Published in final edited form as:

Anesthesiol Clin. 2009 September ; 27(3): 429–contents. doi:10.1016/j.anclin.2009.07.007.

Delayed Arousal

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Keywords

delayed arousal; elderly; geriatric; management

Case Report

A 78 year old female with a six month history of rapid progressive loss of equilibrium, coordination, balance gait and hearing of the left ear presented for suboccipital craniotomy for acoustic neuroma. Her past medical history was significant for hypertension, diabetes, and depression, complicated by a 15 pound weight loss in the past three months.

After application of standard monitors, including a blood pressure cuff, pulse oximeter, and EKG, the patient was induced with midazolam, fentanyl, propofol and succinylcholine. Hemodynamics were originally labile, but stabilized after several boluses of crystalloid. Isoflurane and a fentanyl infusion were used for maintenance of anesthesia. After the end of an eight hour surgical procedure, the patient remained unresponsive 45 minutes after the discontinuation of all anesthetic agents.

Synopsis

Elderly patients have medical and psychological problems affecting all major organ systems. These problems may alter the pharmacokinetics and/or pharmacodynamics of medications, or expose previous neurological deficits simply due to sedation. Delayed arousal, therefore, may arise from structural problems that are pre-existent or new, or metabolic or functional disorders such as convulsive or non-convulsive seizures. Determining the etiology of “delayed arousal” may require clinical, chemical and structural tests. Structural problems

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which impair consciousness arise from a small number of focal lesions to very specific areas of the central nervous system, or from pathology affecting the cerebrum. In general, focal or multi-focal lesions can be identified by computerized tomography, or diffusion weighted imaging. An algorithm is presented that outlines an approach to working up an elderly patient with delayed arousal.

Introduction

What is delayed arousal in terms of states of consciousness?

Multiple terms are used to describe altered states of consciousness. The term that neurologists and neurosurgeons use to describe a mild state of impaired consciousness is “clouding of consciousness,” which refers to a defect in attention. A more severe state of impairment is called “confusional state,” in which stimuli are misinterpreted. As attention becomes progressively more impaired and stimuli become increasingly misinterpreted, patients may be termed “delirious” and in the extreme “obtunded”, “stuporous” or “comatose”. The latter, “coma”, is a state of unresponsiveness to intensely painful stimulation. So, where does “delayed arousal” fit into this spectrum of “clouding of consciousness”? Clearly, one may consider patients under general anesthesia as experiencing “coma”, and under monitored anesthesia care (MAC) as experiencing “clouding of consciousness”. We will define the term “delayed arousal” as referring to a delay in the transition from a state of anesthetic induced “coma” to “clouding of consciousness,” and finally, to fully awake and aware. For the purposes of our discussion we shall define “arousal” as the ability of a patient to follow simple one-step commands which produce simple motor actions or have simple cognitive responses. We will not require more elaborate test performance, such as what might be required for sensory or detailed cognitive responses.

What are the physiological components of consciousness?

The physiological components that define levels of consciousness are based on the capability to attain a state of “arousal” by the central nervous system, the existence and experience of stimuli necessary to stimulate “arousal”, and the mental functions that can be performed in the aroused state.

The “elderly”

Elderly patients, defined as patients 65 years and older, are clearly different than younger patients. One of these differences is reflected in the common observation that elderly patients often experience delayed arousal. In examining why, one must examine the changes that patients experience with aging. Changes usually occur in the physiology of patients with normal aging. Therefore, medications that are given to younger patients will have different effects on the elderly. Often, medical and psychological conditions develop, which affect multiple organ systems. These conditions can also alter the effect of medications. Additionally, some medical problems, for example cerebral infarcts, may not be evident and go “hidden” without a previous neurological workup. With all of these changes, an administered anesthetic may, therefore simply uncover previous neurological deficits ¹. In addition, elderly patients are frequently taking multiple medications, which may affect the pharmacokinetics and pharmacodynamics of medications administered during the course of anesthesia.

Structure of the chapter

This chapter will be divided into three parts. In the first, the anatomic areas of the brain that are involved in consciousness will be discussed along with the neurochemical transmitters

and modulators associated with these areas. The functional changes of these areas that occur with normal aging will be discussed, in addition to their possible implications in delayed arousal. In the second, the pharmacology of medications associated with the aging brain will be discussed to the extent that it is known. And, in the third, an algorithm to determine the cause of delayed arousal, with the previous two components in mind will be presented.

