SPARTEINE SULPHATE AS A MYOMETRIAL STIMULANT

by

N. KISHORE,* M.S., F.A.C.S.

R. KHAMBATTA,** M.S.

R. IDNANI,*** M.S.

Since the introduction by Blair Bell *et al* (1909) of posterior pituitary extract in obstetrical practice, oxytocics have come to stay. Induction of labour and its acceleration is now an accepted obstetric procedure. The search for a better and safer oxytocic however continues.

An ideal oxytocic agent for the stimulation of labour should be one which will with predictable success results in normal labour, raises significantly the resting uterine tonus, allows an adequate period of relaxation between contractions and has no untoward effect on mother and the foetus.

Sparteine sulphate is an alkaloid isolated from scoparious or broom top. Since sparteine sulphate and oxytocin have their major action directly on the muscle fibre an in vitro, it was utilized to test its efficacy.

The present work was undertaken with the following aims and objects:

1. To see the effect of sparteine sulphate on pregnant and non-pregnant human uterine myometrium.

2. To record the effect of sparteine sulphate more extensively on:—

(a) tonus
(b) frequency
(c) intensity

3. To find out the optimum dose of sparteine sulphate to initiate or stimulate uterine contractions.

Material and Methods

Uterine muscle strips were obtained from uteri of pregnant and non-pregnant women operated upon for caesarean section, hysterotomy and hysterectomy. Cases were divided into the following groups:

(1) Non-pregnant, 60 cases.
(a) Strips from corpus, 45 cases.
(i) During proliferative phase, 30.
(ii) During secretory phase, 15.
(b) Strips from isthmus, 15 cases.
(i) During proliferative phase, 10.
(ii) During secretory phase, 5.
(2) Pregnant, 35 cases.
(a) Lower segment, 25.
(b) Upper segment, 10.

The muscle strips from myometrium were preserved in oxygenated Kreb's solution at 37°C. Contractions were recorded on a kymograph after addition of varying concentrations of the drug. The following were studied:—

(a) Amplitude of contractions.
(b) Frequency of contractions.
(c) Duration of contraction.
(d) Contraction phase.
(e) Relaxation phase.

* *Professor and Head of the Department.*
** *Resident Gynaecologist.*
*** *Demonstrator.*
(Department of Obstetrics & Gynaecology, S. N. Medical College, Agra.)
Received for publication on 25-2-1971.

Distribution of the cases according to the concentration of the drug:

15 —100 ug/cc of Sparteine sulphate— 50 strips
105—150 ug/cc — 90 strips
151—299 ug/cc — 20 strips
300—450 ug/cc — 4 strips
450—600 ug/cc — 1 strips

Observations

The observations have been divided into two groups:

1. Sparteine sulphate as a myometrial stimulant.
2. Analysis of kymographic study.

General Factors

Age, parity and period of gestation had no significant effect on myometrial contractions after sparteine sulphate. The motility of uterine myometrium was not modified by the disease for which hysterectomy was done.

Phase of Menstrual Cycle

The response varied during proliferative and secretory phase. In the corpus and isthmus the response obtained was more in proliferative phase as compared to that in the secretory phase (Table 1).

Lag Period

This was taken as the time from the addition of the drug to the start of myometrial contraction, as judged by graphic record on smoked paper. The average lag period was 13.12 minutes with a minimum of 3 minutes to a maximum of 36 minutes. Thirty-eight cases (40%) had a delayed effect of 16-25 minutes.

Dose of Drug

Varying doses of sparteine sulphate ranging from 15-600 ug/cc were used in pregnant and non-pregnant myometrium. The optimum response was obtained with a dose between 105-150 ug/cc.

Effect on Tone, Frequency and Amplitude

In Corpus during proliferative phase: The increase in maximal amplitude was in 76% and remained unchanged in 24%. Contraction frequency increased in 20%, was unchanged in 60% and decreased in 20%. Tone increased in 80%, decreased in 5% and remained unchanged in 15%.

In Corpus during secretory phase: Amplitude was raised in 35%, decreased in 9% and remained unchanged in 56%.

TABLE I

Comparative Study of Tone, Amplitude, Frequency in Pregnant and Non-pregnants Groups in Various Phases of Menstrual Cycle

	Amplitude			Frequency			Tonus		
	Raised	Un Changed	Fall	Raised	Un Changed	Fall	Raised	Un Changed	Fall
Non-Pregnant :									
Corpus :									
Proliferative ..	76	24	..	20	60	20	80	15	5
Secretory ..	35	56	9	30	40	30	55	25	20
Isthmus :									
Proliferative ..	40	50	10	70	26	4	65	30	5
Secretory ..	60	20	20	60	20	20	20	80	..
Pregnant :									
Upper ..	41	41	18	45	38	17	40	50	10
Lower ..	65	30	5	75	20	5	55	45	..

