

How deep is the sleep?

Looking into anesthesia depths

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Most everybody has the idea of Anesthesia as a state in which physical pain is preempted, no matter how gruesome the surgical trauma. Any patient can expect that their general anesthesia will provide oblivion from pain; that their oblivion will be so deep that they neither feel pain nor later recall the experience. Despite powerful drugs it is not always as easy to achieve this state as might be expected. In the first place, losing consciousness is an early step towards a full anesthetic state; by itself, going to sleep does not prevent pain. At times sleep is difficult to distinguish from true unconsciousness, and sometimes sudden severe pain can arouse an "asleep" patient, or cause pain breakthrough into a dimly aware but pain free state. There are other times when a patient's condition is so critical that only the lightest anesthesia is a risk, as in the flicker of a fetus' life before Caesarean section. At any blood level, depth of anesthesia is a balance between surgical assault and central nervous system (CNS) depression, lightened by intense pain, deepened as pain ceases.

In fact, statistics show isolated awareness to be rare, and awareness with pain even rarer. When it occurs, it is almost always due to equipment error: a vaporizer runs dry, a gas supply fails, a leak develops. The other cause is human error that is controllable by routine strict checking protocols, by disciplined training to ensure competent use, and by back-up monitoring, all hallmarks of a good professional department.

The few signs that pinpoint the moment of crossing the threshold from self-control into unconsciousness are difficult to read. It's not made easier when a sign's significance may differ with the two major classes of drugs used for general anesthesia, especially with the modern practice of mixing the two. Classical General Anesthesia by the inhalation of gases and vapors goes back nearly 200 hundred years. It is produced by a small group of simple volatile liquids. They are relatively toxic to the nervous system, in which they produce a shotgun variety of different effects, in combinations that vary with each drug. Strictly speaking, this anesthetic process is a deliberate light poisoning of the nervous system, that is kept safe by the tight control of blood levels by rapid uptake and excretion that is possible with inhaled drugs. Fortunately, the effects are reversible. If today these "smelly" drugs were first offered for i.v. injection they would likely never be accepted.

The first general anesthetics used were ether, chloroform, and nitrous oxide, and the first concept of (five) stages of an-

esthesia came from John Snow in London (1847) who also introduced the idea of monitoring his unconscious patients. The best-known description of Anesthesia Depth is in the (four) stages of anesthesia offered by Guedel in the USA, that was used first during WWI (1917 – 1918). The banning of nurse anesthetists in the US Army from active duty in France was the stimulus for this: Guedel had to train men only, mostly without nursing background, to take over this duty.

Guedel's scheme, published first in 1937, applied mainly to the effects of diethyl ether, and is of lesser value with modern ether anesthetics. Nevertheless it still provides a good working concept of the progression of CNS Depression under General Inhalation Anesthesia. Four stages were distinguished between the Induction of Anesthesia to Imminent Death from Overdose. These are indicated by various physical signs in the pattern of respiration, CVS function, eye signs, autonomic and CNS responses. Through these Guedel maps the changes occur as body control shifts from a highly integrated intellectual state to a more basic survival condition in unconsciousness.

Stage 1. The Descent through Consciousness to Unconsciousness. During this stage, through talking with the patient, one can follow a gradual constriction of their sphere of consciousness as they lose contact through external senses, while simultaneously analgesia increases until ultimately only a microcosmic consciousness of self remains without pain. Time sense fails. Near the end of this stage voluntary control of behavior is lost, heralding unconsciousness. The conventional indicator for the end of Stage 1 is loss of the eyelash reflex.

Stage 2. Turbulence as Consciousness is lost ~ Delirium. With sudden loss of volition, of "conscious control," sometimes-wild aggressive behavior may supervene along with other signs of increased sympathetic activity such as dilated pupils, tachycardia & hypertension, violent purposeless movements, rapidly roving eyes, and irregular respirations. "Higher" control over organ systems seems here to be giving way to primary organ control centers in the medulla.

