A review—uptake and distribution of inhalant agents

CPT MARY C. WEGNER, CRNA
LT COL JOSEPH H. GOFF, CRNA, EdD
U.S. Air Force Nurse Corps
Malcolm Grow USAF Medical Center
Andrews Air Force Base
Washington, D.C.

The authors discuss the processes that enable anesthetic agents to arrive at their site of action. Control of anesthesia by indirect manipulation of gas tensions in the brain is also reviewed.

Multiple and complex mechanisms regulate the body's cardiovascular and respiratory systems enabling them to maintain a proper chemical and physical environment. This is important for the function of all cells. Accordingly, in order to maintain equilibrium throughout the body while achieving effect, the inhalant agents used in anesthesia must necessarily comply with these complex mechanisms.

In this article, we will attempt to show how anesthetics arrive at their site of action and how the anesthetist controls the course of anesthesia by indirectly manipulating anesthetic gas tensions in the brain.

Behavior of gases and vapors

Gases are constantly interchanging between the cells and the external environment through the medium of the extracellular fluid and blood. According to the laws of diffusion, the molecules of each component gas in a gas mixture are distributed evenly in a homogenous medium. Each gas present in such a medium exerts its own partial pressure. The sum total of all pressures of each component gas in the pulmonary alveoli, blood and cells equals atmospheric pressure (760 mmHg).¹

Definition of uptake. The term “uptake” may be used in two distinct contexts. First and literally, uptake refers to the actual amount of anesthetic gas taken up in the body either by the blood or by the body tissues. In this literal sense, uptake may be defined in terms of total amount taken up—that is, how many liters the body has absorbed—or in terms of the amount of anesthetic gas absorbed per unit time—that is ml per minute.

Secondly, uptake may be defined in terms of its effect on the alveolar concentration. In this sense, uptake is the rate at which the alveolar concentration rises towards the concentration of the anesthetic inspired.²

Anesthetic apparatus. When administering an anesthetic, the partial pressure of the gas in the brain is influenced by several elements operating between the gas tanks and the brain. These elements include the anesthetic machine, the lungs and the blood. We can control gas partial pressure issuing from the anesthetic machine. In attempting to control brain partial pressure, we start with a high partial pressure in the tank or vaporizer relative to inflowing gas—from inflowing gas relative to the anesthetic circuit, from the anesthetic circuit relative to the alveoli, from the alveoli relative to the blood and finally from the blood to the brain and other tissues.

February/1979
One factor that influences and speeds induction is lung washout. When a patient arrives in the operating room, his lungs are full of air which must be replaced with a mixture selected by the anesthetist. If a nonrebreathing anesthetic system is used, the minute ventilation determines the rate of lung washout. Conversely, in utilizing the circle system, it is the flow rate of gases into the rebreathing system that determines the rate of lung washout.

The rubber in an anesthetic system also opposes the development of an alveolar concentration by absorbing a portion of the anesthetic introduced. The rubber solubility of the anesthetic is thus the dominant factor in determining the amount of anesthetic absorbed. According to our research, significant rubber solubility is noted in the agents trichloroethylene, methoxyflurane, chloroform, and halothane. Induction with these agents is slowed by rubber uptake. However, rubber saturated with these agents may release anesthetics to the system when an attempt is being made to reduce the agent concentration in the system. Recovery may also be delayed. Current studies indicate that soda lime may also absorb anesthetics.

Factors influencing tension

When a constant tension of a gas is administered by inhalation, the arterial blood tension of the gas approaches the tension of the gas in the inspired mixture. The tension of the inspired gas is commonly called the "inspired tension." To increase the speed of induction, the inhalational anesthetics are initially given in concentrations greater than those ultimately desired, thus producing anesthetic tensions in blood and tissues sooner than would be possible if maintenance concentrations were used for induction. Ventilation. An anesthetic is carried into the lungs by ventilation at a fairly rapid rate. If no anesthetic were absorbed into the blood stream, the rate of rise of alveolar tension toward inspired tension would be very rapid. Opposing the rate of rise of alveolar tension is uptake of anesthetic into the blood. Hence, the rate of rise of alveolar tension toward inspired tension is a balance between input or ventilation and output or uptake.