Contraction frequency was raised in 30%, decreased in 30% and remained unaltered in 40%. Tonus was raised in 55%, decreased in 20% and remained unchanged in 25% of the cases.

The above findings indicate that response of sparteine sulphate was more in proliferative phase as indicated by maximum amplitude and tone.

In Isthmus during proliferative phase: Amplitude was raised in 40%, decreased in 10% and remained unchanged in 50%. Contraction frequency was raised in 70, unchanged in 26%. The tone was raised in 65% and remained unchanged in 30%.

In Isthmus during secretory phase: Amplitude in this series was raised in 60%, decreased in 20% and remained unaltered in 20%. Contraction frequency was raised in 60%, unaltered in 20% and decreased in 20%. Tone was raised in 20% and unchanged in 80%.

In pregnant upper uterine segment: The amplitude was raised in 41%, decreased in 18% and remained unchanged in 41%. Contraction frequency was raised in 45%, decreased in 17% and remained unchanged in 38%. The tonus was raised in 40% and remained unchanged in 50% and decreased in 10%.

In pregnant lower uterine segment: The amplitude was raised in 65%, unchanged in 30% and decreased in 5%. Contraction frequency was raised in 75%, remained unchanged in 20% and decreased in 5%. The tonus was raised in 55% and remained unchanged in 45% of the cases (Table 1).

Complications

Sustained tetanus developed in 4.2% cases after the concentration of 300 ug/cc of sparteine sulphate within 30 minutes. In 1% tetanus was present even at the concentration of 250 ug/cc.

Analysis of Kymographic Study

Amplitude: In non-pregnant corpus in the proliferative phase the mean amplitude before sparteine sulphate was 16.8 mm. and after sparteine sulphate it was 20.23 mm. (76%).

In corpus during the secretory phase, before sparteine amplitude was 24.63 mm. and after sparteine it was 25.4 mm. (35%).

In isthmus during proliferative phase, before sparteine sulphate it was 20.1 mm. and after sparteine sulphate it was 21.55 mm. (40%).

In isthmus during secretory phase, before sparteine sulphate it was 14.3 mm. and after sparteine it was 15.6 mm. (60%).

In pregnant upper uterine segment before sparteine sulphate it was 47 mm. and after sparteine sulphate it was 50.82 mm. (41%).

In lower uterine segment before sparteine sulphate it was 48.46 mm. and after sparteine it was 54.7 mm. (65%).

Frequency

In corpus during proliferative phase, before sparteine sulphate, frequency was 9 cycles/hour and after sparteine sulphate it was 10 cycles/hour.

In corpus during secretory phase, before sparteine sulphate it was 6.6 cycles/hour and after sparteine it was 8.3 cycles/hour (30%).

In isthmus during proliferative phase, before sparteine sulphate it was 6.6 cycles/hour and after sparteine it was 8.3 cycles/hour (70%).

In isthmus during secretory phase, before sparteine it was 10.3 cycles/hour and after sparteine it was 11.2 cycles/hour (60%).

In pregnant lower uterine segment, before sparteine it was 13.8 cycles/hour

and after sparteine it was 15.8 cycles/hour (75%).

In pregnant upper uterine segment, before sparteine it was 11.46 cycles/hour and after sparteine it was 12.2 cycles/hour (45%).

Duration of Contraction

In corpus during proliferative phase, before sparteine it was 1 minute 26 seconds, and after sparteine it was 1 minute 30 seconds.

In corpus during secretory phase, before sparteine it was 1 minute 6 seconds and after sparteine it was 1 minute 15 seconds.

In isthmus during proliferative phase, before sparteine it was 1 minute 3 seconds and after sparteine it was 1 minute 4 seconds. In isthmus during secretory phase, before sparteine it was 1 minute 3 seconds and after sparteine it was 1 minute 14 seconds.

In pregnant lower uterine segment, before sparteine it was 1 minute 28 seconds and after sparteine it was 2 minutes 37 seconds. In pregnant upper uterine segment, before sparteine it was 1 minute and after sparteine it was 2 minutes 27 seconds.

Contraction Phase

In corpus during proliferative phase, before sparteine it was 18.2 seconds and after sparteine it was 30.2 seconds. In corpus during secretory phase, before sparteine it was 29 seconds and after sparteine it was 45.5 seconds.

In isthmuus during proliferative phase, before sparteine it was 21.4 seconds and after sparteine it was 33.4 seconds. In isthmus during secretory phase, before sparteine it was 21.4 seconds and after sparteine it was 25.5 seconds.