In this stage virtually no patient feels or remembers pain but will not be safely "anesthetized" until autonomic and motor reflex activity is controlled, much of which arises in the spinal cord.

Stage 3. Drifting down through Surgical Anesthesia. After

a sometimes-rough ride through Stage 2, organ system control seems to have been regained, marked by immediate onset of regular automatic breathing, stable blood pressure and pulse; slow uncoordinated eye movements that eventually cease. The tears of light anesthesia (and the sweating and salivation) dry. Metabolism slows and temperature control is lost, the body usually drifts with the environment into hypothermia, which, in its turn, intensifies the anesthesia effect.

Guedel distinguished 4 planes in this stage: from an initial stable light surgical anesthetic state that goes over into overdose. About the mid-point, a controlling medullary center seems no longer to be able to manage the direct depression of its organ system by the volatile drug; function falters, and metabolic failure slowly develops. Heightened sympathetic drive can no longer mask increasing myocardial depression. Respiration becomes uncoordinated as intercostal muscles weaken and the response to a raised arterial carbon dioxide level is blunted. Renal and hepatic functions are likewise depressed.

Stage 4. Rock Bottom ~Imminent Failure of all Organ Systems. This is the stage that never should be allowed to develop. Mark it "DO NOT ENTER." If respiration and circulation are eventually allowed to fail resuscitation is impossible.

In general this "shot gun" effect on all organ systems is seen in normal patients with most volatile anesthetics. It comes about because these drugs are more soluble in lipid than in water, so that they tend to concentrate in the lipid membrane of all cells walls. This disturbs a variety of cellular transactions. Interference with the extraordinarily complex neuronal message traffic needed to coordinate the state of consciousness would account for its early failure during anesthesia induction. The effects that follow are more widespread. This does not occur because of any specific synaptic block but is based on high stress overload of a variety of synaptic transmitters through general cellular depression.

If a "normal" patient were to go on to develop organ damage in one system the picture would change; that system will have lost its normal functional reserve, making it more sensitive to the action of depressant drugs. In severe heart failure, for instance, a patient could collapse even before reaching a stable level of surgical anesthesia to start surgery.

It is mainly this problem of the increased risk introduced by pre-existing illness that has turned the search for "magic bullets," specific, single acting, synaptic blocking drugs, to replace the older "shot gun" drugs. (The ideal of a single intravenous drug that safely can produce balanced general anesthesia remains a dream.) These new "bullets" are never volatile and so lose the special safety feature of inhaled drugs of easy uptake AND rapid excretion through the lungs. They must be injected and once in the body may only be removed, sometimes slowly, by metabolic breakdown. Thus the safest drugs to give are those that break down the fastest, making it possible to produce steady blood levels by continuous slow i.v. injection, as volatile drugs now effectively do by inhalation. There appears to be one other advantage with volatile agents: a patient still aware is most often pain free. Pure Hypnosis, by itself, does not come with analgesia.

In designing an anesthetic technique that will use a series of single effect drugs one should start by considering the role anesthesia needs to play in modulating the many responses to a severe trauma. Surgical trauma represents an enormous threat to survival that must trigger a series of powerful protective

reactions. One of these will be escape or aggression, violence only for as long or as briefly as consciousness lasts. This inexorably is followed by long lasting physiological changes aimed at self-preservation and repair in an unconscious body. It is the more important function of anesthesia to optimize such subconscious responses: this will need deeper and different responses than for simple unconsciousness. And these responses are protean: a sudden increase in centrally mediated analgesia; autonomic responses to stabilize circulation by volume maintenance and regional flow control; enhanced blood clotting; shutting down unimportant gastrointestinal and genitourinary functions; raising blood sugar, routing changes in spinal circuits, adrenocorticoid and catecholamine levels; increased muscle tone to protect body cavities or fractured limbs; and later, after surgery, inhibited psychomotor activity as part of The General Stress Response that persists days after injury into the healing phase. How control of all this is achieved is to be found in the detail of anesthetic technique.

