Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 11 (3—4), pp. 201—207 (1970)

Effect of Isoxsuprine on the Foetal Heart

By

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(Received March 12, 1967)

Isoxsuprine has been administered by intravenous drip infusion (0.4 to 0.6 mg per min) to 17 healthy women in the 7th to 9th month of gestation and to 13 likewise healthy parturient mothers. Maternal blood pressure, ECG, foetal ECG or PCG were continuously registered before, during and after the administration of the drug. In cases of labour, intra-amnionic tension was also recorded.

The drug frequently depressed maternal blood pressure and increased the heart rate. The foetal heart rate was also accelerated, even with maternal hypotension. The direct action of isoxsuprine on the foetal heart is accepted as a fact.

The clinical employment of isoxsuprine was preceded by the animal experiments of Lish et al. [12] and the clinical observations of Bishop and Wouters [3], Hendricks et al. [8] and Eriksson and Wiquist [6] who showed that the compound reduced the motility of the pregnant uterus, decreased its tonicity and diminished the intensity and frequency of contractions. In clinical practice isoxsuprine has proved highly efficient for suspending uterine activity in cases of threatening abortion or premature labour, and also for the relief of dysmenorrhoea. Like papaverine, isoxsuprine induces vasodilatation by stimulating the beta receptors and, in large doses, by inhibiting the alpha receptors. Its vasodilator action is most pronounced in the muscles and the skin so that the drug yields satisfactory results in peripheral circulatory disorders as well.

Isoxsuprine, a drug with a structural formula similar to that of adrenaline (Fig. 1), is well-known as an uterine relaxant and vasodilator; in adults it increases the heart rate and depresses blood pressure. To suspend uterine contractions, several intramuscular injections daily or 100—200 mg in intravenous drip infusion are administered; the infusion may be continued during a number of hours and even days.

The effect of the drug on the foetus needs further elucidation. It

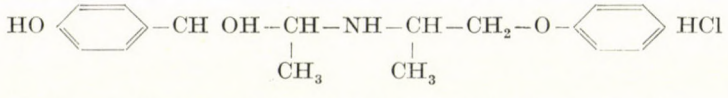

Fig. 1. Structural formula of isoxsuprine hydrochloride

was found by STANDER et al. [17] and SHENKER [16] that isoxsuprine stimulated the foetal heart. The present study was designed to study the effect of the compound on maternal blood pressure, ECG, as also on foetal heart rate.

MATERIAL AND METHODS

Isoxsuprine was administered in intravenous drip infusion to

(1) healthy pregnants in the 7th to 9th mont of gestation;

(2) to pregnant patients in normal term labour; this group included two cases in which the amniotic fluid was contaminated by meconium and the foetal heart sounds were anomalous (Table I).

ad (1). Seventeen pregnants were treated prior to the onset of labour. Before the examination, 5% dextrose solution was dripped into the cubital vein for 30 min during which the maternal ECG was registered from standard leads, maternal blood pressure was determined at 2—3 min intervals, and the foetal phonocardiogram was continuously recorded. Subsequently, 20 mg/100 ml of isoxsuprine was added to the infusion and the drip was so adjusted that the patients received 0.4 to 0.6 mg of the drug per minute. The drip was arrested after further 30—60 min but the said parameters were recorded for another 1—2 hrs. Complaints of the patients were likewise registered.

ad (2). Thirteen women in labour were given isoxsuprine in intravenous infusion after the spontaneous or induced rupture of the foetal membrane. Dosage of the drug and recording of maternal ECG and blood pressure were as above. Uterine activity was continuously registered by means of an intraamnionic (transcervical) catheter, while foetal heart rate was monitored by means of a foetal scalp electrode as designed by HON [9] and modified by KOMÁROMY [11]. An 8-channel Galileo type apparatus was used for the recording of maternal ECG, foetal direct ECG and PCG, and of intrauterine tension.

RESULTS

ad (1). Blood pressure decreased by about 20 mm Hg in 11 of the 17 cases; in two cases the decrease amounted to 35 and 40 mm Hg respectively. Diastolic pressure decreased by 10 to 20, at most by 25 mm Hg. Three patients displayed signs of supine hypotension which was corrected by a change to lateral decubitus. The onset of hypotension occurred 3 to 9 min after isoxsuprine

TABLE I

Effect of isoxsuprine on maternal blood pressure and heart rate, and on foetal heart rate

	Maternal				Foetal	
	blood pressure		heart rate		heart rate	
	decreased	unchanged	increased	unchanged	increased	unchanged
Between 7th and 9th month of gestation (17 cases)	11	6	14	3	12	5
During normal term labour (13 cases)	7	6	8	5	9	4

treatment had started and reached its lowest point after 20 to 30 min. Normalization of blood pressure began 5 to 25 min after cessation of the drip, but in three cases the initial value had been reached before termination of the infusion.