Ventilation can be described as a series of instantaneous breaths; the process also invokes some knowledge of lung volumes and capacities (see Figure 2).

When an inert gas is introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at that partial pressure. Several processes occur each in its own time or at its own rate of change to delay the eventual saturation of the tissues. Initially, the gas is inspired by means of pulmonary ventilation. It dilutes with the functional residual air and is distributed to the alveolar membrane. Diffusion takes place here until equilibrium occurs in the pulmonary blood; then the gas is distributed through the peripheral arteries to the individual tissues. A second diffusion step then occurs across the capillary membrane into the interstitial fluid, and across cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which contributes to the equilibration process occurring at the alveoli. In this manner, the alveolar, arterial, tissue and venous tension of the inert gas gradually rise toward eventual equilibrium with the tension inspired.

Factors influencing uptake

Uptake. The greater the loss or uptake of an anesthetic agent, the lower the alveolar concentration relative to inspired concentration (Figure 3).

Blood solubility. The solubility of an anesthetic in blood refers to the ability of blood to hold that anesthetic. Solubility and uptake are directly related. A high blood solubility means a
great proportion of the anesthetic is distributed to blood at the expense of the concentration in the alveoli. Therefore, the greater the blood solubility, the lower the alveolar concentration relative to inspired concentration.

Solubility is an extremely important factor in the scheme of uptake and distribution, for the more soluble an agent is in the blood, the slower the rate of rise of its alveolar partial pressure. This happens because the agent is rapidly taken up by the pulmonary capillary blood from the alveolus. Knowledge of solubility is equivalent to knowledge of the major characteristics of an anesthetic.9 Anesthetic solubility may be expressed as a partition distribution coefficient, an Ostwald solubility coefficient, or a Bunsen absorption coefficient (Figure 4).

Factors influencing solubility

Anesthetic agent. The anesthetic agent itself influences solubility. Different agents may vary in solubility in the same solvent.

Solvent. The solvent-agent solubility is greatest in lipids, less in protein and least in aqueous solutions.

Temperature. In aqueous media, anesthetic solubility increases with decreasing temperature. Eventually a temperature is reached for each gas above which no further change in solubility occurs with temperature. A decrease in temperature results in a higher fat/gas partition coefficient. Changes in solubility with temperature are not proportionately the same for all gases. Usually, the more soluble the gas, the greater the change in solubility for a given temperature change.

Gas partial pressure. The effect of anesthetic partial pressure on anesthetic solubility is expressed by Henry’s law which states that at a constant temperature, the concentration of gas dissolved in a liquid is directly proportionate to the gas tension above the liquid. This implies that partition coefficients do not change with anesthetic concentration. Henry’s law does not apply to an anesthetic which is completely miscible in a solvent. When an anesthetic is miscible in all proportions in a solvent, an increase in tension results in an increase in the solvent/gas partition coefficient. This applies particularly to the solubility of liquid anesthetics in oil.

Vapor pressure. When a gas dissolves in a liquid, its molecules assume more of the properties of liquids than of gases. The behavior of these solute molecules with respect to solubility can then be defined in terms of Raoult’s law, which states: At a constant temperature and pressure, the vapor pressure of a solute is proportional to its mole fraction in the liquid phase. A vapor overlying a liquid dissolves in the liquid. The amount which dissolves is directly proportional to the partial pressure. Vapors dissolve in the water and obey the same laws as do the permanent gases.10

Cardiac output. Assuming normal physiology is present, cardiac output aids in the removal of anesthetic agents from the alveoli. The higher the cardiac output, the more agent is removed, and the greater the depression of alveolar tension relative to inspired tension. Therefore, increasing cardiac output lowers the alveolar concentrates.11, 12

