

THE LYMPHOGOGUE ACTION OF CALCIUM DOBESILATE ON THE FLOW OF LYMPH FROM THE THORACIC DUCT OF ANESTHETIZED AND MOBILE GUINEA PIGS

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ABSTRACT

Calcium dobesilate increases thoracic duct lymph flow in both anesthetized and mobile guinea pigs. The marked lymphogogue action of this drug may explain in part the improvement in tissue survival with ischemic insult.

The actions and effects of calcium dobesilate and a variety of related benzopyrone substances have been reviewed by Casley-Smith and Casley-Smith (1). These agents may have benefit during treatment of tissue infarction. Thus, calcium dobesilate confers protection to the capillary membrane with improvement in hyperfragility and reduction in hyperpermeability (2,3). These actions influence, thereby, the composition and volume of interstitial fluid and thus the nature of lymph (1).

In cardiac infarction, calcium dobesilate reduces the amount of necrotic tissue, particularly with small infarcts (4). In this respect, an increase in lymphatic transport capacity may further reduce tissue edema and thus the area of injury. In support of this notion, Szlavay et al. (5) have shown that calcium dobesilate results in greater lymphatic filling under conditions of infarction. This response has been further supported by the findings of Piller and Browning (7) that this drug increases the intensity of contraction of lymphangion units. In this context, the effects of calcium dobesilate on the

lymph flow from the thoracic duct of anesthetized and mobile guinea pigs to determine the lymphogogue potential of this drug are now examined.

MATERIALS AND METHODS

Forty male guinea pigs (200-250gms) were fed and watered ad libitum for 5 days followed by 24 hours in which fluid intake was solely milk. This "diet" was supplemented with 200mg ascorbic acid per liter. The guinea pigs were randomly divided into 2 groups. Preliminary anesthesia was obtained by administration of 1ml of Alphathesin per 100gm body mass. In each group a vein on the medial aspect of the foreleg was exposed and a 25-27 gauge needle attached to a cannula filled with isotonic saline inserted and held in place with an epoxy tissue "glue". Catheter patency was maintained by administration of 1 or 2 drops of saline per minute. This access line was used to administer further Alphathesin as required to maintain anesthesia. To cannulate the retroperitoneal thoracic duct, a 15cm polyethylene catheter of internal diameter 0.5-0.6mm was used. One end of the catheter was shaped into a loop of about 4-6mm in diameter and beveled to insure ease of insertion. Prior to manipulation the catheter was filled with isotonic saline with 25u heparin/ml and heat sealed at the free end. The technique was similar to that previously used in the adult rat although the success rate in

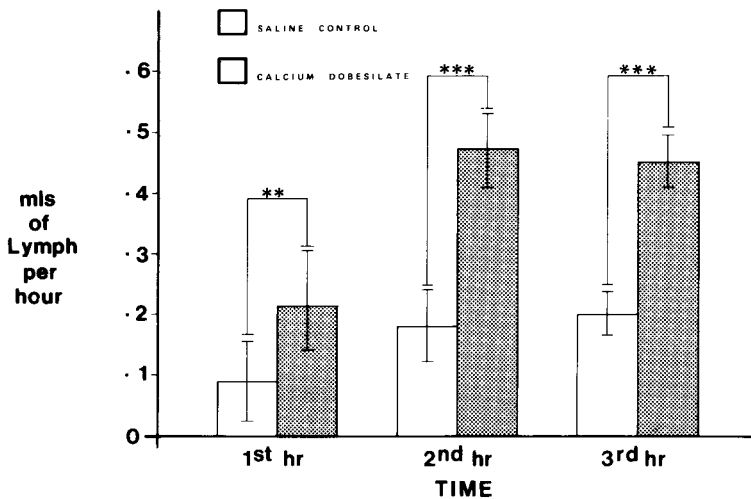


Fig. 1. Effect of calcium dobesilate on lymph flow from the thoracic duct of anesthetised guinea pigs. * $0.01 < p < 0.05$; ** $0.001 < p < 0.01$; *** $p < 0.001$.

guinea pigs was lower in view of the anatomical variation in the cisterna chyli and the thoracic duct which varied from a solitary vessel up to 7 smaller ducts. Where ducts were multiple, all but the largest was ligated.

