Contemporary Issues in Fetal and Neonatal Medicine

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Perinatal Anesthesia

EDITED BY
JOHN WILLIAM SCANLON, M.D.

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Perinatal Anesthesia

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Preface

When first approached by a senior editor of this series to edit a volume on anesthesia during the perinatal period, I was, frankly, reluctant. The subject has already been "done" very, very well. There are many identified mavins within the various interested disciplines.

On reflection, however, there seems to have been recent significant advances in several areas, plus new controversies in others, which require exposition. There certainly are clinical considerations and guidelines which can (and shall) be made. Finally, interactions between anesthetic agents and the many surgical conditions of pregnancy or neonatal life which mandate anesthesia or anesthetic drugs require discussion along the same biological continuum which underlies all perinatal medicine; that is, from conception through the first days of life. Such an approach has not previously been attempted, to my knowledge.

The senior editor also suggested a novel approach to authorship. Rather than choose only authors with well-established reputations in this field, I was free to pick people actively involved, clinically and investigationally, at the cutting edge of any topic. This seemed both eminently practical and consistent with the task at hand. Blackwell's challenge was accepted.

So before you is a potpourri of topics ranging from the esoterically theoretical to the viscerally practical. Recently advanced concepts have been explored, such as behavioral teratology, the beta endorphins and obstetric intravenous fluids as fetally active drugs, with ample discussion and depth of background. Previously (perhaps even overly) reviewed topics have been burnished with new insights from investigators fresh to the field. See, for example, chapters on obstetric anesthesia's impact on newborn neurobehavior or anesthesia for the newly born.

I apologize for any redundancies, for the rare conflicting statement, or for a certain uneveness in style perhaps apparent to the discerning reader. While I am tempted to excuse such foibles as attempts to allow

individual expression, more likely they are simply manifestations of my editorial shortcomings.

I wish to thank all contributors for their significant efforts. Appreciation is also extended to Neil Finer for his confidence that this task could be carried out in a timely fashion and to Richard Zorab, at Blackwell Scientific Publications, for his patience and expertise.

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The Toxicokinetics of Anesthetics and Analgesics During Labor and Delivery

ANTHONY R. SCIALLI and SERGIO FABRO

Introduction

Pain relieving pharmaceuticals are commonly used during labor and delivery. These agents exhibit comparatively different pharmacologic and toxicologic properties in pregnant women and their offspring than in men or nonpregnant women. This chapter describes the principles of pharmacology applicable to the use of pain relieving agents during the specific physiologic process of parturition. These principles are influenced by the profound changes in drug absorption and handling imposed by pregnancy and by the presence of the fetus as a recipient of virtually every medication given to the parturient.

The pain relieving drugs used can be grouped in three categories. Analgesics (a) are systemic medications used to reduce the central perception of pain during labor. Local anesthetics (b) are administered in a specific site to block the transmission of painful stimuli from a targeted area. Injection of these agents into a space containing large amounts of neural tissue can result in anesthesia and paralysis affecting large parts of the body (as in spinal and epidural techniques). Injection near a single nerve can selectively affect a more limited area (as in pudendal block). Finally, even more selective infiltration of a superficial area (e.g., the perineum) is possible with these agents. It should be noted that pain relieving methods that do not abolish all sensation, such as spinal and epidural injection, are strictly speaking analgesia techniques and not anesthesia techniques. In keeping with the common usage of the terms, however, we will speak of spinal anesthesia and epidural anesthesia. General anesthetics (c) are drugs given by intravenous injection or inhalation which produce a loss or modification of consciousness preventing the appreciation of all sensation, including pain.

Drug Disposition In Pregnancy

The physiologic changes of pregnancy begin early in gestation. Many of the alterations in the mother are attributed to elevations in progesterone or estrogens and to the expanding uterus, although several other less adequately explained factors also exist. The absorption, distribution, and metabolism of medications administered during pregnancy may present differently in men or nonpregnant women. It is unfortunate that there are few data on actual drugs used in human pregnancy at term, but the principles of drug handling by the pregnant woman can be outlined and the effects on clinical pain relief therapy inferred.

