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A Preliminary evaluation of a new obstetrical analgesic

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A PRELIMINARY EVALUATION OF A NEW OBSTETRICAL ANALGESIC

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The relief of pain is one of the age-old aims of mankind and a duty of the physician. Probably the majority of the physician's time, no matter what field he is engaged in, is spent in an attempt to relieve pain or find the cause of pain. Keeping in mind the fact that the physician has an important duty to perform in the relief of pain, and considering that there are millions of births every year, which are at best a painful experience, it occured to me that a great deal of suffering could be relieved in this area. That is how I became interested in obstetrical analgesia and the evaluation of a new obstetrical analgesic. And, that is the subject of this paper.

"Divine is the work to subdue pain." So spoke Hippocrates. This still is the challenge of the chemist, the pharmacologist, the obstetrician and the anesthetist who are uniting their efforts towards the safe control of pain in childbirth.

At this point in this paper it seems proper to consider briefly the history of obstetrical analgesics.

The History of Obstetrical Analgesia

The use of analgesics to alleviate the pain of childbirth was unknown before the middle of the 19th century. Nevertheless, historical manuscripts from all the early civilizations described the pain concomitant with childbirth.

The fulfillment of the Biblical prophetic curse. "In sorrow shalt thou bring forth" was described in many of the books of the Old Testament during the 4000 years of Jewish history before Christ. There are many other Biblical quotations on the subject of pain in childbirth.

The Age of the Midwife

There is a prescription for relieving painful childbirth set forth in a manuscript of Zerobabel Endicott of Salem, Mass. in 1659. His prescription included such ingredients as human hair, and ant eggs, mixed in a pint of strong ale.[16] The records give little other information about Endicott except that he was a physician and fined frequently for "excessive drinking."

In France there are recorded instances of painless childbirth during profound intoxication which was not induced for this purpose. Such cases as this are recorded as early as 1818.

The principle analgesic agent until the middle of the 19th century was alcohol. Real progress in obstetrical analgesia began in Edinburgh with James Young Simpson.[6,7] He used Ether and Chloroform analgesia in childbirth in 1847. He reported to the Edinburgh Medico Chirurgical Society the use of Chloroform in 30 painless deliveries the same year. Soon however, he was denounced by the Scottish Calvinists as a blasphemer, heretic, and an agent of the devil. The clergy sent letters to the physicians of the town warning them not to interfer with childbirth by attempts at analgesia. The conflict raged for six years until Queen Victoria used Chloroform analgesia for the birth of her eighth child. Immediately public opinion was turned in favor of analgesia in childbirth. Thereafter, the use of Chloroform analgesia in obstetrics became one of the most important possession of themedical profession.

The Age of the Obstetrician

In 1880, Klikowitsch of Petrograd applied nitrous oxide and oxygen analgesia to obstetrics. He observed 3 or 4 inhalations rendered uterine contractions painless. Dr. J. Clarence Webster was one of the first to use such therapy in obstetrics in America.[16]

In 1902, VonSteinbuchel of Gratz, first suggested the use of Scopolomine and Morphine analgesia in obstetrics. C.J. Gauss of Freiburg made his first report of its use in 1906.[7]

In 1918 the use of "Twilight Sleep" was discovered by the lay press. Within a few months babies by Twilight Sleep became a fad and the relief of pain during labor became one of the chief problems of the average physician. William H. Knipe, R.M. Beach, A.M. Hellman and A.J. Rongy were American Obstetricians who first used this method of obsetric analgesia and modifications of it.

The Battle of the Barbiturates

In 1902, Emil Fischer of Berlin, one of the greatest physiologic chemists of all time, synthesized barbital, the first of the barbiturates. Since that time there have been many controversies about the best agents and their methods of use. The use of these agents alone or in combination with Scopolomine, or the use of "Twilight Sleep" remained the main stay of obstetrical analgesia until the early 1940's. At that time Meperidine, a synthetic analgesic drug was introduced by Eisleb and Schaumann. This drug, alone or in combination with Scopolomine, has been the workhorse of obstetrical analgesia for the past ten

years, more recently it has been used with potentiating agents such as Phenergan and the results have been very good. However, the ideal pharmacological agent to manage pain relief in labor has yet to be developed.[14]

We should consider now before going further the general principles and special problems of obstetrical analgesia. At the outset I would like to say that obstetrical analgesia presents a problem often taken too lightly.

