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# Non-steroidal antiandrogens

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## 1. Introduction

A logical approach for the treatment of androgen-sensitive diseases, especially prostate cancer, is the use of antiandrogens or compounds which block the interaction of testosterone and dihydrotestosterone with the androgen receptor in target tissues. The ideal antiandrogen should thus be a compound which possesses high specificity and affinity for the androgen receptor while not showing any androgenic, estrogenic, progestational, glucocorticoid or any other hormonal or antihormonal activity (Dorfman, 1971; Labrie et al., 1985). Such compounds are called pure antiandrogens (Poyet and Labrie, 1985). So far only Flutamide (Neri et al., 1967) and its derivatives, namely Anandron (Beland et al., 1987) and Casodex (Furr et al., 1987), have been available for clinical use.

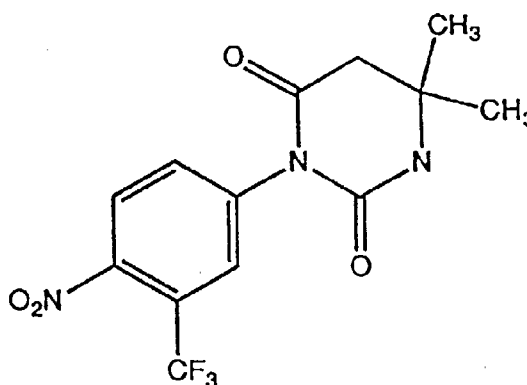
## 2. Mechanism of action

As mentioned above, non-steroidal antiandrogens compete with the androgens testosterone and dihydrotestosterone for binding to the androgen receptor, thus blocking the biological effects of androgens in target tissues, including the prostate (Simard et al., 1988). Due to their lack of intrinsic androgenic activity and their potent antiandrogenic action at the receptor level (Labrie et al., 1985; Poyet and Labrie, 1985), nonsteroidal antiandrogens are the most efficient antiandrogens available. They are especially useful to block the action of androgens synthesized in the prostate from adrenal precursor steroids (Labrie, 1991a). In fact, while testicular androgens can be easily eliminated by orchiectomy or treatment with LHRH agonists (Labrie et al., 1986), non-steroidal antiandrogens represent the most efficient means of interfering with the action of androgens of

adrenal origin which represent on average, 40% of total androgens in adult men (Labrie et al., 1985; Labrie, 1991).

However, such compounds should not be used alone since their neutralizing effect of the inhibitory feedback action of androgens at the hypothalamo-pituitary level leads to increased luteinizing hormone secretion by the anterior pituitary gland which, in turn, results in increased testicular testosterone secretion. The resulting increase in serum testosterone levels progressively neutralizes the inhibitory action of the antiandrogen at the peripheral level. Although such an effect is of minor importance in nonmalignant diseases, it is now well recognized that the nonsteroidal antiandrogens should always be associated with medical (LHRH agonist) or surgical castration for the treatment of prostate cancer.

FLUTAMIDE\*



1. Formula

\* Eulexin®, Euflex®.

## 2. Pharmacokinetics

After oral administration, the absorption of Flutamide is practically complete. Flutamide is very rapidly metabolized to the active compound hydroxyflutamide which accounts for almost all metabolites of Flutamide present in the circulation. The half-life of Flutamide is 5.2 hours.

## 3. Administration

For the treatment of prostate cancer, Flutamide is administered at the dose of 250 mg every 8 hours. For the treatment of hirsutism and androgenic alopecia in women, a twice daily dose of 250 mg was used (Cusan et al., 1990).

## 4. Side effects

- Loose bowel movements or diarrhea is observed in 5-9% of cases. The dose should then be reduced by half for a few days and the drug should be accompanied by food. In almost all cases, the dose can be increased to 250 mg every eight hours after 10 to 14 days at the lower dose.

- No cardiovascular effects are observed.

- No gynecomastia or breast tenderness is observed when the antiandrogen is given in combination with castration.

## 5. Results

### a) Combination therapy in advanced prostate cancer

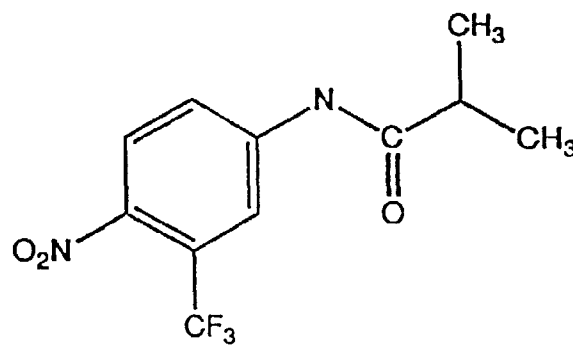
Recent data obtained from two large-scale double-blind and prospective studies have shown that combination of Flutamide and medical castration increases the number of responders, prolongs disease-free survival and, most importantly, increases overall survival by an average of 7.3 months (Crawford et al., 1989) and 15.0 months (Denis et al., 1991) when compared with an LHRH agonist and orchiectomy, respectively. These studies demonstrate that pure antiandrogens should always be given in combination with medical (LHRH agonist) or surgical castration (orchiectomy) as first treatment at the start of therapy. Addition of the antiandrogen after progression of the disease in patients who had monotherapy has less beneficial effects.

### b) Combination therapy in early stage prostate cancer

Randomized studies are in progress in order to assess the potential advantages of temporary (3 months) treatment with the combination of an LHRH agonist and Flutamide prior to radical prostatectomy in early stage prostate cancer. Early data suggest that such treatment facilitates surgery and decreases the incidence of positive margins (Labric, 1991b).

## NITULAMIDE\*

### 1. Formula



\* Anandron®.

### 2. Pharmacokinetics

Nitulamide is well absorbed after oral administration. Its half-life is 45 hours.

### 3. Administration

Nitulamide is usually administered at the daily dose of 300 mg per day once a day for 1 month followed by the daily maintenance dose of 150 mg.

### 4. Side effects

- Visual adaptation to darkness is impaired in 20 to 40% of patients.

- Mild gastrointestinal disturbances in a small proportion of patients.

- Interstitial lung disease has been infrequently seen.
- No cardiovascular effect has been observed.

### 5. Results

Nitulamide given in association with orchiectomy in advanced prostate cancer has shown, in randomized and prospective studies, a greater proportion of responders, a longer duration of disease-free survival and an increase of an average of 5.4 months (Béland et al., 1987) and 7.3 months (Janknegt et al., 1991) in overall survival compared to orchiectomy alone. Data from Brisset et al. (1987) and Navratil et al. (1987) have shown an improved response and an improved quality of life. By analogy with Flutamide, the benefits of Anandron may be superior when given as first treatment.

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