

ADJUVANT EFFECT OF 5-PHENYL-3-METHYLPYRAZOLE (PHEMERAZOLE) ON THE ACTION OF DIETHYLSTILBESTROL ON THE MAMMARY GLANDS OF RABBITS

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In our earlier researches we established some of the pharmacological properties of 5-phenyl-3-methylpyrazole (Phemerazole) [1]. Phemerazole has a tranquilizing action on the central nervous system of experimental animals, lowers their body temperature, counteracts the stimulatory effect of a number of drugs, and enhances the action of soporific drugs [2, 3]. Because of these properties, Phemerazole could be classed as a sedative drug. Such drugs powerfully affect the central nervous system, and also act on certain of the endocrine glands; this latter effect is manifested as enhancement or depression of their function, with corresponding effects on the target organs. An example of this kind of effect is afforded by clinical reports of occurrence of lactation in women, and of mammary enlargement, with formation of secretion, in men, following prolonged treatment with chlorpromazole or reserpine [4, 6, 8]. H. Tuchmann-Duplessis and L. Mercier-Parot [9] have reported mammary enlargement in both male and female rats following 8-15 daily injections of 250 mg/kg of reserpine. The lobules were enlarged, and the ducts were filled with secretion. C. H. Sawyer [7] and J. Meites [5] administered estrogens to rabbits, at dosage levels such as did not have any perceptible effect on their mammary glands. Considerable enlargement of the mammary glands was observed when reserpine was injected intravenously (a single dose of 1 mg/kg), following two preliminary injections of estrogen. The different response of the rabbits to estrogen treatment was evident by the seventh day after reserpine administration. The majority of workers believe that mammary enlargement following chlorpromazine or reserpine administration may be ascribed to increased secretion of lactogenic hormone by the anterior hypophysis, with suppression of luteal function. The way in which these drugs act has not yet been fully elucidated. C. H. Sawyer and J. Meites found that the mammary effects of the drugs appeared sooner, and were more marked, when supplementary doses of estrogens were given.

EXPERIMENTAL METHODS

We examined the effect of Phemerazole on the mammary glands of the rabbit in the same way as did C. H. Sawyer, with supplementary administration of estrogens. The experiments were performed on female rabbits, weighing 2-2.8 kg. The estrogen used was diethylstilbestrol, which was injected subcutaneously as a 2.5% suspension in aqueous alcohol, at a dosage level of 0.1-0.2 mg/kg. Phemerazole hydrochloride was fed as a suspension in water, at dosage levels of 25 and 100 mg/kg. The rabbits were killed 7-8 days after the last injection of diethylstilbestrol.

RESULTS OF EXPERIMENTS

Two daily injections of 0.1 mg/kg of diethylstilbestrol did not give any mammary enlargement or secretion (see table), showing that this dosage level was too low for our purposes. Raising the daily dose to 0.2 mg/kg gave

Results of Combined Administration of Phemerazole and Diethylstilbestrol

Single peroral dose of Phemerazole (in mg/kg)	Time interval between administration of Phemerazole and the first injection of diethylstilbestrol	Dose of diethylstilbestrol (in mg/kg) and the number of such subcutaneous injections given	Number of rabbits per group	Results of examination of the mammary glands of rabbits 7-8 days after the last injection of diethylstilbestrol. Number of rabbits in which we observed:			
				absence of mammary enlargement	slight mammary enlargement	mammary enlargement, with appearance of secretion	considerable mammary enlargement, with plentiful secretion
100	7 days	0.1 × 2	4	3	1	—	—
Control	—	0.1 × 2	4	4	—	—	—
100	7 days	0.2 × 2	4	—	2	2	—
Control	—	0.2 × 2	4	1	3	—	—
100	2 hours	0.2 × 10	4	—	1	1	2
25	2 hours	0.2 × 10	4	—	1	3	—
Control	—	0.2 × 10	4	1	2	1	—
100	2 hours	0.2 × 15	4	—	1	—	3
Control	—	0.2 × 15	4	—	3	—	1

a more or less definite effect on the mammary glands, depending on the number of doses given. Two subcutaneous injections of 0.2 mg/kg gave slight enlargement of the mammary glands in 3 out of 4 animals; the remaining rabbit gave no response. Enlargement of the mammary glands of all four of a group of rabbits was observed when a subcutaneous injection of 100 mg/kg of Phemerazole hydrochloride had been given seven days before the first diethylstilbestrol injection, and secretion was seen in the lobules of two of them.



Fig. 1. Mammary gland of a control rabbit following 10 subcutaneous injections of diethylstilbestrol (0.2 mg/kg per dose). Slight enlargement of lactiferous ducts. Magnification: oc. 8 ×, ob. 10 ×.



Fig. 2. Mammary gland of a rabbit given a preliminary subcutaneous injection of 100 mg/kg of Phemerazole hydrochloride, followed by 10 injections of diethylstilbestrol (0.2 mg/kg per dose). Hyperplasia of the mammary alveoli, and distension of the ducts. Magnification: oc. 8 ×, ob. 10 ×.

In two series of experiments (20 rabbits) subcutaneous injection of 0.2 mg/kg of diethylstilbestrol was begun two hours before the single injection of Phemerazole, and was continued for 10 and 15 days. The control group of rabbits was given diethylstilbestrol alone. The animals were killed 7 days after the last injection of diethylstilbestrol. The mammary glands of the rabbits which had been given both Phemerazole and estrogen were considerably enlarged, and displayed enhanced secretory activity. The lactiferous duct system was highly developed, and the ducts were distended by their large content of watery, sometimes turbid, secretion; numerous alveoli were visible without the aid of a microscope. The peripheral regions of the mammary glands were markedly hyperemic (Figs. 1 and 2).

These changes in the mammary glands were always more pronounced in the animals which had been given Phemerazole than in those receiving diethylstilbestrol alone.

Histological examination of the mammary glands of the rabbits showed hypertrophy and hyperplasia of the lactiferous and alveolar ducts, with considerable distension of their lumina by a protein-containing fluid, in which sporadic clumps of desquamated epithelial cells could be seen. The ducts, and many of the alveoli, were lined with stratified squamous cells, or, less frequently, with cuboidal or columnar epithelial cells. The stroma was sporadically hyperemic, and small clumps of round-cell elements could be seen around some of the alveoli. The mammary glands of the control group of rabbits, which had been given multiple injections of stilbestrol alone, showed slight enlargement, with inconsiderable dilatation of the lactiferous ducts, which in some cases contained small amounts of serous fluid.

Our experiments showed that the action of diethylstilbestrol on the mammary glands of rabbits is intensified by preliminary administration of Phemerazole. In this respect, Phemerazole resembles the sedative drugs chlorpromazine and reserpine.

SUMMARY

The action of diethylstilbestrol on rabbit mammary glands is intensified by administration of Phemerazole (5-phenyl-3-methylpyrazole). Enlargement of the mammary glands is seen, with considerable dilatation of ducts and alveoli, which become filled with secretion. Histological examination showed hypertrophy and hyperplasia of glandular tissue, with considerable dilatation of the lumina, which were filled with protein-containing secretion in which desquamated epithelial cells could be seen.

The control group of rabbits, which received diethylstilbestrol alone, showed only slight dilatation of the lactiferous ducts.

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