EXPERIMENTAL STUDIES OF SPARTEINE SULPHATE ON STRIPS OF HUMAN UTERUS

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Abstract—In the present investigation the action of sparteine sulphate alone and in combination with other drugs has been studied on isolated human uterine strips, from both pregnant and non-pregnant uteri. The effect of sparteine sulphate alone has been found to be dose dependant. Out of various combinations stilbesterol and priscol made a good combination for clinical use, however, further clinical studies on these combinations are indicated.

Sparteine sulphate was first isolated from its parent plant Sarothamnus scoparius by Stenhouse in 1851 (1) but it was not until seventy years later that the property of inducing rhythmic uterine contractions in isolated rabbit uterus was described (2). The drug was introduced into clinical practice as an agent for the induction of labour by Kleine (3).

Recent years have witnessed a marked upsurge of interest in the obstetric potentialities of sparteine sulphate alone or in combination with other drugs (4–10). The drug has been used to induce labour in combination with cardiazol (11–13) and posterior pituitary extracts (14–16). Most of the reports have commented favourably (17) on the value of sparteine as an agent for labour induction and have stressed the lack of tetanic contractions which are often encountered with oxytocin. The assumption that sparteine is devoid of any tendency to induce uterine tetany has recently been challenged by some workers (18–21).

It would thus appear that despite manifest advantages and potentialities in obstetrics, the standard of sparteine sulphate as an oxytocic is still to be clarified. The main object of the present study is to establish a pharmacological basis for the therapeutic use of sparteine sulphate as an oxytocic agent alone and in combination with other agents like DHE, Priscol, calcium etc.

MATERIALS AND METHODS

In the present study the action of sparteine sulphate was observed in vitro on the human uterus. The uterine strips were excised at abdominal hysterotomy for caesarean section or hysterectomy on account of fibromyoma. 22 × 2 mm strips were cut on the pattern of Chambers and Pickles (22) and were immediately immersed in Tyrodes solution maintained at 37°C and oxygenated continuously. The capacity of the bath was 20 ml. After giving rest to the tissue for 2 hr, a dose response was obtained with
sparteine sulphate. Each dose added to the bath was allowed to act for 5 min, then washed out. After washing, spontaneous motility was recorded for approx. 20 min before the subsequent addition of the drug. As mentioned above, after taking the response with sparteine sulphate, individual effects of dihydroergotamine methane sulphonate (DHE), priscoline hydrochloride (Priscol), calcium chloride, potassium chloride and adrenaline hydrochloride were observed (concentration of all these drugs in the bath have been expressed in terms of their respective salts). Thereafter, the response to combination of these drugs with sparteine sulphate was noted in different groups of experiments as follows:

Group 1: Sparteine sulphate (400 µg) + Stilbesterol (400 µg)
Group 2: Sparteine sulphate (400 µg) + DHE (10 µg)
Group 3: Sparteine sulphate (400 µg) + Priscol (10 µg)
Group 4: Sparteine sulphate (400 µg) + Potassium chloride (10 µg)
Group 5: Sparteine sulphate (400 µg) + Calcium chloride (10 µg)
Group 6: Sparteine sulphate (400 µg) + Adrenaline (4 µg)

In each group five experiments were performed for pregnant as well as for non-pregnant uterus.

RESULTS

It was observed that most of the uterine strips which were excised at the time of caesarian section showed no spontaneous motility, known as "G type" activity (23). Few of the strips showed "E type" motility. Non-pregnant uterine strips gave sphincter like contractions. Sparteine sulphate when given in increasing doses of 100 µg, 200 µg and 400 µg resulted in an increase in tone and amplitude of contractions both in pregnant and non-pregnant uteri. The sensitivity of the pregnant uterus was increased (10^-5) as compared to non-pregnant uterus (10^-4). The responses were dose related and spasm was observed with higher doses. The effects of various combinations on amplitude, tone and frequency are shown in Table 1. It may be noted that the responses to various combinations were not significantly different in non-pregnant and pregnant uteri. On the other hand there was a significant increase in tone, amplitude and insignificant increase in frequency when various combinations were compared with sparteine sulphate alone except for the combination of sparteine sulphate and DHE (frequency when various combinations were compared with sparteine sulphate alone except for the combination of sparteine sulphate and DHE).