Since the advent and use of antibiotics to control infection, obstetrical analgesia has gradually crept into the picture to occupy the position of one of the major maternal hazards.

The last 45 years has brought about the gradual reduction in the three main maternal hazards; more time and emphasis has been given to the problems associated with obstetrical analgesics. Twelve percent of the maternal deaths in Philadelphia in the period 1946-1954 were due to attempts at obstetrical analgesia. In a study conducted in St. Louis fourty four percent of maternal deaths were due to similar causes.

I believe that it is significant that there are over 100,000 perinatal deaths in the United States every year, and that one of the major causes thereof is the misuse of

drugs in the first stage of labor. These are preventable deaths. It seems obvious, then, when considering these facts, that if the maternal mortality rates are to be lowered further we need better analgesic agents and methods in labor and delivery.

The sine qua non for proper obstetrical analgesia is saftey for the mother and child. And, the purpose of drugs in the first stage of labor is to produce sedation, amnesia and analgesia without depression of the vital functions of the mother or child. The last two statements encompass the crux of the basic principles of obstetrical analgesia. The relief of pain in labor presents problems which are pecular to this field when compared with analgesia in general. First, in every case of obstetrical analgesia there are two patients to consider, the mother and the baby. The respiratory center of the latter is especially vulnerable to sedatives and analgesic drugs. All of the systemic agents used for obstetrical analgesia at present regularly traverse the placenta. Therefore, the possibility of their jeopardizing the initiation of respiration at birth is apparent. This is not a mere theoretic consideration since some sluggishness of respiration is observed in the majority of infants whose mothers have recieved Morphine or its derivatives or

barbiturates during labor. The effects of the analgesic drug on the maternal respiration is also important because degrees of maternal anoxemia so slight as to be innocuous to the mother may be lethal to the fetus. The effects of the agent on the maternal blood pressure must be considered also because minor degrees of hypotension if prolonged may result in fatal anoxia to the fetus. This especial sensitivity of the fetus to the effects or side effects of almost all forms of maternal analgesia poses one of the most difficult problems in obstetrics.[9] Secondly, while analgesia and anesthesia are manditory in many abnormal labors, in normal labor it is not absolutely necessary because the baby will be born usually satisfactorily without any kind of medication, even though the mother may suffer. Therefore, an anesthetic death in obstetrics is an unnecessary death. Thirdly, pain relief in labor is peculiar in the length of time that the patient must receive analgesics. This may be a period of time of 12 or more hours. Fourth, it is important that the drugs used exert little or no effect on uterine contractions. If contractions cease, labor will be prolonged and the chance of post partum uterine hemorrhage due to uterine atony is increased.

Because of the difficulties presented by the several circumstances enumerated no completely safe and satisfactory method of pain relief in obstetrics has been found.[9]

As a consequence it is sometimes alleged that the hazards of pain relief off set its advantages. This is not true if the attending physician realizes the dangers involved, knows the properties of the drug he uses and knows how to use it. Effective analgesia in labor permits more meticulous care, more gentle and frequently more easy deliveries, resulting in healthier mothers and more living babies.

Since the subject of this paper is an evaluation of an obstetrical analgesic and hence is concerned with the relief of pain in labor, it behooves us to review briefly the concepts of pain. The question arises, just what is "pain" and what are its causes in labor?

The causes of pain in labor are many. When the uterus begins to contract its smooth muscle fibers pull and stretch the nerve fibers in the body of the uterus to initiate uterine cramps. When the cervix is dilating and the contractions are forcing the fetal head through the pelvis pain is caused by:

A. Traction on adjacent and associated organs, or the

tubes and ovaries.

B. Drag upon ligaments attaching the uterus to the pelvis.

C. Pressure on the bladder, urethra, rectum and pelvic musculature.[16]

Now as to the question of what "pain" actually is.

