VALUE OF NALORPHINE IN OBSTETRIC ANALGESIA

by

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The systemic use of pethidine in relieving the pain of the first stage of labour was introduced by Benthinin, 1940, and popularised by Gallenand Prescott in 1944. No doubt pethidine fulfils many of the qualities of an ideal analgesic for the relief of pain in labour, but, in common with other drugs its chief drawback is production of foetal respiratory depression when it has been given in any appreciable amount to the mother. Therefore, the amount usually advocated in obstetric practice has been restricted to between 100-200 mgm. which in some cases is not a sufficient dose for the production of good analgesia during the long first stage of labour. Barnes (1947) concluded that though pethidine does not fulfil all the criteria of perfect obstetric analgesia, it approaches the ideal more nearly than other drugs in current use. This statement was quite true in 1947, but with the advent of nalorphine (Plaza), and its systemic use by Eckenhoff and others, seems to have changed the whole concept of analgesia in the first stage of labour.

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Pharmacology of the drug

Nalorphine per se has a definite pharmacological action and whether it acts as an antagonist to morphine depends on many factors. The important factors include dose of each drug and whether nalorphine is preceded by an additive dose of morphine. This divergent action may be briefly stated as follows:

(a) In a dose of 10 mgm. subcutaneously nalorphine depresses respiration and the body temprature in a manner comparable to morphine. It moderately constricts the pupils.

(b) When a single dose of 10-20 mgm. of morphine is followed by 10 mgms. of nalorphine, about an hour later, the nalrophine will counteract, to a considerable degree, the miotic effect and morphine euphoria, but under these circumstances it will not counteract the respiratory depression caused by morphine.

(c) If, however, the dose of morphine is just sufficient to induce respiratory depression then administration of 10 mgm. of nalorphine promptly restores the normal respiration.

(d) In a patient addicted to morphine, administration of 10 mgm. of nalorphine will provoke a violent abstinence syndrome.

Such diverse effects of nalorphine were demonstrated on experimental and clinical observation.

Review of Leterature

Eckenhoff, Hoffman and Founderberg (1953) working with 1100 expectant mothers, who received higher dose of pethidine, conducted a trial of giving 10 mgms of nalorphine in 2 cc. of normal saline intravenously to the mother, 4.40 minutes prior to the delivery of infants, in half of their series. The remainder served as control cases.

The incidence of asphyxiated babies in the study group was 2%, whereas in the control group it was 8.3%.

The above authors also studied the effects of nalorphine 0.2 mgm. injected directly into the infant's umbilical vein in 12 cases. The results were excellent in eleven cases. The one infant who did not respond satisfactorily was born of a mother who had been given nalorphine 35 minutes before the delivery.

Paterson and Prescott (1954), after seeing the dramatic results obtained by Eckenhoff through nalorphine injection in the umbilical cords of babies, conducted a detailed study of 415 cases, including 212 as a control group. Neonatal asphyxia was present in 34 cases of the control group and in 28 cases in the study group.

Out of 23 babies in the study group who received nalorphine active resuscitation was needed in 12 cases, while in the control group resuscitation was necessary in 31 out of 34 cases; the dose of nalorphine used in this series was 0.5 mgm. in 2 cc. of saline.

Bullough (1954), however, was the first person to use premixed pethidine and nalorphine for obstetric analgesia. The result of his studies shows that increasing doses of premixed pethidine can be used, providing better analgesia for the mother without any corresponding increase in the incidence of neonatal asphyxia.

Baker (1957) conducted a similar clinical trial. His conclusions were: (a) analgesia was good (b) The incidence of respiratory depression of the new-born was reduced comparatively (c) there was no adverse effect on labour.

Material and Method

This study was carried out on 550 patients admitted to the labour room of S.N. Hospital, Agra, from January 1962 to December 1963. The patients were divided into the following groups:

(1) Control Group

(a) Normal labour cases

Primigravidae	..	25 cases
Multigravidae	..	75 cases
		Total 100

(b) Normal labour cases after distilled water as placebo

Primigravidae	..	15 cases
Multigravidae	..	35 cases
		Total 50

(2) Study Group.

This group included 400 normal cases where pethidine injection was given for sedation. The group was further subdivided into four subgroups.

Each sub-group consisted of 75 cases of multigravidae and 25 of primigravidae.

