The effects of hexoprenaline, a β_2-sympathomimetic drug, on maternal glucose, insulin, glucagon, and free fatty acid levels

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Hexoprenaline, an adrenergic β_2-receptor agonist, was administered as a 10 μg intravenous bolus to 9 women in the third trimester of pregnancy. The maternal plasma glucose, serum immunoreactive insulin, plasma immunoreactive glucagon (IRG 30 K), and free fatty acid (FFA) concentrations rose significantly at different times following the bolus injection. Thc serum insulin level increased first and reached a peak at 10 minutes, before the rise in plasma glucose, which reached a maximum at 30 minutes, suggesting that β_2-receptor stimulation affects insulin secretion directly and not via a rise in the glucose level. Plasma glucagon and FFA levels also rose despite the rise in glucose levels. We therefore conclude that β_2-receptor stimulation has direct actions on insulin and glucagon release and on glucose and FFA metabolism. The possible fetal sequelae due to these changes in the maternal metabolic milieu are discussed in relation to the use of a 10 μg intravenous bolus of hexoprenaline as a measure in the treatment of acute fetal distress. (AM. J. OBSTET. GYNECOL. 130: 761, 1978.)

THE β_2-SYMPATHOMIMETIC drugs are used in a wide variety of obstetric emergencies,[1] including fetal distress in labor.[2] This has become possible due to the introduction of the β_2 selective sympathomimetic drugs which have minimal β_1 effects on the maternal heart rate.[3]

Hexoprenaline sulfate, when administered as an intravenous bolus, was found to have the least stimulating effect on the maternal heart rate, compared with equivalent uterine effective doses of fenoterol, ritodrine, and salbutamol.[1] However, the metabolic effects caused by the β_2-sympathomimetic drugs may have important consequences to both the mother and the fetus.

The purpose of this report is to describe the effects of hexoprenaline, administered as a 10 μg intravenous bolus, on the maternal glucose, insulin, glucagon, and free fatty-acid levels (FFA).

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Materials and methods

Nine normal women in the third trimester of pregnancy were studied. Informed consent was obtained after careful explanation of the nature and details of the study to be carried out. The hospital ethics committee approved the study protocol.

Each experiment started at 08:00 hours, the patients having been fasted for 10 hours. With the patient lying comfortably in bed on the left side, an intravenous polyethylene cannula was placed in an antecubital vein and kept patent by repeated small doses of saline/heparin mixture.

Three basal blood samples were drawn at 15 minute intervals. A 4 ml. bolus of 0.9 per cent saline was given and three further samples were taken at 45, 60, and 90 minutes, then 10 μg of hexoprenaline in 4 ml. of diluent was injected and further samples taken at 100, 110, 120, 135, and 150 minutes.

All samples were immediately centrifuged and divided into aliquots. One was used immediately to estimate the plasma glucose by the Neocuprine method on the Technicon AutoAnalyzer. Samples for FFA determination were added to chilled tubes containing heparin; they were immediately centrifuged and the plasma was deep frozen. Samples for glucagon analysis were added to tubes containing heparin and trasylol (Aprotinin-Bayer) 500 K.I.U. per milliliter, cen-

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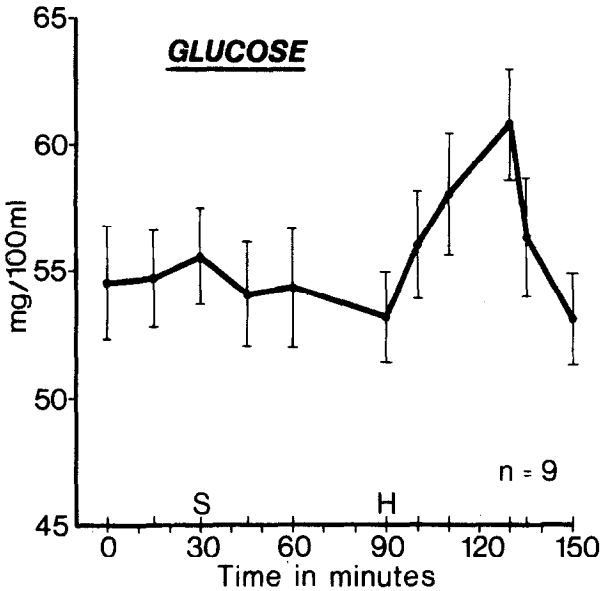

Fig. 1. The effect of hexoprenaline on the plasma glucose. *S*, Saline, 4 ml.; *H*, hexoprenaline, 10 μg.