Cardiovascular Changes

Plasma volume in pregnancy increases by 55 percent to an average of 3850 ml near term (1). Red cell volume may increase over gestation by as much as 30 percent to a total of 1800 ml at term (2,3). The net effect on total blood volume is an increase of about 45 percent with an associated decrease in hematocrit. Perhaps half the increase in blood volume is accounted for by the expansion of the uterine vascular bed. Much of the remaining excess blood volume is located in the venous capacitance vessels of the skin and the lower extremities. It is not known whether the pulmonary vascular space is significantly expanded. It is not unusual, however, to see an increase in pulmonary vascular markings on chest X-ray in normal women at term.

The cause of the increment in blood volume seen in pregnancy is not clear. A considerable influence appears to be exerted by the fetus since blood volume increases more in multiple gestation than in the singleton pregnancy (4). It appears also that adequate expansion of the blood volume correlates with fetal wellbeing and with normal fetal weight at term (5,6). Failure of the blood volume to expand is seen in the toxemias of pregnancy (7,8) although it is not known whether the failed increase in blood volume underlies the hypertensive process or is a consequence of it.

Associated with the increase in blood volume is an increase in cardiac output to 1.5 l/min over the nonpregnant value. The increase in output begins early in the first trimester and reaches its final value by the beginning of the second trimester. There is some evidence that cardiac output is further increased during uterine contractions in labor (9). The increase in cardiac output in pregnancy consists of both an increase in heart rate and in stroke volume. As the uterus enlarges, pressure of the organ on the vena cava may impair venous return to the heart and thus

reduce stroke volume. The consequent decrease in cardiac output may be associated with hypotension and impaired uteroplacental perfusion. Caval compression is more likely when the gravida is supine and pregnant women are therefore advised to lie on their sides to avoid this effect.

Approximately one third of the increase in cardiac output in pregnancy reaches the uterine vascular bed. The remainder is equally divided between the kidney, skin, and other sites. The control of uterine blood flow in pregnancy appears to depend largely on the arterial-venous pressure gradient across the bed and it has not been established that the uterus is capable of adjusting its own blood supply to meet the demands of the organ and its contents. Vasoactive substances have, however, been found in the uterus and it appears likely that uterine blood flow will be shown to be influenced by humoral mechanisms under decidual, placental, or fetal control.

Although estimates of blood volume in pregnancy may be important in predicting achievable blood levels of drugs, most pharmacologic agents are distributed either in the total body water (TBW), extracellular fluid (ECF), or in fat. Pregnancy induced changes in TBW and ECF vary markedly from one gravida to the next. Estimates of the deuterium space (approximately the TBW) in pregnancy show an increase at term of from 7.5 l to 10.8 l over the volume of that space 6–8 weeks postpartum (10). The variation correlates clinically with the amount of edema present. It should be remembered that measurement of TBW in a pregnant woman includes the fetus, amniotic fluid, and placenta, which together may account for nearly 4 l of the TBW increase. ECF in pregnancy increases by 4 l to 6.5 l (9). As much as half of the increase in ECF may be attributable to the contents of the uterus.

Respiratory Changes

Inasmuch as several anesthetic agents are administered by inhalation, an understanding of pregnancy effects on respiration is important. The alteration best appreciated by the pregnant woman at term is the upward displacement of the diaphragm, presumably due to encroachment by the enlarged uterus. This change in diaphragmatic position is offset by a relaxation in the costochondral junctions permitting the ribs to flare and permitting an increase of 5 to 7 cm in the circumference of the thorax.

The various volumes that characterize pulmonary function have been measured serially during pregnancy. Total lung capacity decreases slightly from an average of 4200 cc in the nonpregnant woman to 4000 cc

during gestation. This decrease is accounted for entirely by a decrease in residual volume (the volume of air left after forced expiration) from 1000 to 800 cc (11). The vital capacity (which is the volume from full forced inspiration to full expiration) remains unchanged. Within this vital capacity, the normal tidal volume (the volume of air exchanged during normal quiet respiration) increases in pregnancy from 450 cc to 600 cc. At the same time, the respiratory rate remains unchanged or increases slightly. This results in an increase in the minute ventilation by 50 percent over the nonpregnant state.