The New Gould Medical Dictionary defines pain as:

1. A disturbed sensation causing suffering or distress.

2. A rythmic contraction of the uterus during labor.

I believe that a better definition is that pain is a subjective interpretation of a noxious stimulation. There are two basic factors in the patient's pain:

1. The pain sensation or physical pain.

2. The patients reaction to the pain.[20]

The pain reaction is the response both conscious and subconscious to noxious stimulation. The two basic factors in the patients pain, his perception of the stimulation and his reaction to the stimulation are combined to give rise to the patients pain experience. There are a considerable number of factors which alter the patient's pain experience. Recognition of the importance of these factors and attempts to modify them may have a greater effect on the patients pain than substantual doses of analgesics.[22, 6]

Among these factors which modify the pain experience are:

1. Cultural and Racial factors,- it has been observed that Northern Europeans and Negros have a relatively high reaction threshold and Southern Europeans have a low reaction threshold.

2. Age - Elderly patients have a higher pain threshold in general.

3. Sex - Wilder and Sherman found that women have a lower pain perception and reaction threshold than men.

4. Fatigue - Patients with fatigue have a lower pain reaction threshold. There is also a lower pain reaction threshold of eight to ten percent in patients with mental fatigue or nervous tension.

5. Psychological make up and emotional security. Man reacts not only to actual painful stimuli but is especially sensitive to symbols and threats of danger. Psychic factors have a great importance when one considers that the drugs which effect the most potent analgesia are those which possess the most marked psychic effect.

6. Distraction - If the patient is distracted by excitment or concentration an elevated pain threshold results. Conversly if the patients attention is brought to his situation a lowering of the pain threshold may result.

7. Suggestion attidtude and Mood. These factors also play an important part in the pain experience. Strong beliefs and convictions may result in very high pain reaction threshold as seen in religious devotees who allow themselves to be tortured without evidence of pain. The opposite maybe also seen in the patient who is convinced that an experience is gping to be painful. He sits tense and waiting and in this patient the reaction is out of all proportion to the stimulation.

The success or failure of analgesia is markedly affected by the patients attitude. Realization of the full potential of an analgesic drug is possible only when the physician has the full confidence of the patient.

I would like to discuss at this point some of the aspects concerned in the evaluation of an analgesic agent, and some of the problems encountered in such a study.

From a clinical point of view the study of an analgesic revolves about four factors and three basic principles. The factors are:

1. The patient
2. The medicament
3. The method of testing
4. The investigator

Each contributes a significant component to the end result, the effectiveness of a particular drug under investigation.

The basic principles in such a study are the following. First, one must keep in mind that there is a close correlation between the subjective severity of the pain and the predictability of response to an analgesic. If a patient claims that the pain is severe the likelihood of achieving pain relief with a mild analgesic is remote. The subjectivety of the pain and the response to the pain can not be too greatly emphasized. The investigator may objectively observe pain relief but still must rely on the subjective admission of pain relief from the patient for evidence of analgesic activity. This is one of the problems encountered in the final evaluation; how much emphasis to be placed on objective relief as compared to subjective relief.[1]

The second principle reflects the inability of the patient to distinguish between a palliative or symptomatic relief and a cure of a painful condition. When pain relief is dissipated and pain recurs, the patient may deny any relief at all. Any change in the patients status for the better indicates any one of the following:

1. A placebo action or suggestability.

Suggestability and anticipation of relief with result-

ant alteration in reactivity explain the analgesic effect of placebos. Placebos result in analgesia in as much as forty percent of trials in some analgesic studies. In a series of more than 200 individuals who received an intra-oral placebo injection prior to tooth extraction, about ten percent allowed extraction without further analgesia and denied any pain.[13]

2. The painful state is self limiting and the pain relief co-incidental.

3. The drug being tested is specific for that type of pain.

It is difficult and sometimes impossible from observations obtained in any one patient to determine which of the three is correct.[1] This fact constitutes another difficulty encountered in the evaluation of analgesics.

The third principle in an analgesic study demands that the investigator be able to recognize the reactivity of the patient to the painful state. However, as stated before in discussion of pain, every patient varies to an astounding degree in the factors which modify pain. These factors are cultural and racial factors, fatigue, psychcological makeup, previous experience and training, suggestion attitude and mood. We know that cortical centers may in-

fluence the perception of pain so that excitement or emotional stress may blot out pain or intensify it out of proportion. It is not surprising then, that with the most potent analgesics an important component of action is the alleviation of fear and associated ideas.[17]

It may be seen from these findings that, the diffically of evaluating the subjects reaction because of the various cultural and psychological factors coupled with previous experience and attitude constitutes one of the most difficult problems in evaluation of new analgesics. We have considered the patient to some degree in his reactivity to pain and psychological make up. A word about the investigator and the methods of testing are now in order.

