# HOW TO DEAL WITH A NEW DRUG INTERACTION? EXAMPLE OF THE CONTRAINDICATION ALFUZOSIN–STRONG CYP3A4 INHIBITORS

**N Bensalah, I Carpentier, F Locher, S Garcia.**
**Pharmacie Centrale, Drug Information Center, Saint-Genis Laval, France**
*Hospices Civils de Lyon*

## Background

The French Medicine Agency contraindicates alfuzosin with strong cytochrome 3A4 (CYP3A4) inhibitors, since alfuzosin metabolism is inhibited, thus increasing blood levels. We dispense drugs to hematologic outpatients whose treatments can combine alfuzosin (for lower urinary tract symptoms, LUTS) with anti-infective drugs that are strong CYP3A4 inhibitors. When a contraindication is detected, we make a pharmaceutical intervention to the physician, but so far, no clear and consensual management has been published.

## Purpose

To determine the incidence/clinical importance of this drug interaction (DI) ; how it can be managed and what are the non-interacting alternatives.

## Material and methods

**Review**
Scientific literature, Drug databases, Regulatory documents
→ What is the mechanism, the clinical evidences and the incidence of this DI ?

**Review**
French recommendations on the management of LUTS
→ To identify non or less-interacting alternatives

**Redaction**
Clinical decision tool
→ To help the pharmacist to manage this DI with the prescriber

## Results

### History of drug interaction

| Year | CYP3A4 inhibitor | Decision |
|---|---|---|
| 2005 | Ketoconazole Itraconazole Ritonavir | **Moderate drug interaction** Alfuzosin + Ketoconazole, Itraconazole, Ritonavir, Clarithromycin, Erythromycin |
| June 2006 | Ritonavir | **Contraindication** Alfuzosin + Ritonavir |
| 2011 | Telaprevir | **Contraindication** Alfuzosin + Telaprevir |
| Janury 2014 | All strong CYP3A4 inhibitors | **Contraindication** Extrapolation to all strong CYP3A4 inhibitors (*) |

Table 1. History of drug interaction. *The French Medicine Agency -Drug interactions Working Group*
(*) Increase of plasmatic concentration of alfuzosin

**Treatment of LUTS-BPH**
**Guidelines of the LUTS committee of the French Urological Association (FUA)**

| Alpha1-blockers | 5 alpha-reductase inhibitors | Anticholinergic agents |
|---|---|---|
| Alfuzosin, Doxazosin Terazosin, Silodosin Tamsulosin | Finasteride Dutasteride | Associated to alpha1 blocker |
| Moderate to severe LUTS secondary to BPH | LUTS secondary to BPH + prostate size > 40 ml | LUTS secondary to BPH + post-void residual < 200 ml |

Figure 1. Treatment options of LUTS-BPH according to the recommendation of the FUA

### Review on the DI : Alfuzosin + Strong CYP3A4 inhibitors

| Alfuzosin + Strong CYP3A4 inhibitors | Scientific literature/ Drug databases | Regulatory documents |
|---|---|---|
| Clinical evidence | No data<br>- No case report<br>- No epidemiologic study | 2 studies on healthy volunteers: Effect of ketoconazole on pharmacokinetic and safety of alfuzosin (*) |
| Incidence | No data | No data |

Table 2. Clinical evidence and incidence of Alfuzosin/Strong CYP3A4 inhibitors interaction
(*) No changes in vital signs, ECG, haemodynamic and laboratory data. No Severe adverse events (No hypotension/postural hypotension)

### Therapeutic alternatives

| Drug | Metabolism | | | Receptor selectivity |
|---|---|---|---|---|
| | 3A4 | 2D6 | 2C19 | |
| Alfuzosin | S | | | $\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$ |
| Tamsulosin | S | S | | $\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$ |
| Doxazosin | S | S | S | $\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$ |
| Terazosin | | | | $\alpha_{1B} = \alpha_{1D} > \alpha_{1A}$ |
| Silodosin | S | | | $\alpha_{1A} > \alpha_{1D} >> \alpha_{1B}$ |

Table 3. Therapeutic alternatives regarding the metabolism and alpha 1 blockers selectivity.
$\alpha_{1A}$ = Prostate, $\alpha_{1B}$ = Peripheral vasculature , $\alpha_{1D}$ = Bladder + spinal cord