Fourteen pregnants responded to isoxsuprine by a 15 to 36 per min increase in heart rate and fall in 42/min. Tachycardia usually began after 7 min (from 4 to 13 min) (Figs 2, 3). The heart rate of 5 foetuses rose negligibly, not more than by 10 per min during drug administration. Since slight fluctuations had been registered prior to isoxsuprine treatment also, such cases were classified under the heading "nochange". There was no foetus displaying a decrease in heart rate.

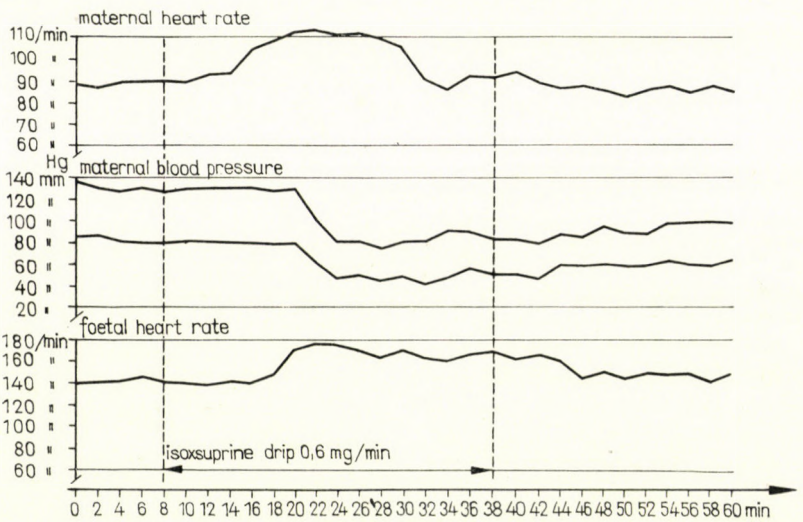

FIG. 2. Changes induced by isoxsuprine in maternal heart rate and blood pressure and in foetal heart rate

blood pressure recorded in 10 cases. In one case, hypotension was not accompanied by an increase in heart rate. Isoxsuprine had no effect on sinus arrhythmia and the course of the ECG curve. The decrease of blood pressure was usually preceded by an increase in heart rate between the 3rd and the 9th min; this usually reached a peak after 12 min, to return to the initial value 5 to 15 min after termination of the drip.

Foetal heart rate was increased in all cases; the maximum increase was

ad (2). Among the 13 pregnants, blood pressure fell in 7 and heart rate rose in 8 cases. Hypotension was so severe in two cases (from 130/80 to 70/50 and from 135/90 to 80/50 mm Hg, respectively) that even a change from supine to lateral position was of no avail so that the treatment had to be stopped. Maternal heart rate, too, was elevated in both parturients but it became slower at the lowest point of hypotension.

Foetal heart rate rose in 9 cases, but the rise was inferior to that

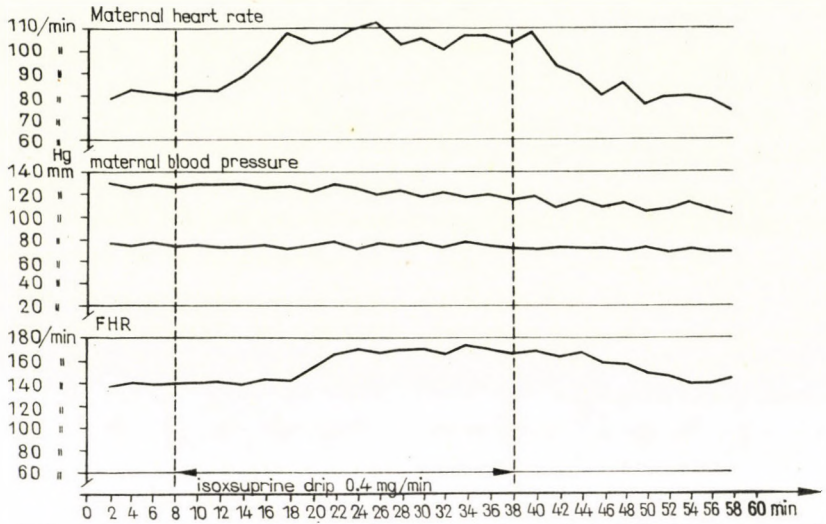

FIG. 3. Effect of isoxsuprine: increase in maternal and foetal heart rate with unchanged maternal blood pressure

registered in the first group; its maximum was 26/min. This may have been due to that foetal heart rate usually decreases during uterine contractions so that these counteract the effect of isoxsuprine. It was remarkable that foetal heart rate did not decrease even in the said two cases of a steep fall of maternal blood pressure.

