ACTA MEDICA IRANICA
Vol. 31, FALL 1993

A NEW APPROACH TO DETERMINE THE DEPTH OF MODERN ANESTHESIA BASED ON DRUG - RECEPTOR PRINCIPLE (INTRODUCING A NEW TEST)

Mohammad Esmaeil Tashayod*, MD

* *Professor, Tehran University of Medical Sciences, Faculty of Medicine, Imam Khomeini Hospital: Department of Anesthesiology.*

SUMMARY

This paper deals with the assessment of the depth of the modern anesthesia. A new classification is proposed and a test is designed for monitoring the movement of the hand during complete relaxation.

KEY WORDS: *Amnesia; Analgesia; Assessment of depth; BZD-receptor effects; Conscious sedation; Modern anesthesia; Monitoring the movements; New classification; Planes of control.*

INTRODUCTION

Guedel (1), in 1937, mentioned his classical table for the assessment of the depth of anesthesia, but eversince no classification of similar nature and significance has been developed for the practice of the modern anesthesia and the problem has remained unsolved.

In the present work, at first the attempt is made to classify the sedative requirement of the patient in confronting the graded noxious surgical stimuli. Only one stage (similar to the first stage of Guedel) covering the whole practice of modern narcosis is proposed. This single stage is subdivided into four planes. Then the author will try to develop the criteria for each plane by adopting the recent drug-receptor effects. They are all summarized in a comprehensive table together with the clinical signs to determine the depth of the plane of narcosis.

THE NEW CLASSIFICATION

Four planes are considered in one single stage as follows:

Plane I: Anti-anxiety
Plane II: Total amnesia + Light sedation
Plane III: Total amnesia + Partial analgesia + Heavy sedation
Plane IV: Total amnesia + Partial to total analgesia + Unconsciousness + Loss of the movements.

	Plane	Graded planes of control	Receptor occupancy	Clinical signs
Stage I / SURGICAL STAGE	1st	Anti-anxiety	BZD receptor block (20-25%)	tranquility
	2nd.	Total amnesia Light sedation consious	BZDs receptor block (25-50%)	vertigo drowsiness
	3rd	Total amnesia Partial analgesia Heavy sedation sedation	BZD receptor block (50%) Opioid receptor block (partial)	ptosis slurred speech cooperative
	4th	Total amnesia Adequate analgesia Unconsciousness Loss of movements Anesthesia	BZD receptor block (60-90%) Opioid receptor block (partial, complete 25%) Muscle relaxant receptor block(60-90%) Inhalational agents < MAC N_2O-IV Hypnotics < ED50	unable to open eye by command; absence of eyelash reflex; no movement in face, extremities
Stages II III IV		Preventable but could not be identified except for ether	Ketamine Thiopentone > ED50 Inhalational agent > MAC	drug-dependent not comparable not measurable

Tashayod's classification of depth in regard to drug-receptor effect, in modern practice of anesthesia

In this paper, we will use either the word "control" (2) or "narcosis" instead of anesthesia for the planes I, II, and III.

DISCUSSION

Guedel, in 1937, published his eminent classification of ether anesthesia which consisted of four stages.

Artusio (3), in 1945, expanded stage I or stage of ether analgesia into three planes as follows:

Plane I: Patient has no amnesia and no analgesia.

Plane II: Patient has total amnesia and partial analgesia.

Plane III: Patient has total amnesia and total analgesia.

Artusio has reported the safety of the first stage of ether anesthesia during the heart surgery.

Unfortunately, these classifications which were proposed for ether anesthesia could not be applied for the practice of modern anesthesia.

Guedel has been criticized for considering only the anesthetic signs whereas ignoring the body's responses to surgical stimuli.

Gray (2) tried to classify the levels of anesthesia by considering the graded body's responses.

In the present table, the author has attempted to combine the two hypotheses.

These days, in our daily practice of anesthesia, we are looking towards the accomplishment of three main goals. We want to have a mentally and physically relaxed patient who does not recall surgical events later on.

