

**INTRA-OPERATIVE FLOPPY IRIS SYNDROME:
AT THERAPEUTIC DOSES ALFUZOSIN DOES NOT
IMPACT ISOLATED RABBIT IRIS DILATOR
SMOOTH MUSCLE WHILE TAMSULOSIN DOES**

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What is IFIS?

- **IFIS (Intraoperative Floppy Iris Syndrome)¹** is a "small pupil" syndrome occurring during cataract surgery, characterized by the following triad:
 - flaccid iris stroma that flutters and billows in response to intraoperative irrigation currents
 - propensity for the iris to prolapse towards the phaco and surgical incisions
 - progressive constriction of the pupil during surgery despite pharmacological measures
- **The pupil must remain stable and dilated properly for effective cataract removal.**
- **IFIS is a potentially serious problem because it might increase the risk of posterior capsular rupture.**

¹Chang DF *et al.* J. Cataract Refract Surg 31: 664-73, 2005

Background

- Recently, BPH patients given tamsulosin, a highly selective α_{1A} -adrenoceptor (α_1 -AR) antagonist, were identified as having an increased risk of IFIS¹.
- The α_{1A} -AR subtype, activated by phenylephrine, seems to be involved in pupil dilation in rats² and rabbits³.
- Therefore, it would be expected that all α_1 -AR antagonists used for treating BPH may cause IFIS.
- However, only isolated cases of IFIS have been reported with other α_1 -AR antagonists, including alfuzosin.

¹Chang DF *et al.* J. Cataract Refract Surg 31: 664-73, 2005

²Yu Y *et al.* J Pharmacol. Exp. Ther. 300: 521-25, 2002

³Yu Y *et al.* J. Ocul Pharmacol Ther 19: 255-63, 2003

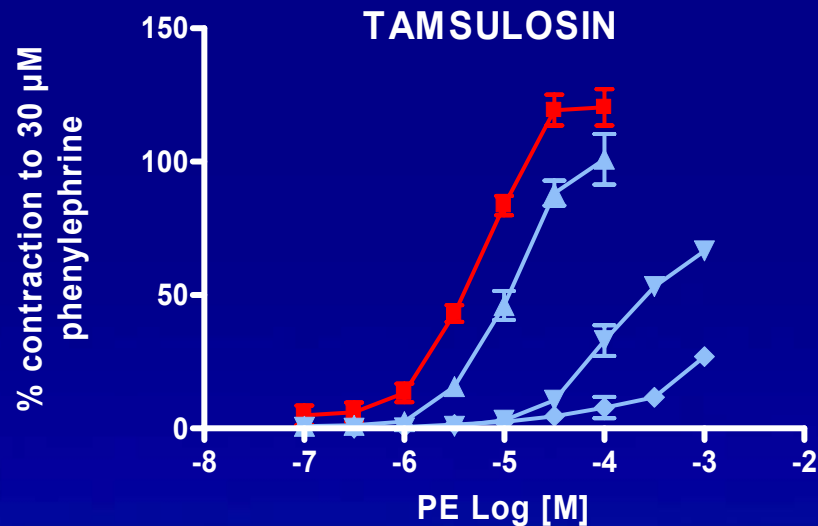
Objective

- To compare the antagonistic potencies of tamsulosin (selective α_{1A} -AR antagonist) and alfuzosin (non-selective α_1 -AR antagonist), on the **isolated prostate and iris dilator smooth muscles**, both known to express α_1 -ARs.
- These investigations were performed in **adult pigmented rabbits**, as it was shown that the pharmacology of α_1 -ARs in humans is similar to that of pigmented rabbits, while it differs in **albino rabbits**¹.