Anatomical Correlates of consciousness: Arousal Pathways & The Effect of Normal Aging

Consciousness was historically believed to be a product of the summation of the activity of the human cerebral hemispheres. However, unilateral dysfunction of the cerebral hemispheres does not cause impairment of consciousness, except if the size of the lesion affects other cortical areas or the diencephalon. In the early 1900s, Von Economo noted a type of encephalitis, encephalitis lethargica, that attacked regions of the brain, specifically the midbrain and diencephalon, and disturbed sleep and arousal.² This is consistent with the current view that there are discrete regions of the central nervous system that are essential for consciousness. In the 1940s, Moruzzi and Magoun experimentally localized the ascending arousal system to the paramedian reticular formation in cats. They found that cats were clinically unresponsive even though they could record cortical evoked potentials in response to electrical stimulation from these areas. Subsequent work demonstrated that electrical stimulation of the midbrain reticular formation and central thalamus desynchronized the large-amplitude slow waves recorded by the electroencephalogram (EEG) induced in anesthetized cats.³ These areas have extensive ramifications throughout the cerebrum. Similar mechanisms are thought to exist in humans.

The ascending arousal system in the brainstem consists of two branches: the first is an ascending pathway to the thalamus and cerebral cortex, and the second bypasses the thalamus, activating neurons in the lateral hypothalamic area and basal forebrain (BF), and throughout the cerebral cortex². It is associated with specific neurotransmitters⁴ (Figure 1).

In this section the known neurobiology of arousal, consciousness and the effect of aging will be discussed.

Thalamic Branch of the Ascending Arousal System

Neuroimaging techniques reveal that there is a decrease in regional activity in the thalamus for all anesthetic classes except for propofol, when compared to awake patients (Figure 2). This observation, in addition to clinical observations that midline thalamic damage results in a vegetative state,⁵ supports the hypothesis that the thalamus plays a critical role in consciousness.⁶

The first branch of the ascending pathway involves the midline nuclei and the intralaminar nuclei of the thalamus, which in turn send information to the cerebral cortex. Their input is from cholinergic cells in the pedunculo-pontine and laterodorsal tegmental nuclei⁷. (Figure 1)

Neurons in these areas fire most rapidly during wakefulness and rapid eye movement (REM) sleep⁸. Action potential generation is effected by the state of wakefulness and anesthetics. Intralaminar thalamic neurons show excitability during wakefulness.⁹ Volatile anesthetics decrease acetylcholine levels in the thalamus, reflecting decreased activation of thalamic neurons¹⁰. The effects of anesthetics in the thalamic region can be experimentally localized: γ -aminobutyric acid (GABA) agonists injected into the intralaminar nuclei cause rats to rapidly fall asleep and slow the EEG¹¹ and rats under anesthetic concentrations of sevoflurane can be awakened by a minute injection of nicotine into the intralaminar nucleus of the thalamus¹².

Non-Thalamic Branch of the Ascending Arousal System

The second branch of the ascending arousal system bypasses the thalamus. (Figure 1) It originates from monoaminergic neurons in the upper brainstem and caudal hypothalamus, including the noradrenergic locus coeruleus (LC), serotonergic dorsal (DR) and median raphe nuclei, dopaminergic ventral periaqueductal grey matter and histaminergic tuberomammillary neurons. This pathway activates neurons in the lateral hypothalamic area and basal forebrain, and throughout the cerebral cortex. The input to the cerebral cortex is augmented by lateral hypothalamic peptidergic neurons (containing melanin-concentrating hormone [MCH] or orexin/hypocretin), and basal forebrain neurons (containing acetylcholine or GABA) ².

Clinically, lesions in the lateral hypothalamus and rostral midbrain cause profound sleepiness and coma ¹³. Similar to the neurons in the thalamic pathway of arousal, neurons in the basal forebrain neurons, including most cholinergic neurons, are active during both wake and REM sleep. ¹⁴⁻¹⁶ The monoaminergic nuclei that contribute to the non-thalamic arousal pathway fire most rapidly during wakefulness and slow during non-REM (NREM) sleep. However, they do not fire during REM sleep ¹⁷⁻¹⁹. Melanin-concentrating hormone neurons are active during REM sleep.

