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Aminoglycoside/imidazoles in the treatment of *Acanthamoeba* keratitis

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Introduction: Aminoglycosides and its derivatives have been recommended for Acanthamoeba keratitis (AK) treatment, Neosporin (Neomycin, Polymyxin and B-Gramicidin) since 2005 or tobramycin. Ishibashi in 1990 published 3 cases successfully resolved using imidazoles alone. Topical aminoglycosides in combination with oral imidazoles, itraconazole has been sowed a good medical treatment too. We describe five cases of culture proved AK and medically treated with netilmicin, a semisynthetic derivative drug of recent medical use, available in intravenous presentation, and useful in ophthalmic topical drops 0.3% concentration (SIFI Laboratory Sicily Italy), alone or in some cases combined with an oral imidazole itraconazole.

Material & Methods: We present five cases of AK culture proved, its clinical diagnosis, treatment and evolution. Case No 1. Female 19 years old, living in Mexico City, contact lens user, she presented with visual acuity loss one week before attention in both eyes. She had received topical gatifloxacin 0.3% and netilmycin 0.3% with no specification of dose and time. At Cornea Department in this Hospital, slit lamp examination was performed: In OD corneal haze and mild keratitis were found; also epithelial edema and perineural infiltrate in temporal inferior quadrant (Figure 1). In OS conjunctiva hyperemia, central cornea stromal opacity and diffuse perineural infiltrate was observed (Figure 3). Patient was diagnosed as OS herpes simplex keratitis, oral Acyclovir was prescribed (400 mg/5 times a day), without clinical response. Sample of both corneas scraps, and both contact lens for bacterial, Fungal and Acanthamoeba was taken at the first medical consultation in the hospital. Laboratory report was Acanthamoeba spp growing in NNA agar covered with live E cloacae after 48hs, in both corneas and both contact lens samples, and culture was negative for bacteria in OS. Stenotrophomonas maltophilia in OD cornea, and contact lens samples. Acanthamoeba strain isolated form cornea sample in OD was identified as Acanthamoeba royreba. After laboratory results and AK diagnosis, topical netilmicin 0.3% eye drops (SIFI Sicily, Italy) and oral itraconazole (100 mg bid) were prescribed for both eyes. The patient was attended 30 days after, at slit lamp examination were observed in OD epithelial edema and perineural infiltrate in temporal inferior quadrant, 30 days after she presented a little inflammatory ring and perineural infiltrate in the same site described before, 12 days after there was observed haze for paracentral corneal, and vascularization, total superficial epithelialization of cornea surface in OD, and 6 weeks later she referred no pain, in the next visit the patient showed no ulcer in OD, inflammatory reaction and perineuritis diminished (Figure 2). In OS cornea, at this visit the patient showed no ulcer in OS cornea, an inflammatory reaction and perineuritis was diminished (Figure 4). The final visual acuity was 20/25 OD and 20/50 OS, perineural infiltrate on left eye continues but was diminished, 3 months later: final best corrected visual acuity 20/20 on both eyes, and haze on OD temporal cornea.

Case No 2:- Female 14 year old living in México City, contact lens user, by an acute ocular pain two days before in OS, was attended in APEC. In clinical exploration was observed; OS red eye, with epiphora +++, and acute pain. At slit lamp examination, was observed corneal ulcer in temporal superior quadrant cornea in OS, des-epitilization, and slight infiltrate surrounding the lesion (Figure 5, 6), she referred the use of CL washed with running water in both LC from both eyes, was administered topical Netilmicin 0.3% and Moxifloxacin 0.3% (Alcon Labs USA) in topical drops each 2hs, alternatively, and Ciprofloxacin ointment by night. Three days after, it was observed epithelialization of corneal ulcer, remaining only a discrete infiltrate. Twenty five days after was observed an superficial inflammatory infiltrate and perineuritis, in direction from infiltrate to central cornea. The laboratory report of Acanthamoeba sp culture in cornea and contact lens samples, was added to previous medical treatment; Itraconazol 100 mgs bid. Thirty days after the first consultation, patient referred no pain and the corneal ulcer was no visible, there was a superficial leucoma, visual acuity 20/60 Final BCVA 20/25

