

MORPHINE SULFATE AS AN OBSTETRIC ANALGESIC*

A CLINICAL ANALYSIS

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IT HAS long been common knowledge that clinically normal babies are sometimes born after the administration of enormous total doses of morphine to patients with toxemia of pregnancy. In one such instance, the child lived and prospered following the administration of 2 gr. of morphine to the mother during the twenty-two hours preceding birth. Similar instances, but with smaller total doses, have been observed with sufficient frequency to prompt an inquiry into the actual and potential dangers of the use of the drug as an obstetric analgesic.

METHOD

Beginning in March, 1941, a record was made on a punch card (Fig. 1) immediately after each labor of: the type, quantity and timing of the analgesic drug, the type and duration of the anesthetic, various maternal complicating factors, the time at which extrauterine, spontaneous breathing began or the nature of the various resuscitative measures which were instituted and the type of labor. Later the subsequent course of the child was added to the record. The onset of spontaneous breathing, although timed and recorded in fifteen-second periods, was analyzed in two thirty-second intervals. The condition of the child at birth was classified into 4 groups: respiratory distress, as evidenced by apnea after spontaneous breathing or cyanosis, paleness, limpness, and circulatory distress including slow, weak, and irregular pulse. The common resuscitative measures included clearing of air passages with a soft rubber bulb syringe, administration of oxygen, surface friction, immersion in warm water, and the introduction of a catheter into the trachea. Analeptics were seldom, if ever, employed. Breast feeding of all babies was encouraged so that the percentage of breast-fed babies represents to some extent a measure of the normality of the course of the child. Since our obstetric patients are commonly discharged on the ninth post-partum day, the infants do not remain in the hospital a sufficient length of time to warrant using the recapture of the birth weight as an index of their hospital course.

Because this study was directed primarily at achieving a clinical evaluation of morphine sulfate when employed as an obstetric analgesic, the general use of the drug was encouraged, but in practice 60 per cent of the patients receiving it were primigravidas.

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PATIENTS

Among a consecutive series of 1,534 parturient women, analgesic drugs of various kinds and combinations were administered to 807, of whom 386 were primigravidas.

Seven hundred and twenty-seven women received no analgesic drug and served as controls. However, only a very few (58) of these patients were primigravidas, a fact which was considered in evaluation and comparison.

ANALGESIC DRUGS

There is no routine obstetric analgesic in the Iowa clinic and the chief concern is individualized medication. The kinds and combinations of analgesic drugs employed in the 807 women of this study are shown in Table I and the quantities of morphine, scopolamine, and sodium pentobarbital administered to essentially normal patients in Table II.

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NAME: <i>Doe, Janet</i> Hosp. number: <i>XX</i> Delivery, Date: <i>7.10.41</i> Time: <i>5:30 am</i> Labor, Duration: <i>1 1/2 hr 37 min</i> 1st St. <i>15-16</i> 2nd St. <i>1-16</i> Hosp. Baby, number: <i>XX</i> Weight: <i>3200 gms.</i> Abnormalities: <i>none</i>																																																	
ANALGESIA: <table border="1"> <thead> <tr> <th>DOSE</th> <th>DRUG</th> <th>QUANTITY</th> <th>TIME GIVEN</th> <th>DATE</th> </tr> </thead> <tbody> <tr> <td>1</td> <td><i>Morphine</i></td> <td><i>gr 1/4</i></td> <td><i>11:39 AM</i></td> <td><i>7.10.41</i></td> </tr> <tr> <td>2</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>3</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>4</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>5</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>6</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>7</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>										DOSE	DRUG	QUANTITY	TIME GIVEN	DATE	1	<i>Morphine</i>	<i>gr 1/4</i>	<i>11:39 AM</i>	<i>7.10.41</i>	2					3					4					5					6					7				
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Chart 1.—A typical card.

During analysis of the data, certain clinic tendencies became manifest. Morphine was not only given more freely to primigravidas than to multigravidas, but also was employed in the presence of complicated labors in general, and toxemia and prolonged labor in particular. Analgesics other than morphine were employed among multigravidas 4 times more often than in primigravidas. Scopolamine was seldom used alone. Although more than 300 patients received the drug, only 36 had no other.

