77

PHARMACOLOGICAL ACTIVITY OF FOUR METABOLITES OF ANANDRON®

TOURNEMINE C. COUSSEDIERE D. COUSTY C. TREMBLAY D. POTTIER J.
Centre de Recherche ROUSSEL UCLAF, Romainville, FRANCE.

Anandron (Nilutamide, 5-5' -dimethyl 3- (4 nitro-3, trifluoromethyl) phenyl 2-4- imidazolidine dione) is a pure antiandrogen.
Urine metabolites of Anandron given as a single radiolabelled dose (14C) to rats, dogs and patients were identified after enzymatic hydrolysis. Two major metabolic pathways are common to the 3 species : partial then complete reduction of the nitrogroup, leading to the hydroxylamino and amino metabolites (M II and M III), oxidation of one methyl of the gem-dimethyl group, leading to the hydroxymethyl M VIII. Association of both pathways leads to the hydroxymethyl amino M IV. These four metabolites were synthetized. Interactions with the androgen receptor (AR) were assayed in vitro and their androgen or antiandrogen activities were measured after SC administration (2-50 $mg.kg^{-1}$) on the prostate of castrated rats. Among the metabolites tested, only the nitro compound M VIII interacted with AR : its RBA was weaker than that of Anandron. In vivo it exhibited a dose dependent antiandrogen activity similar to that of Anandron. M II and M III had a very weak antiandrogen effect only at the highest dose. Compared to its metabolites, Anandron shows greater potency and higher plasma concentrations. It is therefore most probable that the pharmacological and clinical activity of the drug is mainly due to the unchanged compound.

78

CLINICAL EFFECTS OF KETOCONAZOLE ON HORMONE INDEPENDENT PROSTATIC CANCER

J.Trachtenberg and T.Eichenberger
Univ. of Toronto, Dept.of Surgery/Urology,Toronto, Canada

Forty four patients (mean age 69.7 years) with progressing metastatic prostatic cancer were administered 600-1200 mg/day of ketoconazole in a q8h divided dose regime. All patients had previously failed primary hormonal therapy and many had also failed secondary attempts at tumor control (antiandrogens, cytotoxic chemotherapy or wide field irradiation). Patients were initially followed at 2 and 4 weeks of treatment and then monthly. Patients were assessed by NPCP determined response characteristics and a modified Karnofsky performance and pain score. Side effects were frequent in this already debilitated group. Sixty six per cent reported episodes of nausea or lethargy but only 3 patients withdrew because of side effects. Pain relief was dramatic with a 62% improvement in pain by 4 weeks. Changes in other measured parameters were not consistent. The duration of benefit and survival was calculated to be 35.5 and 60.2 weeks respectively. Ketoconazole improves pain in many patients with progressive advanced prostatic cancer. Its effects on survival are not known. It may have an important role to play as an adjunct in the treatment of these patients.

79

PLASMA CONCENTRATIONS (PC) OF ANANDRON® IN PATIENTS DURING LONG TERM THERAPY

TREMBLAY D. DE GERY A. MOUREN M. POTTIER J.
Centre de Recherche ROUSSEL UCLAF, Romainville FRANCE.

During clinical trials of Anandron (Nilutamide) in patients with stage D prostatic carcinoma, blood samples were drawn 1 month (25 to 40 days), 3 months (80 to 104 days), 6 months (160 to 200 days) and 12 months (345 to 405 days) after initiation of treatment. Treatments were : 150 mg/day (50 mg tid, capsule) or 300 mg/day (100 mg tid, capsule or tablet, or 300 mg q tablet). Anandron was assayed in plasma by RIA. The antibody was raised in rabbits receiving an antigen prepared by conjugation of the propanoic derivative on the N3 of the hydantoic moiety of Anandron with BSA. The specificity of the Anandron antibody towards endogenous substances is such that no extraction procedure is required. The cross reactions with 3 of 4 metabolites that have been identified in man are less than 0.2 %. Cross reaction with the fourth which is the only metabolite with intact nitrogroup is 11 %. The PC recorded were compared between different times within each group and between groups for each time point using Student's t test (tid treatment). No significant differences were observed between time points, between capsules and tablets and between 300 and 150 mg doses once PC have been divided by the dose. Means PC were the following : capsule 150 mg/day, 3.61 $mg.l^{-1}$ (N° assays : 100), capsule 300 mg/day, 7.28 $mg.l^{-1}$ (N° assays : 103), tablets 300 mg/day, 6.36 $mg.l^{-1}$ (N° assays : 136). Assays 300 mg q are underway and will be presented. PC remained constant and were proportional to the dose, tablet and capsule were bioequivalent.

80

PLASMA KINETICS OF ANANDRON® IN THE RAT, DOG, AND PATIENT.

TREMBLAY D.* PENDYALA L. COUSSEDIERE D.* POTTIER J.***
*** Centre de Recherche ROUSSEL UCLAF, Romainville FRANCE**
**** Clinical Pharmacology and Therapeutics Department, Roswell Park Memorial Institute, Buffalo NY, USA.**

Anandron (Nilutamide) is a pure antiandrogen which improves the response to castration in patients with prostate cancer.
Plasma levels of radioactivity (R) and of unchanged compound (A) were measured after a single oral bioactive dose of 10 $mg.kg^{-1}$ of 14C Anandron to rats (pool from 5 rats for each time point) and dogs (n = 4). In patients with stage D carcinoma of the prostate (n = 12), 14C Anandron was administered at 150 mg single dose (about 2 mg/kg). Plasma levels of R were measured and unchanged compound was assayed by HPLC. Results are expressed as means in the following table :

	RATS		DOGS		PATIENTS	
	R	A	R	A	R	A
Cmax $mg.l^{-1}$	5.7	4.9	6.2	3.7	1.3	0.9
Tmax h	5	3	6.5	1.8	5.8	2.8
AUC $mg.l^{-1}.h$	119	72	303	60	136	39
t1/2 h	11	7	26	9	87	56

Anandron was rapidly absorbed and showed high plasma concentrations in comparison with the total radioactivity. These high circulating levels and the slow elimination should result in high and constant tissue levels during repeated dosing and should achieve a complete blockade of androgen receptors, explaining Anandron activity in pharmacological and clinical conditions.