EFFECTS OF VARIOUS AMNESIC REGIMENS ON THE HUMAN MATERNAL AND FETAL BLOOD GASES DURING PARTURITION *

JOHN M. BROWN, M.D., AND PERRY P. VOLPITTO, M.D.†

Augusta, Georgia

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Previous investigators have demonstrated that neonatal asphyxia can be produced by a single factor or a combination of factors closely related to parturition (1, 2, 3, 4, 5, 6). Maternal analgesia, prematurity of the fetus, accidents and trauma during delivery and congenital malformations of the fetus are the predominant factors. Quite often, the analgesic regimen becomes the greatest offender (7).

The maternal, uterine and fetal effects of the older analgesic and anesthetic agents and technics are well known (7, 8, 9, 10, 11, 12, 13); however, certain details are missing with regard to amnesic combinations which are so widely employed today during parturition (14, 15, 16, 17, 18).

The purpose of this investigation was to determine the effects of three amnesic combinations when employed in clinically satisfactory dosages on the maternal and fetal blood gases, and to establish their site of action or the mechanism by means of which these agents produce respiratory depression of the infant at birth.

METHOD

To make this study significant, only full-term patients (calculated from the last menstrual period) who experienced normal labors (both

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‡From the Department of Anesthesiology, University of Georgia School of Medicine, Augusta, Georgia.
duration and progression) which terminated in spontaneous delivery of anatomically normal infants were studied. Primiparae and multiparae were studied in approximately equal numbers, and both colored and white patients were included in each of the series.

These patients were classified into four groups, depending upon the agents employed for amnesia during parturition. The first group received no medication prior to delivery and served as controls. The second group received an hypnotic agent combined with an amnesic agent (sodium pentobarbital-scopolamine hydrobromide) which was administered intravenously according to the technic described by one of us (19). The second group received a sedative, analgesic and smooth muscle spasmolytic agent combined with an amnesic agent (isonipecaine hydrochloride-scopolamine hydrobromide) which was administered intravenously according to the technic described by us (20). The fourth group received a new, potent synthetic analgesic agent combined with an amnesic agent (1-isomethadone hydrochloride-scopolamine hydrobromide). The former agent, according to our previous clinical experience, did not produce the degree of sedation and hypnosis obtained with other analgesic agents (21). This combination was administered intramuscularly in a fixed ratio of 20 mg. of 1-isomethadone and 0.64 mg. of scopolamine hydrobromide. The initial dosage was 10 mg. of 1-isomethadone and 0.32 mg. of scopolamine hydrobromide. Succeeding dosage was one-half of the preceding amount and was administered at one to two and three to four hour intervals.

Blood samples were drawn without exposure to the air using greased syringes which had been prepared with heparin, fluoride and mercury. A maternal arterial sample was drawn upon admission of the patient to the floor. Frequently, this sample was taken before early labor could be definitely diagnosed; in all cases it was taken before labor was very far advanced. A sample of maternal arterial blood was drawn within a few minutes after delivery through a previously anesthetized area of skin. Fetal blood samples were taken from the umbilical artery and umbilical vein at birth, using the technic described by Eastman (22).

Duplicate blood analysis was possible in most cases and was performed within two hours of the withdrawal time. Carbon dioxide-oxygen content was determined in the Van Slyke-Neill manometric apparatus (23); the oxygen capacity was determined by fully saturating a blood sample in the manometric apparatus before analysis (24), and checked in many instances by the relationship (25):

$$O_2 \text{ Cap.} = Hb. \text{ (Gm.)} \times 1.36.$$  

The hemoglobin was determined in triplicate by photoelectric colorimetric means (Fisher Electro-Hemometer). Thus, the percentage saturation of the blood was easily calculated:

$$\frac{O_2 \text{ Content}}{O_2 \text{ Capacity}} \times 100 = \text{Percentage saturation.}$$
Blood gas tensions were determined by a direct bubble method described by Riley (26), after tonometer calibration of the technic using a Haldane-Boothby-Saniford gas analysis apparatus (27).

The various laboratory technics occasionally were checked for accuracy by analysis of arterial blood samples from normal nonpregnant patients. Variations of duplicate analyses were within the limits published for each experimental technic.

Each patient was closely observed throughout labor and delivery. The amount of agent administered, the apparent degree of amnesia, the motor activity of the mother and the condition of the fetus at birth were all of paramount importance. These, along with other observations, were recorded at intervals. Whenever operative intervention or any complication of labor occurred, the case was excluded from this series.

