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MONOCROTALINE-INDUCED CARDIOPULMONARY INJURY IN RATS

MODIFICATION BY THE NEUTROPHIL ELASTASE INHIBITOR SC39026

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Abstract—Rats were killed after 6 weeks of continuous ingestion of the pneumotoxic alkaloid monocrotaline (2.2 mg/kg/day), the neutrophil elastase inhibitor SC39026 (60 mg/kg/day), or both. Pulmonary reactions were evaluated by light and electron microscopy. Lung endothelial function was monitored by angiotensin converting enzyme (ACE) activity, plasminogen activator (PLA) activity, and prostacyclin (PGI_2) and thromboxane (TXA_2) production. Lung hydroxyproline content was measured as an index of interstitial fibrosis. Cardiac right ventricular hypertrophy was determined by the right ventricle to the left ventricle plus septum weight ratio (RV/LV + S). Rats receiving SC39026 alone did not differ significantly from untreated control animals with respect to any of the quantitative endpoints, although rarefaction of Type I pneumocytes was observed in the electron micrographs of these animals. Monocrotaline-treated rats, in contrast, developed a significant increase in RV/LV + S, and exhibited pulmonary edema, inflammation, fibrosis, and muscularization and occlusive mural thickening of the pulmonary small arteries and arterioles. These monocrotaline-induced structural changes were accompanied by decreased lung ACE and PLA activities, and increased PGI_2 and TXA_2 production, and by an increase in lung hydroxyproline content. Cotreatment with SC39026 ameliorated the monocrotaline-induced pulmonary vascular wall thickening and the cardiac right ventricular hypertrophy. These data suggest that inappropriate neutrophil elastase activity contributes to monocrotaline pulmonary vasculopathy and hypertension. On the other hand, cotreatment with SC39026 had no significant effect on the severity of the monocrotaline-induced lung inflammatory reaction, the pulmonary endothelial dysfunction, or the increase in lung hydroxyproline content.

Monocrotaline, a pyrrolizidine alkaloid extracted from *Crotalaria spectabilis*, produces pulmonary edema, inflammation, hemorrhage, and interstitial fibrosis [1]. Monocrotaline-treated rats also exhibit occlusive medial thickening of the pulmonary arteries and muscularization of septal arterioles. These reactions are followed by pulmonary hypertension, cardiomegaly, right heart enlargement, and *cor pulmonale* [1]. Monocrotaline-induced lung injury leads to abnormal pulmonary mechanical, ventilatory, and gas exchange functions [2]. While the pathogenesis of monocrotaline pneumotoxicity is not clear, pulmonary endothelial dysfunction is a prominent and early component of the reaction. Monocrotaline-treated lungs exhibit decreased 5-hydroxytryptamine clearance [3], decreased norepinephrine uptake [3], decreased angiotensin converting enzyme (ACE) and plasminogen activator (PLA) activities [4], and increased prostacyclin (PGI_2) and thromboxane (TXA_2) production [4–6], all indicative of vascular endothelial dysfunction.

Because of the pneumotoxicity of monocrotaline, consumption of the parent plant is a veterinary problem in grazing species, and can be a health hazard to herbal tea users [1]. Monocrotaline-induced pulmonary injury also has been advocated as an experimental model of adult respiratory distress syndrome, chronic obstructive pulmonary disease, and idiopathic pulmonary hypertension in humans [2, 5, 7]. We have found the monocrotaline model of lung injury in rats to be a convenient and reproducible system in which to test potential therapeutic agents [8–11].

An early event in the development of monocrotaline pneumotoxicity is the margination and penetration of polymorphonuclear leukocytes through the walls of the pulmonary arteries and arterioles [5, 7, 12]. Fragmentation of the internal elastic lamina of the lung vasculature also occurs within 4 days after a single s.c. injection of monocrotaline, preceding arteriolar muscularization and increased pulmonary artery pressure [13]. These observations suggest that neutrophil elastase may play a role in the pathogenesis of monocrotaline pneumotoxicity, and that inhibitors of this enzyme may be logical candidates as modifiers of monocrotaline lung damage. SC39026 [(±)2-chloro-4-(1-hydroxyoctadecyl)benzoic acid] is a new specific inhibitor of elastase from human, rat, hamster, rabbit and hog neutrophils [14]. Supporting the above hypothesis is a recent report that cotreatment with SC39026 ameliorates pulmonary arterial muscularization and pulmonary hypertension in rats receiving a single s.c. injection of monocrotaline [15]. In the present study, we determined whether SC39026 can intervene in monocrotaline pneumotoxicity in rats ingesting the drugs continuously for 6 weeks, a mode of mono-

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crotaline administration known to produce pulmonary endothelial dysfunction, pulmonary fibrosis and pulmonary hypertension [8–11].