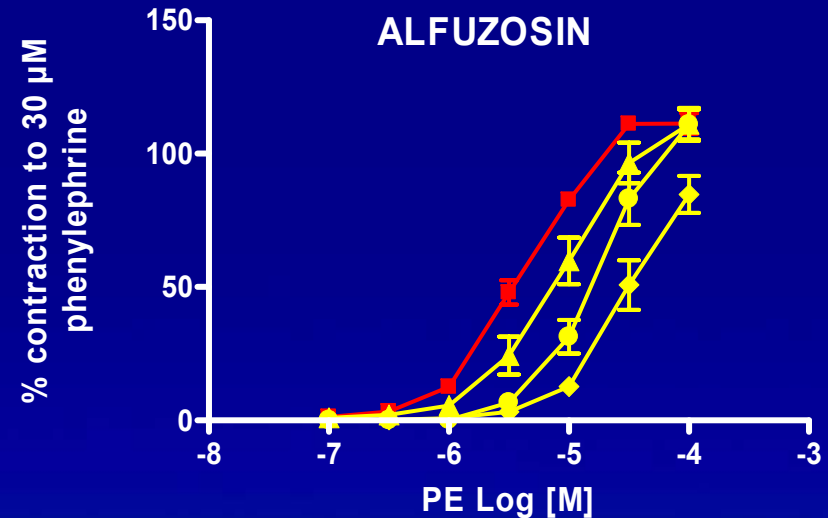
Methods

- Smooth muscle strips from rabbit prostate and iris dilator were placed in organ baths filled with an oxygenated Krebs solution.
- After 1h 30' of equilibration, strips were exposed to 30 μM Phenylephrine (PE) then a first cumulative concentration-response curve to PE was obtained.
- After washouts, tissues were incubated for 60 min with tamsulosin (0.001-0.01-0.1 μM for prostate; 0.01-0.1-1 μM for iris) or alfuzosin (0.1-0.3-1 μM for prostate; 3-10-30 μM for iris).

Results (prostate): alfuzosin & tamsulosin differ in their antagonism profile and potencies



- Control curve (pooled data; n=15)
- Tamsulosin 0.001 μ M (n=5)
- Tamsulosin 0.01 μ M (n=5)
- Tamsulosin 0.1 μ M (n=5)



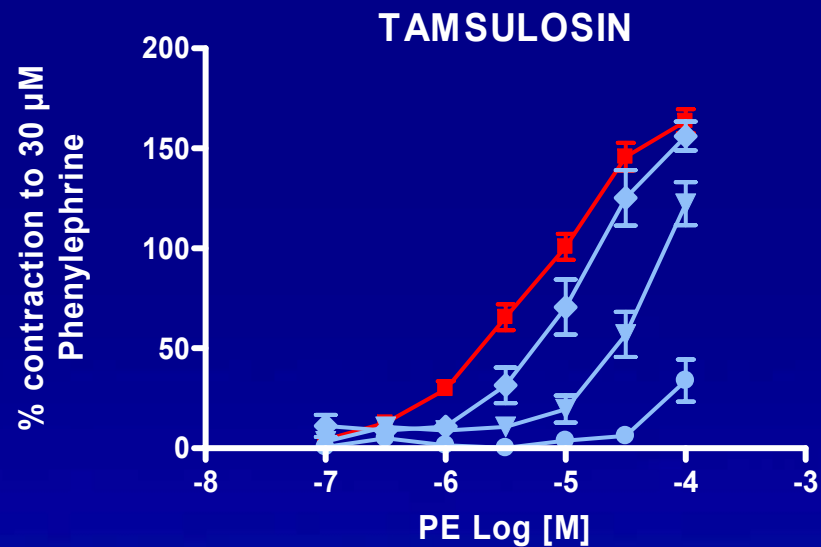
- Control curve (pooled data; n=13)
- Alfuzosin 0.1 μ M (n=5)
- Alfuzosin 0.3 μ M (n=3)
- Alfuzosin 1 μ M (n=5)

Tamsulosin is a non-surmountable antagonist whereas alfuzosin is a competitive antagonist, as in human prostatic adenoma^{1,2}