The orexin peptides, recently discovered in 1998, are produced in the posterior lateral hypothalamus and are a critical part of the non-thalamic arousal pathway. The orexin system has been of particular recent interest in the anesthesia literature in the understanding of arousal. These neurons are most active during wakefulness ^{13,20,21} and play a significant role in narcolepsy (narcoleptic patients have few orexin neurons and low orexin levels in the cerebral spinal fluid).²²⁻²⁴ Orexin producing neurons have processes which project to the cerebral cortex, as well as to all the monoaminergic and cholinergic cell groups of the arousal systems ²⁵. Two receptors exist for orexins: Orexin receptor 1 preferentially binds orexin A over orexin B, whereas orexin receptor 2 binds both ligands with equal affinity. ²⁶

Orexin agonists decrease the duration or depth of anesthesia as monitored by activation of the EEG in rats anesthetized with isoflurane, and administration of an orexin receptor-1 antagonist increases anesthetic duration.^{27,28} Mice bearing a transgene which results in a degeneration of orexin neurons lead to delayed emergence from anesthesia, but do not change loss of consciousness at induction. In addition to orexin playing a key role in clinical anesthetic emergence, anesthetic administration is associated with decreased orexin neuron activation ²⁹. Anesthetics affect orexin receptor function directly ²⁶, and the function of orexin targets. The full understanding of the non-thalamic arousal pathway, and specifically the role of orexin in emergence from anesthesia, and thus arousal, is yet under investigation.

The Ventrolateral Pre-Optic Nucleus: A “sleep system”

Von Economo noted that a small percentage of patients with encephalitis lethargica had a paradoxical response; rather than being sleepy, they became insomniac. These patients had lesions involving the basal ganglia and adjacent anterior hypothalamus. Using animal studies researchers identified a hypothalamic site involving the lateral pre-optic area where lesions caused similar insomnia ³⁰. This region is called the ventrolateral preoptic nucleus (VLPO). Neurons located here send outputs to multiple cell groups in the hypothalamus and brainstem involved in arousal ³¹ (Figure 3). These neurons have increased activity during sleep, and contain the inhibitory neurotransmitters, galanin and GABA ², which innervate diffuse areas of the brainstem ^{2,20,32-34}.

In turn, these ventrolateral preoptic nucleus neurons receive afferent input from monoaminergic systems ³⁴. Both noradrenaline and serotonin inhibit these neurons ³⁵ In

addition, GABA as well as several other potentially inhibitory peptides such as galanin and endomorphin³⁶ from tuberomammillary neurons³⁷ inhibit ventrolateral preoptic nucleus neurons. However, ventrolateral preoptic neurons do not have histamine receptors or orexin receptors³⁸. Since the ventrolateral preoptic neurons can be inhibited by the very monoaminergic and GABA arousal systems that they inhibit during sleep, Saper has described this as a “flip-flop” relationship, in which the ventrolateral preoptic nucleus and the arousal system inhibit each other; the ventrolateral preoptic nucleus inhibits the orexin system, thereby inhibiting the arousal system.²

The Cortex: “The site of end-effect”

While the ascending arousal system with its wide-spread projections to the thalamus and the cortex is clearly important in arousal and the effects of anesthesia, the cortex also plays an important role in arousal and consciousness. Anesthetics slow cortical oscillatory activity in in-vitro studies independently of subcortical activity.³⁹ In rats, inhaled agents at concentrations inducing hypnosis directly decrease discharge rates of cortical neurons by 50%.⁴⁰ In humans, during induction of general anesthesia, slowing of the EEG occurs earlier and is more prominent, compared to the electrical activity of the midbrain⁴¹. Even with light anesthesia (0.7% isoflurane), the cortical somatosensory response may be suppressed without reducing the thalamic response to painful stimulation⁴². Spontaneous thalamic firing during anesthesia is largely driven by feedback from cortical neurons, thus modulating the response of the ascending arousal system⁴³.

Aging

The speed of arousal is known to decline with aging. The mechanism behind this phenomenon is multifactorial, but most likely it involves physiological changes in the cortical, brainstem and diencephalic systems. The lateral hypothalamus affects orexin neurons, and the basal forebrain complex affects cholinergic, histaminergic, and serotonergic transmission.