A next step in designing a "magic bullet" approach comes from looking at characteristics found desirable of "General Anesthesia." Five components are generally accepted, and a sixth ~ post-operative mental status, should be considered. Each alone would be ineffective, but combined they could together make up "Ideal Anesthesia".

HYPNOSIS/SLEEP: although we somehow accept that we must be awake to feel pain, sleep, on its own, does not guarantee freedom from physical pain, although it is a good way to sidestep the anxiety and mental pain that surround surgery. Something more is needed.

AMNESIA: no conscious memory is preserved of an event, even if pain was felt at the time. This is not solely a philosophical point, since memories are sometimes recorded during surgery that are not recoverable without hypnosis, and can leave psychological injury, or, in other words, mental pain. It could be that deeper degrees of amnesia are required than volatile anesthesia sometimes offers. For instance, the sense of hearing remains active in deep anesthesia, well after the perception of physical surgical pain is blanked off. Even so, the "intellect" may still be functional: speech can be detected, translated for meaning, decoded for import, and, if found to be threatening or in other ways significant, registered in some way to influence behavior.

ANALGESIA/PAIN CONTROL: one should expect from any anesthetic technique that the threshold for pain perception be raised. Some agents do this better than others. For instance, it is possible to communicate with a comfortable (and somewhat conscious) patient under ether while body cavity surgery is in progress. Very few true Hypnotic drugs are as good analgesics as this. Most need analgesic supplement. Similarly, many analgesics need an added hypnotic to produce unconsciousness. Indeed, some hypnotic drugs aggravate pain responses if the patient is not fully conscious and in full voluntary control.

MUSCLE RELAXATION: muscle movement in response to noxious stimulus, described as "guarding", is a sign that pain "is being felt" even if it is not being experienced. Curare-like muscle relaxants are commonly used to prevent patient movement in light anesthesia levels. The worry is that patients, being paralyzed, but not analgesic, may feel pain, but cannot signal their protest.

AUTONOMIC STABILITY: severe pain always evokes a

strong autonomic response, usually as sympathetic activity ~ raised pulse and respiration rate, raised arterial pressure ~ and also strong vagal responses ~ bradycardia and hypotension ~ that may be more immediately dangerous.

MENTAL STATUS: the concern is usually limited to the hangover that follows anesthesia intoxication. As this passes, generally there follows a “will to survive” response lasting several days, coinciding possibly with raised adrenal steroid blood levels. The extent of the trauma may also modify mental state: variations in a basic survival instinct, that underpins the opposites of “withdrawal for healing” after severe injury or otherwise a “bounce back” attitude (“escape or play dead” ploys) after a more “minor” infraction.

Without doubt the most severe reactions follow awareness under anesthesia, especially with pain. Severe anxiety states, fear of falling sleep, total insomnia, mental breakdown, all require active psychological intervention. This is the penalty for “too light” anesthesia.

Finally, months after many types of major trauma/surgery a deep depression may develop, long after physical healing is complete. Quite how this might be related to anesthetic technique needs fuller investigation: would better blocking of the noxious input from extreme trauma into the CNS processor change long-term outcome? Anesthesia charting places emphasis on physical values, lacks similar precision in monitoring mental state, and lasts never more than days.

Mixing Drugs: The first five of the above characteristics concern the essential properties of the General Anesthesia state. The problems start with trying to read those indicators of such states that define the depth of anesthesia in patients who can't talk back. And since there are essentially two different classes of drugs in use, there are several ways to define the nervous system depression resulting. “Classical” general anesthetic drugs and a combination of the single action synaptic blockers each produces their own mix of the above 5 properties. Note some of the differences:

RELAXANTS: curare-like drugs can safely prevent muscle tone or movement, provided respiration is supported, with effective, rapidly acting antidotes available. But they do not influence consciousness and must never be used unless unconsciousness can be guaranteed, or torture is the intention.