In two cases foetal heart rate had decreased before isoxsuprine administration (Fig. 4). The drug had no

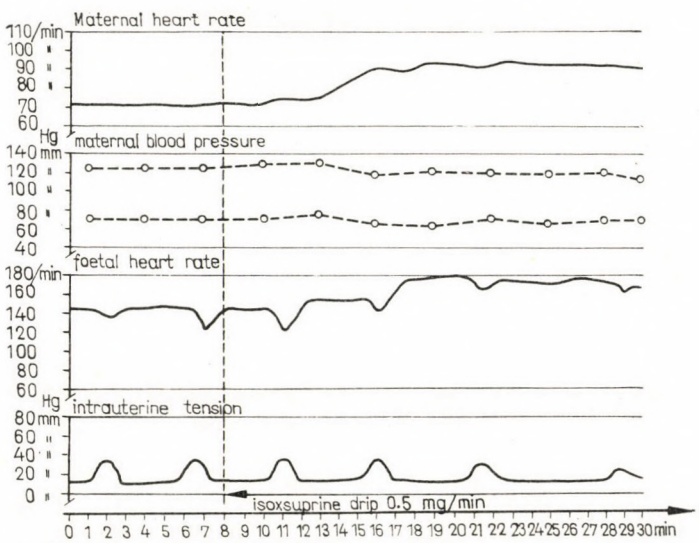

FIG. 4. Administration of isoxsuprine followed by increased maternal heart rate and a slight decrease in blood pressure; reduced frequency and intensity of contractions. While foetal heart rate was accelerated, its decrease during contractions persisted

effect on the foetal ECG although it induced a 6 to 18 rise heart rate both during and between contractions.

Whenever there was a change in maternal blood pressure as well as in maternal and foetal heart rate, the approximate point of time at which the isoxsuprine-induced change had begun, was computed. It was found that maternal heart rate was the first to increase; it was followed after 2—3 min by a rise in foetal heart rate and after another 2 min by maternal hypotension.

Under the effect of isoxsuprine, uterine contractions became less frequent and less intensive, especially at the onset of labour (Fig. 4). In five cases there was no change in uterine activity (where it reached 200 to 250 Montevideo units); in two cases there was a slight diminution in the number of contractions without relief of pain.

Discussion

Isoxsuprine, an uterine relaxant, is mainly employed in cases of threatening abortion or premature labour. The drug often accelerates maternal heart rate and depresses maternal blood pressure. Tachycardia seems to be the more frequent effect: it was observed in 22 pregnants out of a total of 30, while hypotension occurred in 18 cases only. When both phenomena occurred together, tachycardia preceded hypotension by 4 to 5 min.

The foetal cardioacceleratory effect of the drug is of especial importance. Increase in foetal heart rate preceded hypotension but ensued after the rise of maternal heart rate. This would mean that isoxsuprine passing into the foetal circulation, affects the foetal heart in a direct way. The theory would be irrefutable if chemical determination of isoxsuprine in blood were available. As to its passage through the placenta this has been demonstrated for adrenaline, a compound of similar structure.

Maternal tachycardia and hypotension are often associated with an increased foetal heart rate. An obvious explanation of this association would be that foetal tachycardia is a consequence of changes in maternal blood pressure and uterine circulation. Our observations do not, however, support this theory. There were three cases in which foetal heart rate increased, although maternal blood pressure and heart rate remained unchanged. Again, in five cases changes in maternal haemodynamics failed to affect the foetal heart sounds. According to Greiss and Pick [7] the uterine vessels are devoid of beta receptors. Neither can maternal hypotension be the source of increased foetal heart rate because, whenever the two phenomena appeared together, maternal hypotension always occurred a few minutes later. Ebner et al. [5] observed foetal bradycardia during maternal hypotension following spinal anaesthesia; the decrease in foetal heart rate was proportional to the degree and duration of the hypotension. Hon et al. [10] found that a fall in blood pressure in consequence of epidural anaesthesia gave

rise to foetal bradycardia. We, too, observed foetal bradycardia in supine hypotension and in cases of placenta previa accompanied by heavy loss of blood and hypotension. Isoxsuprine did not induce foetal bradycardia in the material of this study, although some of the drops in blood pressure were to levels of 80 and even 70 mm Hg. This observation is in harmony with the finding of SHENKER [16] in that isoxsuprine counteracts the effect of maternal hypotension on foetal heart rate.