METHODS

Male Sprague–Dawley rats (Charles River, Boston, MA) weighing 200–225 g were randomly assigned to one of four treatment groups, each containing ten to twelve animals:

Group 1: control; consumed powdered chow and tap water *ad lib*

Group 2: SC39026; consumed powdered chow containing 835 mg SC39026 per kg chow (60 mg/kg body wt/day), and tap water

Group 3: monocrotaline; consumed powdered chow, and water containing 20 mg monocrotaline (Aldrich Chemical Co., Milwaukee, WI) per liter (2.2 mg/kg/day)

Group 4: monocrotaline plus SC39026; consumed powdered chow as in Group 2 and water as in Group 3.

Body weight, and food and water consumption were measured weekly. The latter were consistent among treatment groups, resulting in average SC39026 doses of 60 mg/kg/day and monocrotaline doses of 2.2 mg/kg/day. All animals were killed after 6 weeks of continuous drug administration.

At autopsy, animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), and exsanguinated from the abdominal aorta. The thoracic organs were dissected en bloc, and the right lung was ligated at the main bronchus and removed. The left lung was inflated via the trachea with 10% buffered formalin at a pressure of 22 cm of water, the trachea was clamped, and the lung was immersed in formalin.

The right lung was separated into the anatomically distinct anterior, medial, and posterior lobes. The right anterior lobe was weighed and stored at −20° until assayed for hydroxyproline (collagen) content by the method of Stegemann and Stalder [16]. Data were expressed as micrograms hydroxyproline (HP) per right anterior lobe (RAL) or milligrams HP per gram wet weight. The right medial lobe was weighed and frozen for measurement of ACE activity by the method of Cushman and Cheung [17]. Protein concentration was determined by the biuret reaction. ACE activity was expressed as units per right medial lobe (RML), units per gram wet weight, or units per gram protein as described previously [18]. One unit of ACE activity is defined as the amount catalyzing the formation of 1 μmol of hippuric acid from the artificial substrate (hippuryl-L-histidyl-L-leucine), supplied by the Sigma Chemical Co. (St Louis, MO), in 1 min at 37° under standard assay conditions. The right posterior lobe of the lung was bisected perpendicular to the spinal axis. The cephalic half was minced, weighed, and incubated at 37° for 10 min in 3.0 ml of Dulbecco's phosphate-buffered saline containing glucose (1.0 mg/ml). Prostaglandin production then was stopped by mixing aliquots of medium with an equal volume of aspirin solution (2 mM). Samples were left at room temperature for 1 hr, frozen in liquid N_2, and stored at −70°. Prostacyclin (PGI_2) and thromboxane (TXA_2) concentrations in the samples were determined by radioimmunoassay of their stable metabolites, 6-keto-$PGF_{1\alpha}$ and TXB_2, respectively (New England Nuclear, Boston, MA). Data were expressed as nanograms of prostanoid produced per milligram wet weight of lung mince during the 10-min incubation. The caudal half of the right posterior lobe was frozen for measurement of plasminogen activator activity by the fibrin plate lysis method [19]. Data were expressed as area (mm^2) of the fibrin plate lysed under standard *in vitro* conditions.

The heart was weighed, fixed in formalin, and later dissected into the right ventricle (RV) and the left ventricle plus septum (LV + S). Right ventricular hypertrophy was evaluated on the basis of the RV/LV + S weight ratio.

A 4 μm mid-sagittal section of the formalin-fixed left lung was stained with hematoxylin-eosin, and examined by light microscopy. All pulmonary arteries whose outer diameter was 20–200 μm were photographed, and the mean wall thickness and outer diameters were determined by computerized image analysis of the photomicrographs. The percentage of severely occluded pulmonary arteries (SOPA) was calculated for each animal. A severely occluded artery was defined as one whose mean wall thickness exceeded 80% of the outer radius of the vessel [9]. In a totally occluded vessel, mean wall thickness is 100% of the outer radius. Three additional animals from each group were anesthetized, and the lungs were perfused via the right ventricle with glutaraldehyde-paraformaldehyde fixative. Lung samples then were processed for transmission electron microscopy [4].

Data were subjected to an analysis of variance and Neuman–Keuls testing [20]. Differences were considered significant when $P < 0.05$. All values are means ± SE.

RESULTS

Survival and body weight

Only one animal, from the group receiving monocrotaline alone, died during the study. Body weight gain in the group receiving SC39026 alone was not significantly different from that of the control group, while weight gain in the two monocrotaline-treated groups was slightly but not significantly less than control (Table 1).

