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TRANSVAGINAL CHEMICAL STERILIZATION :  
CLINICAL USE OF QUINACRINE PLUS POTENTIATING ADJUVANTS

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ABSTRACT

Six years of experience with the use of transvaginal quinacrine as an obliterating agent of the intramural portion of the fallopian tube are presented. Fifteen different forms of treatment using various dosages of quinacrine, alone as well as a combination of quinacrine with several other pharmacological agents were studied. The purpose of these studies was to increase the rate of tubal obstruction, with 1 or 2 instillations of solution. The total experience is based on 638 patients who received treatment according to a prefixed plan. There was a total of 14,677 women months of observation and 437 patients were diagnosed as having tubal obstruction with CO<sub>2</sub> insufflation. Out of this group of 437, 50 pregnancies were observed, none of them ectopic, for a Pearl Index of 4.10. The most effective treatment regimen, quinacrine + xylocaine, with and without epinephrine, after the second instillation had an obstruction rate of 94%. Most of the pregnancies in obstructed patients occurred in the first year and appeared to be due to incomplete obstruction of the oviduct.

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## INTRODUCTION

Earlier studies in the rat have shown that intrauterine instillation of a variety of chemical agents produced significant morphological changes which might have functional significance in fertility control (1). These changes consisted of the transformation of the epithelial tissue into fibrous and granulomatous tissue in the treated horn while implantations in the control horn were normal.

One of these compounds, quinacrine, due to its potential application in humans, has been studied in detail. Preliminary studies with the use of quinacrine in mice and humans have been previously published (2,3). In the mouse, 25 mg/ml of quinacrine in distilled water locally applied to one horn produced only slight morphological changes. Fifty mg/ml produced intense functional alterations which normalized after 2 months. One hundred mg/ml produced obstructive morphological changes that lasted for a period of 3 months. Finally, 200 mg/ml produced apparently irreversible changes in the uterine structure. Similar experiments in the rabbit demonstrated that this species was almost completely insensitive even to doses of 200 mg/ml. This difference in histologic response to quinacrine in the two different species led us to investigate the biochemical basis of the mechanism of action of quinacrine. The results of these investigations have been reported in detail in another publication (4). It was concluded that there was a possibility of sensitization, that is triggering the granulomatous reaction in species refractory to quinacrine, such as the rabbit with the use of pharmacological agents which were called "potentiators". These potentiating agents also evoked the same response to quinacrine in sensitive species by causing previously subeffective doses to become effective. These experimental results led us to investigate, in the human, some physiological studies with various chemical substances that could hopefully increase the rates of obstruction above those previously obtained (3). Due to the impossibility of extrapolating the results obtained with quinacrine and adjuvant substances from one species to another (2-4), it was decided to systematically perform clinical experiments to demonstrate potentiation or depotentiation of some of the agents used as adjuvant. An attempt was also made to determine the importance of the phase of the menstrual cycle in which the instillation was performed. The technique used has been described in previous publications by us (3-5) and others (6).

## MATERIAL AND METHOD

The basic component of the occlusive agent is quinacrine hydrochloride obtained from the Winthrop and Sigma Laboratories, New York, New York. The different components were combined with quinacrine immediately before use and the solution was then instilled into the endometrial cavity from a 10 ml glass syringe through an endometrial biopsy cannula 3.5-4 mm in diameter. Instillation takes approximately one minute. If the patient did not show any adverse reaction, she is sent home one hour later. The patients were given instructions to wash the external genitalia with tap water for 2 or 3 days while the yellow material exuded (Figure 1).

