The intensity and duration of drug effects, including those of anaesthetic agents, may be predicted if the site of action, potency, and methods of uptake, distribution and elimination of these substances in the body are understood. Reliable information on the first two points may be generally available and provided from animal experimentation or clinical study. The methods by which the patient distributes and disposes of the administered agent have not always been as readily understood, mainly because such information is either unsought or its importance is not readily appreciated.

Clinical anaesthetists have administered millions of anaesthetics during more than a century with little precise information of the uptake, distribution and elimination of inhalational and non-volatile anaesthetic agents. Considering how serious is the handicap of not knowing those fundamental and essential facts about the drugs they have used so often, the record of success and safety in clinical anaesthesia is an extraordinary accomplishment indeed. It can in some measure be attributed to the accumulated experience and successful teaching of a highly developed sense of intuition from generation to generation of anaesthetists. It can also be attributed in part to the ability to learn by error after observing patients come uncomfortably close to injury and even to death.

In the last few years, however, sufficient fundamental information has become available to explain more effectively these clinical successes. The empirical process of giving an anaesthetic can be understood better because of the specific data provided by the studies reported in this symposium and by the work of others which has preceded them.

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CONCENTRATION OF ANAESTHETICS IN THE BRAIN

In order that the clinical anaesthetist may appreciate the value of pharmacokinetics to his daily practice, it is essential that he have a practical understanding of the concepts most recently systematized by Kety (1951) which form much of the basis for recent experimental work in this field and provided a significant stimulus for it. It is completely appreciated in clinical practice that the anaesthetic state is correlated in a rather direct fashion with the concentration of the anaesthetic agent in the brain. The concentration of the agent in the brain is dependent upon the uptake of the anaesthetic from the lung, its distribution from the lung by the bloodstream to the brain, and the extent of the solubility of the anaesthetic in blood and brain.

The relationship between the concentration of anaesthetic agent in the blood or brain and that in the lungs is based upon two physical laws. The first of these is the universal gas law which states that the pressure of a gas varies directly with its concentration. The second of these physical laws is Henry's law of solubility which states that the quantity of a gas dissolved in a medium (for example, blood) is proportional to the partial pressure of the gas. At conditions of equilibrium the pressures of the gas in the gaseous phase become equal to those in the phase of the medium. The arterial blood concentration, therefore, is proportional to the pressure of the anaesthetic gas in the lung.

The concentration of the anaesthetic agents about and within the brain cells is then developed from gas dissolved first in the blood which comes to the brain. The brain concentration must therefore ultimately be proportional to the partial pressure of gas in the lung.
uptake process this proportionality will not be exact, but because of the similarity of blood and brain solubility for the anaesthetics as a group, and because the blood flow to the brain is large, a reasonable clinical rule of thumb is to interpret the problem of developing the necessary brain concentration as that of developing the equivalent alveolar concentration. This in turn is itself affected by a series of physical and chemical phenomena which are susceptible to precise analysis. Understanding of these relationships can be used to improve the clinical care of patients, and to help free it from the millstone of empiricism.

An example of the use of the concept of brain concentration is illustrated by the problem of providing a stable level of inhalation anaesthesia where other factors, e.g., surgical stimuli and the effects of haemorrhage, do not require changing depths of narcosis. This goal presupposes a steady level of drug in the brain which, in turn, means the maintenance of a steady partial pressure of the anaesthetic agent in the lung. Although many factors actually influence the concentration of the anaesthetic agent in the alveoli and thereby indirectly its concentration in the brain cells, the two most important factors for the clinician to consider are the solubility of the gas in the blood and other tissues, and the pulmonary ventilation.

**Blood Solubility and Rate of Induction**

The solubility of anaesthetic agents in the blood and other tissues is discussed in great detail elsewhere in this issue (Eger and Larson, 1964). One can derive from this kind of information the fact that an anaesthetic agent which is highly soluble in the blood may be expected to provide for both a slow induction of anaesthesia and a slow recovery from anaesthesia. If ventilation is maintained constant, the alveolar partial pressure of a soluble anaesthetic agent, like ether or chloroform, will reach equilibrium more slowly with the inspired concentration of this agent. Since the partial pressure of the vapour in the brain is ultimately proportional to the partial pressure in the alveoli, a slow build-up in concentration in the alveoli inevitably means a prolonged induction period.

The anaesthetist may accelerate the induction of anaesthesia with an agent which has a high solubility in the blood by the use of “overpressure”, that is, he may, for a limited period, submit the patient to an inspired concentration in excess of that required for maintenance. For example, in many intelligently conducted clinical practices with the use of halothane, trichloroethylene, or diethyl ether, a concentration is inhaled during the induction period which may be four to six times as great as the concentration required for the maintenance of anaesthesia. This is gradually or rapidly reduced to a maintenance level depending on the effects of the anaesthetic agent and its particular solubility characteristics. It will be noted that ether is approximately seven times as soluble as halothane in the blood (Eger and Larson, 1964). The principles of slow induction and its compensation by overpressure are more important with ether and much easier to manipulate with halothane because of its lowered solubility in the blood as compared with ether. Halothane is intermediate in this regard between the highly soluble liquids and the relatively insoluble gases.