Once the main lymph duct and cisterna chyli were located, the thoracic duct was exposed along part of its length by gently tearing the dorsal peritoneum with cotton-tipped fine forceps. The duct was then separated from the dorsal aorta by blunt dissection. A double thread of braided silk was then passed under the duct and the latter cannulated as for a venous cutdown. After incising the chylous lymphatic, outflowing milky lymph was sponged, the catheter inserted, and the inferior suture was tied around the catheter followed by the superior thread. The catheter was exteriorized through the skin near the third nipple on the left side and wounds were closed with interrupted fine sutures. Lymph was collected over 1-hour intervals for each of 3 hours after the end of the cannulation procedure. Only guinea pigs in which lymph flow was "free" were used. After administration of Alphathesin i.v., the guinea pigs were held at this level of anesthesia for 3 hours on a warmed stage and given 5ml of distilled water by intra-

gastric tube. In the "active" group the awakened guinea pigs underwent movement by a continuous gentle mechanical rocking of the cage over a 5 second cycle. One subgroup was given calcium dobesilate at 200mg/kg in isotonic saline whereas the other received an equivalent volume of isotonic saline. This volume or drug was given promptly after cannulation thus providing 1 hour between cannulation and the initiation of the first lymph collection.

RESULTS

A comparison between the lymph flows from the anesthetized (Fig. 1) and mobile control groups (Fig. 2) showed significant increases in both groups for the second and third hours ($p < .001$) but not for the first hour. After treatment with calcium dobesilate a similar but more dramatic effect was seen (Fig. 12).

DISCUSSION

Calcium dobesilate exerts a wide variety of vascular actions including inhibition of vasoactive substances (2) and enzymes such as hyaluronidase (7). It also reduces capillary hyperpermeability

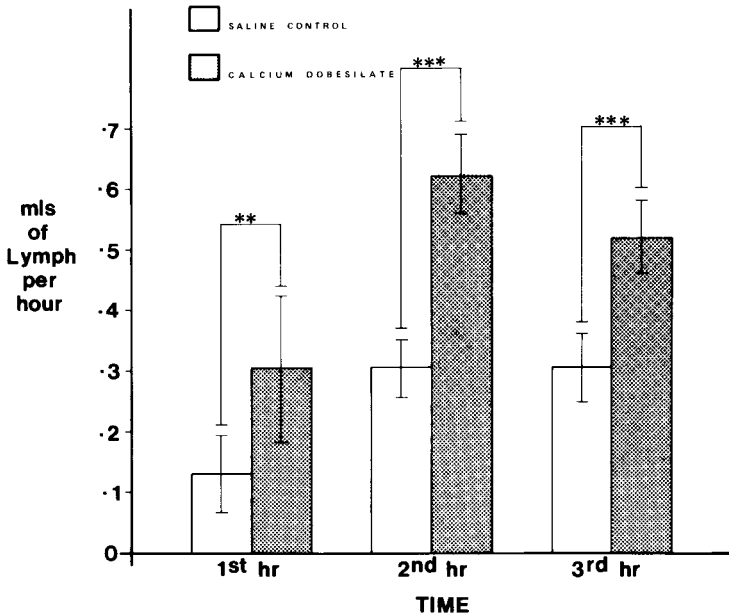


Fig. 2. Effect of calcium dobesilate on lymph flow from the thoracic duct of mobile guinea pigs. * $0.001 < p < 0.05$; ** $0.01 < p < 0.01$; *** $p < 0.001$.

(8). On the other hand, an earlier study in dogs showed that calcium dobesilate had a notable lymphagogue effect (9). In guinea pigs it slows the frequency of contraction of mesenteric lymphatics and increases the time of contraction (6). Observation of the lymphangions with this agent also suggested greater filling and more forceful propulsion of lymph.

The current study supports a lymphagogue action of calcium dobesilate in that thoracic duct lymph flow in both anesthetized and mobile guinea pigs was increased. The ability of calcium dobesilate to increase lymph flow irrespective of the level of host activity (that is, with or without anesthesia) together with its angio-protective effect (10,11) and the effects on blood vascular dynamics (12) suggest that this drug may be useful in minimizing tissue damage during ischemia.

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