In pregnant lower uterine segment, before sparteine it was 34.5 seconds and after sparteine 52.8 seconds. In pregnant upper uterine segment, before sparteine it was 35.6 seconds and after sparteine it was 58 seconds.

Relaxation Phase

In corpus during proliferative phase, before sparteine it was 44.5 seconds and after sparteine it was 58.6 seconds. In corpus during secretory phase, before sparteine it was 57 seconds and after sparteine it was 77 seconds.

In isthmus during proliferative phase, before sparteine it was 45 seconds and after sparteine 66 seconds. In isthmus during secretory phase, before sparteine it was 43 seconds and after sparteine 56 seconds.

In pregnant lower uterine segment, before sparteine it was 66 seconds and after sparteine it was 81 seconds. In pregnant upper uterine segment, before sparteine it was 66 seconds and after sparteine 87 seconds.

Discussion

It is evident from these observations that strips from the corpus and isthmus of non-pregnant group responded in a different manner to the same stimulus and that the response varied during the proliferative and secretory phases. In isthmus and corpus the response obtained was more in the proliferative phase as compared to that in the secretory phase. Amplitude in the proliferative phase was raised in 76% while in the secretory phase it was raised in 35% (Table 1).

Sandberg *et al* (1958) reported an increase in amplitude in 33% of cases.

There was no change in sensitivity of the myometrium to sparteine sulphate at different stages of gestation. Yaman *et al* (1968) working with sparteine also did not find any variation in relation to sensitivity of the uterus.

Dose

The optimum response on the muscle was obtained with a dose between 105-150 ug/cc. No tetanic response was observed in this series. The above findings are in agreement with the findings of Landesman, *et al* (1964) who stated that the optimum response was obtained with a dose above 150 ug/cc. Sustained tetanus was frequent at the level of 300-600 ug/cc.

Lag Period

In the present study the average lag period was 13.12 minutes with a minimum of 3 minutes to a maximum of 36 minutes. 40% cases had delayed effect of 16-25 minutes. In Landesman *et al* (1964) series, 40% cases had delayed effect which lasted from 5-40 minutes.

Such a delayed response could confuse the clinician in giving a second dose before the response comes. This would naturally result in increased tone and at times tetanic contractions.

Effect on Amplitude, Frequency and Tone in non-pregnant and Pregnant Cases

It is evident from the observations that the response of sparteine sulphate was more in proliferative phase as compared to the secretory phase, as indicated by the amplitude and tone (Table 1).

Comparing the findings of corpus and isthmus the response according to percentage amplitude rise in secretory phase was more in isthmus than the corpus (Table 1).

These findings together with the observation of the qualitatively different response of non-pregnant corpus and isthmus to sparteine sulphate may indicate different structural or biochemical composition of the muscle cells in the corpus and isthmus.

In the pregnant group sparteine sulphate showed a greater oxytocic effect as compared to the non-pregnant group and also the effect was more in lower uterine segment as compared to upper uterine segment. Frequency was more significantly affected while the difference in the tone was not striking (Table 1).

Sandberg *et al* (1958) also reported a marked change in frequency and were of the opinion that the response in the lower segment was greater than in the upper uterine segment.

The practical implications of the findings of this nature obviously produce a paradox in relation to the normal functional polarity of the uterus. It could be argued that the difference in response may be due to the structural and biochemical differences in the fibres of the upper and lower uterine segment.

It appears that more work is needed to explain this possible discrepancy of an in vitro response.

Summary

(1) Sparteine sulphate in vitro as a oxytocic agent increases the frequency, amplitude and duration of contraction in the myometrium (all parameters of uterine function).

(2) The distribution of motility was specific, both for the corpus and for the lower uterine segment.

(3) The responsiveness of the myometrium to sparteine is characterized by effective and high degree of variability from patient to patient.

(4) Variability of response extends even to the response to sequential dose in the same patient.

(5) A comparison between pregnant and non-pregnant uterus showed a tend-

ency to increased sensitivity in the pregnant uterus.

(6) Tetanus occurred in 4% cases at the level of 300 ug/cc.

Acknowledgement

We wish to acknowledge with thanks the supply of sparteine sulphate UNITOCIN) by M/s. Unichem laboratories Ltd.

References

1. Landesman, R., Wilson, K. H., and Silverman, F. Obst. & Gynec. **23**: 2, 1964.
2. Sandberg, F.; Sundberg, A. J.: Obst. & Gynec. Brit. Emp. 65; 965, 1958 b.
3. Sandberg, F., Sundberg, A.: J. Obst. & Gynec. Brit. Emp. 65; 484, 1958 a.
4. Yamada, S., Gusberg, S. B., Walker, B.: Am. J. Obst. & Gynec. **101**, 1094, 1964.