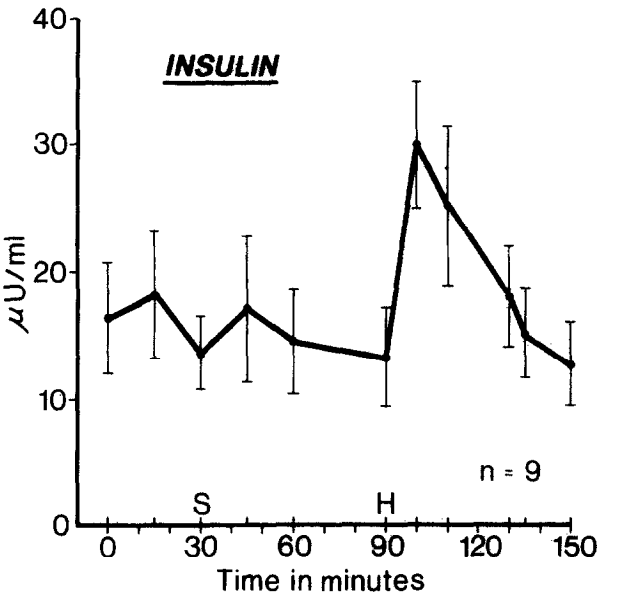

Fig. 2. The effect of hexoprenaline on the serum insulin.

trifuged, and frozen. An aliquot was allowed to clot and the serum frozen for insulin assay.

FFA were measured by the method of Duncombe[4] as modified by Itaya and Ui.[5] Glucagon was estimated with K30 antiserum by a method previously described.[6] Serum insulin was determined with Amersham kits.

Significance was determined with Student's t test for paired observations: p values of <0.05 were regarded as significant.

Results

Maternal pulse. The maximum maternal pulse increase after the administration of the hexoprenaline was 33.0 ± 2.9 (mean ± S.E.M. for all results).

Glucose. The plasma glucose increased from 53.2 ± 1.8 mg. per 100 ml. just before the administration of hexoprenaline to reach a peak of 60.9 ± 2.2 mg. per 100 ml after 30 minutes ($t = 9.29$ $p < 0.001$) and then returned to the initial value within 60 minutes (Fig. 1).

Insulin. The mean serum insulin increased from 13.3 ± 3.9 μU per milliliter just before to 30.0 ± 5.2 μU per milliliter 10 minutes after the administration of the hexoprenaline ($t = 5.94$ $p < 0.001$) and returned to the initial level within 60 minutes (Fig. 2).

Glucagon. The plasma glucagon increased from 65.1 ± 5.8 to 80.8 ± 9.6 pg. per milliliter ($t = 3.19$ $p < 0.02$) 20 minutes after the administration of the hexoprenaline. The increase of 6.1 pg. per milliliter after the administration of the saline was not significant ($t = 1.08$ $p < 0.40$). As with the glucose and insulin values, the glucagon returned to the initial level 60 minutes after the administration of the hexoprenaline (Fig. 3).

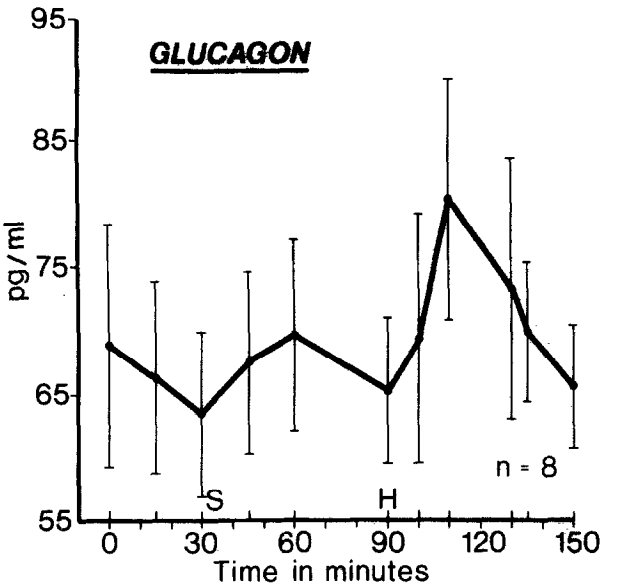

Fig. 3. The effect of hexoprenaline on the plasma glucagon.

Free fatty acids. The FFA increased from 519.3 ± 62.5 μmol., per liter to a maximum of 913.3 ± 48.9 μmol per liter ($t = 6.11$ $p < 0.001$) 30 minutes after the administration of the hexoprenaline. One hour later, the FFA had not yet reached the initial level (Fig. 4).

The sequence of metabolic responses to hexoprenaline is depicted in Fig. 5.