There are numerous experiments to show that tachycardia is among the earliest consequences of a disturbance in foetal oxygen supply. It was shown that the first response of the foetus to incipient hypoxia is an acceleration of the heart beat. Slight hypotension elicited by chlorpromazine was found to be followed by moderate foetal cardioacceleration [1, 2]. Bradycardia ensued only if the drop in maternal blood pressure was considerable or if foetal blood supply was disturbed by a twisting of the umbilical cord. QUILLIGAN and KATIGBAK [14] registered tachycardia in 19 foetuses and demonstrated a simultaneous acidosis in the blood of the umbilical artery. Also BORN et al. [4], further REYNOLDS [15] demonstrated in animal experiments the co-existence of tachycardia and incipient hypoxia.

It will now be evident why we refuse to regard isoxsuprine tachycardia as being due to maternal haemodynamic factors and are convinced that the increase in foetal heart rate is a direct effect of the drug. Tachycardia increases cardiac output and so improves foetal circulation, oxygen supply and carbon dioxide release. Since the elevation of foetal heart rate persists when maternal hypotension would be expected to give rise to pathologic bradycardia, it is safe to assume that isoxsuprine inhibits or delays the development of foetal acidosis. Isoxsuprine does not change the character of anomalous heart sounds; and the decrease in foetal heart rate during uterine contractions remains as before, although the compensatory effect of the increased foetal heart rate may be operative both during and between contractions. It seems therefore justified to determine the effect of isoxsuprine on the evidence of changes in the foetal acid-base balance. Investigations in this respect are in progress.

REFERENCES

1. BIENIARZ, J., FERNANDEZ-SEPULVADA, R., CALDEYRO-BARCIA, R.: Effects of maternal hypotension on the human fetus. I. Fetal heart rate during normal labor. Amer. J. Obstet. Gynec. **92,** 821 (1965).
2. BIENIARZ, J., FERNANDEZ-SEPULVEDA, R., CALDEYRO-BARCIA, R.: Effects of maternal hypotension on the human fetus. II. Fetal heart rate in labor associated with cord around the neck and toxemia. Amer. J. Obstet. Gynec. **92,** 832 (1965).
3. BISHOP, E. H., WOUTERS, T. B.: Isoxsuprine, a myometrial relaxant. A preliminary report. Obstet. and Gynec. **17,** 442 (1961).
4. BORN, G. V. R., DAWES, G. S., MOTT, J. C.: Oxygen lack and autonomic nervous control of foetal circulation in lamb. J. Physiol. (Lond.) **134,** 149 (1956).
5. EBNER, H., BARCOHANA, J., BARTOSHUK, A. K.: Influence of postspinal

hypotension on the fetal electrocardiogram. Amer. J. Obstet. Gynec. **80,** 569 (1960).
6. Eriksson, G., Wiquist, N.: Action of isoxsuprine and its (+) isomer on the pregnant human uterus. Amer. J. Obstet. Gynec. **91,** 1076 (1965).
7. Greiss, F. C. Jr., Pick, J. R. Jr.: The uterine vascular bed: adrenergic receptors. Obstet. and Gynec. **23,** 209 (1964).
8. Hendricks, C. H., Cibils, L. A., Pose, S. V., Eskes, T. K.: The pharmacologic control of excessive uterine activity with isoxsuprine. Amer. J. Obstet. Gynec. **82,** 1064 (1961).
9. Hon, E. H.: Instrumentation of fetal heart rate and fetal electrocardiography. II. A vaginal electrode. Amer. J Obstet. Gynec. **86,** 772 (1963).
10. Hon, E. H., Reid, B. L., Hehre, F. W.: The electronic evaluation of fetal heart rate. II. Changes with maternal hypotension. Amer. J. Obstet. Gynec. **79,** 209 (1960).
11. Komáromy, B.: Új magzati EKG elektród Magy. Nőorv. Lap. **31.** 137 (1968).
12. Lish, P. M., Dungan, K. W., Peters, E. L.: A survey of the effects of isoxsuprine on nonvascular smooth muscle. J. Pharmacol. exp. Ther. **129,** 191 (1960).
13. Lish, P. M., Hillyard, I. W., Dungan, K. W.: The uterine relaxant properties of isoxsuprine. J. Pharmacol. exp. Ther. **129,** 438—44 (1960).
14. Quilligan, E. J., Katigbak, E. B.: Correlation of fetal heart rate and acid-base balance at birth. **3.** Tachycardia. Obstet. and Gynec. **25,** 371 (1965).
15. Reynolds, S. R.: Regulation of the fetal circulation. Its relation to fetal distress. Clin. Obstet. Gynec. **3,** 834 (1960).
16. Shenker, L.: Effect of isoxsuprine on fetal heart rate and fetal electrocardiogram. Obstet. and Gynec. **26,** 104—9 (1965).
17. Stander, R. W., Barden, T. P., Thompson, J. F., Pugh, W. R., Werts, Ch. E.: Fetal cardiac effects of maternal isoxsuprine infusion. Amer. J. Obstet. Gynec. **89,** 792 (1964).

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