THE ACTION OF 2-HYDROXY-3-(3-METHYL--2-BUTENYL)-1,4-NAPHTOQUINONE (LAPACHOL) IN PREGNANT RATS

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SUMMARY

This paper presents a study on the abortive and teratogenic action of the Lapachol in pregnant rats. This antibiotic has been used for treating adenocarcinoma and squamous carcinoma in man.

RESUMO

Este trabalho apresenta o estudo da acção abortiva e teratogênica do Lapachol em ratas grávidas. Este antibiótico tem sido usado contra os tumores adenocarcinoma e carcinoma epidermóide.

1. INTRODUCTION

Lapachol is an antibiotic of the naphtoquinone group, isolated from some *Bigoniaceae* species, which was chemically studied by E. Paternó[10] in 1882 and by Gonçalves de Lima and his colleagues since 1956[2] in relation to its antigerm and antineoplasic activity. Presently, Lapachol is produced by the Laboratório Farmacêutico do Estado de Pernambuco — LAFEPE —, being indicated for the treatment of malignant tumors such as adenocarcinoma and squamous carcinoma. Its clinical use led us to investigate a possible embryotoxic action of this substance in animals, with the objective of determining its toxicity concerning this matter.

2. MATERIALS AND METHODS

Virgin albino Wistar female rats were mated with males of previously confirmed fertility (one male for three females). Vaginal smears were examined each morning for detecting, by the presence of sperm in them, the pregnancy in its first day[5, 6] and the inseminated animals were isolated in cages and divided into 6 groups which were treated with Lapachol according to the following scheme:

Group I — 100 mg/kg from 1st to 5th pregnancy day (8 rats)
Group II — 100 mg/kg from 7th to 12th pregnancy day (8 rats)
Group III — 100 mg/kg from 14th to 19th pregnancy day (8 rats)
Group IV — 500 mg/kg from 1st to 5th pregnancy day (8 rats)
Group V — 500 mg/kg from 7th to 12th pregnancy day (8 rats)
Group VI — 500 mg/kg from 14th to 19th pregnancy day (8 rats)

Each treated group had its corresponding control group. The drug was administered orally, as a suspension in distilled water containing 0,1% of Tween 80 and 0.5% of ethanol, these last substances having been used for improving drug suspension. The control animals received the same amount of liquid but without Lapachol, which was also administered orally.

Each animal was weighted and sacrificed by cervical displacement on the 21st day of the pregnancy. A laparatomy was performed and the uterus and ovaries were removed. Then, the reabsorptions were counted and the viable implantations examined in order to observe the malformations[1, 4, 5, 6, 7, 8, 15].

3. RESULTS

The results are presented in Tables 1 and 2 and were analized by the qui-quadrato test.

As it is observed in Table 1, Lapachol administration from the 1st to the 5th day and from the 7th to the 12th day (groups I, II, IV, V) originated a significant foetus reabsorption. Besides, as it is shown in Table 2, groups II and V, malformations of the implant and viable foetus occurred at the end of the 21st day of pregnancy but was not observed any effect on the foetus already formed (groups III and VI), in spite of several organs showing malformations. A weight decrease of the malformed foetus of about 47% in relation to viable foetus has also occurred.

4. DISCUSSION AND CONCLUSION

The anticancer drugs normally have a teratogenical action in animal and human because they inhibit celular development. These drugs are par-

Table 1 — Incidence of reabsorption in the control and Lapachol treated groups

Group	Implantation	Reabsorption	Reabsorption index (%)
I_t	41	41	100*
I_c	85	00	0
II_t	80	63	78,7*
II_c	84	02	2,3
III_t	85	00	0
III_c	85	00	0
IV_t	43	43	100*
IV_c	86	00	0
V_t	78	70	89,7*
V_c	79	03	3,8
VI_t	81	00	0
VI_c	80	00	0

t = treated; c = control; *p < 0.001

$$\text{reabsorption index} = \frac{\text{number of reabsorptions}}{\text{number of implantations}} \times 100$$

Table 2 — Foetus malformation percentage in the viable implantations observed in the 21st day of pregnancy

FOETUS OBSERVATION	GROUP					
	I	II	III	IV	V	VI
EXOPHTHALMIA	—	5,8	—	—	10	—
LEPORINE LIP	—	11,6	—	—	29	—
ABDOMINAL ORGANS OUTSIDE CAVITY	—	—	—	—	87,5	—

ticularly dangerous because they are used therapeutically in quantities very near to their toxic dosage, and this is the case with Lapachol.

In the above described observations, the administration of Lapachol in dosage of 100 mg/kg by oral via presented great incidence of the blastocistotoxical-antizigotical action and an abortive activity (groups I, II, IV, V), along with malformations (groups II and V).

These observations indicate that the action of Lapachol takes place in the beginning of the egg division periods, as well as during the implantation period[4,5,8,15]. The physiopathological mechanisms of these effects have not yet been full studied and they should be the subject of further investigations.

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