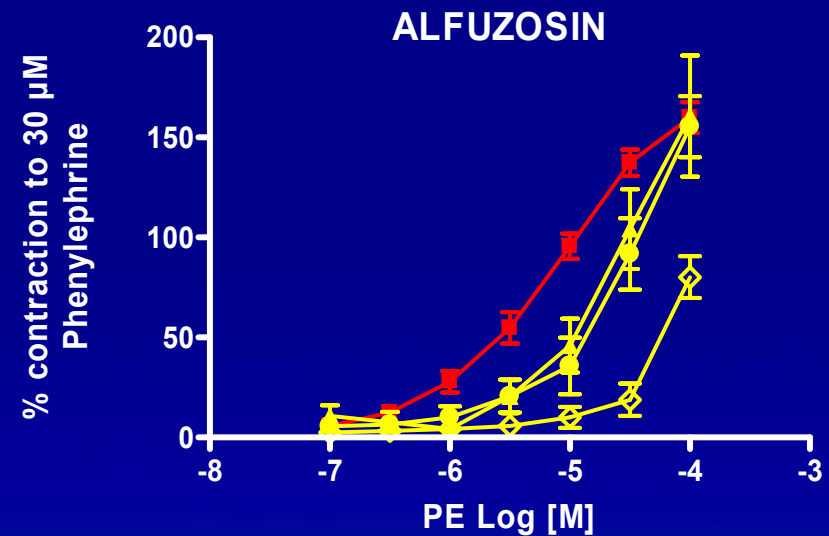
¹ Kenny BA *et al.* Br. J. Pharmacol. 118: 871-78, 1996

² Palea S *et al.* NeuroUrol Urodyn. 19: 431-33, 2000

Results (iris): alfuzosin & tamsulosin differ in their potencies



- Control curve (pooled data; n=13)
- Tamsulosin 0.01 μ M (n=5)
- Tamsulosin 0.1 μ M (n=5)
- Tamsulosin 1 μ M (n=3)



- Control curve (pooled data; n=15)
- Alfuzosin 3 μ M (n=5)
- Alfuzosin 10 μ M (n=5)
- Alfuzosin 30 μ M (n=5)

Tamsulosin is ~300 times more potent than alfuzosin as an antagonist of PE-induced contractions

Comparison of alfuzosin & tamsulosin potencies on recombinant α_1 -AR and rabbit iris dilator

Drug	Bovine α_{1A} (pK _i) ¹	Rat α_{1B} (pK _i) ¹	Rat α_{1D} (pK _i) ¹	Rabbit Prostate (pK _B)	Rabbit Iris (pK _B)
Alfuzosin	8.32±0.14	8.80±0.09	8.66±0.05	6.96±0.03	5.66±0.11
Tamsulosin	10.64±0.28	9.06±0.16	10.06±0.11	9.30	7.90±0.10

The unexpectedly low antagonistic potencies of alfuzosin and tamsulosin on iris dilator suggest that PE could act mainly through activation of receptors different from α_1 -ARs

¹ Data from Michel MC *et al.* J. Auton. Pharmacol. 16: 21-28, 1996

Comparison with human drug levels

Drug	C_{\max} in men	Conc. (μM)	Minimal effective conc. on rabbit iris (μM)	Ratio (C_{\max}/ID)
Alfuzosin 10 mg OD	16 ng/mL ¹	0.037	3.00	0.012
Tamsulosin 0.4 mg OD	11 ng/mL ²	0.025	0.01	2.5

Plasma concentrations of tamsulosin 0.4 mg OD are largely able to antagonize PE in iris dilator whereas those of alfuzosin 10 mg OD are too low to have an antagonistic effect.

¹ McKeage K & Plosker GL. Drugs 62: 633-53, 2002

² RCP Omexel® LP 0.4 mg, France

Conclusions (1)

- In the prostate, tamsulosin and alfuzosin antagonized PE-induced contractions with the expected potencies, similar to those described in **albino rabbits**¹.
- In the iris, tamsulosin and alfuzosin antagonized PE-induced contractions with unusual potencies, much lower than those reported on cloned α_1 -AR subtypes.
- We conclude that, in the rabbit iris, PE could act mainly through activation of receptors different from α_1 -ARs.

Conclusions (2)

- **Our results, if valid in humans, also suggest that plasma concentrations of tamsulosin are able to antagonize PE in iris dilator smooth muscle whereas those of alfuzosin are largely insufficient to have an antagonistic effect.**
- **These findings could explain the high frequency of IFIS in BPH patients treated with tamsulosin.**
- **Further studies will be necessary to validate this hypothesis.**