FDA APPROVED OBSTETRICS DRUGS: THEIR EFFECTS ON MOTHER AND BABY

© 2001 Doris Haire, President, American Foundation for Maternal and Child Health and Chair, Committee on Maternal and Child Health, National Women's Health Alliance

FDA USES ITS OWN DEFINITION OF SAFE

Most Americans, including many health care providers, assume that if the FDA approves a drug for marketing then the FDA has determined that drug is free from harm or injury to the person receiving the drug. They do not know that the U.S. Food and Drug Administration (FDA) bases its approval of a drug on whether, in the Agency's opinion, the benefits of the drug outweigh the risks. Unfortunately the FDA has no way of knowing the true incidence of risk to the patient because there is no law or regulation that requires a doctor or other health care provider to report an adverse drug reaction to the FDA, even if the patient dies.

NO WRITTEN FDA STANDARDS FOR EVALUATING DRUG SAFETY

The Director of the FDA's Center for Drug Evaluation and Research (CDER) acknowledges that the FDA has no written standards for evaluating or documenting the safety of drugs approved for use in obstetric care. The Neurologic and Adaptive Capacity Score (NACS), formerly accepted as a reliable tool for evaluating the neurologic state of the infant, has now been found to be unreliable.

LITTLE MORE THAN A DOZEN DRUGS HAVE BEEN APPROVED BY FDA FOR USE IN OBSTETRIC CARE and more than half of these drugs have had their FDA approved labeling removed from the PHYSICIANS DESK REFERENCE (PDR) by their manufacturers. The manufacturers of these drugs apparently prefer that the information regarding the inherent risks of these drugs be withheld from convenient review by health care providers and consumers.

WHAT IS THE PHYSICIANS DESK REFERENCE (PDR) and WHY IS IT IMPORTANT? The PDR is the only publication that must publish the text of an FDA approved label of a drug exactly as it appears in the drug's package insert.

All other printed sources of drug information can, if they choose, omit mention of risks. The fact that a manufacturer can choose to omit the label of his product from the PDR points to the need for a Federal pharmacopeia that includes the labels of all drugs approved by the FDA.

At the end of this document we have listed some of the drugs that are NOT FDA approved for use in obstetric care, but are nevertheless used for that purpose.

We have also provided a Glossary, defining technical terms you may read in the labeling of the drugs you are offered.

To insure your safety and that of your family it is important that you understand that:

> … The FDA acknowledges that there is major underreporting of adverse drug effects, so neither the FDA nor the public has any way of knowing how frequently adverse drug effects occur. As a consequence, few women realize the inherent risks of oxytocic drugs to themselves and their babies.
>
> … **NONE of the drugs used in obstetric care has been proven safe for the fetus exposed to the drug in utero.** None of the pharmaceutical manufacturers of those drugs approved by the FDA for use in obstetrics has carried out periodic neurological examinations of children exposed to their drug products in utero. The FDA has not required companies to provide such data.
>
> … **Most drugs approved by the FDA have never been tested on women.**
>
> … The FDA acknowledges that drugs trapped in the infant's brain at birth have the potential to adversely effect the rapidly developing nerve circuitry of the brain and central nervous system by altering:

a) the rate at which the nerve cells in the brain mature;

b) the process by which the brain cells develop individual characteristics and capacity to carry out specific function;

c) the process by which the brain cells are guided into their proper place within the brain and central nervous system;

d) the interconnection of the branch-like nerve fibers as the circuitry of the brain is formed; and

e) the forming of the insulating sheath of myelin (fat-like) substance around the nerve fibers which help to assure that the nerve impulses - the messages to and from the brain - will travel their normal routes at the normal rate of speed.

… Research now confirms that the migration of neurons along the fibers within the brain can be altered by changing the normal chemistry of the rapidly developing brain. Yet the FDA does not require, as part of the approval process, that the manufacturer of a drug to be approved for obstetric use commit to carrying out a follow-up study to determine the delayed, long-term effects of the drug on the neurologic development of offspring exposed to the drug in utero.

Health care providers often state that the predominant cause of neurologic impairment in children occurs before labor begins. There is no scientific documentation for this statement.

Please take the time to read "*Just How Safe Is 'Safe': How the FDA Determines the 'Safety' of Drugs*", also at this web site, to understand why one cannot assume that the FDA approval of a drug means that the drug is free from harm or injury to the mother or her baby.

As you read the information in this document keep in mind that:

… Virtually all drugs administered to the mother, including oxytocin, rapidly filter across the placental membranes and enter the blood, brain and other major organs of the fetus within minutes of administration to the mother during pregnancy, labor and birth. There is no such thing as a placental "barrier".

… There have been no adequate and well-controlled studies carried out to determine if this drug may cause fetal harm or damage to the developing fetal brain if administered to a pregnant woman.

… The idea that a maternally administered drug, chemical or food additive can harm the fetus only during the period of organogenesis (the first three months of pregnancy) is scientifically inaccurate.

… As the time of birth nears, the fetal brain is relatively large and rich in blood vessels, and the cerebral blood flow is relatively high in comparison with that of the adult brain. These factors increase the transfer of drugs given to the mother to the fetal circulation, brain and central nervous system. If drugs slow the fetal heart rate and the oxygen saturation of the fetal blood is depleted below the physiologic level, the transfer of drugs administered to the mother, and hence to the fetus, is increased. The one minute APGAR score and the newborn's time to sustained respiration are important barometers of how the fetus fared in utero.

… The fact that the fetal brain's myelin content, the fat-like substance that protects the nerve fibers of the brain, is low when compared with that of the adult brain, makes the fetal and newborn brain and central nervous system more vulnerable to the effects of a drug taken by or administered to the mother.

… The gestational age, the condition of the fetus, and the simultaneous exposure of the fetus to other drugs can

influence the ways in which a drug given to the mother affects the unborn or newborn baby.

… A six week follow up of newborn infants in the U.K. found that bupivacaine, administered in the form of an epidural block, adversely altered brain function in a significant number of newborn infants throughout the six week testing period. A subsequent evaluation in the U.S. found essentially the same results.

CHECK THE OFFICIAL FDA LABEL OF THE DRUG

… To check whether or not a drug has been approved by the FDA for the treatment of your condition ask your pharmacist or doctor for a copy of the drug's official "*package insert*", or read the FDA approved label in the **PHYSICIANS DESK REFERENCE (PDR).**

MANY DRUGS ARE USED "OFF-LABEL".