Heart weight

In rats receiving SC39026 alone, the weights of the whole heart, the left ventricle plus septum (LV + S), the right ventricle (RV), and RV/LV + S were not significantly different from control values, whether the data were expressed as absolute weight or relative to body weight (Table 1). In contrast, animals receiving monocrotaline alone developed a significant increase in absolute and relative weight of the right ventricle. The RV/LV + S weight ratio of monocrotaline-treated rats (38.1 ± 3.0%) also was significantly greater than the control value (24.8 ± 0.9%). However, in animals receiving monocrotaline plus SC39026, right ventricle weight and RV/LV + S were only slightly and not significantly greater than the control values (Fig. 1). Thus, co-

Table 1. Cardiopulmonary reactions in monocrotaline-treated rats: Modification by the elastase inhibitor SC39026*

Response	Control	SC39026 (SC)	Treatment group Monocrotaline (MONO)	MONO + SC
Survival	10/10	10/10	9/10	12/12
Body weight (g)	411 ± 8	436 ± 11	377 ± 14	391 ± 7
Heart weight (mg)	1280 ± 35	1370 ± 39	1422 ± 101	1301 ± 36
Left ventricle wt (mg)	661 ± 18	694 ± 22	590 ± 27	623 ± 20
Left ventricle wt (mg/g body wt)	1.61 ± 0.04	1.59 ± 0.04	1.53 ± 0.06	1.59 ± 0.03
Right ventricle wt (mg)	164 ± 6	152 ± 5	224 ± 19†	180 ± 8
Wet weight (mg/RML)	179 ± 3	193 ± 5	202 ± 8	208 ± 9
Protein (mg/RML)	13.2 ± 0.5	15.5 ± 1.5	15.1 ± 1.4	16.3 ± 1.6
Protein (mg/g wet wt)	73.8 ± 2.5	80.5 ± 6.8	74.6 ± 5.0	79.0 ± 4.1
ACE activity‡ (U/g wet wt)	1.49 ± 0.08	1.42 ± 0.13	0.65 ± 0.17†	0.81 ± 0.07†
ACE activity (U/g protein)	20.4 ± 1.4	18.0 ± 1.5	8.6 ± 1.8†	10.5 ± 1.0†
Wet weight (mg/RAL)	141 ± 8	137 ± 16	164 ± 10	168 ± 7
Hydroxyproline (μg/RAL)	319 ± 7	313 ± 14	386 ± 25†	384 ± 20†
Hydroxyproline (mg/g wet wt)	2.3 ± 0.1	2.1 ± 0.1	2.4 ± 0.1	2.3 ± 0.1

* Rats consumed drugs continuously for 6 weeks. RML = medial lobe of right lung; RAL = anterior lobe of right lung. Values are means ± SE; N = 9–12.

† Different from control, $P < 0.05$.

‡ One unit of ACE activity is defined as the amount catalyzing the formation of 1 μmol of hippuric acid from the artificial substrate (hippuryl-L-histidyl-L-leucine) in 1 min at 37° under standard assay conditions.