Difference in partial pressure

The amount of gas removed by the blood is limited by the amount of gas already in the blood. If the tension in the pulmonary arterial blood is identical to that in the alveoli, then no gas is taken up, regardless of solubility or cardiac output. The partial pressure in venous blood in turn is determined by tissue uptake.11, 12

Concentration is a factor influencing the decrease in tension gradient between inspired and alveolar gases. The higher the inspired concentration, the more rapid the approach of alveolar tension to that inspired. When inspired concentration is 100 percent, the approach of alveolar to inspired tension is most rapid and is identical for all gases, both soluble and insoluble.
matter what quantity of gas is removed from a lung filled with 100 percent anesthetic agent, the gas which remains is still at 100 percent. Solubility or uptake does not affect the alveolar concentration, although lung volume may be decreased. However, if the lung is filled with less than 100 percent anesthetic gas, then the concentration falls as this gas is removed by uptake. That is to say, the proportion of anesthetic gas (falling) to diluent gas (constant) must decrease. The decrease is not proportional to the amount of gas taken up unless this initial concentration is low. The lower the inspired concentration, the more affect solubility or uptake has on the alveolar concentration. The greater the solubility, the slower the approach of alveolar to inspired concentration.¹⁸

Second gas effect. Epstein et al demonstrated that when a constant concentration of halothane was inspired, the rise in alveolar concentration was accelerated by concomitant administration of nitrous oxide. This accelerated rise in alveolar halothane was named the "second gas effect." Epstein et al also postulated that uptake of a large volume of nitrous oxide created a potential subatmospheric intrapulmonary pressure which led to an increased tracheal inflow. This increased inspiratory ventilation was felt to be responsible for the second gas effect.

Stoelting and Eger proposed that the second gas effect is only partially explained by an increase in inspiratory ventilation. Concentration of the second gas resulting from uptake increases the proportion of the residual (second) gases.¹⁴-¹⁶

Circulation influence on uptake and distribution. The tissues are interposed between the arterial and venous circulation. These structures extract the anesthetic agent during the circulation through the body. During induction of anesthesia, the concentration of an anesthetic agent is higher in the arterial blood than in the venous blood return-
Some inhalational agents have approximately the same solubility in principle tissues as in blood. The coefficient of tissue/blood solubility is in the region of 1.0. Halothane is the exception for brain and muscle, with a solubility three times greater than blood. Hence, this tissue remarkably removes halothane from circulation. The remarkable capacity of fat to remove anesthetic agents from the circulation means that this tissue has a vast storage potential.

Blood flow is one of the most important factors in determining tissue uptake of a particular anesthetic agent. Eger in 1964 divided the tissue into four groups according to their blood supply. These groups include:

1. The vessel-rich group (VRG) — brain, heart, liver and kidney (these organs receive 70-75 percent of total cardiac output and hence anesthetic agent tension rises rapidly in these structures;
2. The intermediate group (IG) composed of skeletal muscle and skin;
3. The fat group (FG) comprising the adipose tissue of the body; and
4. The vessel-poor group (VPG) containing relatively nonvascular structures such as ligaments, tendons and cancellous bone; these structures do not influence the uptake of anesthetic agents.19, 20

Factors affecting tension

The tension of an inert gas in the brain depends upon the tension of gas in arterial blood and the supply of arterial blood to the brain (cerebral blood flow).

Tension of gas in the arterial blood depends upon the tension of the gas in the alveoli and the nature of the pulmonary diffusion surface. The pulmonary diffusion surface depends upon the size of functioning lung, the thickness of the diffusion membrane, the presence or absence of edema and the adequacy of pulmonary blood flow. In normal lungs, diffusion is rarely a limiting factor in the uptake of inert gas and hence arterial tension equals alveolar tension.