The following studies were performed. Series A: Two instillations in the same menstrual cycle, 4 groups; 1) proliferative phase, day 7-10 and day 13-14, 2) secretory phase, day 15-16, day 21-23, Groups 1 and 2 were used for comparison with groups 3 and 4 which had adjuvants added, Series B: 11 different groups were

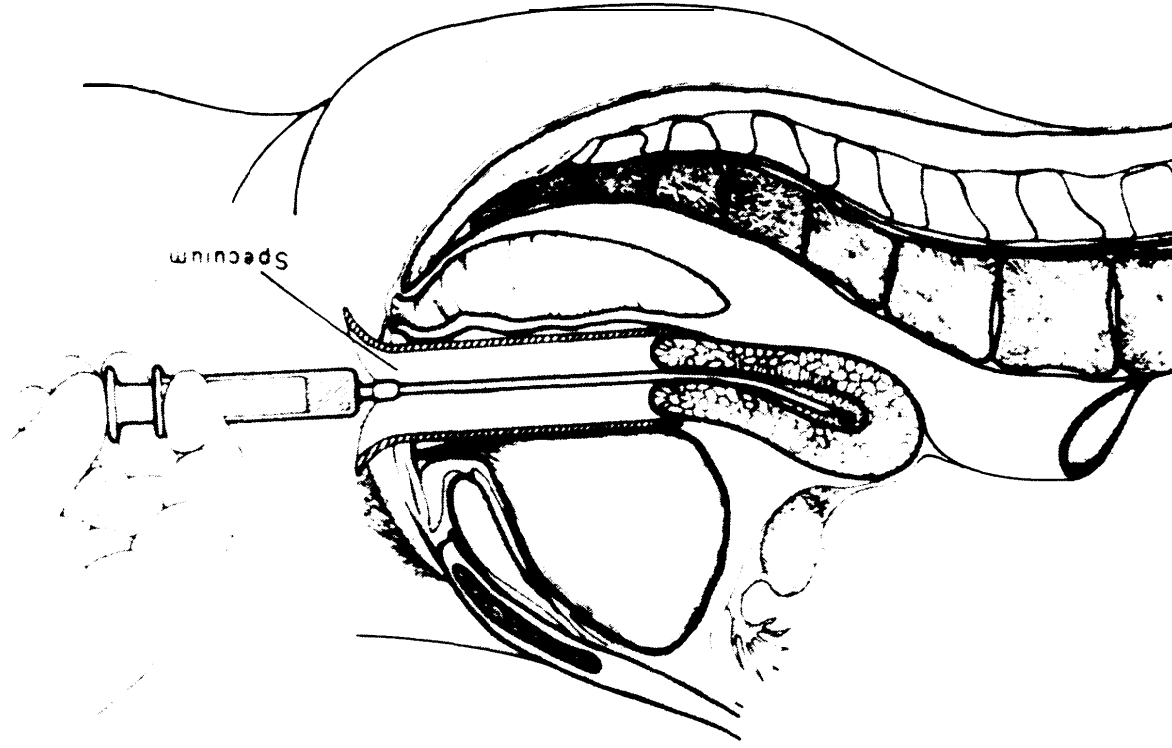


Fig. 1. Technique of Quinacrine Instillation.

formed; instillation was performed once a month for 2 months in two consecutive cycles on days 7-10 of the proliferative phase.

The patients analyzed in this study were enrolled into the clinical study during a 6-year period between August 1967 to September 1973. Analysis of the data was performed in July 1974. Up to the present, more than 800 patients have been instilled but only 638 cases have had post-instillation insufflation to determine "tubal patency". In Series A, two instillations in one menstrual cycle followed by one insufflation, 130 cases are included. In Series B, one insufflation after each instillation, 508 patients are included.

Treatment for each of the 15 different groups were the following:

- Series A:
  - Group 1. Quinacrine 1.5 gr, xylocaine 2% 5 ml; instillation day 7-10 and 13-14 of the same cycle.
  - Group 2. Quinacrine 1.5 gr, xylocaine 2% 5 ml; instillation day 15-16 and 21-23 of the same cycle.
  - Group 3. Quinacrine 1.5 gr, xylocaine 2% 5 ml; epinephrine 20 ug/ml in xylocaine; day 15-16 and 21-23 of the same cycle.
  - Group 4. Quinacrine 1.5 gr, xylocaine 2% 5 ml; epinephrine 100 ug/ml in xylocaine; day 15-16 and 21-23 of the same cycle.

Series B:
 

- One instillation per cycle; two consecutive cycles day 7-10 of the cycle. One insufflation 1 month after each instillation.