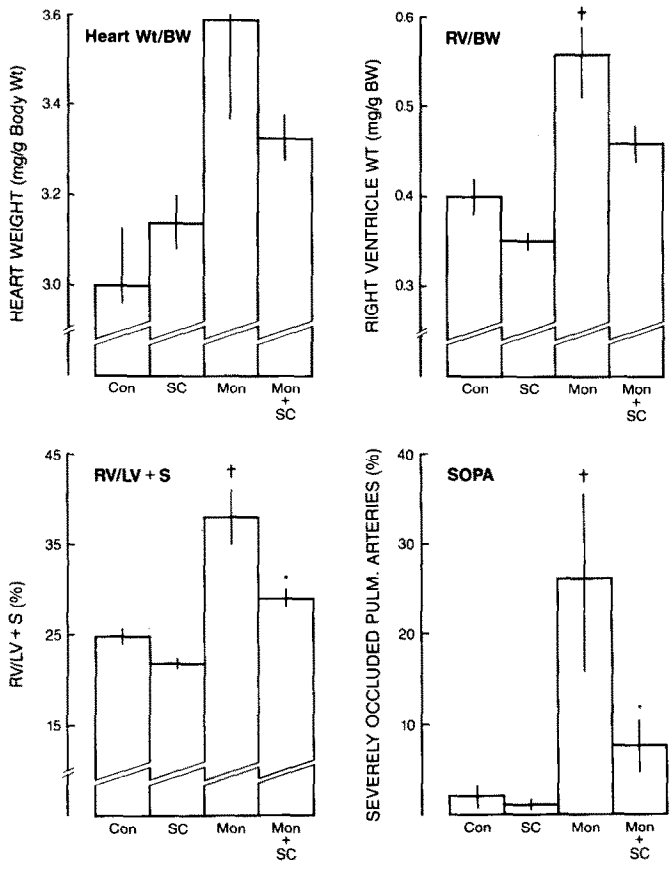

Fig. 1. Anatomic correlates of pulmonary hypertension in rats killed after 6 weeks of continuous consumption of control diet (Con), SC39026 (SC, 60 mg/kg/day), monocrotaline (Mon, 2.2 mg/kg/day), or monocrotaline plus SC39026 (Mon + SC, as above). Values are means ± SE; N = 7–12. Key: (†) different from control, $P < 0.05$; and (*) different from monocrotaline, $P < 0.05$. Upper left: heart weight relative to body weight. Upper right: right ventricle weight relative to body weight. Lower left: right ventricle (RV) to left ventricle plus septum (LV + S) weight ratio. Lower right: percent severely occluded small pulmonary arteries.

treatment with SC39026 more than halved the monocrotaline-induced right ventricular hypertrophy.

Pulmonary endothelial function

Angiotensin converting enzyme (ACE) activity. ACE activity in the right medial lobe (RML) of rats consuming SC39026 alone (276 ± 31 mU/RML) was similar to that of untreated control animals (267 ± 13 mU/RML). Rats receiving monocrotaline alone exhibited a significant reduction in lung ACE activity (136 ± 37 mU/RML) to approximately 50% of the control value. Lung ACE activity in the group receiving monocrotaline plus SC39026 (165 ± 14 mU/RML) also was lower than the control value, and was not significantly different from the monocrotaline-only group (Fig. 2). Similar results were obtained when lung ACE activity was expressed on the basis of wet weight or protein content (Table 1).

Plasminogen activator (PLA) activity. Lung PLA activities in the control (87 ± 5 mm^2) and SC39026-treated (81 ± 6 mm^2) rats were not significantly different, whereas PLA activity in the group receiving monocrotaline alone decreased significantly to 62 ± 6 mm^2 (Fig. 2). Animals receiving both monocrotaline and SC39026 exhibited lung PLA activity intermediate between the control and monocrotaline-only values, and not significantly different from either (Fig. 2).

Prostacyclin (PGI_2) and thromboxane (TXA_2) production. Values for lung PGI_2 and TXA_2 production in rats receiving SC39026 alone were not significantly different from control levels. Monocrotaline-treated rats, in contrast, exhibited approximately a doubling of the normal production rate of both prostanoids, and this effect was not ameliorated by cotreatment with SC39026 (Fig. 2).

Pulmonary hydroxyproline (HP) content

Hydroxyproline content of the right anterior lobe (RAL) of SC39026-treated rats was similar to that of control animals (313 ± 14 and 319 ± 7 μg/RAL, respectively). In contrast, lung HP content in rats