Age-related cognitive decline is understood to be accompanied by changes in cortical neuronal morphology⁴⁴. The complexity of apical dendrites decreases with age: there is a loss in the total number (28–37%) and density (~ 23%) of spines⁴⁵. In humans, neocortical synaptic density declines at a constant rate starting during early adulthood⁴⁶. Although the exact consequence of these changes is still under investigation, dendritic changes are believed to alter the post-synaptic effects of neurotransmitters,⁴⁷ and precede other histological changes found in neurocognitive diseases such as Alzheimer’s disease.⁴⁸

Similar to the loss in complexity of dendrites in the cortex, the orexin neurons of the arousal system show a decrease in complexity with normal aging. Down et al. studied the number of orexin neurons in the lateral hypothalamus of rhesus macaques across their entire life span, from prepubertal development to old age⁴⁹. Similar to the primate studies of the cortex, they did not find a decreased number of orexin neurons, but did find a significant loss of orexin axonal density within the locus coeruleus of old macaques, and a concomitant decrease in tyrosine hydroxylase mRNA expression⁴⁹. This data suggest that age-related decreases in excitatory orexin innervation to the noradrenergic locus coeruleus may contribute to the etiology of poor sleep and delayed arousal in the elderly, specifically with implications to emergence from anesthesia²⁹.

During aging, cholinergic neurons of the basal forebrain complex undergo degenerative changes, including cell atrophy, down regulation of choline acetyltransferase activity (ChAT), and mild cellular loss, resulting in cholinergic hypofunction. Neuropharmacological manipulations that increase or decrease the excitability of basal

forebrain cholinergic projections systematically affect attentional performance and cortical acetyl choline (ACh) efflux⁵⁰. There are quite a number and variety of human brain conditions, notably Alzheimer's disease, in which degeneration of basal forebrain cholinergic neurons have been documented. Therefore, cholinergic changes are important in the arousal system and changes with age likely affect emergence from anesthesia.

Histaminergic neurons play an excitatory role in arousal. The levels of histamine and its metabolites are known to increase in human cerebrospinal fluid with age. In addition, there is a age-related decline in histamine-1 receptor binding in the normal human brain,⁵¹ which is thought to be a result of down-regulation of receptors due to high endogenous histamine⁵².

There are limited and conflicting data in the literature regarding changes in the serotonin (5-HT) system in normal aging. Serotonin receptors are more dense at birth than in the mature brain and may regulate the maturation of cortical neurons⁵³. In addition, several post mortem human studies have reported a reduction in the number of cortical 5-HT_{1A}, 5-HT_{1B/D}, and 5-HT_{2A} binding sites with age in frontal lobe, occipital lobe, and hippocampus^{50,54}. Age-related decline in cortical 5-HT_{2A} binding was also found in living healthy subjects demonstrated by positron emission tomography (PET) imaging with [¹¹C]N-methylspiperone, a ligand with affinity for both 5-HT_{2A} and dopamine D₂ receptors^{50,55}. Age-related decrease in excitatory ascending arousal pathway stimulation would correlate with a decrease in arousal, and possibly a slower emergence from anesthesia.

In addition to the decreases in size and activity of the excitatory components of the arousal system, the inhibitory ventrolateral preoptic nucleus is significantly reduced in size with aging^{56,57}. Degeneration of the ventrolateral preoptic nucleus with age could account for the diminished efficiency and depth of sleep in elderly humans. This difference could be marked, as there is a reported 60% loss of galaninergic neurons in aged versus younger rats in a region that appears to include the ventrolateral preoptic nucleus cluster⁵⁸.

The explanation as to why there are changes with aging in specific cellular populations remains unknown. The perturbation of neuronal calcium homeostasis is a possible explanation⁵⁹. Calcium conductance and the number of calcium channels of the L-type in CA1 pyramidal neurons increase with aging⁶⁰. This high intracellular calcium concentration can activate proteases and induce reactive oxygen species production, which may be neurotoxic⁶¹.

Pharmacology

Delayed arousal may also be due to altered responses to pharmacological agents in the geriatric population. This delay may arise from drug-specific pharmacokinetic or pharmacodynamic changes commonly reported in these patients. Whether these differences in pharmacological parameters are truly age-related independent factors or primarily manifestations of coexistent diseases and/or polypharmacy more frequently seen in the elderly is inconsequential. The net result is the same. Exaggerated pharmacological responses and prolonged duration of action are often seen following the administration of drugs in dosages which seem appropriate for the age and gender of the patient.