### Clinical decision tool

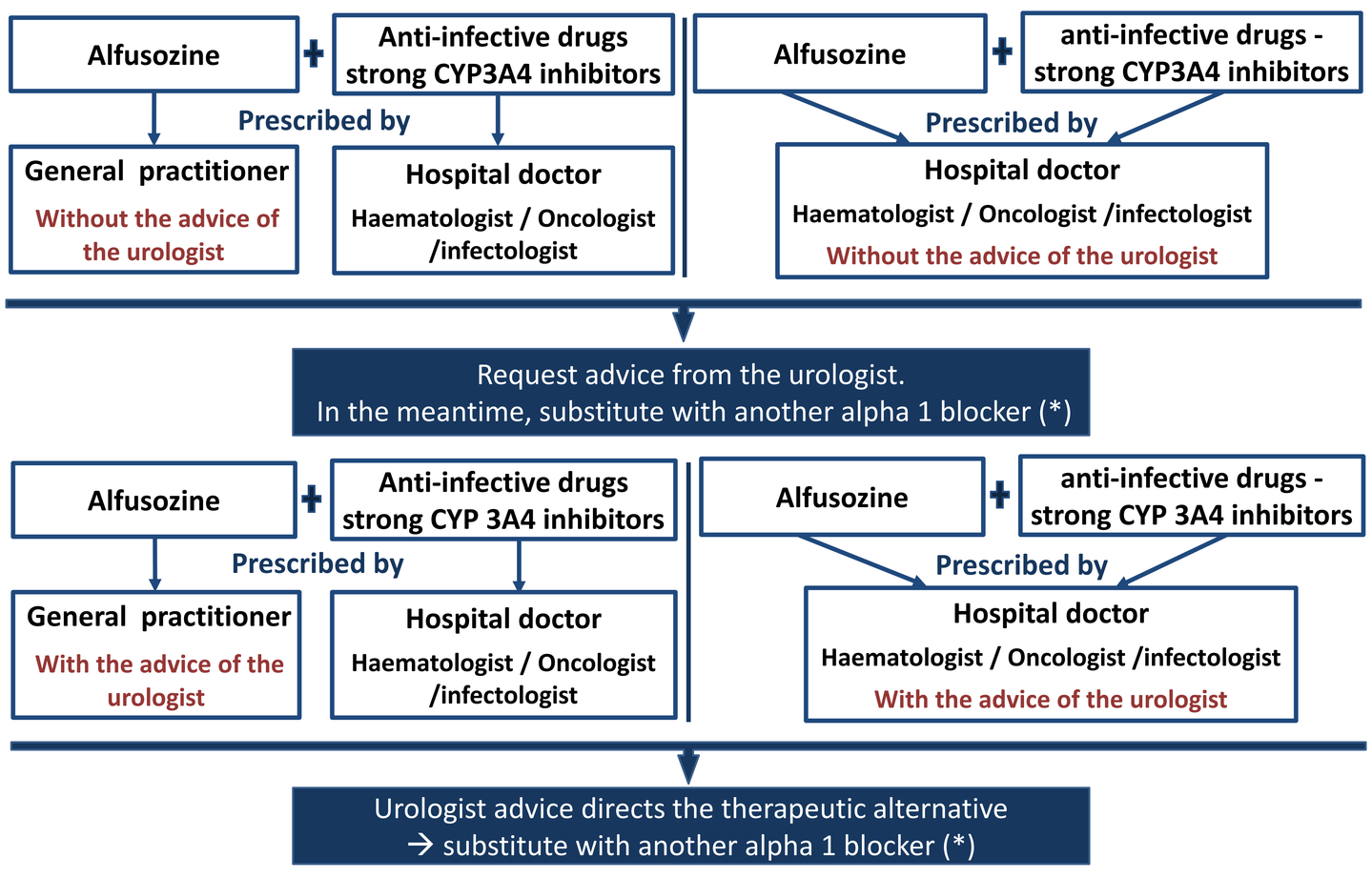


Figure 2. Managing the DI considering the initial prescribing physician of alfuzosin, the presence or not of an urologist advice and the patient's condition.
(*) Alpha 1 blockers are equivalent in effectiveness and efficacy but have slight differences in adverse event profiles. We can propose a substitution with the more specific α1A blocker, tamsulosin and silodosin.
5 alpha-reductase inhibitors and Anticholinergic agents can be used regarding to patient's condition.

## Discussion

Even though the mechanism of the DI is established, no clinical evidence has been found, except for two studies in healthy volunteers that mainly showed an increase of the AUC of alfuzosin when associated with ketoconazole.

Expected side-effects are mainly an increased risk of postural hypotension. The anti-infective drug/CYP3A4 inhibitor generally cannot be stopped due to the infectious risk. Stopping alfuzosin can put the patient at risk for urinary retention, but less or non-interacting alternatives exist for each kinds of LUTS. With our tool, we can argument each option with the prescriber and stronger the PI.

## Conclusion

This work shows that regulatory information may not be sufficient to manage a new DI but appropriate drug information search (e.g. by a Drug information Center) can provide argued PI.

## Acknowledgement

M Boucquin (documentary search)

**CP-029**