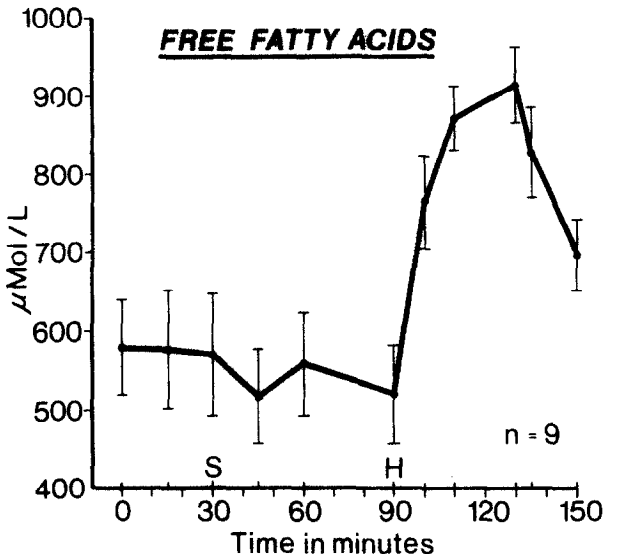

Fig. 4. The effect of hexoprenaline on plasma free fatty acids.

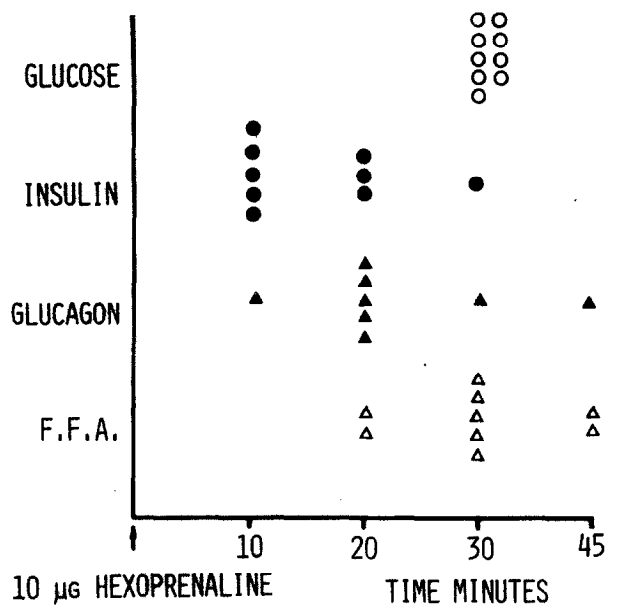

Fig. 5. Time taken for metabolites to reach maximum level.

Comment

We have previously shown that the administration of hexoprenaline to mothers in labor reduces fetal distress.[2] Since acutely administered β_2-sympathomimetic agonists may not immediately cross the placental barrier, the effects of hexoprenaline are likely to be indirect, mediated by changes in uterine contractions, uteroplacental blood flow, and/or transfer of fuel substrates across the placenta.[2]

The administration of a 10 µg intravenous bolus of hexoprenaline resulted in rises in maternal blood glucose and plasma FFA of 15 and 76 per cent, respectively. The fetus uses glucose as the predominant fuel for energy utilization but is capable of utilizing other substrates as well.[7] Glucose crosses the placenta readily as does FFA to a limited degree.[7] Whether or not the rise in concentration of these substrates in maternal blood was of benefit to the fetus is conjectural, but as fuel transfer appears to be dependent on maternal blood levels and not on facilitated transport, the changes were at least in the right direction. Other workers have shown a rise in both maternal and fetal glucose levels during infusion of the β_2 receptor agonist ritodrine.[8] It seems that glycogenolysis and lipolysis are directly stimulated by β_2-receptor agonists in man[9] if not in other species.[10]

The rise in glucose and FFA were not responsible for changes in insulin and glucagon concentrations. The maximum rise in insulin and glucagon occurred before the peak in glucose and FFA and were probably due to a direct action of hexoprenaline on the maternal pancreas. Adrenergic β_2-receptor stimulation is known to release insulin in man[9] but the adrenergic effects on glucagon are less clear.[11, 12] Our study suggests that the adrenergic receptor for glucagon may be of the β_2 variety, but more definitive studies are necessary.

Hepatic glucose output and hence glucose turnover are a resultant of the changing molar ratio of insulin to glucagon.[13] The predominant rise in insulin after hexoprenaline administration might have led to a fall in blood glucose levels, but instead a rise occurred, suggesting that this was mediated by hexoprenaline per se. The changes in insulin and glucagon levels were unlikely to be harmful to the fetus since neither hormone crosses the placental barrier.[14, 15]

We have previously reported that hexoprenaline is beneficial in the treatment of acute fetal distress by its effects on uterine contractions and possibly uteroplacental blood flow[2] and we now conclude that the changes in maternal metabolism too are likely to be beneficial rather than harmful to the fetus. We have confirmed the effects of β_2 receptor stimulation on glucose, insulin, and FFA and suggest that glucagon release may be mediated by adrenergic β_2-receptor agonists.

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