Minoxidil and Cardiac Lesions

To the Editor:

The paper “Minoxidil: Right Atrial Cardiac Pathology in Animals and Man” by Sobota et al. (Circulation 62: 376, 1980) is an inadequate assessment of the potential cardiac toxicity of minoxidil. The authors point out that at least two types of cardiac lesions, involving the right atrium and the left ventricular papillary muscles, are caused by this drug in experimental animals, but they do not present all available information concerning these alterations.

Sobota et al. devote considerable attention to the right atrial lesion, which consists of extravasation of blood, phagocytosis of hemosiderin and formation of new blood vessels and connective tissue. These microscopic changes are accompanied by striking redness of the right atrial appendage. This lesion is claimed to be limited to the beagle dog and to occur when doses of 1 mg/kg or greater of minoxidil are given for at least 1 month. The authors emphasize the species specificity of this lesion to the extent that it seems unlikely that a similar phenomenon could occur in the human or in other species. Some important information regarding these lesions was omitted from this article. Pathologic changes were observed in right atria of beagle dogs after only two daily doses of minoxidil. These alterations included focal deposits of fibrinoid material in the walls of small right atrial coronary arteries; in addition, multiple foci of small, flame-shaped hemorrhages in epicardium and endocardium were observed in many of the animals. A further critical factor is that we have also found atrial lesions in miniature pigs given 3 or 10 mg/kg of minoxidil for 2 days. In miniature pigs, the atrial lesions have been found to be predominantly localized in the left atrium, rather than in the right atrium. The pathogenesis of the atrial lesions is not understood. Nevertheless, the localization of these lesions in the left atrium of miniature pigs (which have an anatomic pattern of coronary circulation that differs from that of dogs and is more similar to that of humans) raises serious questions as to whether minoxidil toxicity can be excluded on the basis of a morphologic study of right atrial lesions in human hearts. Detailed studies of both atria are needed to evaluate the potential toxicity of minoxidil.

Other drugs can produce atrial lesions similar to those of minoxidil. For example, a recent report implicates theobromine as the cause of such lesions in mongrel dogs. These lesions may represent a new, previously unrecognized pathologic and pharmacologic phenomenon that cannot be dismissed as a peculiar, species-specific response of beagle dogs to minoxidil.

Left ventricular papillary muscle lesions constitute the second pathologic change produced in the heart by minoxidil. Sobota et al. acknowledge that this lesion occurs in other species and that it can be induced by other drugs. However, their description of this lesion as “cytoplasmic loss in myocardial cells” is a euphemism for myocardial necrosis. The features of this necrosis have been documented. Sobota et al. state that there is no convincing evidence that the right auricular or the left papillary muscle lesions found in dogs have occurred in minoxidil-treated humans. Nevertheless, the opposite could also be true, as this is strictly a matter of interpretation of anatomic findings. Sobota et al. found lesions that could be ascribed to the drug. For example, they reported that the “only changes seen in autopsied cases were an extension of a left ventricular wall infarction to the left papillary muscle and, in some patients, focal fibrosis.” This focal fibrosis could have been a consequence of healing of drug-induced myocardial necrosis occurring early in the course of therapy. Temporary worsening of electrocardiographic patterns has been observed at the beginning of minoxidil therapy. We conclude that the atrial lesions produced by minoxidil are not limited to beagle dogs, or to the right atrium; that the ventricular papillary muscle lesions are characterized by myocardial necrosis with contraction bands rather than by “cytoplasmic loss;” and that the published studies of human hearts do not exclude the possibility of minoxidil-induced cardiotoxicity.

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