RESULTS

The dosages of the various amnesic combinations shown in table 1 were employed throughout the study:

TABLE 1

<table>
<thead>
<tr>
<th>Agents</th>
<th>Smallest Dosage, mg.</th>
<th>Largest Dosage, mg.</th>
<th>Mean Dosage, mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium pentobarbital</td>
<td>200.0</td>
<td>487.5</td>
<td>341.0</td>
</tr>
<tr>
<td>Scopolamine hydrobromide</td>
<td>0.51</td>
<td>1.25</td>
<td>0.95</td>
</tr>
<tr>
<td>Isopecaine</td>
<td>80.0</td>
<td>190.0</td>
<td>150.0</td>
</tr>
<tr>
<td>Scopolamine hydrobromide</td>
<td>0.51</td>
<td>1.22</td>
<td>0.96</td>
</tr>
<tr>
<td>1-Isomethadone</td>
<td>10.0</td>
<td>25.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Scopolamine hydrobromide</td>
<td>0.32</td>
<td>0.80</td>
<td>0.64</td>
</tr>
</tbody>
</table>

These combinations of sodium pentobarbital-scopolamine hydrobromide and isopecaine-scopolamine hydrobromide produced excellent or satisfactory amnesia in each case in which they were employed. The incidence of fetal depression was comparable to that reported in the literature from other institutions. The arbitrary combination of 1-isomethadone-scopolamine hydrobromide did not always result in total amnesia. The percentage of patients with clinically satisfactory amnesia may be increased, however, by increasing the amount of scopolamine hydrobromide. We have done this since the completion of the series.

DISCUSSION

Statistical methods are required for the interpretation of results which are subject to numerous clinical or laboratory influences. The arithmetic average or mean expresses the general trend of the observations in each category. The variation from this mean in each instance is expressed as the standard deviation from the mean. A comparison of the control group of patients with the medicated groups is desirable. The standard error of the difference between these means is
an expression of the variation which might be expected to occur as a result of chance. If the two means differ by more than twice this value, the difference is considered “significant” and probably occurs as a result of biologic response to an altered situation. If the difference is less than twice this value, it probably occurs as a biologic response to a normal or identical situation and is said to be of no significance. An interpretation of the clinical and laboratory results is now possible.

Normal physiologic mechanisms are somewhat altered as the pregnant human female approaches parturition (28, 29, 30). There is an increase in plasma volume, a reduction in hemoglobin concentration, a reduction in cell count and cell volume (31), a decrease in plasma bicarbonate content (32) and possibly a decreased alkalinity of the blood (33, 34). The oxygen dissociation curve is somewhat flattened and shifted to the right (35). Consequently, experimental data vary to some extent from the established normal values.

The arterial oxygen tension of the full-term patient in early labor is normal (graph 1).

The arterial oxygen content is slightly lower than that found in normal individuals. The mean reduction occurs as a result of specific changes in the blood of the full-term pregnant woman, while individual variations occur as a result of differences in the hemoglobin content of the blood (graph 2).

Saturation of the arterial blood has been reported as normal (36). Variations from 87.5 to 95.5 per cent (mean saturation of 91 to 92 per cent) are present in this series of patients. These values are lower than some investigators have reported, yet the uniform decrease probably can be explained on the basis of decreased alkalinity of the blood and flattening of the oxygen dissociation curve of the blood of the full-term pregnant woman. It is improbable that the slight increase in circulation time of the pregnant woman and the increased “call for oxygen by the tissues” (37) are significant factors in lowering this.
The nasopharyngeal administration of oxygen increases the tension, content and percentage saturation of this blood (38) (graph 3).

The arterial carbon dioxide tension of the full term patient varies from 31.8 to 50.0 mm. of mercury. The mean values (38.7 to 43.8 mm. of mercury) lie within the range of normalcy (graph 4).

The carbon dioxide content of the arterial blood, similar to the oxygen content, is reduced. One would expect this since the plasma bicarbonate is reduced and the carbon dioxide content of the blood is roughly proportional to its alkali content. Normal values range from 48 to 54 volumes per cent (graph 5).

As labor progresses various changes occur. In spite of the unusually heavy demand for oxygen and possible periods of oxygen debt which occur as a result of the muscular effort or work during parturition (39), the maternal arterial oxygen tension, oxygen content and oxygen saturation of the blood remain constant or within limits of experimental error throughout the course of labor and delivery. The ad-
ministration of clinically satisfactory amounts of the three amnesic combinations does not alter any one of these appreciably.

In the unmedicated series of patients, the hyperpnea secondary to each painful stimulus, a fear mechanism and the mental anxiety arising from anticipation of other pains, serves to lower significantly the carbon dioxide tension and the carbon dioxide content of the maternal blood. No significant change occurs in patients who receive 1-isomethadone-scopolamine hydrobromide and sodium pentobarbital-scopolamine hydrobromide. Other patients who receive isonipecaine-scopolamine hydrobromide, in contrast, show a significant increase in maternal carbon dioxide tension and carbon dioxide content of the blood as labor progresses. This increase possibly is related to the decreased respiratory activity of the mother whenever this combination is employed.

The fetus performs its vital functions through the placenta. Torpin et al. have studied the actual intra-uterine pressures developed during pains and have related these to the fetal exchange of gases (40). It
is obvious, therefore, that any agent which has a deleterious pharmacologic action on the uterine musculature will adversely affect the exchange of vital gases to and from the fetus.

The mean fetal blood gas values in the 16 unmedicated patients fall within the range of accepted experimental data. In the 25 patients given sodium pentobarbital-scopolamine hydrobromide, no significant variation from the unmedicated group occurs with regard to oxygen tension, oxygen content or oxygen saturation of the fetal blood. The mean carbon dioxide tension and content are significantly increased over those of the control group of patients. This difference is explained by the relatively lower values established in the control group secondary to the hyperpnea observed, and probably does not represent a pathologically significant increase. Furthermore, Synder and Rosenfield (41) have shown that the fetus can be exposed to increased amounts of carbon dioxide without depressing effects on the respiratory center.