According to Prys-Roberts (3), unconsciousness is a quantal phenomenon. Once the patients reach this level of anesthesia (plane IV) no more anesthesia is desirable while using a muscle relaxant. Indeed, when we continue the flow of anesthetic to the patient, we will get some harmful hemodynamic or respiratory depression.

Besides, the author has noticed that by maintaining the anesthesia in the realm of the first stage, most of the post-anesthetic complications especially post-halothane shivering, agitation, and vomiting will be definitely avoidable.

The diversity and variation of reflex abolitions which are drug-dependent have not allowed any meaningful classification for deeper stages of modern anesthesia. That is why, we should consider stages II, III, and IV the stages of drug overdosage which have purposely been ignored.

In the author's table, the plane IV has been added to the previous arrangement of the first stage because its characteristics are more similar to the first stage with calm and quiet sleep rather than the second stage with its reflex activation and delirium. On the other hand, planes III and IV are easily transformable by little change in drug concentration with visible signs. Plane IV must be considered an end point to clinical anesthesia. Now, we can perform the whole spectrum of surgical procedures in these planes i.e.:

A) Simple endoscopies require only amnesia (plane II).

B) Painful procedures like eye operation, tissue biopsy, colonoscopy, cystoscopy, laparoscopy, ERCP and debridement of burnt tissue all could be performed at plane III.

It is my firm belief that by marketing newer short -acting benzodiazepines (BZDs) and opioids we will be able to perform most of our operations in plane III.

C) Plane IV is the real stage of anesthesia exhibiting unconsciousness along with the loss of movements (4), allowing all kinds of major surgeries.

SELECTED DRUGS

As it has already been mentioned, the main goal of anesthetists is to use special receptor selecting drugs in accordance with "control" of each plane. In the light of recent pharmacological discoveries, we now possess drugs such as BZD (5,6), opiate (7-11), and muscle relaxant (12,13) which show great affinity for special receptors. All we have to do is to find the appropriate site and dosage for them in our table, considering their properties and special potencies in relation to receptor occupation.

Diazepam is a "gold standard" (14-17). In dose of 0.1 mg/Kg (5-10 mg), or 20-25% receptor occupancy provides anti-anxiety effect in pre and post-operative periods.

In dose of 0.2 mg/Kg (10-15mg), or 25-50% receptor occupancy produces a complete amnesia (planes II and III).

In dose of 0.3 mg/Kg (15-25mg), or 60-90% receptor occupancy suffices for the induction of unconsciousness, in a healthy young case. But, in practice, we ought to titrate it according to the patient's requirement.

Of course, the patient can be induced only by thiopentone (4-6mg/Kg) or other IV anesthetics. Although the recovery might be faster, it has the potential risk of the patient's recall of surgical events especially in the lighter plane (III). The author prefers the prior use of BZD (50% receptor occupancy), then at the top, thiopetone (2mg/Kg) being used as a co-induction. The ease of recovery together with the prevention of recall makes this technique safe and desirable. To avoid the local inconvenience of diazepam, it is always mixed with an equal volume of 1% xylocaine. Midazolam is preferred by many authors for its rapid elimination and lack of local venous complication (in $\frac{1}{2}$ $\frac{1}{3}$ dose of diazepam).

Anesthesia is maintained with the help of <MAC6 of an inhalational agent or by performing total IV anesthesia. The patient does not need go deeper than plane IV which is controlled by monitoring the movements.

In regard to analgesics, they can be given more freely and without the fear of changing the level of

narcosis, for example, while 10 micrograms per Kg fentanyl is given for moderate analgesia, doses of30-100 micrograms per Kg weight (25-30% receptor occupancy) produce anesthesia and prevent most of the endocrine and metabolic responses in an open heart surgery. Even at this level of complete receptor occupancy, the awareness during surgery has been reported (18). The same is true for muscle relaxants and they should be used for 60-90% receptor occupancy. While using the clinical doses of BZDs and analgesics, one can be sure that patients never go deeper than plane IV.Thiopentone and inhalational agents (except for N_2O) are inversely able to take the patient into the deepest plane of narcosis rapidly, so extreme economy must be exercised in their use. Ketamine has to be avoided because it is confusing, regarding the assessment of the depth of anesthesia.