… "Off-label" is pharmaceutical jargon meaning that the drug is being used to treat a condition for which the FDA has NOT approved the drug for that treatment. Terbutaline, for example, has not been approved by the FDA to treat premature contractions, yet the drug is frequently used "off label" to treat the condition, rather than use Ritodrine, which has been approved for such treatment.

… Please see the list of drugs frequently used off-label by physicians and other health care providers in the care of maternity patients.

ALWAYS READ THE "*INDICATIONS*" SECTION OF THE PACKAGE INSERT FIRST

… If, for example, the words "obstetrics", "pregnancy", "labor", "delivery", or "lactation" are **NOT** mentioned in the ***INDICATIONS*** section of the package insert, the FDA has **NOT** approved the drug for use under those conditions.

If those conditions are mentioned elsewhere in the text, such as for example, under "*Labor and Delivery*", that does not mean that the drug has been approved by the FDA for such use.

There are many drugs given to or administered to pregnant women that are not approved for such use by the FDA. While drugs such as codeine, morphine, hydromorphone, promethazine, codeine, fentanyl citrate, phenergan, terbutaline, etc, are sometimes used "off label" in obstetric care, they have not been approved by the FDA for obstetric use.

… No drug should be administered to a woman during pregnancy, labor and birth, unless the woman is fully informed of the known risks and the relevant areas of uncertainty regarding the effects of the drug on the physiologic and neurologic development of the woman or her baby. Whenever possible non-technical terms are used to help you and your health care provider discuss the risks as well as the advantages of the drug in question.

… If you have any questions about the drugs listed below, call the manufacturer of that drug and ask to be sent a copy of the package insert for the drug in question. Drug companies, as well as patients, benefit when patients understand the risks, as well as the benefits, of the drugs they are considering. Manufacturers are not accustomed to answering consumer requests for information, so be polite, but firm in your questions.

… NORMAL BLOOD GASES AT BIRTH ARE NO GUARANTEE NEWBORN IS UNSCATHED

Research in animals has found that cord occlusion resulting in short periods of oxygen depletion in the fetus can cause neuronal damage in the offspring that is not reflected by the blood gases measured in the newborn animal. Follow up of animals exposed to such brief periods of occlusion indicates

that there is often a subsequent progressive decline in function.

Research in newborn infants has shown that a drop in fetal heart rate during labor, which reflects a drop in fetal oxygenation, correlates with evidence of CPK enzymes in the newborn's blood indicating damage to the brain, heart and tissue.

… The FDA does not require pharmaceutical manufacturers to advise the physician or the patient if the use of a product is likely to precipitate the need for cascade of obstetrical interventions such as intravenous infusion, catheterization, chemical stimulation of labor, artificial rupture of membranes, cesarean section, episiotomy (incision to enlarge the vaginal opening), fundal pressure (external pressure on the uterus), forceps or vacuum extraction, uterine atony and hemorrhage) or surgical correction to correct postpartum urinary or fecal incontinence.

Nor does the FDA require a drug manufacturer to note in the drug label if the drug is likely to precipitate (a) fetal hypoxia, (b) fetal bradycardia or tachycardia (slowing or speeding of the fetal heart rate), (c) tentorial hemorrhage (blood covering the brain), (d) newborn resuscitation, (e) Erb's Palsy, (f) newborn jaundice, or (g) the need to perform a spinal tap on the newborn to rule out meningitis.

YOUR PHYSICIAN OR OTHER HEALTH CARE PROVIDERS ARE LEGALLY OBLIGATED TO ADVISE YOU OF DRUG RISKS AND TO OBTAIN YOUR INFORMED CONSENT PRIOR TO TREATMENT and you have an obligation to tell the doctor if you know you are pregnant.

FOLLOWING IS A LIST OF DRUGS APPROVED BY THE FDA FOR USE DURING SOME, BUT NOT ALL, OBSTETRIC PROCEDURES.

This document is to assist the reader in identifying the specific FDA approved uses of the drugs listed below and to help the reader understand the risks to both the mother and her baby inherent in their use. For your protection, and that of your family, make sure you understand the risks and let your doctor or other health care providers know whether you wish to accept or forgo the drugs being offered to you.

Each drug is listed alphabetically by its brand name, the generic (chemical) name, and the name of the drug's manufacturer. If the drug is also manufactured by other pharmaceutical companies, we have also noted their names.

If possible, we have included the full name and mailing address of the pharmaceutical company and the telephone number to call for information. Many companies have chosen to remove their label information, their address and their telephone number from the PDR, so we will make them available to the public as soon as they become available to us.

BUPIVACAINE HYDROCHLORIDE: ABBOTT LABORATORIES

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

FDA approved Marcaine for use in labor and delivery.

For information see the <u>MARCAINE</u> entry below.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long term effects of Bupivacaine on pregnant women, or on the neurologic, as well as general, development of children exposed to Bupivacaine in utero.

Abbott Laboratories Inc.
Pharmaceutical Product Division
North Chicago, IL 60064, U.S.A.
Direct inquiries to: (800) 633-9110

CERVIDIL (dinoprostone PGE2) Mnfr: FOREST PHARMACEUTICALS INC.

LABEL IS IN THE PDR, PAGE 1261

Approved by FDA as a cervical ripener in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor.

It is NOT approved for the elective induction of labor, when there is no medical reason for the induction.

Dinoprostone vaginal insert is a thin flat, rectangular polymeric slab with a long tape to serve as a retrieval system. Cervidil is inserted into the vagina in order to "ripen" the cervix. The patient must remain in the recumbent position for two hours after insertion. The drug gradually causes the rigid cervix to become softened, yielding and dilated to allow passage of the fetus through the birth canal.

The use of Cervidil is not without risk. Therefore the drug should only be administered by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities. Since Cervidil is a prostaglandin that can augment the activity of oxytocic drugs, the two drugs should not be administered at the same time. Cervidil must be removed before oxytocin administration is initiated and the patient's uterine activity must be carefully monitored for uterine hyperstimulation. The label also notes that uterine hyperstimulation, sustained uterine contraction, fetal distress, or other fetal or maternal adverse reactions should be a cause for consideration of removal of the insert.

Cervidil should not be administered to women with a history of previous cesarean section or uterine surgery in light of the potential risks for uterine rupture and associated obstetrical complication. If uterine hyperstimulation is encountered, or if labor commences, the vaginal insert should be removed. Cervidil should also be removed prior to amniotomy (the artificial rupture of membranes). If the mother's membranes have ruptured, the chemical stimulation of contractions can increase fetal intracranial pressure. Cervidil is contraindicated when prolonged contractions of the uterus may be detrimental to uterine integrity and fetal safety.

