Estrogenic Effect of Tri-p-anisylchloroethylene (TACE)* in the Human Postmenopausal Female. (19932)

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The study reported here was undertaken to determine the size of the minimal effective dose of Tri-p-anisylcholoroethylene (TACE)* in postmenopausal human subjects. TACE is a synthetic estrogen reported to have a remarkably prolonged effect after oral administration to laboratory animals (rats and monkeys) (1,2); although it has been used therapeutically in human patients(3) almost no reports are available regarding its estrogenic potency in the human subject, and the only comparisons that have been made between it and other estrogens have been done on laboratory animals.

Methods and materials. The subjects were 19 postmenopausal human females, inmates of a county home for the aged. Their ages ranged from 50 to 85 years and the postmenopausal interval, from 3 to 45 years. Each subject included in this study was given a gynecologic examination and judged to be free of pelvic disease. The criterion of estrogenic effect used was the degree of growth of the vaginal mucosa, as judged by the changes in the vaginal smear. All smears were obtained with the subjects in lithotomy position, using a dry cotton tipped swab inserted as deeply into the vagina as possible in the direction of the posterior fornix. On being removed from the vagina, the swab was rolled out on a clean glass slide, and the latter immediately dropped into the fixative solution (equal parts of 95% ethyl alcohol and ethyl ether). The smears were stained either the same or the next day with Schorr's single differential stain(4), and mounted in balsam. The entire area of each smear was examined under low power, and the approximate percentage of cornified, intermediate and basal epithelial cells, leucocytes, debris, and cytolysis estimated, without actually making cell counts of the smears. They were then given an arbitrary grade according to the following scheme: 0—primarily basal cells, with or without leucocytes; +—very few basal cells, with the predominant cells derived from the intermediate cell layers; ++—mostly intermediate cell types, with less than 50% of the cells cornified; +++—same as plus 2, except that at least 50% of the cells were cornified, and the remainder late intermediate cell types. All smears were graded without knowledge of the particular subject or treatment involved. Each subject had a typical postmenopausal smear at the start of the study (grade of 0, according to the above scheme); if she served for more than one test dose, the smear was allowed to return to the pretreatment level before the second or other treatments were started.

Two total doses of TACE were tried: 24.0 and 48.0 mg. The 24.0 mg dose was administered either as a single dose, or as a divided dose of 6.0 mg given on each of 4 consecutive, or on each of 4 alternate days, in either capsule or tablet form. The 48.0 mg dose was given as four 12.0 mg doses on each of four consecutive days, in either tablet or capsule form. Smears were taken before treatment, approximately every other day during the course of, or in the first week following treatment, and then at intervals varying from 3 times to once per week until complete regression was seen.

Results. The results are presented in Table I. It can be seen that 24.0 mg as a single dose is not sufficient to bring about more than a moderate amount of vaginal growth but that the effectiveness of this dose is greatly increased when it is administered as a divided dose on 4 consecutive days; the effect is possibly somewhat less than that produced by 48.0 mg administered in a similar manner. The data also indicate the possibility that the capsule may be a more effective method of

* TACE is the trade-mark of The Wm. S. Merrell Co., Cincinnati, for its brand of chlorotrianisene (tri-p-anisylchloroethylene).

TABLE I. Effect of TACE on Cornification of the Postmenopausal Human Vagina.

Total dose TACE admin., mg	Method of admin.	Total No. subjects	Maximal effect*		Onset of max effect (days)†	Duration of any effect (days)†
			Subjects	Grade		
24	Single dose					
	Capsules	9	6	+	6-10	10-13
			3	++		
	Tablets	8	7	+	6-10	10-13
			1	++		
24	6 mg on each of 4 consecutive days					
	Capsules	9	1	0	5-6	10-14
			1	+		
			4	++		
			3	+++		
	Tablets	5	2	++	5-6	10-14
			3	+++		
24	6 mg on each of 4 alternate days‡	5	2	+	1-2	10-12
			2	++		
			1	+++		
48	12 mg on each of 4 consec. days§	6	1	+	2-6	17
			1	++		
			4	+++		

* See text for description of grades.
† From the time of administration of the last dose.
‡ Administered in capsule form only.
§ Three of these patients received this dose in capsule, and three in tablet form. The differences in effect were too small to justify their presentation as separate groups.

administration than the tablet form but until further studies on a larger number of patients are completed, this must remain in the realm of conjecture.

Since the study was undertaken to determine the minimal effective dose of TACE, prolongation of the estrogenic effect which occurs at higher dosage levels(5) was not expected. Our data show that the duration of maximal effect of these doses of TACE was in the neighborhood of about a week from the time of administration of the last dose, and that a period of roughly 2 to 6 days elapsed after administration of the last dose before the maximal effect was seen. A small comparative study of 2 other oral estrogens (ethinyl estradiol and dienestrol) was run. The ethinyl estradiol was administered as six daily doses of 0.05 mg each, and the dienestrol as 6 daily doses of 0.10 mg each. Both of these induced approximately the same amount of vaginal growth as did 24.0 mg of TACE administered as a divided dose on each of 4 consecutive days. The time of onset of the maximal effect, and the duration of effect with both of these was also roughly equivalent to this dose of TACE.

Conclusions. The minimal effective dose of TACE after oral administration required for virtually complete cornification of the postmenopausal human female vagina is in the neighborhood of 24 to 48 mg administered as 4 daily doses of 6 to 12 mg each. Similar amounts of TACE administered on alternate days do not induce much cornification of the vaginal mucosa, but do lead to some growth of the intermediate cell layers. The duration of effect of these minimal effective doses of TACE was not remarkably different from that of other oral estrogens (ethinyl estradiol, dienestrol), but it is possible that its prolonged effect appears only with doses greater than the minimal ones.

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