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MAXIMAL RESPONSE TO OXYTOCIN OF THE ISOLATED MYOMETRIUM FROM PREGNANT PATIENTS WITH INTRAHEPATIC CHOLESTASIS

E.J. Israel, M.L. Guzman and G.A. Campos

From the Institute of Obstetrics and Gynecology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile

Abstract. Prematurity and fetal death are common complications in patients with cholestasis of pregnancy. Both conditions appear to be associated with abnormal patterns of uterine activity. We studied the oxytocin-induced contractile activity in uterine strips taken from patients with cholestasis of pregnancy (n = 6) and from women with normal pregnancy (n = 6). Contractile activity of the myometrium in response to oxytocin was significantly higher in patients with cholestasis of pregnancy than in normally pregnant patients, at doses of 10^{-6}, 10^{-4}, and 10^{-2} M. We found that there is a greater maximal response to oxytocin in strips of myometrium from patients with cholestasis of pregnancy than from normally pregnant patients.

Key words: Cholestasis of pregnancy, myometrium, pregnancy

Cholestasis of pregnancy is a serious pregnancy complication, commonly associated with prematurity (1) and fetal death (2). The high rate of prematurity and the increased incidence of uterine hypertonus (Campos, GA., unpublished observations) during labor, corroborate observations of abnormal patterns of uterine activity among these patients. However, to our knowledge there are no published studies, either in vivo or in vitro, comparing the response of the myometrium to oxytocin in normally pregnant patients (NP) and in cholestasis of pregnancy (CP).

Bile acids are the main bile product retained in CP (3, 4) and they can stimulate smooth muscle contractions — at least to some extent — by increasing the entry of calcium into the cells (5). It is therefore conceivable that high levels of bile acids in CP may modify either the spontaneous uterine activity or its response to oxytocic agents.

MATERIAL AND METHODS

(a) Patients. Twelve patients were included in this study. Six of them had a normal pregnancy and their gestational ages ranged between 38 and 40 weeks. All of them underwent elective cesarean section because of cephalopelvic disproportion. None of them received oxytocin before surgery.

The remaining 6 patients had cholestasis of pregnancy. Their gestational ages ranged between 34 and 39 weeks. Cholestasis of pregnancy was diagnosed using criteria described elsewhere (6). Itching was the presenting symptom, and serum aminotransferase exceeded 40 units/liter though below 200 units/liter in all the patients. Total serum bilirubin levels ranged between 1.4 and 2.8 mg/100 ml. Hepatitis was ruled out by the absence of typical symptoms as well as by laboratory testing.

After delivery, the clinical symptoms of cholestasis of pregnancy disapeared and the laboratory values returned to normal. The indication for cesarean section in these patients was the need to terminate pregnancy, in the presence of an unfavorable cervix, because of the severity of the disease. None of the patients was in labor or had received oxytocin before delivery. Amniotic fluid was clear in all (12) patients studied, and cesarean section was performed under spinal anesthesia.

(b) Uterine samples. Strips of myometrium of about $2 \times 0.3 \times 0.3$ cm were taken from the upper lip of the hysterotomy during cesarean section in the 12 patients. Once obtained, the uterine samples were placed into a double-walled temperature-regulated (37°) tissue bath (cascade type). The muscle strips were superfused continuously (0.2 ml/min) with Krebs Ringer bicarbonate (pH 7.4). The uterine samples were kept oxygenated with 95% O_2 and 5% CO_2. Contractions were measured with a tension transducer (Statham F-10) connected to a Grass 7 Polygraph (Grass Medical Instruments, Hato Rey, Puerto Rico). After a stabilization period of 90 min, spontaneous uterine activity was recorded for 20 min, the myometrium was superfused with different concentrations of oxytocin (10^{-8} to 10^{-2}) for intervals of 20 min for each dose, allowing an interval of the same length between each dose as a wash-out period.

Uterine activity was quantitated by measuring the total area during contractions for the last 10 min of recording for each dose and for the wash-out period. Values are means±SE. The Dunnet t-test and the Scheffé test for Multiple Comparisons were used for statistical analyses. A p-value of less than 0.05 was considered significant.

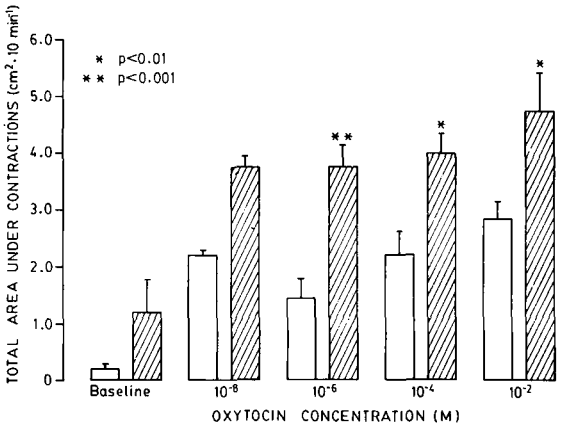

Fig. 1. Effect of oxytocin on myometrial strips taken from patients with cholestasis of pregnancy (▨) and from normal pregnancy patients (□).

RESULTS

Although spontaneous myometrial activity was greater in the CP group (1.20±0.58 cm^2) than in the NP group (0.2±0.16 cm^2) the difference was not significant. When induced contractile activity was compared between the groups, a significantly greater ($p<0.01$) response to oxytocin was observed in the CP group for the doses of 10^{-6}, 10^{-4}, and 10^{-2} M (3.78±0.40 vs 1.44±0.41 cm^2; 4.00±0.35 vs 2.22±0.41 cm^2; and 4.75±0.68 vs 2.86±0.29 cm^2) respectively (Fig. 1).

Within each group of samples the differences observed between the doses were not statistically significant.

DISCUSSION

When the plotted results of these experiments are analysed, it can be concluded that the slope of the dose–response curve for oxytocin lies below 10^{-8} M, and that above this dose, maximal effect is reached. It is also evident that the maximum effect of this hormone is greater in strips of myometrium taken from patients with CP, than from NP patients.

Bile salt levels are noticeably high in patients with CP (3, 4). Since bile salts are able to labilize cell membranes, thus facilitating calcium entrance to the cells (5, 7) it can be postulated that the myometrium of patients with CP, subjected for a long time to the detergent effect of high serum levels of bile salts, may have less stable plasma membranes. Under the effect of oxytocin, the latter may have facilitated either the entry of calcium into the myometrium cells, or the release of the calcium bound to the plasma membrane.

Further experiments are now in progress to study the effects of physiological doses of oxytocin in strips of myometrium taken from patients with CP and the interactions between oxytocin and bile salts on uterine contractility in NP patients.

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G.A. Campos, MD
Instituto de Obstetricia y Ginecología
Facultad de Medicina
Universidad Austral de Chile
Casilla 567
Valdivia
Chile