During a normal contraction the maternal blood vessels that carry oxygenated blood through the uterine wall to the placenta are constricted. During these periods of diminished blood flow the oxygen in the mother's blood, stored up in the placenta's intervillous space **between** contractions, maintains the fetal brain with a relatively constant supply of oxygen. Any uterine stimulant or drug which foreshortens these oxygen-replenishing intervals between contractions, by making the contractions too long, too strong, or too close together, increases the likelihood that fetal brain cells will be adversely affected. Uterine activity, fetal status and the progression of cervical dilatation and effacement should be carefully monitored.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long term effects of Cervidil on pregnant women, or on the neurologic, as well as general, development of children exposed to Cervidil in utero.

For more information from the manufacturer call or write:

Forest Pharmaceuticals, Inc.
13600 Shoreline Drive
St. Louis, Missouri 63045
Direct inquiries to: (800) 678-1605

DEMEROL (meperidine Hcl) Mnfrs: ABBOTT LABS., ELKINS-SINN, AND SANOFI-SYNTHELABO

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR.

Approved by FDA for obstetrical analgesia.

Demerol (meperidine), called Pethidine in Europe, is a narcotic analgesic used to relieve moderate to severe pain. The drug has multiple actions similar to those of morphine. Demerol crosses the placenta and enters the fetal circulation, brain and other organs within minutes of administration to the mother. Demerol also appears in breast milk.

The major risks of meperidine, as with other narcotic analgesics, are respiratory distress, circulatory depression, respiratory arrest, shock and cardiac arrest. Overdose of meperidine can result in hypertension, severe respiratory depression, cyanosis, coma and death. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe and occasionally fatal reaction in patients who have received such agents within 14 days. Other adverse reactions noted in the label/package insert are hyperexcitability, convulsions, bradycardia or tachycardia (slowing or speeding of the fetal heart), hyperpyrexia (high fever), hypertension or hypotension (high or low blood pressure), coma, severe respiratory depression, and cyanosis (bluish discoloration of skin due to diminished oxygen).

If meperidine is given intravenously, the injection should be given very slowly,preferably in the form of a diluted solution. Rapid intravenous injection of narcotic analgesics, including meperidine, increases the incidence of adverse reactions such as severe respiratory depression, apnea, hypotension, peripheral circulatory collapse and cardiac arrest. Meperidine should not be administered intravenously unless a narcotic

antagonist and the facilities for assisted or controlled respiration are immediately available.

The package insert states that the major hazards of meperidine, as with other narcotic analgesics, are respiratory depression, circulatory depression, respiratory arrest, shock and cardiac arrest.

Under "Nervous System" the package insert cites adverse effects such as euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, severe convulsions, transient hallucination and disorientation, and visual disturbances. The inadvertent injection of the drug about a nerve trunk may result in sensory-motor paralysis which is usually, but not always, transitory.

Under "Cardiovascular" the package insert cites adverse effects such as tachycardia, bradycardia, palpitation, hypertension, syncope, and phlebitis following intravenous injection.

Urinary retention and pruritus (itching) are also noted by the manufacturer.

FETAL EFFECTS:

The FDA has allowed the manufacturer to imply, by the following ambiguous paragraph, that meperidine has been proven safe for the fetus when administered to the mother during labor. Under **Usage in Pregnancy and Lactation** the package insert states:

> "Meperidine should not be used in pregnant women prior to the labor period unless in the judgment of the physician the potential benefits outweigh the possible hazards, *because safe use in pregnancy prior to labor has not been established relative to possible adverse effect on fetal development.* When used as an obstetrical

> analgesic, meperidine crosses the placental barrier (editor's note: the placenta is not a barrier) and can produce depression of respiration and psychophysiologic function in the newborn. Resuscitation may be required."

The manufacturer does not describe in the package insert the type of psychophysiologic dysfunctions that may be precipitated when the fetus is exposed in utero to meperidine during labor and delivery. The ambiguity of the statement arises from the fact the drug has never been subjected to a long-term, scientifically controlled follow-up to evaluate the effect of the drug on the subsequent neurologic development of the offspring exposed to the drug during labor and delivery.

Meperidine rapidly filters across the placental membranes and enters the blood, brain and other organs of the fetus within seconds or minutes of administration to the mother. Drug induced alterations in the brain chemistry of the fetus can cause the fetal heart to slow or to speed up to non-physiological levels. The drug's official label notes that meperidine, like all pain relieving drugs, tends to increase cerebral spinal fluid pressure.

We have no way of knowing how frequently these adverse effects occur under normal clinical conditions because, as mentioned earlier, the law does not require physicians or other health care providers to report adverse drug reactions to the FDA, even if the patient dies.

The FDA has allowed the manufacturers of meperidine to provide only a minimum of information in the label in regard to the drug's adverse effects on the fetus and newborn infant. The label acknowledges that the drug does cross the placenta and can increase the likelihood that the newborn infant will require resuscitation. However, the label does not make it clear that:

(a) meperidine given to the mother during labor can impede the normal transfer of oxygen from the mother's circulation to that of her fetus,

(b) prolonged oxygen depletion can cause the fetal brain to swell,

(c) the drug can interfere with the newborn infant's normal ability to self- regulate his/her internal temperature, or

(d) a severely narcotized newborn infant is more prone to aspirate its gastric fluids if the drug has blunted or paralyzed his protective gag reflex.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Demerol on pregnant women, or on the neurologic, as well as general, development of children exposed to Demerol in utero or during lactation.

For more information from the manufacturer call or write:

Abbott Laboratories Inc.
Pharmaceutical Product Division
North Chicago, IL 60064, U.S.A.
Medical Information, Tel: (800) 633-9110

and also

Elkins-Sinn Inc.
2 Esterbrook Lane
Cherry Hill, N.J. 08003
Direct inquiries to: (800) 934-5556

Sanofi-Synthelabo Inc.
90 Park Avenue

New York, New York 10016
Direct inquiries to: 212) 551-4000

FERRO-FOLIC 500 (ferro-folic-500/iberet-folic-500)

Mnfr: ABBOTT LABORATORIES

LABEL IS IN THE PDR, PAGE 449

Approved by FDA for use in pregnancy for the prevention of iron deficiency and to supply a maintenance supply of folic acid.

However, the manufacturer cautions that, because studies cannot rule out the possibility of fetal harm, these drugs should be used during pregnancy only if clearly needed.

Ferrous sulfate is the principal ingredient of Fero-Folic.