The investigator represents an important component in the effectiveness of an analgesic. His mere presence is sufficient to alter the reactivity of the patient to pain. Add to this the administration of a drug, repeated observations and the interests of physician and the patient desires to report a beneficial result. Hence another problem in the evaluation.[1]

It is also noted that the practice of utilizing only one or two observers may give misleading results since

other investigators may not be able to confirm their conclusions. The effectiveness or satisfactory action of an analgesic agent should be the conern of every member of the medical and nursing staff that may come in contact with the patient. The comments and observations of many persons should be integrated for the final result.

Efforts must be made to introduce the drug as a "double blind", that is unknown to the investigator and to the patient, to eliminate bias. It is difficult to eliminate bias even with this method because ward personel tends to begin forming opinions about one constituent of the study as compared to another. To illustrate this I refer to an analgesic study carried out in London. Three sets of colored tablets were given at random to compare the substance under trial with an established analgesic and an inert control. However, ward nurses became biased in favor of tablets of one color or another and tended to give the ones they considered effective.[8] Bias is a definite problem in these drug studies and without the double blind technique elimination of bias would be impossible.

The final component in the study is the drug itself. Clinical analgesia means satisfactory analgesia based on

the relief of pain and the occurence of toxic effects or untoward reactions. This is simply another way of stating that the analgesic posseses a theraputic range. The decrease in the perception of pain may be marked, but if the patient maniefests undesirable side effects, the analgesic maybe unsatisfactory for clinical use. Therefore, the side effects must also be considered in the final evaluation of the drug. Hence, another problem to be considered by the investigator.

After considering the preceeding factors which should be studied in the clinical evaluation of a compound for the relief of pain, it is possible to establish a list of criteria that should be attained by an ideal analgesic.

1. The physician should be assured of the greatest likelihood of relief of pain without untoward reactions, regardless of the severity, type, or origin of the pain.

2. The resultant analgesia should occur promptly and last for at least 3 to 4 hours.

3. The degree and duration of analgesia should not be influenced by tolerence.

4. Sedation or narcosis should be absent or minimal.

5. Concomitant depression or stimulation of brain areas other than those involved in analgesia should be slight.

6. The analgesic should influence the function of smooth muscle organs minimally if at all. In this regard any pharmacologic action should preferably be antispasmodic.

7. The cardiovascular, renal and respiratory system should not be affected by theraputic doses.

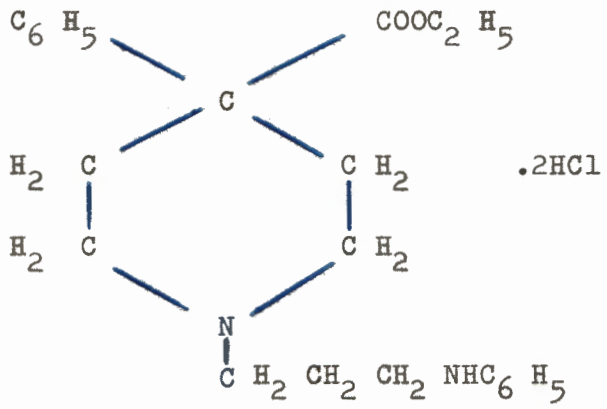
8. The drug should be applicable for pain relief for all patients regardless of age, cause of pain or accompanying conditions that may alter the elimination or dissipation of the drug from the body.

9. Idiosyncrasies or unpredictable side reactions should be rare.

10. It is desirable that the drug be non addicting.

It is evident that the ideal analgesic is yet to be discovered or synthesized. The field is far from closed. Numerous compounds have been, and are being prepared which strive to meet these criteria. One such compound is Ethyl 4 - phenyl - 1-3- (Phenylamino) propyl piperidine - 4 - carboxylate dihydrochloride - called Win 14,098.

Win 14,098



The producers of this new analgesic requested a clinical trial for their product. After studying their data on the properties and effects of the drug, it was given a clinical trial as an obstetrical analgesic.