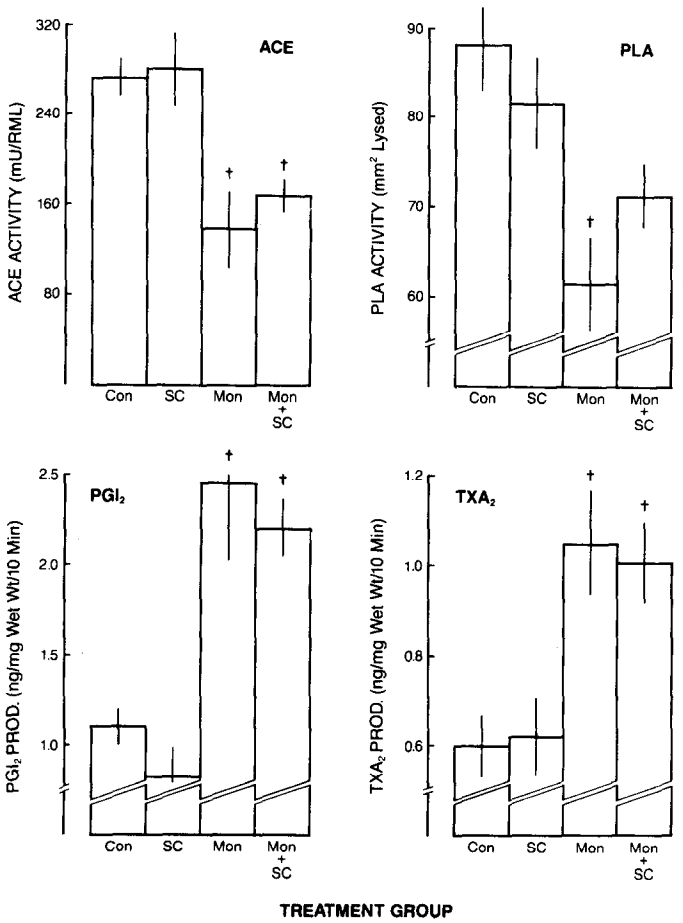

Fig. 2. Pulmonary endothelial function in rats killed after 6 weeks of continuous drug administration. See legend to Fig. 1 for treatment regimens. Values are means ± SE; N = 7–9. Key: (†) different from control, $P < 0.05$. Upper left: angiotensin converting enzyme (ACE) activity. One unit of ACE activity is defined as the amount catalyzing the formation of 1 μmol of hippuric acid from the artificial substrate (hippuryl-L-histidyl-L-leucine) in 1 min at 37° under standard assay conditions. Upper right: plasminogen activator (PLA) activity. Lower left: prostacyclin (PGI_2) production. Lower right: thromboxane (TXA_2) production.

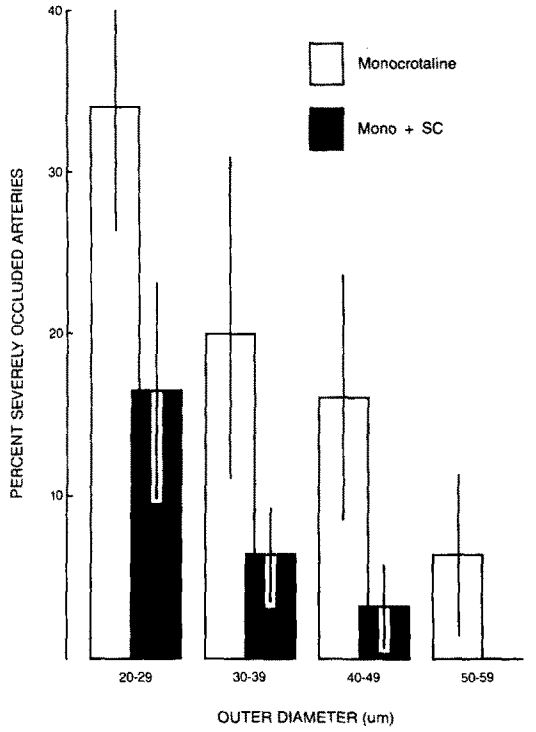

Fig. 3. Percent severely occluded pulmonary arteries as a function of arterial outer diameter in rats killed after 6 weeks of continuous ingestion of monocrotaline (open bars) or monocrotaline plus SC39026 (solid bars). A severely occluded artery was defined as one whose mean wall thickness exceeded 80% of its outer radius. Severe occlusion was rare in arteries with outer diameters greater than 59 μm. Values are means ± SE; N = 12.

receiving monocrotaline increased significantly to 386 ± 25 μg/RAL, and this increase was not prevented by cotreatment with SC39026 (Table 1). The monocrotaline-induced increase in lung HP content was accompanied by a slight but nonsignificant increase in lung wet weight. As a result, lung HP concentration ranged from 2.1 ± 0.1 to 2.4 ± 0.1 mg/g wet weight among the four groups, and was independent of treatment (Table 1).

Pulmonary histology and ultrastructure

Light microscopy. The lungs of both untreated and SC39026-treated animals exhibited occasional focal perivascular inflammatory cell infiltrates and hypercellularity. In all other respects the lungs of the two control groups were normal. In contrast, severe histopathologic changes were noted in the lungs of monocrotaline-treated rats. Perivascular edema and inflammatory cell infiltrates (polymorphonuclear leukocytes, lymphocytes and macrophages) were widely distributed. Airspaces contained debris and proteinaceous fluid, and excess numbers of macrophages, polymorphonuclear leukocytes, and erythrocytes. Occasional hemosiderin-containing cells were noted. The media of the pulmonary arteries and arterioles was thickened and exhibited an increase both in the number of smooth muscle cells and in the quantity of extracellular connective tissue. This mural thickening became partially and even completely occlusive, particularly in the small arteries and arterioles. Of these histopathologic reactions, only the severity of the monocrotaline-induced pulmonary vascular wall thickening appeared to be spared by cotreatment with SC39026.