WARNING: Keep this product out of reach of children.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Ferro-Folic on pregnant women, or on the neurologic, as well as general, development of children exposed to Ferro-Folic in utero.

For more information from the manufacturer call or write:

Abbott Laboratories Inc.
Pharmaceutical Product Division
North Chicago, IL 60064, U.S.A.
Direct inquiries to: (800) 633-9110

MARCAINE (bupivacaine hcl) ABBOTT LABORATORIES

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR.

FDA approved Marcaine for use in labor and delivery.

The FDA approved labeling for bupivacaine hcl (Marcaine) reads:

LABOR AND DELIVERY: Local anesthetics rapidly cross the placenta, and when used for epidural, caudal or pudendal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity... Adverse reactions in the parturient, fetus and neonate involve alteration of the central nervous system, peripheral vascular tone and cardiac function..."

Under "**ADVERSE REACTIONS. Neurologic**" the official labeling continues:

> "Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.....Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery."

Epidural analgesia can cause disruptions in normal uterine function that cannot always be completely corrected by the use of oxytocin. The package insert does not mention that such disruption can precipitate the need for forceps or vacuum extraction of the baby, or the use of fundal pressure (external pressure applied to the mother's lower abdomen) to help push the baby out). Forceps and vacuum extraction carry

risks to both mother and baby, as does fundal pressure. Fundal pressure increases the likelihood of uterine inversion, and that an episiotomy will be extended into a rectal tear. Fundal pressure has the potential to increase fetal intracranial pressure if the membranes have ruptured.

The incidence and degree of bupivacaine toxicity depends on the (a) procedure performed, (b) type and amount of drug used, (c) technique of drug administration (d) gestational age of the fetus, (e) condition of the fetus, (f) and previous and concomitant exposure to other drugs. Relative hypoxia and various pathological conditions can affect how a drug given to the mother will affect her fetus during labor, birth and the infant's development following birth. Hypoxemia and a build up of lactic acid in the fetal blood during labor and birth can increase the uptake of a maternal drug by the fetal brain and heart.

Rosenblatt and her fellow investigators in Britain found that bupivacaine administered to the mother during labor can have prolonged adverse effects on the early development of the exposed offspring. The investigators concluded:

> "Significant and consistent effects of bupivacaine throughout the assessment period can be demonstrated. Immediately after delivery, infants with greater exposure to bupivacaine in utero were most likely to be cyanotic and unresponsive to their surroundings. Visual skills and alertness decreased significantly with increases in the cord blood concentration of bupivacaine, particularly on the first day of life, but also throughout the next six weeks. Adverse effects of bupivacaine levels on the infant's motor organization, his ability to control his own state of consciousness and his physiological response to stress were also observed."

A similar investigation carried out by Sepkoski, Brazelton and colleagues supports the earlier findings of Rosenblatt et al. See References at end of document.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies sponsored by Abbott to determine the delayed, long-term effects of Marcaine on pregnant women, or on the neurologic, as well as general, development of children exposed to Marcaine in utero or during lacation.

For more information from the manufacturer call or write:

Abbott Laboratories Inc.
Pharmaceutical Product Division
North Chicago, IL 60064, U.S.A.
Direct inquiries to: (800) 633-9110

MEPERIDINE Mnfr: BAXTER PHARM. PROD. AND ELKINS-SINN, INC.

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

SEE DEMEROL ENTRY ABOVE FOR INFORMATION ON MEPERIDINE

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Meperidine on pregnant women, or on the neurologic, as well as general, development of children exposed to Meperidine in utero or during lactation.

For information from the manufacturers call or write:

Baxter Pharmaceutical Products INC
96 Spring St., New Providence, N.J. 07974
Direct inquiries to: (800) 262-3784

or

Elkins-Sinn, Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003
Direct inquiries to: (800) 934-5556

METHERGINE (Methylergonovine maleate) Mnfr: Novartis Pharmaceuticals

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR.

Approved by the FDA for use only AFTER the delivery of the anterior (front) shoulder.

Methergine acts directly on the smooth muscle of the uterus and increases the resting tone, rate and strength of uterine contractions. Methergine is used to induce a rapid and sustained spasmodic uterine contraction to shorten the third stage of labor and reduce blood loss.

The manufacturer of Methergine acknowledges that the drug can result in sudden and severe blockage of blood to the heart. The use of Methergine has diminished because of the drug's action to constrict blood vessels.

The label of Methergine warns against intravenous administration of the drug because of the possiblity of inducing a sudden hypertensive or cerebrovascular accident (stroke). Under full obstetric supervision, Methergine may be given in the second stage of labor following delivery of the anterior (front) shoulder. The timing of Methergine administration is of upmost importance, since premature administration can cause the baby's body to become "trapped" by the constricting uterus, making the infant difficult to extract by forceps, vacuum extraction or manually.

The manufacturer of Methergine reports infrequent cases of acute myocardial infarction, transient chest pains, labored breathing, thrombophlebitis (inflamation of a vein resulting from the formation of a stationary blood clot along the wall of a blood vessel, hematuria (blood in the urine), water intoxication (an undue retention of water, marked by vomiting, depression of core temperature, convulsions; halllucinations, leg cramps, dizziness, tinnitus, diarrhea, profuse sweating; irregular heart rate, and coma.

The official label of Methergine mentions that several infants have been accidentally injected with Methergine and that all but one infant recovered. The label provides no information as to the long term effects of the drug on the neurologic development of those infants injected with Methergine.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Methergine on pregnant women, or on the neurologic, as well as general, development of children exposed to Methergine in utero.

For more information from the manufacturer call or write:

Novartis Pharmaceuticals
59 Route 10
East Hanover N.J. 07936
Direct inquiries to: (888) 669-6682

NAROPIN (ropivacaine hcl) Mnfr. ASTRAZENECA

LABEL APPEARS IN THE PDR, Page 579

Approved by FDA for obstetrical procedures, but requires the manufacturer to warn against the use of Naropin in a paracervical block, retrobulbar block, spinal anesthesia

(subarachnoid block), and Bier block (intravenous regional anesthesia).

Naropin rapidly filters across the placental membranes and enters the blood, brain and other organs of the fetus within seconds or minutes of being administered to the childbearing woman. The onset, depth, and duration of sensory block are similar to bupivacaine. When used for epidural block Naropin can cause varying degrees of maternal, fetal and neonatal toxicity.

The manufacturer of Naropin cautions that resuscitative equipment, oxygen and other resuscitative drugs should be immediately available when Naropin is administered. A well-recognized risk of lumbar epidural block anesthesia is the unintentional injection of local anesthetic into the subarachnoid space and tissue surrounding the spinal cord.

