approx 20% reduction in joint swelling which was sustained for 8 weeks up to the time of sacrifice (Table 1). Joint temperature was not significantly reduced. By contrast, the intra-articular injection of catalase (6.4 mg) alone or linked to Dauno (50µg) had a marked pro-inflammatory effect, increasing both joint swelling and temperature for the duration of the experiment (Table 1).

The generation of superoxide radicals (O_2^-) and subsequently hydrogen peroxide by phagocytosing cells is thought to contribute to the inflammatory response. Since catalase promotes the breakdown of hydrogen peroxide and protects synovial fluid from degradation (Greenwald & May, 1980), its pro-inflammatory effect was unexpected. Superoxide dismutase, an O_2^- scavenger, might be more suitable for linking with Dauno for intra-articular therapy. Moreover, linking Dauno to a protein increases its molecular size, and might be expected to delay its clearance from the injected joint and prolong its local action, as appeared to occur with Dauno linked to BSA.

Table 1. Reduction in diameter (mm) of treated joints compared with contralateral control arthritic joints (mean ± s.e. mean, n = 3)

Treatment	Days after treatment				
	3	7	21	35	49
Dauno	0.30±0.15	1.23±0.18*	1.07±0.09*	0.90±0.40	0.83±0.43
Dauno + BSA	+0.29±0.17	0.03±0.03	1.43±0.27*	2.03±0.23*	1.67±0.37
Catalase	+1.90±0.40**	+1.80±0.40**	+1.43±0.52**	+1.20±0.42*	+0.90±0.26*
Dauno + catalase	+1.93±0.52*	+1.80±0.12**	+1.23±0.18*	+1.07±0.26*	+0.70±0.53*

+ = increase in joint diameter; *P < 0.05; **P < 0.01.

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