ANESTHETIC DRUGS

Since the group of 727 patients receiving no analgesia represents a natural selection of essentially normal multiparas, the type of second stage medication was quite distinct from the other group. Thus, the average normal multipara with no premedication tended to receive chloroform as an analgesic drug intermittently with the pains. It is emphasized that chloroform was never used to produce complete unconsciousness. Obstetric procedures necessitating surgical anesthesia

were always performed with the patient under the influence of some other appropriate medium.

On the other hand various types of inhalation and block anesthetics, selected according to existing exigencies, were administered during the second stage of labor to the 807 women of the group receiving analgesia during the first stage. The types and combinations employed are listed in Table III. In general, patients requiring obstetric operations received cyclopropane.

TABLE I. ANALGESICS EMPLOYED IN ORDER OF FREQUENCY

1. Morphine alone	217
2. Morphine and scopolamine	161
3. Sodium pentobarbital	135
4. Morphine, scopolamine, and sodium pentobarbital	85
5. Morphine and sodium pentobarbital	64
6. Scopolamine alone	36
7. Sodium pentobarbital and scopolamine	35
8. Morphine and miscellaneous (not included above)	28
9. Sodium amylal alone	22
10. Rectal ether	17
11. Miscellaneous (not included above)	7
Total	807
Total receiving morphine alone and in combination	564
Total receiving all other drugs	243

TABLE II. QUANTITY OF THREE MOST COMMONLY EMPLOYED ANALGESIC DRUGS

MORPHINE			SCOPOLAMINE			SODIUM PENTOBARBITAL		
GRAINS	PRIMI-GRAVIDA	MULTI-GRAVIDA	GRAINS	PRIMI-GRAVIDA	MULTI-GRAVIDA	GRAINS	PRIMI-GRAVIDA	MULTI-GRAVIDA
$\frac{1}{8}$	14	14	$\frac{2}{600}$	2	4	$\frac{3}{4}$	0	0
$\frac{1}{6}$	90	80	$\frac{3}{600}$	43	48	$1\frac{1}{2}$	30	14
$\frac{1}{4}$	68	67	$\frac{4}{600}$	75	68	3	60	94
$\frac{1}{3}$	40	5	$\frac{5}{600}$	1	1	$4\frac{1}{2}$	16	60
$\frac{3}{8}$	23	8	$\frac{6}{600}$	8	5	6	13	5
$\frac{1}{2}$	47	4	$\frac{7}{600}$	6	4	$7\frac{1}{2}$	5	5
$\frac{5}{8}$	2	0	$\frac{8}{600}$	8	0	9	2	0
$\frac{3}{4}$	6	1	$\frac{9}{600}$	0	0	$10\frac{1}{2}$	0	1
1	2	0	$\frac{10}{600}$	4	1			
$1\frac{1}{4}$	1	0	$\frac{11}{600}$	3	0			
			$\frac{12}{600}$	0	0			
			$\frac{13}{600}$	1	0			
Totals	293	179		151	131		126	179

Records of all patients with premature babies, pregnancy complications, and fetal death clearly not due to the analgesic medium were excluded.

TABLE III. ANESTHETICS AMONG 807 WOMEN RECEIVING FIRST STAGE ANALGESICS (ORDER OF FREQUENCY)

1. Chloroform, alone and in combination	343
2. Cyclopropane, alone and in combination	289
3. Nitrous oxide, alone or with ether	90
4. Block anesthesia	43
5. Ether alone	8
6. None	34