(a) Pethidine alone. 100 cases.
(b) Pethidine I.M. followed by nalorphine 10 mgms. I.V. 10-15 mts. before the expected time of delivery. 100 cases.
(c) Premixed pethidine and nalorphine injection (100 mgm: 2.5 mgm). 100 cases.
(d) Premixed pethidine and nalorphine injection (100 mgm: 5 mgm). 100 cases.

Only normal patients with good uterine contractions and no abnormalities were selected. As soon as the patient was admitted a thorough history was taken with special reference to age, parity, duration of labour, the time of start of true labour pains and in cases of multigravidae the nature of previous labours. A general examination was made and the mental make up of the patient was studied in great detail. According to the psychological and mental make up the mothers were graded as follows:

A. Normal, mentally balanced.
B. Nervous and upset.
C. Frightened and apprehensive.

The duration of pregnancy, presentation position and foetal heart sounds were determined by abdominal examination.

Vaginal examination was also performed, with full aseptic precaution, to confirm the presentation, position and station of the head; cephalopelvic disproportion was excluded. Dilatation of cervix was determined.

For all practical purposes the duration of the first stage was calculated from 4 cm. till full dilatation of cervix. It was found very difficult to determine the actual onset of the first stage, for no patient gave a correct history of the start of true labour pains and the patients were generally admitted with 3-4 cm. of cervical dilatation.

The first injection of 100 mgm. pethidine, pethidine plus nalorphine or distilled water was given according to the group when cervix was 4 cm. dilated, with the exception, in few cases, where due to poor general condition of the patient, the dose was restricted to 50 mgm. only. The subsequent injections were repeated at 3-4 hourly intervals, depending on the dilatation of the cervix, and subjective and objective relief of pain.

The duration of the second stage was also noted. Episiotomy was used in all the primigravidae as a routine and occasionally low forceps applied to cut short the second stage.

Observations and Results

A persual of findings shows that minimum age in the control and study groups was 17 and maximum 45. There is hardly any difference in age groups. The duration of gestation varied from 36-40 weeks. In all cases there were good uterine contractions and none had cephalopelvic disproportion.

Mental make up and psychology:

According to the mental make up and psychology the mothers were graded as A B, and C. The average dose of pethidine in mgms. required in different grades of patients in the different series is also shown in Table I.

According to psychological make up 25 fell in group A in control series whereas groups B and C consisted of 10 cases in primiparae. In the multiparae, however, group A consisted of 81 cases, B 17 and C 12 cases. In the study group in primiparae, 47 fell in psychological grade A, 34 in B and 19 in C. Figures in the multiparae were respectively 212, 60 and 28 according to psychological grading.

Average dose of pethidine according to psychological grade was:

TABLE I

Average dose of pethidine in mgms. required in different sub-groups depending on the psychology of the patient

	Average dose		
	A	B	C
Primipara	177.25	198.25	242.5
Multipara	118.5	154.5	187.5

The patients who were frightened and apprehensive were graded as groups B and Cs and required larger amounts of pethidine, alone or in combination, with appreciably less subjective relief, though the co-operation of the patient during delivery was improved, as compared to the control group.

Duration of the first stage of labour: The maximum, minimum and average duration of the first stage of labour, both in primiparae and multiparae in different groups is shown in Table 2.

TABLE II

Average duration of labour from 4 cm. to full dilatation

Series	Primipara	Multi-para
Control	9 Hrs.	5.3 Hrs.
Distilled water	9 Hrs.	5.3 Hrs.
Pethidine	8.5 Hrs.	5.1 Hrs.
Peth. & Nal I.V. (10 mgms.)	8.2 Hrs.	5.1 Hrs.
Peth. & Nal (2.5 mgms.)	8.7 Hrs.	5.1 Hrs.
Peth. & Nal (5 mg.)	8.8 Hrs.	5.1 Hrs.

Doses of Pethidine and assessment of pain relief

The relief of pain by pethidine alone or in combination, and with distilled water, as assessed by subjective and objective symptoms is depicted in Table III given below:

The condition of the baby at the time of delivery was assessed by apgar scoring method.