ANALGESICS: boosting analgesia is safe, again provided the accompanying respiratory depression is supported, and the antidotes are to hand. These drugs more reliably produce apnea than sleep or amnesia, and so are generally used together with AMNESIC & HYPNOTIC DRUGS when anesthesia must be very “light.” One of the actions of amnesic drugs is to render unpleasant experiences less significant, less registrable in memory.

It is difficult to mix drugs having a single specific effect with any but very light levels of the mixed effects of general anesthetic drugs because the traditional signs of anesthetic depth ~ breathing, circulation, muscle tone, eye movement ~ are eliminated. Making matters more difficult is that anesthesia potency is traditionally measured by the MAC scale: the Minimum Alveolar Concentration of a volatile drug that prevents response to a defined stimulus in 50% of patients. Somewhere above this 50% Effective Dose (ED50) will loss of awareness appear on the therapeutic horizon. There is no other comparable depth of anesthesia scale. Using a MAC value derived from suppression of the autonomic response, reflected in arterial pressure and heart rate (the MACBAR), gives more

realistic values of an Effective Dose, although not everyone responds to pain by tachycardia and hypertension. This criterion shows endotracheal intubation to be more stimulating than the skin incision that follows. Commonly, values around 1.2 – 1.5 MAC are usually combined with the single effect relaxant, analgesic, and amnesic drugs, observing two caveats. Firstly, the low potency of nitrous oxide cannot achieve more than about 75% of MAC: most cases of awareness are when N₂O is combined with opiates. Secondly, the end expired concentrations of anesthetics reflect the true dose administered, not the mixture as delivered by the machine.

As old patents expire, to be superseded by “improved” psycho-pharmaceuticals, there will be many more strings to the Anesthesia marionette. This means that new ways of looking at anesthetic depth have to be developed. A major goal is to find reliable signs of awareness in the organ of consciousness. Exactly where to look for this telltale brain activity is debatable. One obvious source is the EEG waveform, even though awareness may well have its seat in the deep interior of the brain, below the cerebral cortices. Possibly rapid PET monitoring of metabolic activity at deeper brain levels may yet give the most precise information. The EEG waveform, subject to fast Fourier transformation of short epochs of activity, separates the signal into its constituent sine waves, and detects phase shifts and power distribution across a spectrum of 1.0 – 40 Hz. The distribution of activity at different frequencies can be visualized by techniques as Spectral Edge Frequency or a Compressed Spectral Array, the latter displaying frequency shifts in the power spectrum. These methods seem better indicators of anesthesia depth below the threshold of awareness. More recently, processing of the power and frequency spectrum with phase shifts has produced a Bispectral Index Scale (BIS)⁽¹⁾, a dimensionless number between 0 – 100, related to brain silence or activity. This tracks the awareness threshold more clearly at around 60.

Other avenues give other views into brain: along EMG pathways that indicate protective muscle tone, or indicators of the triggers for the hormonal stress response. Normally subconscious functions, such as the activity in hollow muscular organs, have been used. This reflects autonomic activity. Because hearing is the last sensory function that persists in the brain, reliable signs come from auditory evoked potentials. There must be, somewhere, a sign of precisely when awareness is “locked in,” even of awareness that never emerged into remembrance. But the presence of awareness is just one consideration; anesthesia must do more than peace the sleep. There is much evidence that an uncontrolled stress response does delay immediate physical recovery and healing, making outcome ultimately more damaging.

And yet, when all is said and done, there may be no need to worry over what Depth of Anesthesia that should accompany a particular type of surgery. By blocking entry of injury data into the processing system that is the Central Nervous System, Local or Regional Analgesia provide excellent control of pain, and of most of the usual physiological responses to trauma.

And one injection, of one drug, once, may suffice.

Reference

1. Johansen JW, Sebel PS. *Anesthesiology* 2000; 93:1336-1344. Development and Clinical Application of Electroencephalographic Bispectrum Monitoring