- Group 1. Quinacrine 500 mg, H2O 4 ml.
- 2. Quinacrine 1 gr, H2O 6 ml.
- 3. Quinacrine 1.5 gr, xylocaine 2% 5 ml.
- 4. Quinacrine 3 gr, xylocaine 2% 5 ml.
- 5. Quinacrine 1.5 gr, oxytocyn 1 I.U., H2O 5 ml.
- 6. Quinacrine 1.5 gr, tetmcycline 250 mg, xylocaine 2% 5 ml.
- 7. Quinacrine 1.5 gr, tetmcycline 250 mg, xylocaine 2% 5 ml, Tris pH 7.3.
- 8. Quinacrine 1.5 gr, xylocaine 2% 5 ml, epinephrine 20 ug/ml in xylocaine.
- 9. Quinacrine 1.5 gr, cortisone 100 mg, H2O 5 ml.
- 10. Quinacrine 1.5 gr, xylocaine 2% 5 ml. A TCu 200 intrauterine device was inserted before the instillation.
- 11. Quinacrine 1.5 gr, versenate 2.5 mg/ml, H2O 5 ml.

The number of patient included in each series, plus the months of observation, are specified in Table I and II with the results.

RESU LTS

Table I summarizes the results obtained in Series A ( 2 instillations in one cycle). It is evident that epinephrine acts as a potentiating agent for quinacrine as is observed in the obstruction rates. The secondary effects of the increase of the doses of epinephrine from 20ug/ml in xylocaine to 100 ug/ml will be discussed in the special comments section. If two instillations are performed in one cycle, the proliferative phase is more adequate than the secretory. Table II (Series B, groups 1-11 ) summarizes the results obtained with different quinacrine concentrations, solvents and adjuvants. It is evident that both xylocaine 2% and epinephrine, act as active potentiators of the occlusive action of quinacrine in the human. Doses more than 1.5 gr of quinacrine, group 4, do not increase obstruction rates. Two instillations in the proliferative period of two different cycles show rates of occlusion superior to those of two instillations in the proliferative period of the same cycle.

Figures 2 and 3 summarize the time of conception in those pregnancies which occurred in patients instilled who later had insufflation tests to determine patency. All the patient patients (36) who were not given additional protection (surgical sterilization or contraception) became pregnant. The average months of sexual exposure until I conception were 6.4. Pregnancy appearance in time follows a normal pattern. One ectopic pregnancy was recorded.

Figure 3 shows the pregnancy curve in obstructed patients, 50 cases in total; 94 women obstructed in Series A plus 343 women in Series B for a total of 437 women. In relation to the patient series, the onset of pregnancy shows a slight displacement to the right with an average of 10.2 months of exposure after treatment. Most pregnancies appear in both series in the first year, apparently indicating incomplete obstruction in the non-patent series. In this group, there were no ectopic pregnancies reported.

Secondary effects. In the 800 women instilled with one and two instillations, there were two cases of acute excitation of the central nervous system that were controlled with intravenous barbiturates, thiopental and pentobarbital. This complication forced us to keep the patient in the hospital until the cortical excitation disappeared in approximately 24 hours. In one case, the excitation appeared 1 hour after the instillation. A neurologic study of these patients after symptoms disappeared showed no abnormalities. The incidence of this disturbance seems to be approximately 1 in 700 instillations. One patient had a laparotomy on the 4th day post-treatment to rule out uterine perforation. There were no signs of quinacrine in the peritoneum. In group 4 of series A, in which 500 ug of epinephrine were used, 6 cases of acute abdominal pain were reported immediately after instillations, these symptoms lasted for more than 48 hours in spite of analgesics. One of these women had subsequent surgical sterilization and it was observed that there was an absence of quinacrine in the abdomen and no visceral lesions. There was also one case of