I would like to present now the basic data concerning this agent.[21]

Analgesic Activity

A. Rats

The analgesic activity of Win 14,098 was evaluated in rats, using the Bass-Vander Brook method in which a thermal pain stimulus is provided by a lamp shining on the tip of the tail. When the lamp is turned on a stop watch is started simultaneously. Movement of the rats tail exposes a photo cell beneath the tail, causing the watch and

the stimulus to automatically stop. An increase in the reaction time of the animal is taken to indicate an analgesic effect of the test compound.

Table 1 gives the analgesic effect of subcutaneous and intraperitoneal doses of Win 14,098 and compares it with that of Demerol.

TABLE 1

Analgesic Effect Of Subcutaneous And Intraperitoneal Doses Of Win 14,098 And Demerol.

Compound	Dose mg./kg.	Average increase in reaction time (seconds) 30 min after medication		Number Dead	Number Medicated
		i.p.	s.c.	i.p.	s.c.
Win 14,098	15.0	14.9		3/18	
	7.5	12.8		1/18	
	3.75	3.3	17.0	0/18	0/18
	1.88		13.0		0/18
	0.94		6.4		0/18
	0.47		1.2		0/18
Demerol	120.0		12.6		2/26
	60.0	10.1	9.2	1/24	1/24
	45.0	5.8	4.0	0/24	0/12
	30.0	3.4	4.0	0/30	0/24
	15.0	1.7	4.0	0/24	0/12

In these rats the ratio of activity of Win 14,098 to Demerol was 55 when given subcutaneously and 9.2 by intraperitoneal administration, as calculated from the dose to required to produce equivalent analgesia.

B. Monkeys

No attempt was made to determine the threshold analgesia in monkeys, but a rough estimate of the analgesic activity of Win 14,098 was made during the course of the tolerance studies in monkeys. The evaluation was based on the pain response to pinching sharply the nail beds of the fingers and toes. Win 14,098 was administered I.M. once daily to two rhesus monkeys starting with a dose of 0.00625 mg./kg. and doubling the dose each day in two alternate monkeys until severe physiological effects were produced. For comparism, Demerol was given daily to two other monkeys begining with a dose of 0.1 mg./kg. and doubling this each day.

Monkeys medicated with 0.025 mg./kg. of Win 14,098 did not respond to the painful stimulus. Demerol gave a comparable amount of analgesia in a dose of 12.8 mg.kg. This indicates that Win 14,098 is about 500 times more active than Demerol in the monkey.

Effect on Blood Pressure

The effect of Win 14,098 on the blood pressure of two trained unanesthetized dogs was determined. Control values were taken preceding the I.M. injection of 0.36 mg./kg. of Win 14,098, a dose whose analgesic potency is equal to that of 20 mg./kg. Demerol as evaluated by rat analgesic methods. The dogs' blood pressures were determined 5, 10 and 15 minutes after equipotent injections of Win 14,098 and Demerol.

TABLE 2

Effects On Blood Pressure Of Equipotent Intramuscular Injections Of Win 14,098 And Demerol.

Compound	Dog	Dose mg./kg.	Blood Pressure: Systolic/Diastolic, mm. Hg			
			Control	5 min	10 min	15 min
Win 14,098	1	0.36	126/90	112/80	108/80	108/80
	2	0.36	140/90	140/90	140/80	130/80
Demerol	*	20.0	156/112.5	120/84.7	126.3/92	129.7/95.7
	**	20.0	131/83.3	133.3/103	144/113.3	135.7/101.3

* Average of 6 dogs whose control diastolic pressure was 100 mm. Hg or above.

** Average of 6 dogs whose control diastolic pressure was 90 mm. Hg or below.

As can be seen from the results the changes in Blood pressure after I.M. injections of equipotent doses in trained, un-

anesthetized dogs are slight and transient.

Acute Toxicity

The acute intravenous toxicity of Win 14,098 was determined in mice and rats.

A. Mice

Doses of 20.0, 25.0 and 31.6 mg./kg. of Win 14,098 were administered to three groups of ten mice each. The deaths resulting from respiratory arrest were preceeded by tonic and clonic convulsions and occurred within one minute after injection. The surviors demonstrated atoxia (10 - 15 min.), deep respitory depression (15 - 20 min.), and generalized depression for 30 - 40 minutes after injection. There were no delayed deaths. The $L.D._{50} \pm$ s.e. was computed to be 25 ± 1.7 mg./kg.

