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Anti-implantation activity of 2 derivatives of *o*-hydroxy naphthaquinones in rats

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AIM: To search for female contraceptive agents. **METHODS**: 2-Hydroxy-3-methyl-1, 4-naphthoquinone monosemicarbazone (HMNQS) and 2-hydroxy-1, 4-naphthoquinone monothiosemicarbazone (HNQTS) were screened for anti-implantation activity in rats. **RESULTS**: Both compounds showed a dose-dependent activity, and HNQTS was more potent. An 100 % anti-implantation activity was observed with HNQTS 150 mg kg^{-1} ig. Its LD_{50} was found to be >2 g kg^{-1} ig in mice. **CONCLUSION**: HNQTS was more potent than HMNQS for anti-implantation activity in rats.

KEY WORDS naphthoquinones; synthetic oral contraceptives; estrogen antagonists

Antifertility activity has been found with quinone derivatives[1-5]. Two new derivatives were synthesized by the method described earlier[6], 2-Hydroxy-3-methyl-1, 4-naphthoquinone monosemicarbazone (HMNQS) and 2-hydroxy-1, 4-naphthoquinone monothiosemicarbazone (HNQTS). In this paper, we report the anti-implantation activity of the 2 compounds.

MATERIALS AND METHODS

Albino rats (Charles Foster strain) and mice bred in the Animal House of Regional Research Laboratory, Jammu, were kept on a 14-h light: 10-h dark schedule in air-conditioned rooms (25±0.5 ℃); relative humidity 50 %—60 %. The animals were put on a standard pellet diet (Lipton India Ltd) with free access to water. For anti-fertility study, the ♀ rats were caged with coeval ♂ rats of known fertility in the evening of the proestrous stage. The presence of sperms in the vaginal smear taken in the following morning was designated as d 1 of pregnancy. The 2 compounds were suspended in 0.5 % carboxymethyl cellulose (CMC) and were administered orally from d 1 to d 10. Control rats received CMC. Laparotomy was made on d 11 under light ether anesthesia. All the implantation sites observed on d 11 were living. They were allowed to go to term. The delivered pups were kept under observation for any teratogenic effect for 1 month.

For estrogenicity test, immature ♀ rats (weighing 40—50 g) were divided into 6 groups of 5 each: Group A, oil 0.05 ml sc; Group B, estradiol valerate 0.1 μg d^{-1} in ground-nut oil sc; Group C, HMNQS 150 mg kg^{-1} ig; Group D, HNQTS 150 mg kg^{-1} ig; Group E, estradiol (B) + HMNQS (C); Group F, estradiol (B)+HNQTS (D).

The treatment was given for 3 d. The rats were killed 24 h after the last dosing; uteri were examined.

For acute toxicity studies, mice of either sex were used. The animals, 5 in each group, were given ig the compounds 1, 1.5, and 2 g kg^{-1}. They were observed for any signs of toxic symptoms and mortality for 48 h.

RESULTS

When HMNQS and HNQTS were tested at 50 mg kg^{-1} ig, pregnancy occurred in only 1 out of 5 rats. At 100 mg kg^{-1}, HMNQS inhibited pregnancy in 2 out of 5 rats and HNQTS was effective in 3 out of 5 rats. With HNQTS 150 mg kg^{-1}, no implantation sites were found at laparotomy on d 11. But only 60 % activety was noted with HMNQS

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150 mg kg^{-1}. All the control rats delivered normal pups at term, the number being similar to the number of implantation sites recorded at laparotomy (Tab 1).

Tab 1. Anti-implantation activities of HMNQS and HNQTS. $\bar{x} \pm s$.
$^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Durg/ mg kg^{-1}		Rats	Rats not implanted	Implanation sites
Control	0	15	0	7.50 ± 1.56
HMNQS	50	5	1	4.60 ± 0.35^a
	100	5	2	2.80 ± 0.24^b
	150	5	3	1.60 ± 0.20^c
HNQTS	50	5	1	4.00 ± 0.24^a
	100	5	3	1.60 ± 0.24^b
	150	5	5	0.00^c

No gross teratogenic effect was found in any of the pups.

Estradiol valerate 0.1 $\mu g\ d^{-1}$ produced a marked increase in the uterine weight compared to control ($P < 0.001$). On the other hand, HMNQS and HNQTS produced no significant increase in the uterine weights *vs* the control (Tab 2).

Tab 2. Effects of HMNQS and HNQTS on uterine weights. $n = 5$ rats. $\bar{x} \pm s$. $^cP < 0.01$ *vs* Group B.

Groups	Body wt/g	Uterus wt (mg/kg body wt)
A	44.80 ± 0.58	572 ± 56
B	44.50 ± 0.20	$3\,124 \pm 312^c$
C	43.10 ± 0.16	602 ± 89
D	44.00 ± 0.20	585 ± 62
E	44.30 ± 0.13	$2\,784 \pm 210^c$
F	44.5 ± 0.13	$2\,558 \pm 263^c$

When HMNQS and estradiol were given together, a decrease in uterine weight was seen *vs* that with estradiol alone ($P < 0.01$). With the combination of HNQTS and estradiol, a further decrease in the uterine weight was obtained.

In mice, no toxic sign or mortality was observed for 48 h with both compounds.

DISCUSSION

Both HMNQS and HNQTS have shown a dose-dependent anti-implantation tests in rats. At doses of 50, 100, and 150 $mg \cdot kg^{-1}$, HMNQS showed 20 %, 40 %, and 60 % activities, and HNQTS showed 20 %, 60 %, and 100 % activities, respectively.

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