Epidural anesthesia has been shown to prolong the second stage of labor by removing the laboring woman's reflex urge to bear down or by interfering with her motor function.

During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur resulting in (a) the depression of the myocardium, a major muscle within the heart), (b) decreased cardiac output, (c) heart block, (d) hypotension (non-physiological drop in blood pressure), and (e) non-normal heart rates such as bradycardia, tachycardia, arrhythmias, and fibrillation, and cardiac arrest. The manufacturer advises the physician to discuss the various adverse reactions to the drug with the patient if appropriate.

In addition, the unintentional penetration of the subarachnoid space by the catheter or needle during lumbar epidural block may result in subsequent neurologic reactions such as (a) spinal block of varying magnitude (including high or total spinal block), (b) hypotension secondary to spinal block, (c) urinary retention, (d) urinary incontinence (loss of bladder

control), (e) loss of perineal sensation in the vagina, and (f) loss of sexual function. Other neurological adverse effects include persistent anesthesia, abnormal sensations, weakness, paralysis of the lower extremities, and fecal incontinence (loss of sphincter control), all of which may have slow, incomplete or no recovery.

Other reported adverse effects in the woman during labor include septic meningitis, meningismus (meningitis-like fever but no infection), slowing of labor, loss of the bearing down reflex during labor, increased incidence of forceps or vacuum extraction, cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid, and headache. A high spinal in the laboring woman is characterized by paralysis of the arms, loss of consciousness, respiratory paralysis and slowing of the heart.

Central nervous system reactions to Naropin include excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors, possibly proceeding to convulsions. This may quickly be followed by drowsiness, merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions resulting from high doses or unintentional intravascular injection include decreased cardiac output, heart block, hypotension, non-normal heart rate (bradycardia and ventricular arrhythmia) and possibly cardiac arrest. Local anesthetic induced convulsions have demonstrated a rapid lowering of oxygen in the blood, an excess of carbon dioxide in the blood, and an excess of acid in the blood within a minute of the onset of convulsions.

In addition to warning that resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use when Naropin is administered, the manufacturer cautions that the lowest dosage that results in effective anesthesia should be used in order to avoid high blood levels and serious adverse effects. Epidural anesthesia has been reported to prolong the second stage of labor by

removing the laboring woman's reflex urge to bear down or by interfering with motor function. Injection of repeated doses of local anesthetic may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug.

The manufacturer of Naropin acknowledges this fact in the label and cautions that Naropin should not be used during pregnancy unless clearly needed. The The manufacturer then advised the reader that such a warning does not preclude the use of Naropin after organogenesis, the first three months of pregnancy, or use during labor and delivery. The FDA officer that confirmed the Agency's approval of the drug for obstetric procedures is apparently unaware that changes in the placenta as pregnancy advances heighten the transfer to the fetal circulation of all drugs used in obstetric analgesia and anesthesia. Like other local anesthetics Naropin rapidly filters across the placental membranes and enters the blood and brain of the fetus within seconds or minutes of being administered to the mother during labor and delivery. The manufacturer does not mention that alterations in the brain chemistry of the fetus and newborn infant may alter the dendritic arborization (the millions of thread-like neurologic connections in the rapidly developing newborn brain).

No specific information is available on the treatment of overdosage with Naropin.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Naropin on pregnant women, or on the neurologic, as well as general, development of children exposed to Naropin in utero or during lactation

For more information from the manufacturer call or write:

ASTRA usa
Westborough, MA 01581

or

AstraZeneca LP
Wilmington, DE 19850
Direct inquiries to: (800)236-9933

NUBAIN (nalbuphine HCl) Mnfr: ENDO LABS

LABEL APPEARS IN THE PDR, PAGE 1208

Approved by FDA for obstetrical analgesia during labor and delivery.

Nubain is a potent analgesic which relieves pain but does not remove it. The analgesic potency of Nubain is essentially equivalent to that of morphine on a milligram basis. The manufacturer advises that Naloxone, a drug used to counteract the effect of nubain, resuscitative and intubation equipment and oxygen should be readily available.

The manufacturer acknowledges that safe use of Nubain in pregnancy has not been established and that Nubain should be administered to pregnant women only *if clearly needed.* The transfer of Nubain across the placental membranes is high, rapid, and variable.

Central Nervous System Effects: The manufacturer notes in the label (package insert) of Nubain the drug's CNS effects when the drug is administered to the mother during labor and delivery. These include nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucination, dysphoria, feeling of heaviness, numbness, tingling, sense of unreality, hypertension, hypotension, bradycardia, tachycardia (non physiological increase in heart rate), respiratory depression, and dyspnea (labored breathing).

Allergic Reactions: Increased allergic reaction leading to respiratory distress, and other serious hypersensitivity reactions have been reported following the use of Nubain and may require immediate, supportive medical attention. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema, stridor (high pitched breathing), bronchospasm, wheezing, edema, rash, pruritus (itching), nausea, vomiting, diaphoresis (profuse sweating), weakness and shakiness.

Fetal and Neonatal Effects: The manufacturer of Nubain advises that Nubain should be used with caution in women during labor and delivery, that the fetus exposed to the drug in utero should be carefully monitored during labor and delivery, and that the newborn infant should be monitored for respiratory depression, apnea, bradycardia, and arrhythmias. Nubain, like most pain relieving drugs, can elevate cerebrospinal fluid pressure in the fetus. Adverse fetal effects of Nubain include fetal bradycardia (slowing of the fetal heart rate) and fetal arrhythmias (abnormal fetal heart rate). Severe and prolonged fetal heart bradycardia has been reported following fetal exposure to Nubain. Permanent neurological damage attributed to fetal bradycardia has occurred. The manufacturer suggests that administering naloxone (Narcan) to the mother during labor has normalized these effects in **some** cases. However, naloxone is not FDA approved for use during labor.

Neonatal effects of Nubain include respiratory depression at birth, apnea (cessation of breathing), cyanosis (severe reduction of oxygen in the fetal blood) and hypotonia (diminished tone of skeletal muscles). Severe and prolonged fetal bradycardia (non-normal slowing of the fetal heart rate) has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Nubain on pregnant

women, or on the neurologic, as well as general, development of children exposed to Nubain in utero or during lactation.

For more information from the manufacturer call or write:
Endo Pharmaceuticals Inc.
223 Wilmington West Chester Pike
Chadds Ford, PA 19317
Direct inquiries to: (800) 877-3636

NUMORPHAN (oxymorphone HCl) Mnfr: ENDO PHARMACEUTICALS

LABEL APPEARS IN THE PDR, PAGE 1209

Approved by FDA for the relief of moderate to severe pain in obstetric care.

