Histopathologic alterations induced in the lungs of sheep by use of α_2-adrenergic receptor agonists

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Objective—To study effects of central- and peripheral-acting α_2-adrenergic receptor agonists on lung parenchyma, platelets, and pulmonary intravascular macrophages (PIM) of sheep.

Animals—12 healthy mature female sheep.

Procedure—Group-1 (control, n = 2) sheep received 5 ml of physiologic saline solution IV and were euthanatized 3 minutes later. Sheep of group 2 (n = 8) received xylazine (150 µg/kg of body weight, IV), then 2 sheep each were euthanatized 3, 10, or 60 minutes, or 12 hours later. Sheep (n = 2) of group 3 were given ST-91 (30 µg/kg, IV), then were euthanatized 3 minutes later. Immediately after euthanasia, the lungs were fixed intratracheally and tissue was obtained for light and electron microscopy after 1 hour.

Results—Pulmonary parenchymal damage or morphologic alterations in PIM and platelets were not evident in control sheep. Three minutes after xylazine administration, morphologic changes in PIM were appreciable. After 10 minutes, extensive damage to the capillary endothelium and alveolar type-I cells, intra-alveolar hemorrhage, and interstitial and alveolar edema were evident. Most PIM had complete internalization of the surface coat. Similar changes were seen 60 minutes after xylazine administration; however, by 12 hours, morphologic features of PIM and lung parenchyma were almost completely restored. Evidence of PIM activation, obvious damage to capillary endothelium, and extensive pulmonary edema also were evident 3 minutes after ST-91 administration.

Conclusions—Xylazine induces severe pulmonary parenchymal damage when administered at clinical sedative doses in sheep; morphologic changes in PIM within 3 minutes after administration of these drugs are substantial; and platelet aggregation is not apparent. (*Am J Vet Res* 1999;60:154–161)

Alpha$_2$-adrenergic receptor agonists (α_2-agonists), such as xylazine, are commonly used as sedative analgesics in veterinary medicine. These agents induce severe hypoxemia in sheep when administered IV at nonsedative and sedative doses.[1-5] In conscious sheep, a comparable degree of hypoxemia is induced by IV administration of various α_2-agonists, irrespective of their reported variable selectivity and affinity for α_2-versus α_1-adrenoceptors.[2,3] Furthermore, an α_2-agonist that does not cross the blood-brain barrier, ST-91, also induces hypoxemia, indicating involvement of a peripheral component in hypoxemia.[3,5] In conscious sheep, hypoxemia is accompanied by a substantial increase in respiratory frequency and maximal **change in transpulmonary pressure (Ppl)**.[2,3] Significant increase in airway pressure after α_2-agonist administration has also been reported in anesthetized, ventilated sheep.[4,6] The increase in Ppl and airway pressure is suggestive of a change in pulmonary mechanics.

Taken together, these results indicate that α_2-agonists might induce structural alterations in lung parenchyma, in turn inducing hypoxemia and an alteration in pulmonary mechanics. Eisenach[5] hypothesized that α_2-agonists induce transient platelet aggregation, leading to pulmonary microembolism and hypoxemia; however, morphologic study was not done to support this hypothesis.

It is an interesting coincidence that species that manifest a hypoxemic response to α_2-agonists also have a unique population of macrophages called **pulmonary intravascular macrophages (PIM)**. For instance, ruminants, which have a rich population of these cells,[7-9] also develop a severe hypoxemic response after administration of α_2-agonists.[1-5] On the other hand, PIM in the pulmonary capillaries of dogs have not been reported,[10] and α_2-agonists do not cause appreciable lowering of Pa_{O_2} values in that species.[11,12] The PIM are highly reactive to endotoxins[13]; antiplatelet serum[14]; tracer particles, such as monastral blue[9] drugs (eg, heparin[8]); and the pharmacologic vehicle propylene glycol.[15] Recently, it was reported that equine PIM were markedly affected by halothane, an inhalant anesthetic agent.[16] Once stimulated, PIM are capable of producing a battery of vasoactive mediators, such as arachidonate metabolites and cytokines.[17] According to Brain,[18] PIM are central to the chain of events leading to altered ventilation and perfusion, and finally to respiratory distress, in ovine and porcine experimental models of pulmonary damage.

In the study reported here, the central- and peripheral-acting α_2-agonist xylazine was administered to

Received for publication Jul 24, 1997.
Accepted May 19, 1998.
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Supported in part by the Canadian Commonwealth Fellowship Fund and the Ontario Ministry of Agriculture, Food and Rural Affairs.
This report represents a portion of a thesis submitted by the senior author to the graduate school as partial fulfillment of the requirements for the PhD degree.
The authors thank Dr. L. Viel for assistance with interpretation of the histologic data, Kanwal Minhas for technical assistance with electron microscopy, and Boehringer Ingelheim for providing ST-91.