DISCUSSION

In the present study the experiments were performed on human uteri in vitro because in vivo experiments are complicated by reflex and other indirect effects. In these experiments on human uterine strips, the concentration for the oxytocic action of sparteine sulphate was found to be 10^-4 for non-pregnant human uterus and 10^-5 for pregnant human uterus. The sensitivity of the strips taken from uterus whether in proliferative or progestational phase was found to be the same. In a pregnant uterus with a concentration
**Table 1.** Action of sparteine sulphate and the combination with other drugs on non-pregnant and pregnant human uterine strips in vitro.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Drugs</th>
<th>No. of exp.</th>
<th>Non-pregnant uterus</th>
<th>Pregnant uterus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amplitude of contraction in mm (mean ± S.E.)</td>
<td>Tone</td>
</tr>
<tr>
<td>1</td>
<td>Sparteine sulphate</td>
<td>5</td>
<td>10.2 ± 1.74</td>
<td>Increase</td>
</tr>
<tr>
<td>2</td>
<td>Sparteine sulphate + Stilbesterol</td>
<td>5</td>
<td>25.8 ± 2.86</td>
<td>Increase</td>
</tr>
<tr>
<td>3</td>
<td>Sparteine sulphate + DHE</td>
<td>5</td>
<td>12 ± 2.23</td>
<td>Decrease</td>
</tr>
<tr>
<td>4</td>
<td>Sparteine sulphate + Priscol</td>
<td>5</td>
<td>28.4 ± 1.16</td>
<td>Increase</td>
</tr>
<tr>
<td>5</td>
<td>Sparteia sulphate + Potassium chloride</td>
<td>5</td>
<td>15.2 ± 1.74</td>
<td>Increase</td>
</tr>
<tr>
<td>6</td>
<td>Sparteine sulphate + Calcium chloride</td>
<td>5</td>
<td>19 ± 2.23</td>
<td>Increase</td>
</tr>
<tr>
<td>7</td>
<td>Sparteine sulphate + Adrenaline hydrochloride</td>
<td>5</td>
<td>15.4 ± 2.54</td>
<td>Increase</td>
</tr>
</tbody>
</table>

Action of sparteine sulphate alone or in combination with other drugs on non-pregnant and pregnant uteri was not statistically significant P > 0.05.

The difference in amplitudes of uterine contractions with sparteine sulphate alone or in combination with other drugs was always statistically significant P < 0.05 except sparteine sulphate + DHE. P > 0.05.

The percentage increase in frequency with sparteine sulphate alone and in combination with other drugs was not statistically significant P > 0.05.

* Sparteine sulphate with DHE caused a decrease in frequency which was significant P > 0.02.
of $10^{-4}$ of sparteine sulphate, a spasm was produced and spontaneous rhythmicity did not return to normal for about one hr even after repeated washings. Similar observations have been made by Kreitmair and Sieckmann (24) with sparteine sulphate in pregnant cats and by Rosenblum and Stein (17) in isolated non-pregnant human uterus. Development of contracture appears to be a dose dependent phenomenon. This may explain the uterine hypertonia observed by some workers (7, 25, 26) and not observed by others (4, 27) in their clinical cases. By careful adjustment of the dose, accidents reported in literature for example, incomplete and complete rupture of uterus (20, 29) can be avoided. Titration of the dose to the needs of individual patient may be desirable as marked individual variations to the response of sparteine sulphate have been reported (26).

**Effects with stilbesterol:** Experiments with stilbesterol on isolated strips showed an increase in amplitude and tone of contractions and when used in combination with sparteine sulphate there was marked increase in the tone leading to a sustained spasm but this returned to normal after repeated washings within a period of half an hour. These in vitro findings throw considerable light on the theory that estrogen pretreatment sensitizes the uterus to oxytocic agents. Earlier reports reveal that estrogen treatment increases the spontaneous activity (30-32). It is well known that estrogens are essential for building up the actomyosin complex and high energy phosphates which together form the contractile system of the myometrial cell (33). The spontaneous contractile impulses are generated at such a rate that strong rhythmic activity occurs whenever the uterus is under estrogen domination. It has been shown that estrogens in particular are concerned in bringing about an endocrine milieu in which myometrium responds to mechanical stimuli (34).

**Effects with sympatholytics:** For the present studies of sparteine sulphate with sympatholytic agents, DHE and Priscol were selected as they are pharmacodynamically active on uterus and that their effects on this preparation with sparteine sulphate have yet to be described. DHE caused relaxation of human uterine strips when used alone. In combination with sparteine sulphate there was very little rise in amplitude and tone. Thus it did not form a suitable combination with sparteine sulphate to be used as an oxytocic rather this observation may form the basis of its use as an antispasmodic. The responses obtained were the same in pregnant as well as in non-pregnant uterus. With priscol there was a marked stimulation of the myometrial strips as indicated by increased tone, motility and amplitude and spasm with high doses. The pregnant myometrium was slightly more sensitive than non-pregnant one. When sparteine sulphate was added to the bath containing Priscol, stimulant effects were much more exaggerated. Priscol has been shown to be a stimulant of uterus in all species though non-pregnant rat uterus is said to be less responsive (35). Such stimulant effects of Priscol could reasonably be explained on the basis of its histamine like, parasympathomimetic and sympathomimetic actions besides its sympatholytic effects.

**Effects with calcium and potassium chloride:** In experiments with varying concentrations of calcium, stimulation of uterine strips was observed with $2 \times 10^{-4}$ as indicated by
increased tone and motility and sustained contracture as a result of higher concentrations. Optimum concentration of calcium was found to be essential for normal uterine motility. These effects are in accordance with the results obtained by Hellar and Holtz (36), and Bleir Bell and Datnow (37). Further, presence of calcium chloride potentiated the effects of sparteine sulphate.

Similar results were obtained with potassium chloride.

Effects with adrenaline: Adrenaline increased the tone, amplitude and frequency of movements of the isolated uterine strips. It potentiated the action of sparteine sulphate. No significant difference was found in pregnant and non-pregnant uterine strips, these findings being in agreement with those of others (38–40).

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