Pulmonary arterial wall thickening. Pulmonary vascular changes were quantitated more precisely by computer-assisted digital image analysis. Mean wall thickness and outer diameter were measured in photomicrographs of a total of 1380 pulmonary arteries from thirty animals in the four treatment groups. The data were expressed as percent severely occluded pulmonary arteries. An artery whose mean wall thickness exceeded 80% of its outer radius was defined as severely occluded. Severe arterial occlusion occurred in only 4 of 189 arteries from untreated control lungs and in 2 of 177 arteries from SC39026-treated animals. In the two groups receiving monocrotaline, however, the frequency of pulmonary arterial occlusion was inversely proportional to vessel outer diameter, and was significantly higher in rats treated with monocrotaline alone than in the combined drug group (Fig. 3). Since almost all of the severely occluded arteries had outer diameters of 20–49 μm, these were grouped into a category termed "small" arteries for statistical analysis. A total of 26.1 ± 9.7% of the small pulmonary arteries from monocrotaline-treated rats were severely occluded, and this value decreased significantly to 7.8 ± 2.7% in the combined-drug group (Fig. 1).

Transmission electron microscopy. Pulmonary ultrastructure in untreated control and SC39026-treated rats was generally normal. The only unique ultrastructural change observed in the lungs of SC39026-treated animals was the loss of electron density in many alveolar Type I epithelial cells (Fig. 4). This rarefaction was due to an apparent decrease in cytoplasmic organelles in the Type I cells.

Ultrastructural changes in monocrotaline-treated rat lungs were striking and confirmed the light microscopic findings. These included increased collagen bundles and interstitial cells in the alveolar septa, increased polymorphonuclear leukocytes in and out of capillary lumens, and an increased macrophage population in the alveolar spaces (Fig. 5). All of these reactions were observed in the lungs of rats receiving both monocrotaline and SC39026. This group also exhibited the rarefaction of Type I epithelial cells noted in animals receiving SC39026 only.

DISCUSSION

These data demonstrate that the neutrophil elastase inhibitor SC39026 can intervene in the pathogenesis of monocrotaline-induced cardiopulmonary damage in rats consuming the drugs continuously for 6 weeks. This observation confirms a previous report in which SC39026 was administered by twice daily gavage, from 12 hr before to 8 days after a single s.c. injection of monocrotaline [15]. While SC39026 ameliorates some monocrotaline-induced cardiopulmonary reactions, the inhibitor appears to act selectively. In the present study, cotreatment with SC39026 reduced both the frequency of occlusive wall thickening in small pulmonary arteries, and the