RESULTS

A gross comparison among all patients receiving no analgesia, those with morphine alone or in combination, and those with all other analgesic drugs (Table IV) seems to indicate that morphine, alone and in combination, was associated with the highest percentage of respiratory and circulatory difficulties at birth and of fetal death. Moreover, the percentage of low forceps operations in the morphine group was 3 times higher than among the patients receiving other analgesics and 9 times greater than in the control group. Since too many extraneous factors are introduced by study of combinations of other drugs with morphine, or in fact by study of any set of combinations, series of patients receiving single drugs were analyzed. Consideration of the 217 patients who received no analgesic other than morphine, however, did not appreciably alter the figures. Since morphine tended to be employed in the unusual type of patient, it was decided to make certain standard exclusions throughout the remainder of the analyses. These included: all cases where the infant weighed less than 2,500 Gm. at birth, all cases with ante-partum maternal complicating factors, such as placenta previa, abruptio placentae, severe maternal toxemia, and all stillbirths and neonatal deaths at term where the fatality was clearly due to some proved factor other than analgesia, such as macerated fetuses, death associated with diabetes, eclampsia, ruptured uterus, craniotomy, and erythroblastosis. Where no such well-defined and definite entity existed, fetal fatalities were included.

TABLE IV. COMPARISON OF INFANTS RECEIVING NO ANALGESIA, MORPHINE ALONE AND IN COMBINATION, AND ALL OTHER ANALGESICS

(FIGURES REPRESENT PERCENTAGES)

		NO ANALGESIA	MORPHINE	ALL OTHER ANALGESICS
PATIENTS, NUMBER		727	564	243
Spontaneous breathing	1-30 sec.	95.5	79.6	91.4
	31-60 sec.	1.9	10.8	5.8
Fetal distress immediately postnatal	Respiratory	4.3	26.3	15.6
	Pale	1.1	4.1	0.4
	Limp	0.7	9.0	4.1
	Circulatory	0.4	7.9	2.5
Resuscitative measures	Bulb	7.7	18.5	10.7
	Friction	17.2	34.1	14.8
	O ₂	1.4	15.6	5.4
	Tub	1.4	17.6	6.6
	Intratracheal catheter	1.1	6.6	3.5
Breast feeding		73.5	66.0	74.2
Stillbirth and neonatal death		2.3	5.9	2.9
Labor	Spontaneous	94.5	75.2	90.9
	Low forceps	1.9	17.9	5.4
	Other operations	3.9	6.4	3.7

Table V compares 3 series: no analgesia, morphine alone, and sodium pentobarbital alone, after such standard exclusions. The discrepancies among these groups are not so large as in the previous table. Nevertheless, the use of morphine still appears to be attended with considerable respiratory embarrassment, some interference with breast feeding, too many fetal deaths, and too many low forceps operations.

Despite the exclusions previously made, the feeling persisted that comparable series had not been obtained. The group receiving no analgesia was composed almost entirely of multigravidas, while the majority of the patients in the morphine group were primigravidas. A final subdivision of the groups into primigravidas and multigravidas was, therefore, made and tabulated (Table VI). Morphine still seems to be a more dangerous drug than sodium pentobarbital. However, the differences are not so marked, especially in the comparisons among the multigravidas. In fact, in the latter group, the principal point of difference seems to be in the greater percentage of respiratory difficulties, which included mild cyanosis and apnea following spontaneous respiration.

TABLE V. COMPARISON OF GROUPS RECEIVING NO ANALGESIA, MORPHINE ALONE AND SODIUM PENTOBARBITAL ALONE (STANDARD EXCLUSIONS)

(FIGURES REPRESENT PERCENTAGES)

		NO ANALGESIA	MORPHINE ALONE	SODIUM PENTOBARBITAL ALONE
PATIENTS, NUMBER		666	172	127
Spontaneous breathing	1-30 sec.	96.7	84.9	90.4
	31-60 sec.	1.8	9.3	7.1
Fetal distress immediately post natal	Respiratory	3.6	24.4	14.2
	Pale	0.8	1.7	2.4
	Limp	0.3	6.9	4.7
	Circulatory	0.0	2.3	3.2
Resuscitative measures	Bulb	8.1	15.1	11.0
	Friction	17.3	23.3	14.9
	O ₂	0.9	12.2	5.5
	Tub	0.8	12.2	5.5
	Intratracheal catheter	0.8	4.1	3.2
Breast feeding		79.9	55.2	77.9
Stillbirth and neonatal death		0.9	1.7	0.8
Labor	Spontaneous	95.3	80.8	89.7
	Low forceps	1.1	16.3	6.3
	Other operations	3.3	2.9	3.9

By the time so many "breakdowns" have been made, the series becomes too small to be of great significance. Nevertheless, it is felt that only by such limitation of extraneous factors is it possible to attain true comparisons. Many papers extolling the virtues of this or that analgesic medium or technique have failed to consider all the factors involved.