Numorphan is an opioid, a synthetic opiate analgesic that is indicated (FDA approved) for preoperative medication, for support of anesthesia, and for obstetrical analgesia. The analgesic action of Numorphan is ten times that of morphine sulfate. Opioid analgesics such as Numorphan exert their principal pharmacologic effects on the central nervous system and the gastrointestinal tract. Pinpoint pupils are a common sign of opioid overdose, while extreme dilatation of the pupils may be seen with worsening hypoxia.

Numorphan should be used with caution during labor. Opioid analgesics cause the pooling of blood in the extremities and can adversely effect the heart by decreasing the flow of blood returning to the heart. Non-normal fetal heart rate patterns can occur with the use of Numorphan. Opioids can (a) cause respiratory depression, (b) elevate cerebrospinal fluid pressure, (c) depress the cough or gag reflex, (d) slow digestion in the small intestine, (e) disrupt function of the colon, (f) diminished the normal amount of urine secreted by

the body, and (g) induce spasms in the urinary tract causing difficulty with urination.

The manufacturer warns that Numorphan interacts with other central nervous system depressants resulting in additive CNS depression.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Numorphan on pregnant women, or on the neurologic, as well as general,

development of children exposed to Numorphan in utero or during lactation.

For more information from the manufacturer call or write:

Endo Pharmaceuticals Inc.
223 Wilmington West Chester Pike
Chadds Ford, PA 19317
Direct Inquiries to: (800) 877-3636

OXYTOCIN INJECTION Mnfr: AMERICAN PHARMACEUTICAL PARTNERS

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

For information see the following entry for PITOCIN

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Oxytocin on pregnant women, or on the neurologic, as well as general, development of children exposed to Oxytocin in utero or during lactation.

For more information from the manufacturer call or write:

American Pharmaceutical Partners

PITOCIN (oxytocin) Mnfr: MONARCH PHARMACEUTICALS, INC

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

PITOCIN has been approved by the FDA for the medical induction and stimulation of labor. Pitocin has not approved for the elective induction or stimulation of labor.

Oxytocin crosses the placenta and enters the blood and brain of the fetus within seconds or minutes. There appears to be a correlation between fetal exposure to oxytocin and autism in the exposed offspring.

The manufacturer of oxytocin warns the provider in the package insert:

"Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, fetal deaths and permanent CNS or brain damage of the infant due to various causes have been reported to be associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor."

Because oxytocin is used so commonly to stimulate labor we note here that, in addition to the more benign effects of uterine stimulants, such as nausea and vomiting, the manufacturer of Pitocin (oxytocin) points out in its package insert that oxytocin can cause:

(a) maternal hypertensive episodes (abnormally high blood pressure)

(b) subarachnoid hemorrhage (bleeding in area surrounding spinal cord) (c) anaphylactic reaction (exaggerated allergic reaction)

(d) postpartum hemorrhage (uterine hemorrhage following birth)

(e) cardiac arrhythmias (non-normal heart rate)

(f) fatal afibrinogenemia (loss of blood clotting fibrin)

(g) premature ventricular contraction(non-normal heart function)

(h) pelvic hematoma (blood clot in the pelvic region)

(i) uterine hypertonicity (excessive uterine muscle tone)

(j) uterine spasm (violent, distorted contraction of the uterus)

(k) tetanic contractions (spasmodic uterine contractions)

(l) uterine rupture

(m) increased blood loss

(n) convulsions (violent, involuntary muscle contraction(s).

(o) coma (unconsciousness that cannot be aroused)

(p) fatal oxytocin-induced water intoxication (undue retention of water marked by vomiting, depression of temperature convulsions, and coma and may end in death.

Fetal and Newborn Effects

The following adverse effects of maternally administered oxytocin have been reported in the fetus or infant:

(a) bradycardia (slow fetal heart rate)

(b) premature ventricular contractions and other arrhythmias (non-normal heart function

(c) low 5 minute Apgar scores (non-physiologic neurologic evaluation)

(d) neonatal jaundice (excess bilirubin in the blood of the neonate.

(e) neonatal retinal hemorrhage (hemorrhage within the innermost covering of the eyeball)

(f) permanent central nervous system or brain damage

(g) fetal death

Uterine stimulants which foreshorten the oxygen-replenishing intervals **between** contractions, by making the contractions too long, too strong, or too close together, increase the likelihood that fetal brain cells will die.

The situation is analogous to holding an infant under the surface of the water, allowing the infant to come to the surface to gasp for air, but not to breathe. All of these effects increase the possibility of neurologic insult to the fetus. No one really knows how often these adverse effects occur, because there is no law or regulation in any country which requires the doctor to report an adverse drug reaction to the FDA.

These findings underscore the importance of the midwife managing the woman's labor in a way that will avoid the need for Pitocin and the pain relieving drugs that are often administered to help the woman cope with the contractions intensified by Pitocin.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Pitocin on pregnant women, or on the neurologic, as well as general, development of children exposed to Pitocin in utero or during lactation.

For more information from the manufacturer call or write:

Parkedale Pharmaceuticals, Inc.
870 Parkedale Road, Rochester, Mich. 48307
Direct Inquiries to:(248) 651-9081

or

Distributor: Monarch Pharmaceuticals
501 Fifth St., Bristol, TN 37620
Direct inquiries to: (800) 776-3637

PREPIDIL GEL (dinoprostone) Mnfr: PHARMACIA & UPJOHN

LABEL IS IN THE PDR, PAGE 2637

> ***Approved by FDA for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction. For more information see the entry for Cervidil above, which is the same basic drug.***
>
> Prepidil gel has been shown to be poisonous to the embryos of rats and rabbits. Any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.
>
> Prepidil Gel contains dinoprostone as the naturally occurring form of a hormone, prostaglandin E2. The manufacturer states that, in addition to an oxytocic effect, there is evidence suggesting that this agent has a local cervical effect in initiating cervical ripening the softening, effacement, and dilatation of the cervix. Prepidil Gel administered endocervically (at the inner, uterine end of the cervix) may stimulate the muscles of the gravid (pregnant) uterus to contract in a manner similar to contractions seen in the term uterus during labor.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Preperdil on pregnant women, or on the

neurologic, as well as general, development of children exposed to Prepidil in utero.