TABLE III

		Control Group	Study Group			
			A	B	C	D
Subjective	Good ..	3	50	60	54	53
	Fair ..	5	30	26	29	28
	Poor ..	42	29	14	17	19
Objective	Grade I ..	3	72	80	75	72
	Grade II ..	8	15	12	14	17
	Grade III ..	39	13	8	11	11

TABLE IV

Grading of babies according to apgar classification in different groups

Baby	Control Group	Study Group			
	B	A	B	C	D
Grade I	49	80	85	84	91
Grade II	1	14	11	12	6
Grade III	0	6	4	4	3

The relationship of the time of delivery and percentage of depression in babies was also noted in different sub-groups of the study series. In this the percentage of depression was noted within two hours and later. The striking feature was that there was 75% depression in the pethidine series, 33.3% in pethidine plus nalorphine series, in cases where delivery took place within two hours. In deliveries after two hours the percentage of depression was 9.5% and 6.3% respectively in pethidine and pethidine plus nalorphine series.

In series B it was possible to give the 10 mgm. nalorphine intravenously to only 54 mother (out of 100) 6.15 minutes before delivery. In the others delivery took place either before or after this.

Out of these 54 cases 18 were primiparae and 26 multiparae; out of 18 primiparae, in 9 cases forceps were applied for obstetric indications. The time interval was between 8-12 minutes.

It was thought interesting to note the condition of babies born to the mothers in these cases. In 54 cases, 44 mothers were well sedated, in these the babies were grade I after nalorphine injection, except one who had slight peripheral cyanosis.

In 10 cases having poor sedation after intravenous nalorphine, condition of babies was as follows:

Grade I 6, Grade II 3, Grade III 1.

Out of the remaining 46 cases, 17 cases delivered 15 minutes after nalorphine injection, 12 were heavily sedated, and foetal outcome was good amongst 5 cases which were less sedated; the condition of babies was as follows:

Grade I 16, Grade II 6, Grade III 2.

In five cases with poor sedation all the babies were grade I.

From the above observations the following deductions can be made:

(1) It is very difficult to give nalorphine to all the expectant mothers within 6-15 minutes before the delivery. In this study we could give it only in 54 out of 100 cases. In other cases of the series, either the delivery took place before or after the expected time. This was due to the fact that it was difficult to anticipate the exact time of delivery of the infant specially in multiparae. However, in forceps delivery such planning was possible.

(2) In mothers who were well sedated nalorphine acted in time, and the outcome to the new-born was good (grade I).

(3) In cases where the effect of pethidine was waning, if nalorphine was given it further depressed the mother, and the outcome to the infant was not satisfactory. This was

due to the fact that nalorphine acted synergestically on the mother and affected the mothers and babies adversely.

(4) In cases where delivery did not occur within 10-15 minutes but was prolonged up to 25 to 30 minutes after the nalorphine injection, less cooperation and sedation of the mother was noticed, indicating that nalorphine counteracted the analgesic action of pethidine; but babies were in grade I.

(5) In cases where delivery took place within 5 minutes of nalorphine injecction, we have found a high incidence of neonatal asphysia. This shows that nalorphine takes certain time to reach the foetal circulation to counteract the action of pethidine, probably more than 5 minutes.

(6) While calculating the dose of nalorphine, we must take into consideration the dose of pethidine received by the mother, and its effect. It has been noticed that mothers with good sedation required higher doses of nalorphine and vice versa. This indicates that we can not suggest a uniform dose of nalorphine to be used in all cases.

Instrumental delivery

The incidence of instrumental delivery in different sub-groups of both control and study groups in shown in the Table V:

TABLE V

Incidence of Instrumental Delivery

Sub group	Primi	Multi	Total
Control	5	1	6
Placebo	3	—	3
Pethidine	7	3	10
Peth. & Nal (I.V. 10 mgm.)	9	3	12
Peth & Nal (2.5 mgm.)	7	2	9
Peth. Plus Nal (5 mgm.)	7	3	10

Comments

The dose of pethidine alone or in combination required in our series in primiparae ranged from 100-350 mgms. whereas in multiparae the dose was 50-250 mgm. However, a large number of cases received a dose between 100-250 mg. as compared to the series of Gallen and Prescott, the total dose required in our series is less. This is due to the fact that the general health and weight of Indian women, on an average, is low and they are psychologically tuned towards child-birth. This important fact should always be borne in mind when calculating the dose.

The dose in mgm. per hour in primiparae was less than in multiparae. This increase in multiparae was due to shorter duration of first stage of labour. As compared to the Baker series our mg. per hours dose was on the higher side, which is due to the fact that they have considered the duration of the first stage from the first painful contractions, whereas we have taken this from 4 cms. of dilatation of the cervix.

