EVALUATION OF THE ANDROGEN ANTAGONIST POTENTIAL OF QUINOLINE (CAS: 91-22-5) IN SURGICALLY CASTRATED PERIPUBERTAL MALE RATS

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ABSTRACT

The potential effects of the Quinoline as androgen antagonist was quantified in the Hershberger Bioassay using castrated male Wistar rats. A total of 30 rats were divided into 5 groups comprised of 6 rats. Negative control [Testosterone propionate (TP) – 0.4 mg/kg b. wt./day; subcutaneous)], positive control [Flutamide (FLU) – 3 mg/kg b. wt./day; oral + TP-0.4 mg/kg b. wt./day; subcutaneous)] and three groups of Quinoline (50, 100 and 200 mg/kg b. wt./day; oral + TP – 0.4 mg/kg b. wt./day; subcutaneous) were treated for 10 consecutive days. All animals were sacrificed approximately 24 hours following the last dose. No treatment related mortality was observed during the study. Weakness and lethargy were observed in 200 mg/kg b. wt./day Quinoline group. Body weight, body weight gain and feed consumption of the 100 and 200 mg/kg b. wt./day Quinoline groups were statistically significant decreased compared to the negative control group. Body weight, body weight gain and feed consumption of the positive control group were comparable with the negative control group. Terminal body weight of the 100 and 200 mg/kg b. wt./day Quinoline groups were statistically significant decreased as compared to the negative control group. Absolute liver weight of the 100 and 200 mg/kg b. wt./day Quinoline treated groups were statistically significant increased compared to the negative control group whereas no effect on terminal body weight and absolute liver weight was seen in positive control group as compared to the negative control group. Absolute and relative organ weights of androgen dependent organs (glans penis, LABC, cowper's gland, ventral prostate and seminal vesicle) of Quinoline treated groups were comparable to the negative control group. Statistically significant decreases in absolute and relative organs of androgen dependent organs were observed in the positive control group as compared to the negative control group. Based on the result of study Quinoline showed no evidence of androgen antagonist activity.

INTRODUCTION

During the last fifty years many synthetic pesticides, plasticizers, detergents and cosmetics that become environmental contaminants have been shown to alter endocrine function. Some of these chemicals can produce toxic effects at surprisingly low doses. Many researchers hypothesize that exposure to these endocrine disruptor chemicals (EDCs) during critical periods of development could result in adverse effects to wildlife and humans[5, 9]. EDCs have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body and responsible for the maintenance of homeostasis and the regulation of developmental processes[4].

The rodent Hershberger bioassay was first described in 1953 by Hershberger and colleagues as a screening assay for androgenic and anabolic agents[3]. The rodent Hershberger assay is a short-term, *in vivo* screening assay designed to detect compounds with potential to act as androgen receptor (AR) agonists, antagonists and 5-α reductase inhibitors. The maintenance of assessory sex tissue weights depends upon androgenic signals (i.e., typically, testosterone and dihydrotestosterone); therefore, the Hershberger assay detects chemicals that act as AR agonists, antagonists, or 5-α reductase inhibitors[1, 2, 6]. An immature Hershberger model was proposed, but this model was less sensitive at detecting weak antiandrogens, and therefore was not included as part of the test guidelines[2].

Quinoline is a hygroscopic, pungent odor, colorless liquid. It is used as solvent and intermediated for various chemicals. It is derived from petroleum, coal processing, wood preservation, tobacco smoke and shale oil. It is considered genotoxic and likely to be carcinogenic in humans[11]. When released to soil, Quinoline is likely to leach quickly into groundwater. Most of the compounds studied pesticides and industrial pollutants-exhibit weak receptor affinities compared with endogenous hormones but can produce endocrine responses both *in vitro* and *in vivo* at environmentally relevant doses[10]. Androgenic activity in surface waters near intensive livestock farms may be high enough in some places to cause endocrine disruption in some aquatic organisms[7]. Quinoline was suspected endocrine disruptor. Therefore, it was included in second list of 109 endocrine disruptor chemicals published by EPA June 14, 2013.

OBJECTIVE

The objective of this study was to quantify the effects of the Quinoline co-administered with the reference Testosterone Propionate (TP) as a potential androgen antagonist in the Hershberger Bioassay using the male animals with minimal endogenous androgen production.