B. Rats

Win 14,098 in doses of 7.94, 12.6 and 20.0 mg./kg. was administered to three groups of 10 rats each. Plastic rigidity, respiratory depression, respiratory arrest and death occurred 2-4 minutes after injection. The survivors demonstrated plastic rigidity and respiratory depression for 30 minutes, to 2 hours followed by ataxia (>1 - <15 hours). There were no delayed deaths. The $L.D._{50} \pm$ s.e. was computed to be 12.4 ± 1.3 mg./kg.

Table 3 summarizes the results of these experiments and compares the toxicity of Win 14,098 with that of Demerol.

These data indicate that the acute intravenous toxicity of Win 14,098 is about 1.4 and 2.5 times that of Demerol in mice and rats respectively.

TABLE 3

Acute Intravenous Toxicity Of Win 14,098 and Demerol In Mice And Rats.

Compound	Specie	Dose mg./kg.	No. dead/ No. Medicated	LD_{50} ± s.e. mg./kg.
Win 14,098	Mice	20 25 31.6	1/10 3/10 10/10	25 ± 1.7
	Rats	7.94 12.6 20.0	0/10 4/10 9/10	12.4 ± 1.3
Demerol	Mice			* 36 ± 2
	Rats			* 31 ± 2

* Mean LD_{50} of several determinations in the Winthrop Laboratory.

Tolerence

The tolerance of monkeys to Win 14,098 was determined.

Four rhesus monkeys were injected I.M. with Win 14,098 daily starting at a dose of 0.00625 mg./kg. This dose was doubled each day in two alternate monkeys until severe physiologic effects were produced. Demerol was used as reference drug and administered in steadily increasing daily doses to two other monkeys.

The monkeys were carefully observed many times daily throughout the experiment. Particular emphasis was placed on changes in rate and amplitude of respiration, the eye changes, the alimentary tract, and the production of sedation.

Hematologic studies were done before medication and at the end of the experiment to determine the effect of the drug on the red and white blood cell count, the differential count and hemoglobin concentration.

Win 14,098 was very well tolerated by rhesus monkeys when administered I.M. in a single dose of 0.00625 mg./kg.

A dose of 0.0125 mg./kg. produced slight depression of the respiratory rate in one monkey. At a dose of 0.025 mg./kg. both monkeys had severe respiratory rate depression, mydriasis, and severe sedation. Win 14,098 at 0.05 mg./kg. produced prostration, severe depression of the respiratory rate and severe sedation. One monkey medicated with 0.1 mg./kg. developed severe depression of respiratory rate, severe sedation and mydriasis and clonic convulsions within eight minutes. A dose of 0.2 mg./kg. produced prostration, severe sedation and respiratory depression in both monkeys. Respiratory arrest and death occurred in one monkey in 25 minutes. The other monkey recovered in about two and one half hours.

Demerol was very well tolerated by rhesus monkeys when administed I.M. in single daily doses of 0.1, 0.2, 0.4, 0.8,

1.6, and 3.2 mg./kg. At doses of 6.4 and 12.8 mg./kg. slight to moderate respiratory rate depression occurred which lasted one to three hours. One monkey at 25.6 mg./kg. died of respitory arrest. The other monkey at the same dose level survived after severe sedation, weakness, and respitory depression.

No blood dyscrasia was observed in any of the monkeys receiving either Win 14,098 or Demerol. Respiratory arrest due to Win 14,098 occurred at a dose approximately 1/100 that of Demerol in these monkeys.

The theraputic ratio of Win 14,098 in rats, as determined by comparing the analgesic activity to acute toxicity is twenty two times that of Demerol.

The theraputic ratio of Win 14,098 in monkeys, computed by comparing the approximate analgesic ratio to the dose producing respiratory arrest is approximately four times that of Demerol.