Those inhalational anaesthetic agents which are relatively insoluble in the blood, e.g., nitrous oxide, cyclopropane and ethylene, are agents which produce a rapid induction of anaesthesia. This phenomenon is to be expected in clinical experience since the alveolar partial pressure of these agents, and therefore the cerebral concentration of the anaesthetics, approach the inspired concentration much more rapidly than with the soluble anaesthetic agents. The low solubility of these anaesthetics in blood allows for a fast build-up of alveolar partial pressure.

For instance, induction of anaesthesia with nitrous oxide and oxygen is completed in a relatively few minutes. Recovery is equally fast. The differences between nitrous oxide and cyclopropane are most interesting and can be explained to the clinical practitioner on the basis of their solubilities in the tissues (Eger and Larson, 1964). Cyclopropane is considerably more soluble in body fat than is nitrous oxide. Their solubilities in blood and aqueous tissues are very similar. Therefore, in a brief anaesthetic procedure, of perhaps 30 minutes, the similarities between nitrous oxide and cyclopropane predominate so that induction with both anaesthetic agents is rapid and recovery is approximately equally rapid. However, where anaesthesia is prolonged, cyclopropane dissolves in
body fat to an appreciable extent. If enough time has elapsed in prolonged anaesthesia the difference in fat content of gas will become quite obvious and the recovery period from cyclopropane will be considerably longer than from nitrous oxide. Accordingly, in long cases of cyclopropane anaesthesia it becomes necessary to begin to empty the breathing bag of anaesthetic mixtures repeatedly much earlier in the course of anaesthesia than is the case with nitrous oxide. This procedure has an important clinical benefit in providing a patient who is more alert early in the course of his recovery than would otherwise be the case. It also seems likely that the opportunities for post-cyclopropane hypotension are lessened if an earlier termination of anaesthesia is secured. This phenomenon of hypotension is more dramatic and more frequent in longer periods of cyclopropane anaesthesia than in shorter ones. Although its precise mechanism is unknown, its occurrence can be diminished by this process. This characteristic of cyclopropane also provides a rational explanation for the clinical practices of those who terminate cyclopropane anaesthesia with nitrous oxide and oxygen. This, in effect, is one way of ending a cyclopropane anaesthesia earlier than would take place otherwise. There does not appear, however, to be a compelling need to use nitrous oxide for this purpose; it can be just as easily accomplished with oxygen or mixtures of air and oxygen except that nitrous oxide provides some insurance against premature awakening. In this way the knowledge that the heightened solubility of cyclopropane in fat must be dealt with in terms of recovery from anaesthesia is exploited for clinical purposes.

PULMONARY VENTILATION

In addition to the influence of blood solubility of anaesthetics, pulmonary ventilation has an important effect upon the uptake of inhalation anaesthetic agents. It is generally recognized by most practitioners that the greater the pulmonary alveolar ventilation the more rapidly the partial pressure of the anaesthetic agent will rise, with a concomitant and subsequent increase in the concentration of the anaesthetic agent in the brain. Speed of induction is correlated with pulmonary ventilation if these assumptions are reasonable. The greater the ventilation the more rapid will be the speed of induction and the speed of recovery.

Variations in inhalation anaesthetic techniques also have an influence on the rate at which the alveolar partial pressure of an anaesthetic agent approaches that of the inspired concentration. A non-rebreathing method allows for a faster increase in the concentration of agents in the alveoli than does a closed circle system (Severinghaus, 1963). The reason for this phenomenon is that there is no dilution of the inspired gas with exhaled air in the non-rebreathing technique. In
clinical practice, therefore, when one is choosing a method for the administration of an anaesthetic agent, the non-rebreathing method can provide for more rapid induction when such is desired as compared with a closed circle system.

CLINICAL COMPROMISES

One can summarize these concepts from a clinical point of view by stating that the fastest possible induction of anaesthesia can be accomplished by hyperventilating a patient with a potent agent relatively insoluble in the blood with the use of over-pressure (or excessive concentration in the inhaled atmosphere) and employing a non-rebreathing circuit. Conversely, one could anticipate a slow induction and a slow recovery if the patient is permitted to hypoventilate with a relatively non-potent anaesthetic agent which is highly soluble in blood in a circle system. Both methods, of course, may be dangerous. The rapid induction can become a matter of hazard because of the pharmacological properties of the anaesthetic agents. In this discussion, consideration of these particular properties of the anaesthetics was omitted, although it is quite obvious that they are highly important. The question of potency of an anaesthetic agent and the specific effects of these agents upon the various tissues and organs of the body must also be known by the clinician in his administration of anaesthesia. It is assumed in this discussion that these properties are familiar and will be used in exploiting the pharmacokinetic aspects of anaesthetic administration.