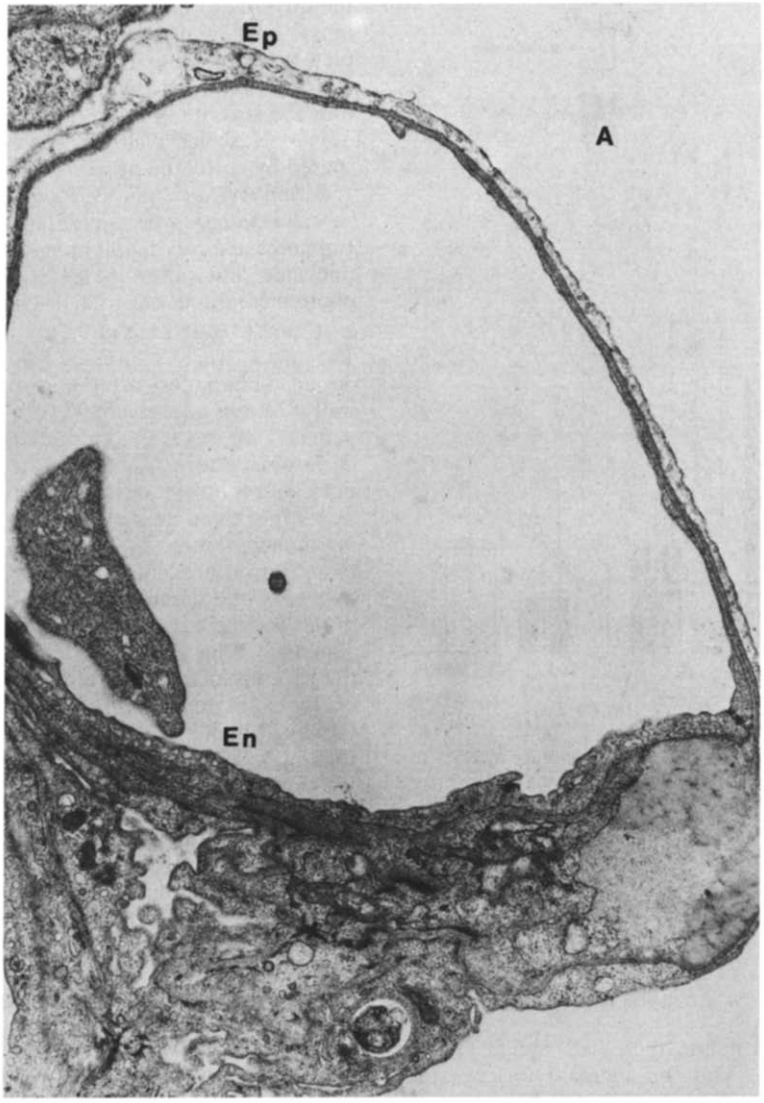

Fig. 4. Electron micrograph of the lung of a rat killed after 6 weeks of continuous ingestion of SC39026 (60 mg/kg/day). Note rarefaction of the Type I epithelial cell (Ep). This was the only difference between the control and SC39026-treated animals noted in the present study. Alveolar spaces (A) are clear, and endothelial cells (En) exhibit normal ultrastructure. Magnification: ×12,740.

cardiac right ventricular hypertrophy observed in monocrotaline-treated rats. At the same time SC39026 did not influence the severity of pulmonary inflammation, hydroxyproline accumulation, or endothelial dysfunction in these animals. The monocrotaline reactions spared by concomitant SC39026 administration are anatomic correlates of pulmonary hypertension. Thus, the present data provide indirect confirmation that SC39026 ameliorates monocrotaline-induced pulmonary hypertension. A similar therapeutic action of SC39026 has been demonstrated by direct determination of pulmonary artery pressure in rats receiving a single injection of monocrotaline [15]. These data suggest, therefore, that inappropriate neutrophil elastase activity contributes to the pulmonary vasculopathy and hypertension in monocrotaline-treated rats.

The point at which SC39026 intervenes in the pathogenesis of monocrotaline-induced pulmonary hypertension remains to be determined. However, SC39026 clearly does not influence the pulmonary endothelial dysfunction observed in monocrotaline-treated rats. Suppressed lung ACE and PLA activities and increased PGI_2 and TXA_2 production represent nonspecific responses of the pulmonary endothelium to insult, inducible not only by monocrotaline [4], but also by thoracic irradiation [21] and bleomycin administration [22]. While these endpoints are fairly specific markers of endothelial function, alternative cell types in the lung can exhibit ACE and PLA activities, and PGI_2 and TXA_2 production [21]. However, as measured in this study, we believe these endpoints largely reflect endothelial status [21]. In the present study, cotreatment with