Neonatal depression can be produced by two methods whenever this combination is employed. Large dosage may directly depress the fetal respiratory apparatus. Such babies are not markedly cyanotic at birth, exhibit relatively normal blood gas values and often feebly cry following external stimulation. They are depressed for some time following birth in spite of adequate resuscitative measures. (Two cases occurred in this series.) On the other hand, large dosage of this amnesic combination may interrupt labor contractions. These babies are markedly cyanotic, exhibit significant changes in the blood gas values, yet rapidly respond to resuscitative measures. (One case occurred in this series.) It is feasible that a combination of these two conditions may occur, although the former mechanism seems to take place more frequently in our clinical experience with this amnesic combination.

In the 25 patients who were given isonipecaine-scopolamine hydrobromide amnesia the mean umbilical vein oxygen tension, content and saturation were lower than the levels observed in the unmedicated series. Inspection of each individual case in the series reveals that this significant variation was produced in only 2 cases, and that if these 2 cases are excluded, the mean values become of no significance. In each of these 2 patients, the normal progression of labor was temporarily interrupted, and lowering of the fetal umbilical vein oxygen tension, content and saturation resulted. Cyanosis was present and resuscitation was necessary at birth. Both patients rapidly improved.

Other patients, the so-called "hypertonic" type, maintain relatively normal fetal oxygen values. This fact suggests that the relaxing effect of isonipecaine on the uterus is possibly of value in the dystocia dystrophy syndrome. "They spontaneously deliver a breathing baby without the usual distressing outcome of this condition on the fetus during labor" (42). Furthermore, all babies in this series in which labor was not interrupted breathed spontaneously at birth. Fetal de-
pression occurs only infrequently as a direct result of drug depression on the infant.

Clinically, mild cyanosis is oftentimes observed in infants who have lowered oxygen tensions, yet the babies exhibit no slowing of the heart rate and breathe spontaneously. Glass et al. (48, 44) have shown that the full term fetus (laboratory animals) is particularly resistant to anoxia, and often survives after the death of the mother. Other authors have shown that anoxia itself, of a mild degree, does not produce respiratory depression in the infant unless there is a drug depression of the fetal nervous system.

The mean carbon dioxide tension and content of the fetal umbilical vein and artery are significantly increased. The former is physiologically necessary to assure gaseous diffusion from the infant to the maternal blood stream, and the latter occurs secondary to the increased carbon dioxide tension.

The group of 11 patients who received 1-isomethadone-scopolamine hydrobromide amnesia shows a mean lowering of the umbilical oxygen values similar to that of the isonipecaine series. In this group, also, one individual case produced this significant graphical variation from the control group. In this case, labor pains were temporarily slowed, the umbilical oxygen tension and content were reduced and the baby was moderately cyanotic at birth. Fetal depression with this combination and dosage of agents is probably the result of an action of 1-isomethadone on the uterine musculature and placental exchange of gases. No consistent type of uterine dysfunction was noted clinically, yet a peculiar elevation of the carbon dioxide content of the fetal blood makes one strongly suspect that this might be the mechanism involved.

The dosage of scopolamine was inadequate for total amnesia in 3 of 11 cases; however, it is possible to increase this dosage and obtain a greater degree of amnesia with this combination of agents.

The pharmacologic characteristics of the drugs administered to these patients are adequately reported elsewhere. Scopolamine hydrobromide is employed in each regime solely as an amnesic agent. As a psychic depressant it is desirable in the combination, yet extensive trials and massive dosage have shown it to be without analgesic effectiveness and that it does not directly affect either the uterine musculature or depress the fetal respiration. One may safely conclude, therefore, that the agent which is combined with the scopolamine hydrobromide in an amnesic regime is primarily responsible for the observed deviations from the normal.

Summary

Clinically effective combinations of sodium pentobarbital-scopolamine hydrobromide, isonipecaine-scopolamine hydrobromide and 1-isomethadone-scopolamine hydrobromide were administered to 61 patients during parturition. Sixteen patients received no medication and served as controls.
Significant changes can occur in the carbon dioxide tension and carbon dioxide content of the maternal blood as labor progresses. These changes are modified by the administration of amnesic drugs to the parturient female.

Overdosage of isonipecaine-scopolamine hydrobromide and 1-isomethadone-scopolamine hydrobromide can result in fetal depression at birth owing to interference with normal uterine contractions and relaxations during labor. Patients with a dystocia dystrophy syndrome or "hypertonic" type of uterine contraction may benefit by the use of isonipecaine-scopolamine hydrobromide amnesia.

Large dosage of sodium pentobarbital-scopolamine hydrobromide can produce fetal depression at birth through an interruption of labor or, more frequently, as a direct drug depression of the fetal respiratory apparatus.

REFERENCES

42. Torpin, Richard: Personal communication to the Authors.