There are important consequences of these respiratory changes. The exchange of a larger volume of gas over a given period of time results in a more rapid induction of anesthesia with inhalation agents. Minute ventilation may be further increased during labor by pain or apprehension. This results in accentuation of the mild respiratory alkalosis normally seen at term which may influence the degree of ionization of local anesthetics. This degree of ionization is an important determinant of drug distribution.

Renal Changes

Renal blood flow and the glomerular filtration rate increase by 30–50 percent from the first trimester until term (12,13). A late pregnancy decrease has been noted in some of the measurements approximating the glomerular filtrations rate (e.g., creatinine clearance). However, it is likely that any such decrease is related to caval compression by the third trimester uterus and not to a decrease in renal function. Renal tubular function changes in such a way that increased resorption of water and salts compensates for the increased glomerular filtration of these substances. Tubular resorption of amino acids and sugars may also be increased to compensate for the increased filtered load. At least in some instances however, tubular function is unable to increase and glycosuria and aminoaciduria result (14,15).

Hepatic Changes

Blood flow through the liver appears unchanged during pregnancy and most measurements of liver function are normal throughout gestation. The major pregnancy induced change in drug handling attributable to the liver is a change in the concentration of binding proteins. Albumin, the most important binding protein, decreases by 5–10 g/l. This decrease in albumin concentration is compensated by an increase in blood volume and the total amount of circulating albumin available for drug bind-

ing is probably not different from that before pregnancy. Globulins, which are important in the binding of a few drugs, are increased in pregnancy (16).

The hepatic metabolism of drugs may be divided into two phases. First-phase reactions involve modifications of the drug molecule to make it more polar, generally by oxidation, reduction, or dealkylation. Second-phase reactions result in the synthesis of a larger compound through conjugation of the first-phase product with glucuronic acid, glycine, or acetyl moieties. The first-phase reaction may deactivate the drug; however, often the product is a very reactive species which may be toxic. Rapid conjugation results in a loss of biological activity and ready excretion into bile.

Among the most important of the first-phase reactions are oxidations or hydroxylations. These reactions are catalyzed by a system of enzymes, called mono-oxygenases or mixed function oxygenases, located in the microsomal compartment of the hepatocyte. Cytochrome P–450 is a protein mediating oxygen transfer for many such drug transformations and this cytochrome is often measured as an indicator of the activity of the system.

There is evidence that the metabolism of some drugs changes during pregnancy. In monkeys, for example, the metabolism of phenytoin appears to increase as pregnancy progresses (17). Several of the steroid hormones normally elevated during pregnancy, including estradiol, progesterone, testosterone, and glucocorticoids, have been shown in vitro to inhibit hepatic microsomal oxidation of ethylmorphine and hexabarbital and the metabolic transformation of aniline and aminopyrine (18,19). Animal studies have shown a reduction in drug metabolism during pregnancy which may be attributable to an inhibitory effect of progesterone or one of its metabolites. In human gravidas, however, a decrease in hepatic metabolism of drugs is more difficult to document. Some studies suggest a pregnancy associated increase in the activity of hepatic enzymes (20).

The Placenta and Fetus

The pregnant woman has an added "organ" through which drugs may be distributed and metabolized, namely, the fetoplacental unit. As discussed above, half the increase in extracellular fluid seen in pregnancy may be located within the uterus. There is great concern about the effect of maternal medication on the fetus. Alterations in maternal drug handling imposed by the products of conception are also of concern in calculating medication dosages and administration intervals.

Placental and Fetal Drug Metabolism

The placenta contains most of the enzymes necessary to biotransform drugs and it is considered a likely metabolic site for at least some agents administered to the pregnant woman (21,22). Documentation of drug metabolism by the human placenta has been presented for only a few agents. Most chemicals known to be metabolized by the placenta are steroid hormones, such as estradiol, for which the placenta appears to have an enormous metabolic capacity (23). Other agents metabolized by the placenta include environmental pollutants such as benzo[a]pyrene. In fact, placental transformation of some of these agents may render them more toxic to the developing conceptus (24).