**TABLE I**  
EFFECT OF DIFFERENT POTENTIATING AGENTS ON TRANSVAGINAL STERILIZATION WITH QUINACRINE IN WOMEN

GROUP	TWO INSTILLATIONS AND INSUFFLATION			PREGNANCIES AFTER NON PATENCY (I <sub>2</sub> )	WOMEN MONTHS OF OBSERVATION IN NON PATENT	
	N° PATIENTS	NON PATENT	%		N°	PEARL INDEX
1	48	34	70.8	4	850 5.6	
2	25	15	60	2	345 7.0	
3	31	23	74.1	1	483 2.5	
4	26	22	84.6	2	616 3.9	

**SUMMARY**

<b>TABLE I</b>	130	94	72.3	9 (9.5%)	2294	4.7
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**TABLE II**

EFFECT OF DIFFERENT POTENTIATING AGENTS ON TRANSVAGINAL CHEMICAL STERILIZATION WITH QUINACRINE IN WOMEN

GROUPS	ONE INSTILLATION (I <sub>1</sub> ) ONE INSUFFLATION			TWO INSTILLATIONS (I <sub>2</sub> ) AND INSUFFLATION			CUMULATIVE % OF NON-PATENCY (#)	PREGNANCIES AFTER TUBAL OCCLUSION		WOMAN MONTHS OF OBSERVATION IN NON-PATENT
	N° PATIENTS	NON PATENT (I <sub>1</sub> )	%	N° PATIENTS	NON PATENT (I <sub>2</sub> )	%		I <sub>1</sub>	I <sub>2</sub>	
1	68	24	35.2	41	24	58.5	73.8	4	1	3456 2.4
2	39	26	66.6	9	8	55.5	88.5	1	1	1860 2.6
3	141	91	64.5	24	17	70.8	93.9	12	0	2332 6.2
4	33	15	45.4	12	9	75	88.8	0	0	216 0.0
5	29	15	51.7	5	2	40	85	1	0	187 6.4
6	46	27	58.6	10	2	20	78.3	1	0	1131 3.2
7	30	15	39.4	0	0			1	0	540 6.7
8	40	28	70	6	4	66.6	94.1	4	0	1024 4.7
9	25	10	60	5	1	20	80	1	0	432 2.8
10	23	10	43.4	0	0			3	0	560 6.4
11	26	11	50	0	0			1	0	556 5.5

**SUMMARY**

<b>TABLE II</b>	508	279	54.9	112	50	57.1	87.7	37 (13.2%)	4 (6.2%)	12383	4.0
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# THE CALCULATION OF THE CUMULATIVE PERCENTAGE OF OBSTRUCTION (OR NON PATENCY) WAS OBTAINED CONSIDERING AS NUMERATOR THOSE OBSTRUCTED WITH I<sub>1</sub> PLUS THOSE OBSTRUCTED WITH I<sub>2</sub> AND AS DENOMINATOR THE NON PATENT WITH I<sub>1</sub> PLUS THE TOTAL NUMBER THAT RECEIVED I<sub>2</sub>

TABLE III

SUMMARY OF TABLES I AND II

N° OF WOMEN STUDIED	NON PATENT WITH $I_1$ AND $I_1 + I_2$	PREGNANCIES IN NON-PATENT	WOMEN MONTHS OF OBSERVATION	PEARL'S INDEX
638	437(68.4%)	50	14.677	4.1

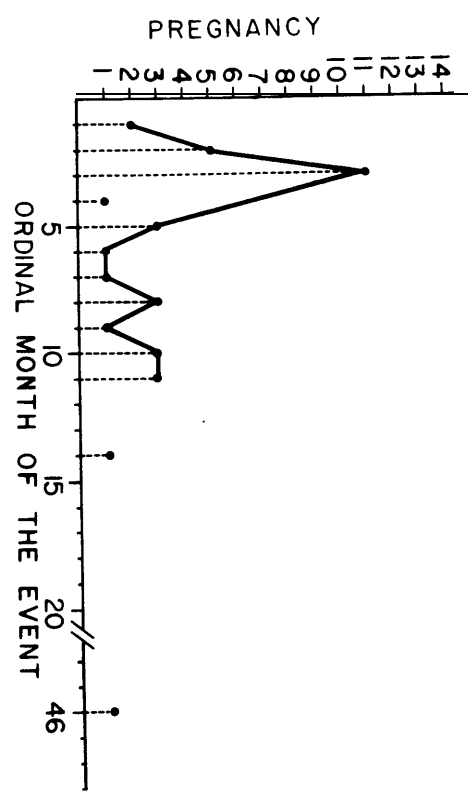


Figure 2 Distribution of pregnancy in patent women quinacrine treatment.

