ORAL CONTRACEPTIVES—PART VII
ANTIMALARIALS AS ANTIFERTILITY AGENTS[1]

By

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Six typical antimalarials have been studied for their effect on the fertility, on the mating behaviour of mice and on their oestrus cycle. The schizonticidal drugs chloroquine, camoquin and mepacrine were found to be devoid of antifertility effect when tested at dose levels equivalent to their usual therapeutic doses. The gametocidal drug pamaquine, on the other hand, produced significant antifertility effect in mice. Paludrine and daraprim were found to be too toxic in mice and need testing in some other species.

The antifertility effect of some anthelmintics was reported by Sareen *et al.* (1961). The encouraging results obtained in that series indicated the possibility that some antimalarials, which, by virtue of the structural similarity of their active centres, possess in general a similar mode of action on the protozoa and thus share to some extent their anthelmintic action, may also possess antifertility effect. Besides, the hypothesis that mepacrine, an electropositive dye (Keller, 1949) abolishes the electrochemical forces responsible for the attachment of the scolex of the worm to the intestines (Mustakallio and Saikkonen, 1954), suggested the further possibility that it might also elicit a similar action on fertilization or implantation during the mammalian reproductive process. On the basis of these assumptions six typical antimalarials were selected for testing their antifertility effect.

METHODS

Albino mice weighing 18-25 g were employed in the screening experiments. The effect of the drugs on the fertility and on the mating behaviour of the animals, on their oestrus cycle and the approximate lethal dose (ALD) were studied according to methods described in the earlier communications (Sareen *et al.*, 1961). The following antimalarials were screened at dose levels calculated from their usual therapeutic doses: Chloroquine, Camoquin

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and Mepacrine edch 12 mg/100 g, orally, daily for 15 days before and for 15 days during cohabitation; Pamaquine, three doses were used: 12, 6 and 3 mg/100 g, orally, daily for 10 days, 5 days before and 5 days during cohabitation; Paludrine, two doses were used: 4 and 2 mg/100 g, orally daily for 15 days before and 15 days during cohabitation; Daraprim, two doses were used : 5 and 3.75 mg/100 g, orally, biweekly.

RESULTS AND DISCUSSION

The effect of the drugs on fertility, on the mating behaviour of mice and on their oestrus cycle is recorded in Tables I, II and III. Out of the six drugs tested only two (pamaquine and daraprim) showed a significant reduction in the fertility rate of the animals (Table I).

The antimalarials selected for the testing belonged both to the schizonticidal and the gametocidal series. It is evident from Table I that the schizonticidal drugs chloroquine, camoquin and mepacrine, in doses of 12 mg/100 g daily for 30 days (15 days before and 15 days during cohabitation) did not possess any significant antifertility effect although chloroquine (Camero, 1951) and mepacrine (Culbertson, 1940; Neghme, 1940) were known to possess fairly potent anthelmintic activity. The gametocidal drug pamaquine, on the other hand, when given at a dose level of 6 mg/100 g daily for only 10 days (5 days before and 5 days during cohabitation), produced infertility in 95 per cent of the animals when both females and males were treated, 84 per cent when females alone were given the drug and 72 per cent when only males were treated. The higher dose (12 mg/100 g) proved to be equally potent, but was more toxic; the lower one (3 mg/100 g) was inactive. The approximate lethal dose of pamaquine in mice was found to be 200 mg/100 g body weight. Although the 6 mg/100 g dose (the equivalent of the usual therapeutic dose) was found to be safe and did not produce any untoward effect, it would be worthwhile to investigate the antifertility effect of still less toxic gametocidal 8-amino-quinolines like primaquine, particularly when these drugs have to be used for long periods. Pamaquine is known to produce severe toxic and other side effects, especially hemolytic anaemia. The biguanide paludrine and the diazine daraprim (which resembles the triazine metabolite of the former) are carried by the gametocytes into the mosquito in which the male and the female gametes unite (cf. mammalian fertilization) but fail to develop beyond the sporocyte stage (Wilson and Schild, 1959). Paludrine at dose levels of 4 and 2 mg/100 g daily produced 60 and 43 per cent infertility when the females were treated. Daraprim at

TABLE I

Effect of the antimalarials on the fertility of mice

Drugs	Dose (mg/100 g)	Treated females						Normal females					
		Treated males			Normal males			Treated males			Normal males (control)		
		No. of females	No. of infertile females	% infertile females	No. of females	No. of infertile females	% infertile females	No. of females	No. of infertile females	% infertile females	No. of females	No. of infertile[1] females	% infertile females
Chloroquine	12	10 (3)[2]	2	29	10 (1)	3	33	10	2	20	10 (i)	2	22
Camoquin	12	10 (2)	2	25	10	2	20	10 (2)	1	13	10 (1)	2	22
Mepacrine	12	10 (1)	3	33	10 (1)	3	33	10 (1)	1	11	10 (1)	2	22
Pamaquine	12	20 (8)	12	100	20 (10)	9	90	20 (12)	6	75	20	4	20
	6	20 (1)	18	95	20 (1)	16	84	20 (2)	13	72	20	2	10
	3	20 (1)	5	26	20 (1)	4	20	20 (2)	3	16	20	4	20
Paludrine	4	10 (2)	3	37	10 (5)	3	60	10	2	20	10 (1)	2	22
	2	20 (9)	3	27	20 13)	3	43	20	8	40	20	4	20
Daraprim	3.75 (biweekly)	10 (3)	3	43	10 (1)	3	33	10 (1)	1	11	10	1	10
	5.0 (biweekly)	—	—	—	6 (1)	4	80	—	—	—	6 (1)	0	0