On the basis of these data, which indicate that Win 14,098 is a more potent analgesic than Demerol, it was recommended that the drug be given a clinical trial as an analgesic agent. This was done in the following manner. The drug was evaluated as an obstetrical analgesic as compared to Demerol. 20 mg. of Win 14,098 was calculated to be equipotent to 100 mg. of Demerol, therefore these drugs were put into 10 cc blank vials contain-

ing 20 mg./cc and 100 mg./cc respectively. Then, the vials were coded as Drug A,B,C, and D. The identity of the contents were known only to the pharmacist who made up the code. Each cc contained an analgesic equivalent to 100 mg of Demerol. The analgesic study was done as a "double blind"; that is neither the patient nor the observer knew the identity of the drug used for analgesia on that particular patient. The drugs were administered in 1 cc doses as soon as it was established that the patient was in active labor and in moderate to severe pain. A base line blood pressure and respiratory rate were taken. The analgesic agent used was then evaluated subjectively by the patient and objectively by the observer. Subjective evaluation was carried out during labor by questioning the patient as to pain relief and also by post partum interview of the patient. Objective evaluation was carried out by the observer using the following criteria for efficiacy of the drug:

1. The extent to which the patients apprehension was alleviated.

2. The presence or absence of respiratory depression.

3. Changes in the blood pressure.

4. Changes in the pulse rate.

5. The alleviation of agitation during uterine contraction and production of relaxation between contractions.

6. The effect of the drug on the frequency of uterine contractions.

7. The duration of the patients pain during a uterine contraction.

8. The presence or absence of sweating during active labor.

9. The amount of crying out and moaning during uterine contractions.

10. The presence or abscence of co-operation after administration of the drug.

11. The amount of sedation, sleep and mental confusion produced by the drug.

12. The presence or absence of respiratory depression in the baby.

13. The amount of amnesia for labor.

The various drugs were evaluated according to the above listed criteria. The notes taken during each observation and the subjective evaluation by the patient were then reviewed. The four drugs were then graded as to excellent, good, fair, or poor in their analgesic activity.

Results

A total of twenty-eight patients were included in this analgesic study. Of these, twelve recieved Demerol for analgesia. The results in these patients were as follows:

1. Decrease in the frequency of uterine contractions

after administration of the drug occurred in none of the twelve patients given Demerol.

2. Adequate analgesia with adequate sedation and relaxation with relief of apprehension, as judged by objective observations was present in ten of the twelve receiving Demerol.

3. Over sedation was not found in any of the twelve receiving Demerol.

4. Excellent or good analgesia and amnesia as judged subjectively by the patient was present in nine of the twelve receiving Demerol.

5. Respiratory depression in the fetus was present in none of the twelve patients receiving Demerol.

Out of the twenty-eight patients included in this study, sixteen received Win 14,098 for obstetrical analgesia. The results in these patients were as follows:

1. Decrease in the frequency of uterine contractions after administration of the drug occurred in three out of the sixteen patients.

2. Adequate analgesia with adequate sedation and relaxation as judged objectively was present in nine out of sixteen patients.

3. Over sedation was not found in any of the sixteen patients.

4. Excellent or good analgesia as judged subjectively by

the patient was present in eight of the sixteen. Conversely eight patients denied any benefit as to analgesia from the drug.

5. Respiratory depression was present in three out of the sixteen babies delivered of the patients that received Win 14,098.

The comparison of the analgesic activity and side effects of Demerol and Win 14,098 as obstetrical analgesics are tabulated in Table 4.

TABLE 4

Comparison of Win 14,098 and Demerol as Obstetrical Analgesics.

	Demerol - 12 pts.	Win 14,098 - 16 pts.
1. No. of pts. with decreased frequency of uterine contractions after administration of the drug.	0/12	3/16
2. Adequate analgesia, sedation and relaxation judged objectively.	10/12	9/16
3. Adequate analgesia judged subjectively by patient.	9/12	8/16
4. Inadequate analgesia judge subjectively by patient.	3/12	8/16
5. Over sedation in the patient.	0/12	0/16
6. Respiratory depression in the fetus.	0/12	3/16

Conclusions

The results in this study of Win 14,098 compared to Demerol as an obstetric analgesic indicate the following:

1. Where as none of the patients receiving Demerol had a decrease in frequency of uterine contractions, 18.8% of patients receiving Win 14,098 did.

2. 83.3% of patients receiving Demerol had adequate analgesia and sedation evaluated objectively.