If the patient still remains unconscious at the end of the operation, we should titrate flumazenil as an antagonist to BZDs to bring him back to plane I or II i.e, lightly sedated fluently speaking patient with the orientation of time and place (19).

PREDICTION AND ASSESSMENT OF DEPTH

As it has already been mentioned, special receptor acting drugs exert their effect mostly in the realm of the first stage. So, by titrating them to the desired level of narcosis, we can be sure of getting the expected depth. For instance:

A) By giving 5-10mg diazepam, a state of calmness and anti-anxiety supervens which is pre and post-operatively beneficial (plane I).

B) By giving 10-15mg diazepam (50% receptor occupancy), the patient will manifest total amnesia though talking fluently (plane II).

C) When analgesic is also used, we will reach the plane III of narcosis. In this plane, talking becomes gradually more difficult. Slurred speech with ptosis is indicative of plane III. Meanwhile, the patient's cooperation is preserved and he may ask for more analgesia. Eyelash reflex has been intact so far.

D) When the patient is unable to open his eyes by our verbal command, this is the beginning of plane IV (16). The eyelash reflex becomes abolished now though the eyes still remain wet.

About the same level of narcosis, movements disappeared provided the patient received enough analgesic. Analgesia should always be tailored to the magnitude of surgical stress.

By giving a precalculated depth of anesthesia, aiming at special receptors, we leave the major part of the brain untouched; therefore, a reversible anesthesia is produced with stable physiology and free from side effects which means that we are getting close to the definition of an ideal anesthesia.

Beyond this stage of anesthesia, the drug-dependent signs and symptoms of patient's response to surgery are hard to be classified. Perhaps the hypotension with dry eyes will be produced by most of anesthetics. So, we should avoid entering the deeper stage by sticking to MAC of inhalational agents and titration of thiopentone to its lowest dosage during the induction of anesthesia, keeping in mind the intense synergism of thiopentone with the BZDs at the site of GABA receptor (20).
However, when the depth of anesthesia goes unexpectedly deeper than the desired level, the flow of the anesthetics must be discontinued, and we should wait and look for the lacrimation to occur.

On the other hand, whenever the anesthesia is getting too light, it is recognised by the changes in respiratory pattern, lacrimation, opening eyes, and appearing of the movements in face and extremities.

However, when total IV anesthesia is used, we have either rely on the autonomic manifestation (BP+HR) or try special tests.

SPECIAL TESTS

The appearing of the movements is a good indication of analgesia, anesthesia inadequacy, but they are prevented by the use of muscle relaxants. To mitigate this inconvenience, Tunstall (21) used the isolated forearm. The forearm is isolated by applying a tourniquet before the administration of muscle relaxant. Tunstall noticed that 44% of patients showed the hand's movement after N_2O and fentanyl anesthesia, but only in a few recall of events occurred. The prolonged inflation of tourniquet at a high pressure and at a limited time together with

non-perfused arm which is a source of pain production, make this technique inconvenient fordaily practice.

Tashayod (22), in 1983, made an arm resistant to paralysing effect of muscle relaxant for the detection of movements during surgery.

This test is consisted of the following steps:

1) A plastic needle is inserted at the back of one hand.
2) Forearm is made totally ischemic by means of Smarch rubber bandage.
3) Tourniquet is inflated to 250 mm Hg.
4) Now, 0.5 mg neostigmine diluted in 40 ml saline is injected intravenously.
5) The pressure of tourniquet is maintained for three minutes, then it is released.
6) We wait for one minute.
7) The desired dose of muscle relaxant may be injected through the same needle.
8) The prior binding of neostigmine to the receptors of this arm makes them resistant to paralysing action of muscle relaxant and provides a useful monitoring of hand movement for up to three hours when the whole procedure can be repeated.