1 Infertile mice were those which had sterile mating, abortion, resorption, still births or pseudopregnancies.

2 The figures in brackets represent the number of females that died before mating.

5 mg/100 g biweekly for 10 days produced 80 per cent reduction in the fertility rate of mice when the females were treated. However, at 3.75 mg/100 g biweekly for 30 days it produced only 43 per cent infertility when both the females and males were treated and 33 per cent when only the females were treated. As the doses employed in the above experiments were equivalent to their usual therapeutic doses, it was thought advisable not to go beyond these limits to obtain a better response, if any.

All the drugs except pamaquine showed very little effect on the mating behaviour of mice (Table II).

TABLE II

Effect of the antimalarials on the mating behaviour of mice when females were treated

Drugs	Dose (mg/100 g)	No. of females	No. of matings	Days between cohabitation and the first mating	
				Mean	Range
Control	—	20 (1)	21	5.1	1— 9
Chloroquine	12	9 (1)	8	5.3	1—12
Camoquin	12	10	11	5.5	3— 8
Mepacrine	12	9	10	5.9	1— 9
Paludrine	4	7 (1)	4	6.0	2—10
Daraprim	3.75	9	10	5.8	1— 9
(Control)	—	20	20	4.2	1— 6
Pamaquine	12	20 (8)	12	9.5	2—14
,,	6	20 (1)	16	9.0	4—13
,,	3	20 (1)	19	9.5	5—14

The figures in parenthesis indicate the number of females which did not mate during the cohabitation period of 15 days.

In the case of mice treated with the different doses of pamaquine, the mating was prolonged to a mean value of 9.5, 9 and 6.5 days having a range 2 to 14, 4 to 13 and 5 to 14 days between cohabitation and mating with the respective doses as compared to that of control (a mean value of 4.2 days with a range of 1 to 6 days). Likewise, a statistically significant prolongation in the oestrus cycle and the dioestrus phase was observed with the two higher doses of pamaquine (Table III); the lowest dose (3 mg/100 g) showed no change at all as compared to the 15 days period prior to the drug treatment. As the oestrus is usually followed within 12 hrs by ovulation and the dioestrus represents quiescent phase (Allen, 1922) it may be suggested that the antifertility effect may be due to its prevention or delaying of ovulation by keeping the animal 'n hormonal quiescence for a longer period than normal.

TABLE III

Effect of pamaquine on oestrus cycle in mice

Drug	Dose mg/100 g	No. of animals	No. of cycles Mean±S.E.	Days of dioestrus Mean±S.E.	Days of oestrus Mean±S.E.	Duration of cycle		
						Days Mean±S E.	t	P
(Control)	—	20	2,86 ± 0,15	5,42 ± 0,21	3,21 ± 0,15	4,93 ± 0.21	—	—
Pamaquine	3		2,99 ± 0,11	5.31 ± 0,20	3,21 ± 0,15	4.92 ± 0.21	—	—
(Control)	—	20	3,2 ± 0,20	4,78 ± 0,19	3,42 ± 0,18	4,32 ± 0.21	—	—
Pamaquine	6		1,64 ± 0.18	8,14 ± 0,20	1,71 ± 0,11	8,54 ± 0·44	8,5	0,001
(Control)	—	20	3,46 ± 0,20	5.41 ± 0,21	3,58 ± 0,05	4,32 ± 0,22	—	—
Pamaquine	12		1,95 ± 0,15	8,33 ± 0,21	2,08 ± 0,10	8,78 ± 0,39	9,8	0,001

As the antifertility effect was elicited only by the gametocidal drugs or by those which had an unfavourable effect on the protozoal gametes, it seemed there may be some parallelism in these bioresponses though their nature remains obscure (cf. the selective gametocidal and the schizonticidal action elicited by 8-amino- and the 4-amino-quinolines).

Paludrine and daraprim proved to be highly toxic to mice in the doses employed. The former was found to be lethal to about 50 per cent and the latter to about 10 to 30 per cent of the animals. The ALD of paludrine and daraprim in mice was found to be 200 and 100 mg/kg respectively when given orally and the doses used in the screening experiments were approximately 1/5th and 1/3rd of the ALD respectively. Since these drugs are known not to be so toxic in higher animals including man, their antifertility effect should also be tested in some other species before they are discarded.

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