Solvents and Chemicals

Quinoline, Testosterone propionate and Flutamide (Manufacturer by Sigma-Aldrich, USA), Ketamine HCl Inj. IP (Manufacturer by Toikaa pharmaceuticals Ltd. India), Xylazine (Manufacturer by Indian Immunologicals Ltd., India) Meloxicam Inj. (Manufacturer by Intas Pharmaceuticals Ltd., India) and Povidone Iodine (Manufacturer by Win-Medicare, India) were purchased..

Study Design – For Antagonist

Group	Test Item	Dose Level (mg/kg b. wt./day)	Duration of Dosing	Number of Animals (Castrated Male Rats)
G1	TP**	0.4		6
G2	TP** + FLU*	0.4 + 3.0		6
G3	TP** + Quinoline*	0.4 + 50	For 10 days	6
G4	TP** + Quinoline*	0.4 + 100		6
G5	TP** + Quinoline*	0.4 + 200		6

Key: * = Administered orally, ** = Administered by subcutaneous injection

Results – For Antagonist

Group/ Parameter	G1	G2	G3	G4	G5
Mortality	Nil	Nil	Nil	Nil	Nil
Clinical observation	Normal	Normal	Normal	Normal	Lethargy, Weakness
Body Weight	-	Comparable	Comparable	↓	↓
Body Weight Gain	-	Comparable	↓	↓	↓
Feed Consumption	-	Comparable	Comparable	↓	↓
Organ Weight					
Liver	-	Comparable	Comparable	↑	↑
Glans penis	-	↓	Comparable	Comparable	Comparable
LABC		↓	Comparable	Comparable	Comparable
Cowper's gland	-	↓	Comparable	Comparable	Comparable
Ventral prostate	-	↓	Comparable	Comparable	Comparable
Seminal vesicle	-	↓	Comparable	Comparable	Comparable
Gross pathology	NAD	NAD	NAD	NAD	NAD

Key: LABC = Levator ani-bulbocavernosus, = Significantly higher than control, - Significantly lower than control, NAD = No abnormalities detected

Study Design – For Agonist

Group	Test Item	Dose Level (mg/kg b. wt./day)	Duration of Dosing	Number of Animals (Castrated Male Rats)
G1	Corn Oil*	0		6
G2	TP**	0.4		6
G3	Quinoline*	100	For 10 days	6
G4	Quinoline*	200		6

Key: * = Administered orally, ** = Administered by subcutaneous injection,

Results – For Agonist

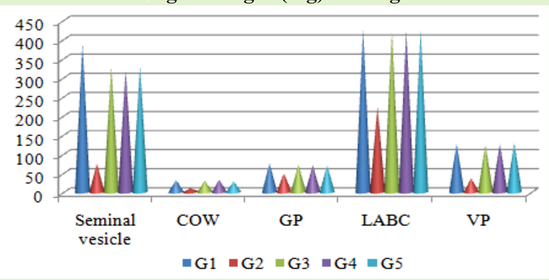
Group/ Parameter	G1	G2	G3	G4
Mortality	Nil	Nil	Nil	Nil
Clinical observation	Normal	Normal	Normal	Lethargy
Body Weight	-	Comparable	Comparable	↓
Body Weight Gain	-	↑	↓	↓
Feed Consumption	-	↑	↓	↓
Organ Weight				
Liver	-	Comparable	↑	↑
Glans penis	-	↑	Comparable	Comparable
LABC		↑	Comparable	Comparable
Cowper's gland	-	↑	Comparable	Comparable
Ventral prostate	-	↑	Comparable	Comparable
Seminal vesicle	-	↑	Comparable	Comparable
Gross pathology	NAD	NAD	NAD	NAD

Key: LABC = Levator ani-bulbocavernosus, = Significantly higher than control, - Significantly lower than control, NAD = No abnormalities detected

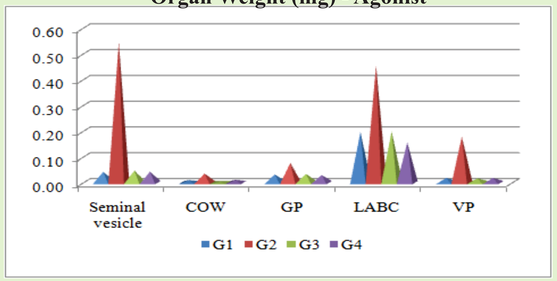
CONCLUSION

Based on the results of the study, Quinoline showed no evidence of androgen agonist and androgen antagonist activity.

Organ Weight (mg) - Antagonist



Organ Weight (mg) - Agonist



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