The dark side of fluoroquinolones

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Once, fluoroquinolones were considered safe antibiotics that treat infection beneath the waist by killing everything smaller than a squirrel. Fluoroquinolones were easily administered orally and were often widely used, even prophylactically, for recurrent urinary tract infection.¹ Soon, tendon ruptures were observed in patients using fluoroquinolones.² A recent clinical study suggests that fluoroquinolones are linked with aortic aneurysm and dissection and that extracellular matrix, collagens, and fibroblasts of the aortic wall may behave analogously to the collagen of tendon tissue.³ It is disturbing to acknowledge the dramatic shift of fluoroquinolones from drugs with a benign reputation into agents with evil side effects.

The study presented in this issue of the *Journal* by Guzzardi and colleagues⁴ sheds fascinating light on the mystery association of fluoroquinolones and aortopathy. Human aortic myofibroblasts were procured from patients undergoing surgery for the ascending aorta. After exposure to fluoroquinolones, degradation of extracellular matrix of these cells was investigated with a 3-dimensional microgel assay, and collagen-1 expression was assessed by immunoblotting and immunofluorescent staining. Cell apoptosis and metabolic activity were investigated. This in vitro study showed that the interaction of myofibroblasts with fluoroquinolones resulted in a molecular imbalance involving matrix metalloproteases and tissue inhibitors of matrix metalloproteases, leading to the degradation of essential aortic wall collagens. A beautiful set of figures is presented to delineate the key findings.

A sequel of exciting questions now emerges. Can these seemingly unharmed fluoroquinolones really have such a hidden dark side effect on the aorta? The role of antibiotics during evolution of the aortic wall in general is most controversial as tetracyclines, another family of antibiotics, may in contrast inhibit aortic aneurysm formation by inhibiting metalloprotease activity.⁵ The study does not demonstrate whether fluoroquinolones aggravate already diseased myofibroblasts, and it is therefore possible that they are not a trigger of the onset of aortopathy but rather add to the progression of a preexisting disease. Aortopathy is a

The dark side of fluoroquinolones may explain iatrogenic aortopathy.

Central Message

Aortic wall metalloproteases and their inhibition may be investigated in vitro with the aid of fluoroquinolones.

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generalized term that clinically encompasses many events: aortic dissection, aortic dilatation, aortic aneurysm formation, aortic rupture, and aortic wall sclerosis, to name but a few. The samples in this study were obtained from the proximal part of the aorta, which is embryologically derived from neural crest cells that may be susceptible to a different aortopathy than the rest of the aorta.⁶ The samples were procured from only 9 patients with aortopathy, and bicuspid aortic valves were present in most of the patients; aortopathy may genetically differ in some patients according to aortic valve morphology.⁷ As Guzzardi and colleagues⁴ state, this is clearly a preliminary work.

For the first time, the wild theory of fluoroquinolone-associated aortopathy has a molecular hint that is based on collagen degeneration and progression of aortic disease. Metalloproteases and their inhibitors are intertwined and form a basis for a metabolic matrix tissue stability that may be interrupted pharmacologically. This theory is in line with previous observations revealing antifibrotic activity⁸ and decreased collagen-1 protein expression with fluoroquinolones.⁹ The enigmatic puzzle of the progression of some aortic events may alarmingly be iatrogenic, and the clinician may wisely consider a prudent use of fluoroquinolones in patients with aortic dilatation.

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