Many of the drug metabolizing enzymes present in the adult liver are also present in the fetal liver and, to some extent, in the fetal adrenal. Activity of these enzymes is not prominent until late in pregnancy and it is possible that inhibition of these enzymes occurs in early gestation. Such an inhibition of fetal drug metabolism may be protective since the products of first-phase reactions can be highly reactive and toxic. In addition, nearly all drug transformations result in creation of more polar molecules. Since polar molecules do not cross the placenta as readily as nonpolar molecules, first-phase reactions occurring in the fetus might result in drug trapping in the fetal compartment.

The fetal liver has been shown capable of metabolizing a number of drugs including aminopyrine, carbamazepine, chlorpromazine, diazepam, phenytoin, ethanol, ethylmorphine, halothane, hexabarbital, meperidine, and prazepam (25). The contribution of fetal metabolism to the overall rate of metabolic transformation of drugs by the mother is, however, likely to be insignificant.

Placental Transfer

It is no longer tenable to view the placenta as a barrier protecting the fetus from substances administered to the mother. Most chemicals are capable of passing across the placenta to at least some extent and many drugs reach similar equilibrium levels in maternal and fetal blood. The mechanisms by which substances pass across the placenta may include pinocytosis, active transport, facilitated diffusion, and simple diffusion. It appears that only the last of these, simple diffusion, accounts for the passage of virtually all drugs that gain access to the fetus.

The placenta may be thought of as a lipid membrane for which there are five factors determining the likelihood and rate of simple diffusion of a drug: (1) lipid solubility of the drug, (2) its degree of ionization, (3) its

molecular weight, (4) the concentration gradient for the drug, and (5) the surface area and thickness of the membrane. The first factor, lipid solubility, is an important characteristic of many pain relieving drugs, enhancing entry of these agents into the central nervous system. It can, in fact, be assumed that the ease of passage of an analgesic or anesthetic into the fetus parallels passage of the same agent into the brain. The only group of anesthetics which do not rely on lipid solubility for passage into the central nervous system are the local anesthetics which are injected directly into the subarachnoid or epidural spaces. The second factor, the degree of ionization of a drug, may inhibit or retard drug passage, although even ionized agents will cross the placenta if the molecular size of the drug is not too large. The degree of ionization, rather than serving as an absolute determinant of whether or not the drug will cross the placenta, is more of a determinant of the equilibrium concentration of the drug in the maternal and fetal compartments. Local anesthetic agents, for example, may be distributed according to their degrees of ionization and the relative maternal and fetal blood pH. Most of these agents are amines capable of accepting protons in an acid environment:

$$R\text{-}NH_2 + H^+ \Leftrightarrow R\text{-}NH_3^+$$

Since the pH of fetal blood is considerably lower than that of the mother during labor, it is possible that ionization and trapping of amine anesthetics in the fetus occurs. It should be noted, however, that the clinical importance of this biochemical possibility has not been established.

The third factor, molecular weight, inhibits the placental diffusion of molecules greater than 1000 daltons. Most drugs have molecular weights of 600 daltons or less and are not inhibited by considerations of size. The fourth factor, concentration gradient, is the major factor determining the rate of diffusion across a membrane. For the placenta, the rate of diffusion is given by the formula:

$$Q/t = KA(C_m - C_f)/T$$

where Q/t is the rate of diffusion, K is the diffusion constant, A the area of the membrane, T the thickness of the membrane, and C_m and C_f the concentration of drug in the maternal and fetal compartment respectively. The diffusion constant is specific for each drug and depends on the molecular size, lipid solubility, ionization, and spatial configuration of the molecule. As can be seen from the formula, the rate of diffusion of an agent given rapidly to the mother by intravenous injection or inhalation (as is the case with most analgesics and anesthetics) will be most