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Case No 3:- Female 17 years old, Living in Mexico City, contact lens user, she was attended after 21 days of onset by pain++ in OD, palpebral edema, and conjunctiva hyperemia ++. At slit lamp examination in OD was observed, cornea perineural inflammation, corneal ring surrounding a central desepthelization, after laboratory Acanthamoeba sp. culture confirmation in corneal sample, was started topical Brolene, Netilmicin and artificial tears each 2 hours alternatively, an oral Itraconazole 100 mgs each 2 hours. Because perforation risk in OD the patient was submitted to TPK (tectonic), the corneal tissue was submitted to laboratory studies cultures and microscopic observation (Figures 7) after three weeks, was adjusted one corneal suture, and presented in central donor cornea a visible desepthelization. For a peak of intraocular pressure was installed by surgery an intraocular Ahmed valve in OD with the regularization to 10 mmHg pressure, after 6 months the central donor cornea was reepitilized and the patient was maintained only in observation, remaining a visible central scar in her OD cornea.

Case No 4:- Female 14 years old contact soft lens user in right eye, 45 days before she had foreign body sensation, and have a central corneal ulcer diagnosed as corneal ulcer related to seasonal conjunctivitis, she received medical therapy with topical prednisolone and sodium cromoglycate, after increasing pain and loss vision, the patient was attended in Corneal service of our hospital. At slit lamp examination OD; infectious 5.6 and 6.3 mm in diameter central ulcer in the right eye, immune ring with light infiltrate surrounding the ulcer, inflammation in anterior chamber, hipopyon (Figure 8), VA; HM, severe conjunctivitis, and pain. In the smears from scrap sample taken was observed Acanthamoeba cyst (Figure 9) and in the culture Acanthamoeba sp. For medical treatment was administered topical Tobramycin 0.3% (Laboratorios Sophia, Mexico) each 2 hours day and night, and oral itraconazole 100 mgs bid, and was recommended do not use the contact lens in the right eye. Lab report was culture positive for Acanthamoeba castellani. Twenty four days days after was observed conjunctiva hyperemia, ciliar reaction 360 grades, some clear cornea, and no ulcer (Figure 10) was suspended oral itraconazole, and was added topical dibromo propamidine-isotionate (brolene) each 4 hours for 6 months. After 6 months OD, FVA 3/10 (.) 6/10

Case No 5:- Female 30 years old, refractive contact lens user in OS, referred intense pain 24 hours before, VA 20/200. At slit lamp observation; Ciliary 360 inflammatory reaction, central and superior paracentral cornea infiltrates in OS, VA 20/300(.)20/200, Tyndal +, Cells in anterior chamber +, immune ring and perineuritis (Figure 11). Samples for CL cultures was taken and yielded abundant colonies of *P aeruginosa* and cyst and trophozoites of Acanthamoeba sp, the diagnosis was AK, medically treated with topical netilmicin 0.3%, neomycin eye drops each 2 hours, the evolution taken 74 days, and was good. The patient showed central slight leucoma, FBCVA 20/20 (Figure 12).

Discussion: Nowadays, there are no single drug that eliminate from the cornea lesion Acanthamoeba cyst and trophozoites, for all the drugs tested the susceptibility is higher for trophozoites than for the cyst. Aminoglycosides interfere with the normal process of ribosomal function, and imidazols change the pathway at the synthesis of ergosterol in Acanthamoeba cells membrane. The combination is synergistic, and finally the action over the new Acanthamoeba trophozoites and cyst replicating in the cornea tissue, is expressed healing the keratitis in cases with early diagnosis.

Conclusion: In early diagnosis of AK the topical netilmicin/oral itraconazole can be a good choice for medical treatment; both medical drugs in pharmaceutical presentation are available in Mexico and are not so expensive.

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