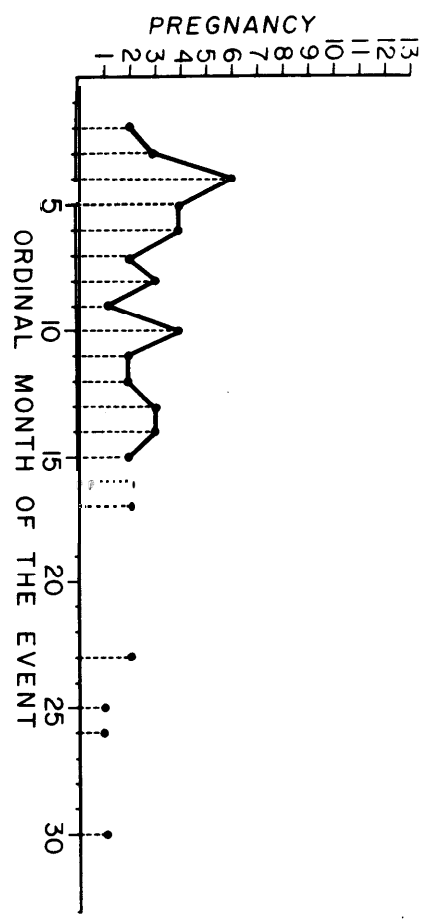


Figure 3. Distribution of pregnancy in non patent women after quinacrine treatment.

skin rash which persisted for more than a week. Seven women experienced amenorrhea of 3 months duration; endouterine adhesions were found in 4 of these women. Four patients presented moderate chemical vaginitis. These were associated with a specific lot of quinacrine.

The summary of this experience showed that of the 638 patients studied for a total of 14,677 women months of observation, 437 were obstructed. Fifty pregnancies were observed in this group of obstructed patients during this observation period, for a Pearl Index of 4.10 per 100 women years (Table III).

Pregnancies reported in patients with 1 instillation (I 1) were 37 of a total of 279 patients shown to be obstructed (13.2%). Pregnancies reported in patients with 2 instillations were 13 of a total of 158 cases with 2 instillations (8.2%). The total number of obstructions as determined by both the first and second insufflations, in successive cycles, totaled 87.7% rising to 94% in groups 3 and 8 of series B.

CONCLUSIONS

1. Apparently the rat is an acceptable experimental animal to determine the drugs that potentiate the action of quinacrine.
2. If the hypothesis of potentiation or depotentiation of the action of the drug is accepted, three mechanisms would have to be taken into account: a) the possibility that the drug does not reach the intramural region of the tubes due to spasmodic reactions of this segment shown by studies of Moulding and Thompson (7); b) that once the drug reached the tubes, it does not act due to a depotentiating factor present; and c) potentiating drugs might also act as relaxing agents at the tubal-uterine sphincter, thus permitting the drug to pass.
3. The adrenergic system seems to play an important role in the pharmacology of quinacrine in the three different species studied.
4. Of the combinations used, xylocaine and epinephrine seem to be the most promising one. Epinephrine must be used in low concentrations since when associated with quinacrine in concentrations higher than 20 ug/ml, it produces uterine pain in some patients.
5. The role of insufflation as a factor in opening previous obstruction must be considered.
6. Pregnancies produced after occlusion has been demonstrated are probably due to incomplete occlusion of the oviduct.
7. The technique is associated with a low morbidity; the only serious complication observed was cortical excitation which can be treated with intravenous barbiturates (thiopental).
8. The risk of ectopic pregnancies appears minimal.
9. The best results seem to be offered by 2 instillations in successive cycles in the proliferative phase of the cycle.
10. It seems possible that potentiating drugs can be found that provide an obstruction rate close to 100% with 2 instillations.

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