



The mechanisms of increasing outflow facility by AR-13324M in human eyes

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Purpose: AR-13324 is an inhibitor of Rho kinase/norepinephrine transporter currently in Phase 3 clinical development for the treatment of glaucoma. We investigated the effects of AR-13324M, the active metabolite of AR-13324, on the outflow facility (C), hydrodynamics, and morphology of the trabecular outflow pathway in enucleated human eyes.

Methods: Five pairs of eyes were perfused with phosphate buffered saline containing 5.5 mM glucose (GPBS) at 15 mmHg for baseline C. One eye of each pair was then exchanged (5mL) and perfused with 0.3 μ M AR-13324M for 3 hours, while the contralateral eye was treated with vehicle in GPBS. The anterior chambers of both eyes were exchanged and perfused with a fixed volume of fluorescent microspheres (150 μ L) to trace the outflow patterns prior to perfusion-fixation. The trabecular meshwork (TM) and episcleral veins (ESVs) were imaged from the anterior segment using a global imaging technique. Frontal sections of anterior segments were imaged by confocal microscopy. The percent effective filtration area (PEFA) was calculated from the measured lengths of tracer distribution in the TM, ESVs, and along the inner wall (IW) of Schlemm's canal (SC). Morphological changes, including TM thickness and cross-sectional areas of ESVs, were analyzed by light and electron microscopy. Student's t-test and correlation analysis were performed.

Results: C increased by 51% and 102% after 3-hr perfusion with AR-13324M when compared to the baseline ($p < 0.01$) and controls ($p < 0.01$), respectively. A significant increase in PEFA in both IW and EPVs was found in the treated eyes. In control eyes, the PEFA was similar between the ESVs and IW; however, in treated eyes, PEFA in the ESVs was significantly higher than in the IW ($p < 0.01$), which is associated with increased cross-sectional areas of ESVs ($p < 0.01$). PEFA in ESVs was positively correlated to the percent change in C. TM was significantly expanded ($p < 0.05$) in high versus low tracer regions in control eyes, and this expansion was found in both low and high tracer regions in treated eyes.

Conclusions: AR-13324 acutely increases C by increasing the area of actively filtering tissue in the trabecular outflow pathway, expanding TM and dilating ESVs in normal human eyes. These effects need to be followed in the diseased trabecular outflow pathway of glaucomatous patients in long-term treatment.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.: