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Clinical Studies
on Bis-(p-Acetoxyphenyl)-Cyclohexyldenemethane (Sexovid)
and on 6-chloro-9 β ,10 α -pregna-1,4,6-triene-3,20-dione
(Ro 4-8347)

CHARLOTTE NEALE, G. BETTENDORF and G. TREU

We have studied the effect of Sexovid in a group of 103 patients with different kinds of ovarian insufficiency in 157 treatment cycles (Table I). In women with hypogonadotropic ovarian insufficiency no ovulation occurred. In 3 treatment cycles a bleeding resulted without an increase in BBT (basal body temperature).

In the group of patients with hypergonadotropic ovarian insufficiency there also was no evidence for ovulation.

90 patients with normal gonadotropin excretion were treated in 136 treatment cycles. In this group we observed in 32% a bleeding following a biphasic BBT. 4 patients became pregnant. There was no reaction in 40% of the treatment cycles.

In Table II this group is subdivided. It shows that the highest rate of suggested ovulation is found in patients with oligomenorrhoea and an-ovulatory cycles. There is hardly any response in that group of women with secondary amenorrhoea lasting longer than 2 years.

The BBT increased in 56% between the 2nd and 15th day after the start of treatment with Sexovid. The luteal phase in 42% was between 13 and 14 days, and in 30% it was shorter than 13 days. According to our studies the optimal dose amounts about 5 times 400 mg to 10 times 400 mg. 88% of the biphasic cycles with subsequent bleeding resulted after that dose. In hardly any case women who did not respond to this dose do so to higher dosages (Table V). There were hardly any side effects. 2 patients complained of headaches, 3 of vasomotoric symptoms. Especially no ovarian enlargement was seen.

The effect of the retroprogesterone Ro 4-8347 was studied in a group of 55 patients during 89 treatment cycles. In the eugonadotropic ovarian in-

Table I
Effect of Sexovid in different types of ovarian insufficiency

Ovarian insufficiency	Number of		No reactions	BBT increase bleeding		"Withdrawal" bleeding	Successive spontaneous biphasic cycles
	pat.	treatment cycles		no	yes		
eugonadotropic...	90	136	55 (40%)	37 (27,2%)	43 (32%)	1 (0,8%)	6 (4,4%)
hypergonadotropic	5	8	7 (88%)	1 (12%)		—	—
hypogonadotropic	8	13	8 (62%)	3 (23%)	—	2 (15%)	—
Total	103	157	70	45	43	3	

Table II

	Amenorrhoea		Corp. lut. insuffi- ciency	Anovul- atory cycles	Oligo- menor- rhoea	Total
	primary	secondary				

<i>Effect of Sexovid in patients with eugonadotropic ovarian insufficiency</i>						
Number of patients	6	38	4	23	19	90
Number of treat- ment cycles	8	55	5	40	28	136
Bleeding following biphasic BBT ..	2	5	4	16	16	43

<i>Effect of Ro 4-8347 in patients with eugonadotropic ovarian insufficiency</i>						
Number of patients	3	19	6	15	9	52
Number of treat- ment cycles	10	26	8	21	17	82
Bleeding following biphasic BBT ..	—	2	6	5	5	18

sufficiency no ovulation occurred. In two of the treatment cycles BBT showed an increase without subsequent bleeding.

In patients with normal gonadotropin excretion no reaction was seen in 28%, anovulatory bleeding occurred in 23%, bleeding following biphasic BBT in 22%, and in 27% withdrawal bleeding occurred. That means that bleeding started in the first 5 days after the end of Ro 4-8347 administration.

Table III
Increase of BBT after starting of treatment

Between day	Number of cycles	Between day	Number of cycles
<i>After therapy with Sexovid</i>		<i>After therapy with Ro 4-8347</i>	
6 and 10	2 (5%)	6 and 10	2 (11%)
11 and 15	24 (56%)	11 and 15	11 (61%)
16 and 20	11 (25%)	16 and 20	3 (17%)
21 and 25	6 (14%)	21 and 27	2 (11%)

Table IV
Length of luteal phase

Length of hyperthermic phase	Number of cycles	Length of hyperthermic phase	Number of cycles
<i>After therapy with Sexovid</i>		<i>Without therapy</i>	
8 days	1	9 days	2
10 days	1	11-12 days	4
11-12 days	11	13-14 days	8
13-14 days	18	15 days	1
15-16 days	4	16 days	1
19-20 days	2		
27 days	1		
57 days	1		

On Table II the patients with normal gonadotropin excretion are subdivided in different groups. The following results could be obtained. In none of the 10 cycles of patients with primary amenorrhoea ovulation was evident. In secondary amenorrhoea lasting more than two years a bleeding following biphasic BBT could be observed in only 2 out of 26 cycles. In 5 out of 21 cycles of women with anovulatory cycles ovulation could be suggested. In this 28% of the biphasic cycles ovulation was not only suggested by a BBT increase but also by endometrial biopsy. In oligomenorrhoea a bleeding after a biphasic BBT resulted in 30%.

In 61% the shift in BBT was between the 11th and 15th day after the start of treatment. In most of the cycles with biphasic BBT the length of the hyperthermic phase was around 14 days, but in nearly the same percentage shorter than 12 days (Tables III and IV).

At the beginning of our studies we did not know the optimal dosage and we still are not sure of it. Table V shows the effect of different doses and different durations of therapy with Ro 4-8347. It seems that the best effects were seen in the group of patients receiving 4 mg of Ro 4-8347 per day. After that dose we observed 61% of biphasic cycles with subsequent

Table V
Effect of different dosage of Sexovid and Ro 4-8347 respectively

	Number of days	Sexovid	Number of cycles	BBT biphasic bleeding
	10	200 mg	1	1
	20	300 mg	1	1
	5	400 mg	33	12
	8	400 mg	3	—
	10	400 mg	75	26
	20	400 mg	6	—
	25	400 mg	5	—
	45	400 mg	1	—
	10	600 mg	5	2
	15	600 mg	4	1
	20	600 mg	2	—

	Number of days	Ro 4-8347	Number of cycles	BBT bi-phasic bleeding	BBT mono-bleeding	“Withdrawal” bleeding
	3	8 mg	1	—	1	—
	4	8 mg	1	—	—	—
	5	8 mg	8	—	2	3
	8	8 mg	4	1	—	—
	8	6 mg	1	1	—	—
	10	6 mg	4	2	—	—
	5	6 mg	1	—	—	—
	2	4 mg	1	1	—	—
	3	4 mg	15	2	3	6
	4	4 mg	2	1	1	—
	5	4 mg	5	—	2	1
	8	4 mg	15	6	6	2
	10	4 mg	14	1	4	6
	3	2 mg	2	—	—	2
	4	2 mg	1	—	—	—
	5	2 mg	1	—	1	—
	10	2 mg	3	2	—	1

bleeding. On the other hand, the rate of withdrawal bleeding is the highest in this group (72%). Those women who had an ovulatory response did so mostly in the first treatment cycle.

Up to now we have had two pregnancies after this treatment.

There were no side-effects during or after the administration of Ro 4-8347. Besides Sexovid and Ro 4-8347 we use clomiphene in patients with normal gonadotropin excretion and ovarian insufficiency. Though clomiphene is up to now the more effective medicament, there are patients who did not respond on it, but did to Sexovid or Ro 4-8347. In Table VI are listed

Table VI
Effect of Ro 4-8347, Clomid and Sexovid in the same patients
(— no response, + ovulation)

Patient	Ro 4	Clomid	Sexovid	Patient	Ro 4	Clomid	Sexovid
1. A. W.	—	+	+	1. G. S.		+	+
2. F. S.	—	+	+	2. I. R.		+	+
3. E. K.	—	+	+	3. I. B.		+	+
4. C. Sch.	—	+	—	4. G. L.		—	+
5. A. C.	—	+	—	5. E. O.		—	+
6. H. M.	—	—	—	6. M. G.		—	+
7. D. H.	—	—	—	7. G. K.		—	+
8. H. v. H.	—	—	—	8. C. O.		—	+
9. R. H.	—	—	—	9. G. S.		—	+
10. I. K.	—	—	—	10. K. B.		—	+
11. U. P.	—	+	—	11. E. M.		—	+
12. C. M.	—	+	—	12. C. K.		—	—
13. G. N.	—	+	—	13. H. G.		—	—
14. H. Sch.	—	—	—	14. E. H.		—	—
15. M. O.	—	—	—	15. U. S.		—	—
				16. F. W.		—	—
1. K. M.	—		—	17. I. D.		—	—
2. E. L.	—		—	18. U. Z.		—	—
3. D. P.	—		—	19. C. G.		—	—
				20. R. G.		—	—
1. J. M.	+	—		21. B. S.		—	—
2. L. L.	+	—		22. R. R.		—	—
3. B. C.	+	—		23. P. S.		—	—
4. K. S. K.	+	—		24. H. L.		—	—
5. K. M.	+	+		25. E. R.		—	—
6. M. S.	+	+		26. v. M. O.		+	—
7. G. N.	—	+		27. C. B.		+	—
8. G. M.	—	+		28. L. D.		+	—
9. B. J.	—	+		29. C. K.		+	—
10. U. P.	—	+		30. E. K.		+	—
11. B. R.	—	—		31. G. S.		+	—
12. B. D.	—	—		32. C. B.		+	—
13. D. E.	—	—		33. J. R.		+	—
14. A. D.	—	—		34. I. S.		+	—
15. E. B.	—	—		35. E. S.		+	—
				36. C. H.		+	—
				37. Ch. H.		+	—
				38. M. H.		+	—
				39. K. B.		+	—
				40. B. B.		+	—
				41. M. B.		+	—
				42. U. G.		+	—

groups of patients who got all three or two of the medicaments. Out of 15 patients who were treated with the three preparations 8 responded to clomiphene, 3 to Sexovid (these 3 also responded to clomiphene and none to Ro 4-8347). On the other hand, the administration of Ro 4-8347 was successful in 7 patients, 4 of them did not respond to clomiphene, and in the last group 11 patients showed ovulation after treatment with Sexovid; 8 of them did not respond to clomiphene.

For example the response of a 30-year-old woman with anovulatory cycles will be discussed. This patient showed ovulation after Pergonal. Clomiphene did not have any effect, not even with the additional medication of HCG. After that, the patient was treated with Sexovid. During the 6 treated cycles, 3 times biphasic BBT resulted. During the last turn the patient became pregnant. Meanwhile she has been delivered of a healthy child.

Comparing the ovulation rate we observed after treatment with clomiphene to that after Sexovid and Ro 4-8347 we got 70% ovulations after clomiphene, 31% after Sexovid and 22% after Ro 4-8347.

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Discussion

E. DICZFALUSY: What was the dosage of clomiphene and what was the dosage of Sexovid?

G. BETTENDORF: We usually started with 5 times 50 mg of clomiphene and then increased the dosage, if there was no effect, to 5 times 100 mg or 10 times 50 mg. With the Sexovid we have a treatment schedule of 400 mg daily for 20 days.

E. DICZFALUSY: 400 mg. Not 600 mg as they suggest?

G. BETTENDORF: No, 400 mg.

R. RICHTER: Which were the side effects in the patients who have been treated with all three compounds, i.e. with Sexovid, clomiphene, and Ro 4-8347?

G. BETTENDORF: I mentioned that we have not seen any side effects in the patients who were treated with the retroprogesterone. With Sexovid we only had a small percentage of side effects. Sometimes we had eye symptoms, but very few and no other ones. With clomiphene we had the usual well-known side effects: abdominal pains, eye symptoms, etc.

J. GUÉGUEN: Il y a quatre sujets qui ont répondu au Ro 4-8347 et qui n'ont pas répondu au Clomid. Je voudrais savoir quelle a été la chronologie du traitement. Est-ce que le Ro 4-8347 a été donné après ou avant le Clomid?

G. BETTENDORF: We always start with Ro 4-8347. When we have no success, no positive results, we go on to the Sexovid and the last will be the clomiphene and this followed by human gonadotrophins.

J. GUÉGUEN: Quand il y a eu un succès avec le Ro 4-8347, le Clomid a-t-il été donné après?

G. BETTENDORF: Yes. In these four cases it was negative, however, only in these four cases.