3. 75% of the patients stated that they had adequate analgesia from Demerol, but only 50% admitted to adequate analgesia with Win 14,098.

4. Where as none of the babies born of mothers receiving Demerol maniefested respiratory depression, 18.8% of the babies born of mothers receiving Win 14,098 did show some depression.

These results indicate that, in this study at least, Demerol is the more efficient obstetrical analgesic. Demerol in this series produced a higher incidence of adequate analgesia, both objectively to the observer and subjectively to the patient. Demerol also produced a lower incidence of decrease in the frequency of uterine contractions, thus not interfering with the progress of labor. Also, the incidence of respiratory depression in the fetus was much lower in the patients treated with Demerol.

It is to be stressed here that this study was a preliminary evaluation of an obstetrical analgesic. The number of patients presented in this series is far too small to derive any definite conclusions as to the value of this drug as an obstetrical analgesic. Also, attention should be recalled once more to the problems in evaluating analgesic activity objectively, this is because the psychological make up, cultural training and previous experience vary widely from patient to patient, and these are the factors which determine the manner in which the subject reacts to pain.

SUMMARY

This paper presents a preliminary evaluation of a new obstetrical analgesic. It gives a brief history of obstetrical analgesia. Since a subject of this type is concerned with the relief of pain during labor, some of the concepts of pain; the special problems of obstetrical analgesia and some of the problems found in analgesic studies are presented. The basic data concerning the new analgesic agent is then presented. The method of evaluation follows, along with the results and conclusion.

The special problems of obstetrical analgesia which are discussed include:

1. The fact that two patients are to be considered in each case of obstetrical analgesia.
2. The special sensitivity of the fetus to the effects, or side effects, of most forms of obstetrical analgesia.
3. The length of time which patient may need to be treated with analgesic drugs.

The concepts of pain presented in the paper point out that a subjects' pain is actually composed of two components:

1. The actual physical stimulus.
2. The reaction to this stimulus.

These two components are combined to form the pain experience for any one subject. It is also pointed out that the pain

experience is modified by factors which vary from person to person. Among these factors are:

1. Cultural and Racial factors.
2. Age.
3. Sex.
4. Fatigue.
5. Psychological make-up.
6. Distraction, suggestion, and mood.

After consideration of the concepts of pain some of the difficulties and problems of evaluating analgesic drugs are presented. The problems which are encountered in analgesic studies include:

1. How much credibility should be placed in the objective observation of analgesia by the observer as compared to subjective evaluation of analgesia by the patient.
2. The difficulty in determining if analgesic action is due to suggestion or placebo action, or actually due to the action of the drug.
3. The difficulty in evaluating pain relief due to the wide variety of manners in which subjects react to pain.
4. The elimination of bias in the evaluation of the agent being tested.
5. The integration of side effects into the final evaluation of the agents.

The basic data of the new agent which was evaluated in this study is then presented. The agent has the chemical name of Ethyl 4-phenyl-1-3 (phenylamino) propyl piperidine-4-carboxylate dehydrochloride. It was estimated by its producers to have the following properties:

1. In rats the analgesic activity of the agent was determined to be 55 times that of Demerol subcutaneously and 9.2 times by intraperitoneal administration.
2. Changes in blood pressure after I.M. injection of equipotent doses of the agent and Demerol are slight.
3. The theraputic ratio of this agent in rats as determined by comparing the analgesic activity to acute toxicity is 22 times that of Demerol. The theraputic ratio in monkeys is four times that of Demerol.

Considering this data, the agent was given a clinical evaluation as an obstetrical analgesic. It was compared with Demerol in a double blind analgesic study. The results were reviewed in a series of twenty-eight patients. It was found that the incidence of slowed labor and respiratory depression were higher in those patients receiving the new analgesic agent as compared to Demerol. Subjective admission of analgesia on the part of the patient and objective observation of analgesia was found in a higher percentage of patients receiving Demerol.

These findings indicate that the new agent, ethyl - phenyl - 1 - 3 (phenylamino) propyl piperidine - 4 - carboxylate dihydrochloride, is not as efficient as Demerol as an obstetrical analgesia. It is emphasized that this is a preliminary evaluation and the series is much too small for any final conclusions.

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