A final analysis concerning the fetal effects of morphine in relation to the time interval before delivery was made (Table VI). In general the results agree with those obtained by Shute and Davis,¹ namely, that administration of morphine during the third and second hours preceding delivery is attended by the highest percentage of fetal difficulties. During the first hour, and after the third or fourth hour, the effects of the drug on the fetus are minimal.

Also analyzed, but not presented in tabular form, was the effect of morphine on 22 immature infants weighing between 1,500 and 2,499 Gm. More than one-third of them exhibited respiratory distress at birth, and nearly one-third ultimately died.

TABLE VI. COMPARISON OF GROUPS RECEIVING NO ANALGESIA, MORPHINE ALONE AND SODIUM PENTOBARBITAL ALONE (STANDARD EXCLUSIONS)

		PRIMIGRAVIDAS			MULTIGRAVIDAS		
		NO ANALGESIA	MORPHINE SULFATE ALONE	SODIUM PENTOBARBITAL ALONE	NO ANALGESIA	MORPHINE SULFATE ALONE	SODIUM PENTOBARBITAL ALONE
PATIENTS, NUMBER		54	97	20	612	75	98
Spontaneous breathing	1-30 sec.	90.7	82.5	93.1	97.3	83.0	89.7
	21-60 sec.	3.7	7.2	3.4	1.6	12.0	8.2
Fetal distress immediately post natal	Respiratory	5.6	24.7	10.3	3.4	24.0	15.3
	Pale	1.9	0.0	3.4	0.7	4.0	2.0
	Limp	1.9	10.3	0.0	0.2	2.7	6.1
	Circulatory	0.0	2.3	0.0	0.0	2.7	4.1
Resuscitative measures	Bulb	12.9	15.5	3.4	7.7	14.7	13.3
	Friction	22.2	25.8	6.9	16.8	20.0	17.3
	O ₂	5.6	15.5	3.4	0.5	8.0	6.1
	Tub	5.6	16.5	3.4	0.3	6.7	6.1
	Intratracheal catheter	5.6	6.2	0.0	0.3	1.3	4.1
Breast feeding		59.2	38.1	65.4	81.7	77.3	81.6
Stillbirth and neonatal death		0.0	2.3	3.4	1.0	1.3	0.0
Labor	Spontaneous	88.8	70.1	89.6	96.2	94.7	89.7
	Low forceps	7.4	25.8	6.9	0.5	4.0	6.1
	Other operations	3.7	4.1	3.4	3.3	1.3	4.1

TABLE VII. RELATION OF TIME OF ADMINISTRATION OF MORPHINE TO CONDITION AT BIRTH, NECESSITY FOR RESUSCITATION AND FATE OF BABY (STANDARD EXCLUSIONS). FIGURES REPRESENT PERCENTAGES.) (NO ANALGESIC EXCEPT MORPHINE ADMINISTERED.)

		FIRST HOUR	SECOND HOUR	THIRD HOUR	MORE THAN THREE HOURS
PATIENTS, NUMBER		31	37	36	65
Condition at birth	Breathed 1st 30 sec. within	90.4	83.8	72.8	82.1
	2nd 30 sec.	6.5	13.5	8.3	9.2
	Respiratory difficulties	16.1	13.5	30.6	15.4
	Pale and limp	3.2	13.5	8.3	10.8
Necessity for resuscitation	Mild measures	25.8	35.2	41.6	38.5
	Other incl. O ₂	6.5	21.6	38.9	38.5
Fate of child	Breast fed	74.2	70.3	61.2	69.3
	Dead	0.0	0.0	5.6	1.5
	Spontaneous labor	83.8	83.8	80.6	76.9
	Low forceps	12.9	16.2	11.1	20.0

In three cases time interval is not stated.