An illustration of the difficulties of enhancing the speed of an induction by overpressure or hyperventilation is the danger of serious cardiocirculatory depression which can be caused by a potent anaesthetic agent like halothane or ether if its uptake is encouraged by the use of hyperventilation in the form of controlled respiration with high concentrations. This compromise on a clinical level is an important one in everyday practice. The competent clinical anaesthetist, by knowing the methods of controlling the speed of his induction and weighing them against the possible harmful effects produced by the pharmacological properties of the agent, should be able to arrive at some reasonable compromise which provides for an acceptable speed of induction without hazard to the patient. In daily practice this problem can be obviated by using those agents whose potency is weak so that the undesirable depressant pharmacological effects upon the various organ systems do not occur. This concept is the basis for the clinical practice which suggests that nitrous oxide and oxygen can be used as practically universal anaesthetic agents if supplemented by muscle relaxants. Hyperventilation with nitrous oxide will simply bring the alveolar concentration into equilibrium with the inspired concentration more rapidly. The effect due to the nitrous oxide will remain modest because the agent's intrinsic pharmacological properties are such that it cannot produce an undue depression of the brain and the heart and other vital organs. Hyperventilation per se may, of course, produce other physiological alterations. It is interesting that the practice of non-potent gas anaesthesia with muscle relaxants has grown on an intuitive basis for so long. An appraisal of the pharmacokinetics of the uptake and distribution of nitrous oxide could have predicted this course of events during clinical anaesthesia or at least made its practice more rational at an earlier time.

The problem of slow induction of anaesthesia may also prove a hazard when a prolonged excitement stage ensues with the potential of respiratory obstruction, serious cardiac arrhythmias, and the possibility of body injury. The intelligent clinician can, by considering these various factors in the light of the disease processes which affect his patients, select a proper approach to ensure a rapid and safe induction of anaesthesia, a steady maintenance of anaesthesia and a reasonably rapid recovery.

UPTAKE AND DISTRIBUTION IN CHILDREN

A word should be said about the information provided by the uptake and distribution of anaesthetics in children. Quantitative studies are not yet available on these problems in children and in infants. However, it can be predicted with reasonable confidence that the uptake and excretion of anaesthetic agents in infants will be more rapid than in adults in view of their relatively larger cardiac output and alveolar ventilation and smaller functional residual capacity per unit of surface area or body weight (Rackow, personal communication). There-
fore a more rapid approach to overdose of potent anaesthetic agents is likely during the maintenance of anaesthesia should the inspiratory concentration of an agent like halothane or ether be increased. It is recommended to the clinician that the technique of overpressure with a relatively soluble anaesthetic agent such as halothane or ether be used either not at all or with very great caution in the youngest patients. The use of overpressure with relatively insoluble anaesthetic agents like cyclopropane during the maintenance period is not necessary. Again the previously mentioned importance of anaesthetic potency comes into a consideration of paediatric problems. The lack of potency of nitrous oxide explains why clinical anaesthetists have become increasingly happy with its use for infants and children. As with adults there is an automatic fall to fixed depths of anaesthesia, and stability of anaesthetic levels is easier to obtain. It also explains why cyclopropane is considered by many to be a useful agent in infants and children. This probably has not as much to do with the high potency of the anaesthetic as it has with the insolubility of this agent in the blood, making it easier to attain equilibrium conditions early and to maintain them in a more stable condition than with the more soluble agents.

MATHEMATICAL AND ELECTRONIC ANALOGUES

A word is required for the clinician concerning mathematical and electronic analogue models. This whole problem is discussed more fully and more competently elsewhere in this symposium (Mapleson, 1964), but the clinician should be able to decide how he can use these data in his practice. It must be stated that mathematical and electronic analogue data are neither sacred because of their highly intellectualized formulations nor are they to be discarded because they do not represent actual clinical or experimental procedures. These methods are in fact only as accurate as the data which is fed into them, whether in mathematical formulae or in analogue manipulations. Unfortunately, many of the data required for the complete presentation of the behaviour of an anaesthetic agent are lacking. For example, we do not have adequate knowledge of the effects of the various anaesthetic agents on individual organ blood flow. Therefore these methods, while highly deserving of study, must be considered approximations. They are useful educational and experimental tools and they are even more useful in aiding in the design of appropriate experiments to test their predictions in intact animals and patients. Significant contributions from these methods can be expected increasingly as they become more sophisticated and as data fed into them become more reliable. At the present time the clinician would be well advised to look at these data with interest and from the standpoint of aiding him in a shortcut method until experimental data add information for clinical practice.

A final point to make in the consideration of pharmacokinetics of inhalational anaesthetic agents is a look to the future about newer and as yet undeveloped anaesthetic agents. If the anaesthetist studies the pharmacology of these agents and understands their pharmacokinetic properties, he can with reasonable certainty predict which of these newer anaesthetic agents will hold promise for clinical utility. Obviously the last answer is found in the administration of a new agent to a patient who requires a surgical procedure. It is respectfully suggested, however, that the clinician can spare his patients much danger and his own work many hardships if he is aware of the importance of the physico-chemical and pharmacological knowledge of new agents. The anaesthetist is then free of the problems that have beset him for almost a century of having to learn intuitively by trial and error with the risk of misleading experience. He is rather in the position of the scientist testing in a patient the reasonable, predictable effects that a new anaesthetic agent should have. If for no other reason, this kind of knowledge should prove invaluable to the competent clinician.

REFERENCES