Factors that influence alveolar—arterial tension are respiratory minute volume, lung volume, pulmonary blood flow, blood solubility and the partial pressure of the gas in mixed venous blood.

All gases taken in by the body are breathed into the lungs. Effective respiratory minute volume is a factor that regulates alveolar tension. Respiratory minute volume is the liters per minute of inspired gas which reaches the functioning diffusion surface. This function is equal to the output of the vascular structure multiplied by the rate of respiration.

Lung volume refers to the volume which dilutes each inspired breath of gas.

Pulmonary blood flow is important in regulating the alveolar partial pressure of gases. It is the pulmonary blood flow that carries the anesthetic gases from the alveoli partial pressure. Associated with pulmonary blood flow is another factor influencing alveoli tension and that is the blood solubility or partition coefficient. The partition coefficient equals the ratio of the concentration of that gas in blood to the concentration of that gas in air at equilibrium. The solubility in blood and the pulmonary blood flow are the factors responsible for the loss of gas from the alveoli.

The last factor affecting alveolar tension is the partial pressure of the gas in the mixed venous blood that returns to the alveoli. This blood raises the alveolar tension. If the tension in venous blood is rising rapidly, this will permit alveolar tension to rise rapidly, but if venous tension stays low, it will keep alveolar tension low longer. Mixed venous tension of an inert gas depends upon three factors including cardiac output, the mass of muscles and fat and the partition coefficient of the gas between fat and blood. A high fat solubility causes large amounts of gas to be removed from the blood to the adipose tissue. This keeps the venous blood ten
sion low, hence keeping the alveolar tension low and prolonging anesthesia.\textsuperscript{21-23} The second factor regulating the tension of anesthetic gas in the brain is the rate of cerebral blood flow. The more rapid the cerebral blood flow, the more anesthetic that will go to the brain per minute, therefore permitting a more rapid accumulation of tension in the brain and more rapid induction of anesthesia. Cerebral blood flow depends upon mean arterial blood pressure and cerebrovascular resistance.

\textbf{Variables affecting anesthetic gas uptake}

\textit{Variations in solubility of the agents.} Some agents are more soluble than others and this has an important influence on alveolar concentration. Clinically, anesthetics with a high solubility in blood give a slow induction and a slow recovery; the opposite occurs with agents of low solubility.

\textit{The concentration effect.} The importance of this effect is that the alveolar concentration increases toward inspired concentration more rapidly when a high concentration is administered. The concentration effect is best seen in anesthetic agents with high blood solubilities.

\textit{The diffusion hypoxia.} This is also called the Fink phenomenon and is the reverse of the concentration effect. This condition, if noted, usually occurs during emergence from a nitrous oxide-oxygen anesthetic and is due to a sudden outpouring of nitrous oxide into the alveoli, which dilutes the inspired air, reducing its oxygen content and also reducing arterial oxygen saturation.

At the conclusion of the anesthetic, the mask is removed and the patient breathes room air. This room air then fills the alveoli with a mixture of nitrogen, oxygen, carbon dioxide and water vapor. However, there is still an appreciable amount of nitrous oxide in the circulation and tissues which is 34 times more soluble than nitrogen; hence, the blood can carry more nitrous oxide than nitrogen. During the first few minutes of breathing room air, large amounts of nitrous oxide leave the body. In essence, the volume of expiration exceeds inspiration, and more carbon dioxide tension of the blood reduces the stimulus to respiration and brings about a depression of ventilation.

An even more important effect of this mass movement of nitrous oxide into the alveoli is that it dilutes the concentration of oxygen present to the extent that some hypoxia may ensue.