Most patients received $\frac{1}{4}$ gr., some $\frac{1}{6}$ gr., 19 received more than $\frac{1}{4}$ gr.

DISCUSSION

It is generally recognized that morphine stands supreme as an analgesic drug. Therefore, its use in labor is indeed rational, if the attendant dangers are not too great. On the other hand the drugs usually employed in reasonable dosages during labor generally produce amnesia rather than analgesia. Because morphine is admittedly a respiratory depressant, most obstetricians use it with caution, if at all. There are, however, others who feel that the fetal dangers resulting from the employment of morphine during the first stage of labor have been exaggerated. Such figures as have been obtained seem to indicate that morphine is not without danger to the fetus, although those dangers are not so excessive as generally believed. One is inclined to agree with Cole, Kimball, and Daniels² that "all sedative drugs increase the incidence of asphyxia" and the danger to the fetus "in direct proportion to the amounts used."

Since morphine is not without effect on the fetus, it is of interest to understand how the effect is produced. Snyder and Lim³ have shown that rhythmical breathing of rabbit fetuses observed within the unopened uterus in a bath of warm Ringer's solution persisted despite administration to the mother of more than 15 times the analgesic dose of morphine. In another publication,⁴ these authors report the effect of morphine on labor following delivery of rabbit fetuses from heavily morphinized mothers in two ways, hysterotomy and spontaneous labor. "In striking contrast to delivery by hysterotomy the incidence of stillbirths amounted to 70 per cent when the birth occurred spontaneously." They feel that the "chief damage of morphine is on the labor mechanism rather than directly on the fetus." Such an interpretation would explain the high percentage of respiratory difficulties and fetal death following morphine administration to the mothers of 22 premature infants where admittedly the trauma of labor is relatively severe.

Unquestionably, many factors combine to determine the effect of the drug upon the newborn infant. Two have been mentioned, the timing of the administration in relation to delivery, and the trauma of labor. Other factors include the size of the dose, the anesthetic and accessory drugs. Morphine in therapeutic doses probably does not exert a deleterious effect upon the fetus in utero. In other words, a pregnant woman may be given morphine without stint and without fear for her child. It is only when the drug is administered to parturient women, and then within two to three hours of delivery, that respiratory embarrassment may be anticipated. Even so, Shute and Davis¹ point out, "It is interesting to note that a large number of infants born under optimum conditions for the production of narcosis showed no trace of the effects of the drug." As an example, an infant of the present series breathed and cried immediately, and showed no sign of any difficulty after the hypodermic injection to the mother of $\frac{1}{2}$ gr. of morphine two

hours and fifty minutes before delivery. In another instance (mentioned in the opening paragraph of this communication), an 18-year-old primigravida suffering from severe pre-eclampsia received 2 gr. of morphine in $\frac{1}{4}$ gr. doses during the twenty hours preceding her delivery by low forceps under pudendal block anesthesia. She was in active labor for fourteen hours of this time and received $\frac{3}{4}$ gr. of morphine during the last six hours of labor. The child, weighing 2,930 Gm. at birth, breathed spontaneously, was entirely breast fed and gained weight prior to discharge. On the other hand infants occasionally exhibited respiratory embarrassment and required resuscitative measures following doses as small as $\frac{1}{6}$ gr. In light of the data presented, this question cannot be adequately answered.

CONCLUSIONS

1. The employment of morphine sulfate as an obstetric analgesic is not without some risk of postnatal, fetal, respiratory difficulty, which, however, is readily combated by the usual resuscitative measures.
2. The administration of morphine during the second- and third-hour period preceding delivery probably should be avoided.
3. Morphine seems to offer an excessive risk in premature infants.
4. On the basis of these observations, there is no good reason for the complete discontinuance of morphine as an analgesic in normal labor although its limitations should be recognized.