This test enables the anesthetists to find the minimum concentration of anesthesia sufficient for different surgeries to be accomplished. It is observed that this concentration is considerably lower than concentration normally administered.

REFERENCES

1) Guedel, AE. (1937). Inhalational anesthesia: A fundamental Guide. New York: Macmillan.
2) Gray, TC. (1960). The triad of anaesthesia. *Irish J. Med. Sci. 419,* 499.
3) Prys-Roberts, C. (1987). Anaesthesia: A practical or impossible construct? *Br. J. Anaesth., 59,* 134.
4) Eger, EL, S. Aidman, LJ, & Brandstater, B. (1965). Minimum alveolar anesthetic concentration: A standard of anesthetic potency. *Anesthesiology, 26,* 765.
5) Squires, RF, & Braestrup, C. (1977). Benzodiazepine receptors in rat brain. *Nature, 266,* 732.
6) Amrein, R, Hetzel, W, Harmann, D, & Lorscheid T. (1988). Clinical pharmacology of flumazenil. *Eur. J. Anaesthesiol., 2,* 65.
7) Pert, CB, & Synder, SH. (1973). Opiate receptor: Demonstration in nervous tissue. *Science, 179,* 1011.
8) Terneius, L. (1973). Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fractions from rat brain. *Acta Pharmacol. Toxicol., 13,* 377.
9) Simon, EJ, Hiller, JM, & Edelman, I. (1973). Stereospecific binding of the potent narcotic analgesic [3H] etorphine to rat homogenate. *Proc. Natl. Acad. Sci., 70,* 19-74. USA.
10) Stanley, TH, L Eysen, J, Niemegeers JE, *et al* (1983). Narcotic dosage and central nervous system, opiate receptor binding. *Anesth. Analg., 62,* 705.
11) Lauven, PM. (1990). Pharmacology of drugs for conscious sedation. Sedation and monitoring in endoscopy at the world congress in endoscopy (pp. 1-6). Australia: Sydney.
12) Wand, BE, & Waud DR. (1970). On estimation of the margin of safety of neuromuscular transmission during recovery from block by a competitive and antagonist. Paper presented at the meeting of the American society of anaesthesiologists.
13) Feldman, S. (1973). The rational use of relaxants in muscle relaxant. London: Saunders.
14) Shane, SM. (1983). Conscious sedation for ambulatory surgery. Baltimore: University Park Press.
15) Scanman, FL, Klein SL, & Choi, WW. (1985). Conscious sedation for procedures under local or topical anesthesia. *Ann. Otol. Rhinol. Laryngol., 94,* 21.
16) McCloy, KF, & Pearson RC. (1990). Which agent and how to deliver it? Sedation and monitoring in endoscopy at the world congress in endoscopy (pp. 7-11). Australia: Sydney.
17) Pointdexter, AN, Abdul-Malak, M., & Fast JE. (1990). Laparoscopic tubal sterilization under local anesthesia. *J. Obst./Gyn. 75,* 5-8.
18) Hilgenberg, JC. (1981). Intraoperative awareness during high dose fentanyl-oxygen anaesthesia. *Anesthesiology, 54,* 341.
19) Thompson, D, & Gelles, *et al* (1990). Midazolam and flumazenil: The agonist-antagonist concept for sedation and anaesthesia. *Acta Anesthesiol. Scand., 92,* 108-109.
20) Olson, RW. (1981). GABA benzodiazepine - barbiturate receptor interaction. *J. Neurochem, 37,* 1.
21) Tunstall, ME. (1977). Detection of wakefulness during general anaesthesia for cesarian section. *Br. Med. J., 1,* 1321.
22) Tashayod, ME. (1983). The nature of acetylcholine receptor. *Acta Medica Iranica, 25,* 14-44.