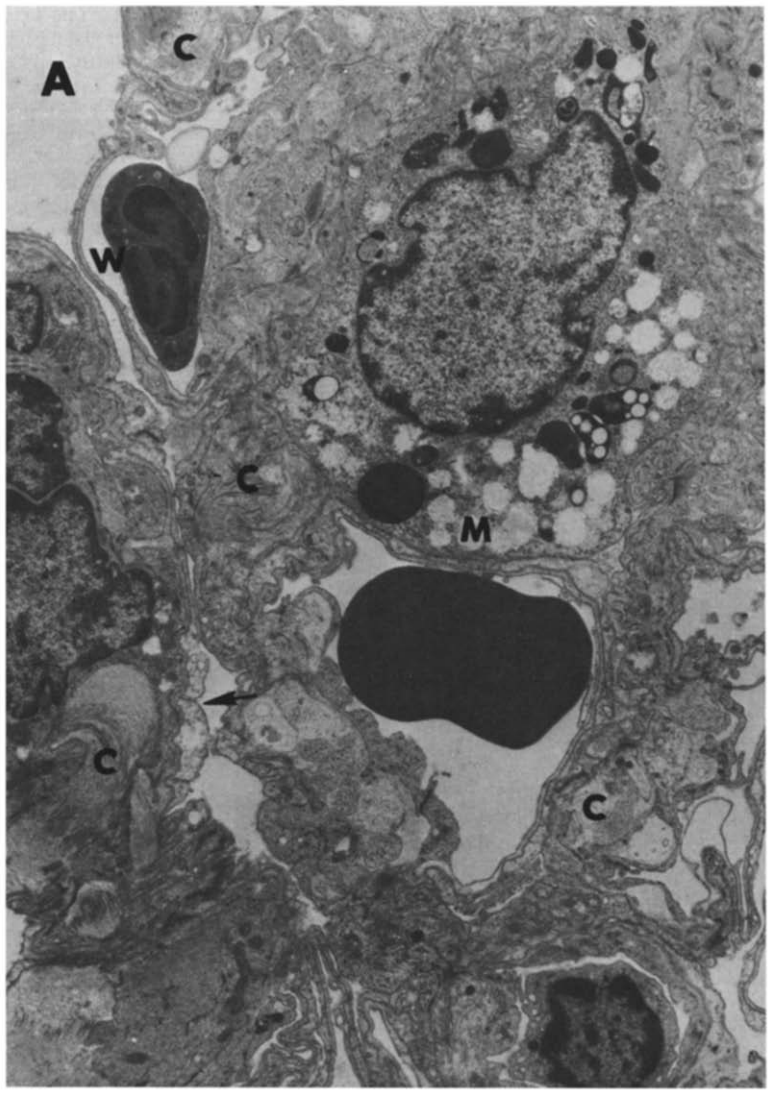

Fig. 5. Electron micrograph of the lung of a rat killed after 6 weeks of continuous ingestion of monocrotaline (2.2 mg/kg/day). Note the increase in interstitial collagen (C). A polymorphonuclear leukocyte (W) is present in one capillary. Note the interstitial macrophage (M), and the rarefaction of a Type I epithelial cell (arrow). A = alveolus. Magnification: ×6000.

SC39026 did not ameliorate any of these endothelial functional responses to monocrotaline. Similarly, Ilkiw *et al.* [15] observed that a therapeutic regimen of SC39026 does not spare ultrastructural changes in the pulmonary endothelium of monocrotaline-injected rats. Of the successful modifiers of monocrotaline pulmonary hypertension tested previously by our laboratory, including penicillamine [8] and six ACE inhibitors [8–11], none has been found to ameliorate monocrotaline-induced pulmonary endothelial dysfunction. The endothelial cell damage which accompanies lung inflammation is thought to be mediated, at least in part, by products of polymorphonuclear leukocyte (PMN) metabolism, including elastase [23] and hydroxyl radicals [24]. While SC39026 might not be expected to influence the latter, there was reason to hope that it would reduce the former damage. Yet SC39026 had no effect on monocrotaline-induced pulmonary endothelial damage, whether the damage was assessed functionally (Fig. 2) or ultrastructurally [15]. Nor did cotreatment with SC39026 reduce the severity of the inflammatory reaction or the influx of neutrophils, as evaluated by light microscopy of monocrotaline-treated lungs. It is possible that SC39026 inhibits inappropriate neutrophil elastase activity in the extravascular compartment of the lung, an area inaccessible to the natural elastase (protease) inhibitors such as α1-antitrypsin and α2-macroglobulin [14]. Neutrophil elastase degrades not only elastin but also types III and IV collagen [25]. Thus, elastase-induced alterations in extracellular matrix may modulate cell morphogenesis, chemotaxis, proliferation, and/or connective tissue metabolism in

the vessel wall [26–28]. By intervening in this process, SC39026 may reduce the muscularization [15] and the occlusive wall thickening (Fig. 3) of the small arteries and arterioles of monocrotaline-treated lung. This intervention then may ameliorate the increase in pulmonary artery pressure [15] and the right ventricular hypertrophy ([15], Fig. 1) which accompany monocrotaline pulmonary hypertension. Since only one time point (6 weeks) has been evaluated in the present study, it also is possible that SC39026 simply delays the onset rather than prevents monocrotaline toxicity. Whatever its mechanism of action, SC39026 must be added to the already extensive list of agents capable of modifying monocrotaline-induced cardiopulmonary injury [11]. The list of successful modifiers seems too diverse to propose a common mechanism of action. Indeed, the pathogenesis of monocrotaline pneumotoxicity is so complex that multiple points of intervention seem reasonable.

Animals receiving SC39026 alone did not differ significantly from untreated control rats with respect to any of the endpoints quantitated in the present study. However, the observation that pulmonary Type I epithelial cell rarefaction was common only in electron micrographs from animals receiving SC39026, either alone or in combination with monocrotaline, merits further study. In its ability to provide therapy without quantifiable side-effects, SC39026 resembles penicillamine [8] and is superior to the same dosage of ACE inhibitors such as Captopril [8] and CL242817 [9] in this monocrotaline model. Unlike Captopril and CL242817, however, SC39026 and penicillamine do not ameliorate monocrotaline-induced hydroxyproline (collagen) accumulation in rat lung [8, 9].

In conclusion, cotreatment with the neutrophil elastase inhibitor SC39026 ameliorated monocrotaline-induced occlusive wall thickening of small pulmonary arteries, and cardiac right ventricular hypertrophy in rats. SC39026 reduced these anatomic correlates of pulmonary hypertension without modifying pulmonary inflammation, fibrosis or endothelial dysfunction in the monocrotaline-treated animals. Furthermore, SC39026 was effective at a regimen (60 mg/kg/day, p.o.) which appears to be relatively free of side-effects for at least 6 weeks of continuous drug administration in this species.

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