For more information from the manufacturer call or write:

Pharmacia & UpJohn
100 Route 206 North
Peapack, New Jersey 07977
Direct inquiries to: (888) 768-5501

RITODRINE Mnfr: ABBOTT LABORATORIES

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

Approved by the FDA for use as a tocolytic agent to manage preterm labor in suitable patients.

When administered intravenously, Ritodrine will decrease uterine activity and prolong gestation in the majority of suitable patients. Intravenous infusion of 0.05 to 0.30 mg/min or single oral doses of 10 to 20 mg/min decrease the intensity and frequency of uterine contractions.

Ritodrine Hydrochloride, once sold under the brand name Yytopar, is the only tocolytic drug approved by the FDA to forestall premature labor. The manufacturer cautions that IV administration of Ritodrine should be supervised by persons having knowledge of the pharmacology of the drug and who are qualified to identify and manage complications of drug administration and pregnancy. Beta-adrenergic drugs such as Ritodrine increase cardiac output. Even in a normal healthy heart this added demand can lead to a reduction in the flow of oxygenated blood to the myocardial muscle - the major muscle in the heart. This disruption in blood flow can result in myocardial necrosis (death of heart muscle); non-physiological heart rates, such as arrhythmias, atrial and ventricular contractions, ventricular tachycardia; and heart pain, with or without EEG changes. Because cardiovascular responses are common and more pronounced during

intravenous administration of Ritodrine, cardiovascular effects, including maternal pulse rate and blood pressure and fetal heart rate, should be closely monitored.

The label of Ritodrine notes that pulmonary edema (accumulation of fluid in the lungs) has been reported in patients treated with Ritodrine and cautions that patients must be closely monitored in the hospital, and sometimes **after** the delivery of the infant. Maternal death from this condition has been reported.

Ritodrine contains sodium metabisulfite, a sulfite which may cause an allergic-type reaction, including serious allergic symptoms that can become life-threatening.

When Ritodrine is used for the management of preterm labor in a patient with premature rupture of the membranes, the benefits of delaying delivery should be balanced against the potential risks of development of chorioamnionitis (inflamation of fetal membranes).

Ritodrine crosses the placenta, enters the fetal circulation, brain and other major fetal organs. How this alteration of brain chemistry affects the neurologic development of the exposed offspring is unknown. The label of Ritodrine notes that neonatal symptoms of hypoglycemia and ileus (intestinal obstruction due to inhibition of bowel motility) are infrequently reported. Although clinical studies did not demonstrate a risk of permanent adverse fetal affects from Ritodrine, the possibility cannot be excluded; therefore, Ritodrine should be used only when clearly indicated.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Ritodrine on pregnant women, or on the neurologic, as well as general, development of children exposed to Ritodrine in utero.

For more information from the manufacturer call or write:
ABBOTT LABORATORIES
Pharmaceutical Product Division
North Chicago, IL 60064, U.S.A.
Medical Information, Tel: (800) 633-91104

SCOPOLAMINE HYDROBROMIDE Mnfr: AMERICAN PHARM. PARTNERS

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

APPROVED FOR USE IN OBSTETRICS

Scopolamine is a sedative and tranquilizing depressant to the central nervous system. The drug can produce restlessness, hallucinations, or delirium, especially in the presence of severe pain.

The manufacturer advises in the label that Scopolamine crosses the placenta and that use during labor may cause respiratory depression in the neonate, and that Scopolamine may contribute to neonatal hemorrhage due to a drug induced reduction in the clotting factor (fibrin) in the neonates blood.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Scopolamine on pregnant women, or on the neurologic, as well as general, development of children exposed to Scopolamine in utero.

For more information from the manufacturer call or write:

American Pharmaceutical Partner
10866 Wilshire Blvd
Los Angeles, CA 90024
Direct inquiries to: (310) 470-4222

SENSORCAINE (bupivacaine HCl) Mnfr: ASTRAZENECA LP

LABEL IS IN THE PDR, PAGE 599

Approved by FDA for obstetrical analgesia and anesthesia. It is NOT approved for paracervical block or spinal anesthesia

FOR ALSO THE ENTRY FOR MARCAINE ABOVE.

Sensorcaine is a local anesthetic drug, prepared with and without epinephrine, and is chemically related to mepivacaine and lidocaine. The drug has a rapid onset and is long lasting. The drug blocks the generation and the conduction of nerve impulses to the brain. Like all local anesthetics, Sensorcaine has a primary depressant effect on the brain.

Only the 0.25 and 0.5% concentrations of the drug are FDA approved obstetrical anesthesia.

It is essential that aspiration for blood or cerebrospinal fluid be done prior to injecting any local anesthetic, both the original dose and all subsequent doses. A negative aspiration does not, however, ensure against an intravascular or subarachnoid injection of the drug, since the catheter carrying the drug may migrate into the subarachnoid space surrounding the spinal cord.

At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility and peripheral vascular resistance are usually minimal. Toxic blood concentrations depress cardiac function, which may lead to cardiac arrest, sometimes resulting in fatalities. The manufacturer of Sensorcaine notes in the package insert that recent reports suggest that these cardiovascular changes are more likely to occur after intravascular injection of Sensorcaine. Since a physician is not required to report an adverse drug reaction to the FDA there is no way of knowing how often this mistake occurs.

Incremental dosing is necessary to protect the safety of the fetus, as well as the mother.

Local anesthetics are rapidly absorbed by the mother's circulatory system and within minutes the anesthetic in the mother's blood filters across the placenta and enters the blood and brain of her baby. Local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremor and shivering, progressing to convulsion, followed by depression and coma, progressing ultimately to respiratory arrest. The depressed stage may occur without a prior excited stage.

Local anesthetics are distributed to some extent to all body tissues, with high concentration found in highly perfused organs such as the brain, lungs, liver and heart. After injection of Sensorcaine for caudal, epidural or peripheral nerve block peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a gradual decline to insignificant levels over the next 3 to 6 hours, unless the dose is repeated. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, the technique of administration and the condition of the mother and the fetus. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function. Maternal hypotension has resulted from regional anesthesia. How this slowing of blood pressure affects the oxygenation of the fetus is not discussed.

The manufacturer of Sensorcaine cautions against the use of its product for obstetrical paracervical block anesthesia. This technique has resulted in fetal bradycardia and death. The manufacturer also cautions that the drug should not be used in children less under twelve years of age.

Epidural, caudal, or pudendal anesthesia can alter the normal physiology of birth by disrupting the mother's normal uterine

contractility and her reflex urge to bear down. Such disruption may increase the need for vacuum extraction, forceps extraction and uterine stimulants, all of which increase the risk to both mother and baby.