Clinically, diffusion hypoxia is of significance when nitrous oxide is the anesthetic agent because it is the only anesthetic used in high concentration. The prevention of this type of hypoxia consists of administering 100 percent oxygen at the close of anesthesia to ensure adequate respiration.\textsuperscript{24,25}

\textit{Variations in ventilation.} The rate at which a high tension in the blood is achieved determines the speed of anesthesia induction. Additionally, the height of the agent's tension relates to the depth of anesthesia. An anesthetic agent with a low solubility rapidly achieves a high tension in the blood while one with a high solubility requires a longer period of time, even though the blood absorbs large quantities. Hence, the alveolar tension or concentration is the critical factor. This is a balance between input from ventilation and removal or uptake by circulation. If ventilation increases and cardiac output is unchanged, then the alveolar tension must be raised. A sudden increase in ventilation will lead to a rise in both alveolar and arterial blood tension. This is demonstrated when changing from spontaneous to controlled respiration.\textsuperscript{26,27}

The speed of induction is affected by lung washout. Lung washout aids in the rise of arterial and alveolar tension. The rate of washout depends upon the ratio of effective minute volume of respiration to lung volume.\textsuperscript{28}

\textit{Variations in cardiac output.} Alveolar tension tends to drive the anes-
thetic vapor into circulation. An increase in cardiac output means a greater amount of anesthetic vapor is removed from the alveolus, and subsequently, there is a fall in alveolar tension. If cardiac output is reduced, then this raises the alveolar tension and leads to an increase in the depth of anesthesia. 29

Variations in ventilation/perfusion ratio and right or left shunt. A portion of the cardiac output bypasses the lungs when any right to left shunt exists due to a heart defect. In some disease processes, alveoli may be perfused but not ventilated; in others, the alveoli may be ventilated but not perfused.

When one lung is blocked, the other lung receives double its normal ventilation. The blood picks up the anesthetic vapors in the capillaries but on draining into the pulmonary vein, the tension of the anesthetic vapor in blood is diluted to half by blood coming from the nonventilated lung. 30

Variations in body temperature. Generally, the solubility of a gas in blood increases as the temperature falls. The lower the body temperature, the less anesthetic the patient requires.

Summary

In order to understand and appreciate the principles governing the uptake and distribution of inhalant agents, it is necessary to consider several influencing factors, such as the anesthetic apparatus, the lungs, circulation and the tissues.

The uptake and distribution of inhalant agents places great emphasis on uptake from the lungs and uptake by the body tissues. Uptake from the lungs is directly related to the factors of blood solubility, cardiac output and the anesthetic tension gradient between alveoli and pulmonary blood. Tissue uptake depends on blood flow, solubility and the arterial to tissue partial pressure difference. Solubility is an extremely important factor in uptake and distribution because it basically refers to the ability of blood and tissue to hold the anesthetic agent.

Applying the knowledge of the basic properties involved here reveals pertinent information as to the speed of induction, the safety of anesthesia administration and the rate of recovery from a particular agent.

REFERENCES

(4) Eger, E. I., 1974. Uptake, Distribution and Elimination of Inhalation Anesthetic. Paper and tape from a presentation at Emory University, Atlanta, Georgia.
AUTHORS

Mary C. Wegner, CRNA, is a graduate of St. Joseph's School of Nursing, Philadelphia, Pennsylvania. She attended Alvernia College in Reading, Pennsylvania and Our Lady of Angels College in Glen Riddle, Pennsylvania. Captain Wegner graduated from the Wilford Hall USAF Medical Center Nurse Anesthesia Residency Program and is presently a staff anesthetist at Malcolm Grow USAF Medical Center, Andrews Air Force Base, Washington, DC.

Joseph H. Goff, CRNA, EdD, currently serves as senior medical service consultant to the USAF Surgeon General, Nurse Anesthesia, and also as chief nurse anesthetist at Malcolm Grow USAF Medical Center, Andrews Air Force Base, Camp Springs, Maryland. Dr. Goff received his nursing diploma from McLean Hospital School of Nursing, Belmont, Massachusetts and his BSN from Boston College, Chestnut Hill, Massachusetts. Additionally, he received an MEd from Massachusetts State College, Worcester, Massachusetts and earned an EdD from North Texas State University, Denton, Texas.