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DISCUSSION

DR. ARTHUR H. BILL, CLEVELAND, OHIO.—I have on various occasions heard members of the profession make the remark that if there were but one drug in the pharmacopeia or if they had access to only one, they would choose morphine. Dr. Mengert has pointed out some limitations and dangers associated with the use of morphine in obstetrics and has emphasized the fact that, although its administration during pregnancy and the early part of labor is without harm to the child, there is a real danger of causing apnea when it is given during the two or three hours preceding the birth. This, in my opinion, is his most important conclusion and conforms perfectly with the practice which I have followed in its use. For the most part I have used morphine in combination with other drugs, notably scopolamine. At the Cleveland Maternity Hospital, this combination has been given in a very large number of cases, more than 25,000, including both private and ward patients, with most satisfactory results and, we believe, absence of danger to the child.

There has been a strict rule that neither morphine nor scopolamine be given within three hours of the birth, and this rule has been faithfully observed in this entire series, practically the only exceptions being the occasional emergency case in which more immediate delivery seems to be imperative. We attribute the safety of this method in a very large degree to the adoption of this rule. This practice, of course, practically eliminates its use in cases of multiparas, but retains for

primiparas a method which is, with little doubt, the most satisfactory combination of analgesia and amnesia.

In compiling statistics on the effect of morphine on the child one should be very careful not to include in the morphine group cases in which the effect of labor itself may have caused fetal distress. Dr. Mengert has carefully excluded most of the cases in which there were other obvious causes of fetal distress. However, more consideration could be given to the numerous accidents of labor. I mention one typical example: a case in which during a protracted labor morphine was given to produce a period of rest. During several hours of sleep labor progressed normally and after six hours the head was on the perineum. At this time there was an unusual amount of bloody discharge and the fetal heart rate increased to 180. The baby was immediately delivered and examination of the placenta showed that there had been a partial separation. The baby lived but was limp and required resuscitation. The fact that morphine had been given during the labor obviously had nothing to do with the fetal distress. Cases similar to this one, and there are many, should be excluded from the list of those in which morphine had been administered when compiling statistics of this kind.

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—Dr. Mengert has used meticulous care in attempting to evaluate the effect of morphine but no one can do this with absolute certainty. For example, in a clinic where there is no fixed routine the primiparas who are more likely to receive morphine are the cases of inertia uteri where it is desired to give the patient a rest for eight or ten hours and it is in just these cases that there occurs the highest proportion of respiratory distress in the fetus.

In some of Dr. Mengert's cases the doses seemed rather high. In our clinic where morphine has been used by preference for some thirty years, the dosage is limited to $\frac{1}{6}$ grain in twenty-four hours unless suppression of convulsions be required.

I feel that if a patient is given analgesia by some other drug within three or four hours of delivery to a degree comparable with that produced by morphine the effect upon the fetus will be almost identical. It is even common practice in some clinics to give morphine a short time before delivery. With regard to the elective sections done in our clinic $\frac{1}{6}$ grain of morphine is given as a preliminary sedative before the section is begun.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I never hear a discussion on the subject of analgesics in labor cases that I am not reminded of an incident at Professor Sellheim's clinic in Leipzig some years ago. I was discussing with him the analgesic procedure employed in his clinic. He said, "I have a very simple little mixture here," and showed me a 250 c.c. bottle filled with a light brown liquid. He said, "It is particularly applicable to these younger primiparas. One-half dozen bottles are put into their room and they are told to take one-half the contents of a bottle when their pains become strong, and after a certain period to take another half bottle and repeat it until the labor is completed. It has no bad effects on the mother or the fetus." I asked what it was and he said, "It is just ordinary cognac, and these girls are so inebriated they do not mind labor pains."

DR. MENGERT (closing).—I am glad that Dr. Bill emphasized the rule that morphine should not be given within three hours of labor. Of course, one cannot always calculate the length of labor so accurately, but whenever possible such administration should be avoided.

DR. CURTIS.—Would you mind expressing your views in regard to giving morphine preliminary to cesarean section?

DR. MENGERT.—Generally we have not used it, although on a few occasions we have employed doses of $\frac{1}{6}$ gr. In the few cases where morphine was used prior to cesarean section, we have seen no harmful effect from it.