In series C and D where we used a mixture of pethidine and nalorphine in proportion of 100: 2.5 mgm. and 100: 5 mgm. we found that there was very little difference in percentage, as regard the subjective and objective relief of pain, as compared to series A where pethidine alone was used (Table 4) but on the other hand the doses of pethidine required in series C and D were higher as compared to

that in series A (Table 1). In other words, we can say that to get the same amount of analgesia, both in subjective and objective form, we require a higher dose of pethidine when we use the mixtures of pethidine and nalorphine than with pethidine alone. Our findings are in conformity with those of Baker (1957) and Bullough (1959).

This increase in amount of pethidine required when it is used with nalorphine is said to be due to the fact that nalorphine not only antagonises the respiratory depressing effects but also antagnosies the analgesic potency of pethidine. This is evident from our study, the dose of pethidine required to get the same amount of analgesia was higher when we used it with nalorphine. Acceptable techniques to quantitate analgesia in man are complex and tedious. Even with adequate control small differences are difficult to distinguish.

Pethidine alone or in combination does not seem to affect the normal contraction of uterus, but there is evidence that it reduces the smooth muscle spasm of the cervix thus shortening the first stage of labour.

From the above observations it is obvious that there is definite reduction of the first stage of labour by the use of pethidine alone, or in combination, in normal cases.

It is seen in the present series that the mothers who received higher doses of pethidine, alone or in combination, had a high incidence of instrumental delivery. This, however, was due to the fact that it was thought expedient to shorten the second stage for other reasons than with the effect of drug itself.

It is certain that pethidine passes through the placenta and affects the baby adversely. In our pethidine series there were 24% grade II babies and 6% grade III babies in comparision to 2% grade II babies in the placebo group.

In the mixture series C and D where we used pethidine and nalrophine in proportion of 100:2.5 mgm. and 100:5 mgm. we found that in series C there were 12% grade II babies, and 4% grade III babies, whereas in series D number of grade II babies was 6% and III 3%. From the above observations it is obvious that nalorphine also passes through the placenta as does pethidine, and counteracts the narcotic effects of pethidine to some extant. Baker and Bullough's also reported that nalorphine passes through the placenta.

In grade II babies no active resuctitation was required, only wiping, suction and nasal oxygen was needed. In grade III babies active resuctitation, e.g. suction, endotracheal oxygen and stimulants were necessary. We had 6 grade III babies in the pethidine series, in which we injected nalorphine 0.2 mgm. through the umbilical vein and found dramatic results in all the cases. Mothers of these six babies were adequately sedated with pethidine.

In pethidine and nalorphine series we gave nalorphine through the umbilical vein only in two cases out of four in grade III. These two cases were from the mothers in whom delivery took place within 5 minutes of

the intravenous injection of nalorphine to the mothers. The results in these two cases were satisfactory.

In the mixture series C and D where we used pethidine and nalorphine together, we had 4 cases of grade III babies in series C and 3 cases in series D. We thought fit not to inject nalorphine per umbilical vein in these cases considering the dual pharmacology of nalorphine. However, we resuscitated the babies by usual means.

Summary and Conclusion

1. The literature is briefly reviewed.

2. A total of 550 cases has been studied in two groups, 150 control and 400 study group.

There was definite reduction in duration of the first stage of labour when pethidine alone or in combination was administered intramuscularly in normal cases with good uterine contractions.

4. The ideal combination for maximum subjective and objective relief of pain with minimum foetal asphyxia was noted by giving 10 mgm. of nalorphine intravenously 10 minutes before the expected time of delivery, but the method was not of great advantage, as is evident in our study; we could give the drug intravenously in scheduled time only in 54 per cent of cases, out of which most were low forceps deliveries.

5. For practical purposes, the ideal combination is premixed pethidine and nalorphine in proportion of 100 mgm.: 5 mgm., as it gives maximum subjective and objective relief of pain to the mother with minimum depression to the babies.

6. The average dose of pethidine and nalorphine mixture (100:5 mgm.) required was 100-250 mgm. and it should be given when the cervix is two fingers dilated.

7. In pethidine series there were 14% grade II babies and 6% grade III, whereas in pethidine plus nalorphine series (100:5 mgm.) there were 6% grade II babies and 3% grade III.

8. In pethidine series for grade III asphyxiated babies nalorphine 0.2 mgm. injected through the umbilical vein, gave dramatic results, provided mothers of these asphyxiated babies were well sedated with pethidine.

9. Nalorphine is a specific antagonist to the opiates and not a panacea for the treatment of asphyxia neonatorum. It should not be administered to the infants who are apnoeic due to any other cause than opiate narcosis.

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