The injection of repeated doses of local anesthetics can cause significant increases is blood levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression or drowsiness may be early warning signs of central nervous system toxicity.

Neurologic Effects: Following unintentional subarachnoid administration during epidural or caudal anesthesia may include spinal block by varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the low extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery; headache; backache; septic meningitis; menigisumus; slowing of labor; increased incidence of forceps delivery (and vacuum extraction); or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid. A high spinal is characterized by paralysis of the legs, loss of consciousness, respiratory paralysis and bradycardia. The label advises against the use of Sensorcaine in an obstetrical paracervical block, and in a Bier block, the intravenous injection of Sensorcaine.

The label (package insert) of Sensorcaine warns: "Local anesthetic should only be employed by clinicians who are well versed in diagnosis and management of dose-related toxicity and other acute emergencies which might arise from the block to be employed, and then only after insuring the immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel

resources needed for proper management. Delay in proper management of dose-related toxicity, underventilation from any cause and/or altered sensitivity may lead to the development of acidosis, an non-physiologic balance of blood gases), cardiac arrest and, possibly, death".

The incidence and degree of bupivacaine toxicity depends on the (a) procedure performed, (b) type and amount of drug used, (c) technique of drug administration (d) gestational age of the fetus, (e) condition of the fetus, (f) and previous and concomitant exposure to other drugs. Relative hypoxia and various pathological conditions can affect how a drug given to the mother will affect her fetus during labor, birth and the infant's development following birth. Hypoxemia and a build up of lactic acid in the fetal blood during labor and birth can increase the uptake of a maternal drug by the fetal brain and heart.

Rosenblatt and her fellow investigators in Britain found that bupivacaine administered to the mother during labor can have prolonged adverse effects on the early development of the exposed offspring. The investigators concluded:

"Significant and consistent effects of bupivacaine throughout the assessment period can be demonstrated. Immediately after delivery, infants with greater exposure to bupivacaine in utero were most likely to be cyanotic and unresponsive to their surroundings. Visual skills and alertness decreased significantly with increases in the cord blood concentration of bupivacaine, particularly on the first day of life, but also throughout the next six weeks. Adverse effects of bupivacaine levels on the infant's motor organization, his ability to control his own state of consciousness and his physiological response to stress were also observed."

A similar investigation carried out by Sepkoski, Brazelton and colleagues supports the earlier findings of Rosenblatt et al. See References at end of document.

The manufacturer suggests that the physician should discuss the possible adverse effects of Sensorcaine with their patients when appropriate. It is hard to imagine when such a discussion would not be in the best interests of mothers and their babies.

DELAYED OR LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Sensorcaine pregnant women, or on the neurologic, as well as general, development of children exposed to Sensorcaine in utero or during lacation.

For more information from the manufacturer call or write:

AstraZeneca LP
Wilmington, DE 19850
Direct inquiries to: (800) 236-9933

SUFENTA (sufentanil citrate) Mnfr. Acorn Pharmaceutics.

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

Sufenta is FDA approved for epidural administration as an analgesic combined with low dose bupivacaine during labor and vaginal delivery.

SUFENTANIL CITRATE is also mnfr. by Baxter and Elkin Sinn

Sufenta is a potent opioid. The drug can produce muscular rigidity that involves the skeletal muscles of the neck, trunk and the extremities. The manufacturer warns that skeletal muscle rigidity is related to the dose and speed of administration of Sufenta. The drug can cause respiratory drive to decrease and airway resistance to increase. At high doses, a pronounced decrease in pulmonary exchange and apnea (transient cessation of breathing) may be produced.

The FDA approved label/package insert of Sufenta cautions that the drug should be administered incrementally and that the proper placement of the needle or catheter in the epidural space is essential. The intravascular injection of Sufenta can result in a serious overdose including acute muscular rigidity in the trunk area, and apnea (impaired respiration). A intrathecal injection of the full sufentanil/bupivacaine epidural dose and volume can result in a serious overdose, including acute truncal muscular rigidity and apnea that can, in turn, produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery and death.

The FDA approved Sufenta label cautions:

> (a) that the drug should be administered only by persons specifically trained in the use of intravenous and epidural anesthetics and the management of the respiratory effects of potent opioids.
>
> (b) that an opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available, and
>
> (c) that the facility should be fully equipped to handle all degrees of respiratory depression, and provide for post operative monitoring and ventilation of patients administered Sufenta. Muscular rigidity has been reported to occur or recur infrequently in the extended postoperative period.

The label advises that (a) the most serious and significant effect of an overdose of Sufenta is respiratory depression, (b) that the intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression, and (c) that respiratory depression can recur in the postoperative period.

The patient must be carefully and continuously monitored since the duration of respiratory depression produced by Sufenta may last longer than the countering effects of the opioid antagonist. If the patient's gag reflex continues to be blunted by the opioid after the effects of the opioid antagonist has worn off, there is increasing possibility that the patient may aspirate her stomach contents, which could result in neurologic injury or death.

Respiratory depression may be intensified when Sufenta is administered in combination with volatile inhalation agents and or other central nervous system depressants such as barbiturates, tranquilizers, and other opioids.

Indwelling catheters appear to be standard with the use of epidural Sufenta in order to avoid urinary retention. The return of normal bladder activity may be delayed.

The manufacturer of Sufenta states that there are insufficient data to critically evaluate the effects of Sufenta on the neuromuscular and adaptive capacity of the neonate following recommended doses of maternally administered epidural sufentanil with bupivacaine. If larger than recommended doses are used for combined local and systemic analgesia during delivery, the impaired neonatal response to sound and light can be detected for 1-4 hours and if a dose of 80 mg is used, impaired neuromuscular coordination can be detected for more than 4 hours.

DELAYED LONG TERM EFFECTS: There have been no adequate and well-controlled studies to determine the delayed, long-term effects of Sufenta on pregnant women, or on the neurologic, as well as general, development of children exposed to Sufenta in utero or during lactation.

For more information from the manufacturer call or write:

Acorn Pharmaceuticals
150 Wyckles Rd. Decature, Il 62522
Direct Inquiries: (217) 428-1100

SYNTOCINON (oxytocic) Wyeth-Ayerst Pharmaceuticals

ALL INFORMATION HAS BEEN OMITTED FROM THE PDR

For information see entry for PITOCIN above

The risks inherent in the use of Pitocin (see above) and Syntocinon are essentially the same since they are both oxytocin.

For more information from the manufacturer call or write:

Wyeth-Ayerst Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101
Direct inquiries to: (800) 999-9384