Pharmacokinetic alterations can be characterized by changes in initial and steady state volumes of distribution, clearance rates, redistribution and elimination half-times. The decrease in initial volume of distribution, V_i , reflects the age-associated decrease in blood volume, which may result a higher than expected initial concentration of drug following an intravenous bolus injection. Changes in steady state volumes of distribution, V_d , are less consistent, such that the increase in body fat, decrease in lean body mass and decreased total

body water will result in an increased V_d for lipophilic drugs and a decrease for hydrophilic drugs. Although an increased V_d is associated with a lower concentration of drug, the elimination of drug is likely to be more prolonged. In addition, the decreased plasma protein binding in the elderly results in an increase in the free plasma concentration for drugs such as midazolam, fentanyl and propofol, which are highly protein bound.⁶²

The aging process is generally accompanied with a gradual decline in organ function.⁶³ While the decrease in renal function resulting from diminished renal blood flow, glomerular filtration and tubular secretion predictably leads to increased serum concentration and prolonged presence of drugs dependent renal excretion, the disposition of drugs dependent on hepatic metabolism is less consistent. Phase II metabolic pathways do not seem to be much affected by age, while the effect of age on phase I metabolism is unclear.⁶⁴ The decrease in liver mass and blood flow in the elderly would predict a delay in the elimination of drugs with a high extraction ratio, such as midazolam, fentanyl and sufentanil. Clinical studies however, have not consistently demonstrated an increased elimination half life.⁶⁵

With the exception of a few drugs whose behavior can be described by a one compartment model, classical pharmacokinetic parameters are not accurately predictive of the rate of decrease of drugs from the central compartment. Thus, although the elimination half life of sufentanil is much greater than fentanyl (9.5 vs. 3.7 h), sufentanil is more rapidly cleared from the circulation, at least after prolonged (> 2h) infusions. The triexponential function derived from 3-compartment models characterizing the elimination of most agents administered in the course of anesthesia are descriptive of a scenario where distribution-redistribution between the fast and slow compartments may be the primary factor affecting the disappearance of drug from the central compartment. The complex interaction between compartment sizes, clearance and intercompartmental rate constants is well characterized by the “context sensitive half-time”.⁶⁶ The premise of the context sensitive half-time is that with large doses or long infusions drug eliminated from the central compartment may be rapidly replaced by drug redistributing from the slow peripheral compartments, thus hindering the decline in central compartment drug concentration. Thus, context sensitive half-time estimates the amount of time for the concentration of drug to fall by 50% in the context of the duration of the drug infusion.

Despite providing an improvement over elimination half-life, context sensitive half-time does not fully explain recovery from anesthesia.⁶⁷ Contributory factors to this problem include the fact that any selected infusion regimen is likely not to reliably yield a constant targeted plasma concentration. In addition, it is rather unlikely that recovery occurs at exactly 50% of the concentration at the end of the infusion.

Although the pharmacokinetics of anesthetic drugs in the elderly has been extensively studied, pharmacodynamics in the elderly has not received equal attention. The presence of pharmacodynamic alteration is often surmised by the observation of an exaggerated or prolonged effect for a drug for which pharmacokinetic studies failed to discern any difference between age groups. There is a paucity of studies that examine the relationship between measured plasma concentration or modeled effect compartment concentration and clinical effect.⁶⁸ Clinical experience, nonetheless has demonstrated that the elderly are more sensitive to anesthetics, with the consensus opinion that for most agents this effect is primarily, or at least in part, due to pharmacodynamic changes.

Factors invoked to explain pharmacodynamic changes include altered receptor density and binding, changes in signal transduction and impaired cellular responses.⁶⁹ As a result of or in addition to these factors, the elderly exhibit a decrease in homeostatic mechanisms. Any

drug induced perturbation may be longer lasting, requiring a greater length of time for restoration of the steady-state.⁷⁰

For drugs such as anesthetics where the primary effect is binary, i.e. awake versus asleep, or movement versus no movement, the pharmacodynamic response is best defined by the Hill equation:

$$P = 100 \cdot C^\delta / (C^\delta + C_{50}^\delta),$$

where P is the probability of effect (0 to 100%), C is the plasma concentration and C₅₀ is the concentration at which 50% of subjects exhibit the desired effect. A plot of the Hill equation, dose or plasma concentration against probability of the desired effect, yields a sigmoid curve. The steepness of the curve is defined by the variable delta (δ). When delta is large, as for example, alfentanil and sufentanil, the curve is steep, such that most patients can be expected to respond at doses near the C₅₀. Conversely, smaller values of delta, as for example, propofol and midazolam, are associated with greater variability, with the therapeutic response, as well as the termination of the therapeutic effect occurring at a more variable and less predictable plasma concentration (Figure 4).⁷¹

Combining pharmacokinetics and pharmacodynamics, intuition would dictate that for a drug with a steep delta, one would know with relative certainty what concentration of drug would be required for the desired effect. Presumably, it might, for illustrative purposes, be assumed that 50% of this concentration could be associated with a 5% probability of this effect, thereby implying that 95% of patients will have recovered at that point. In this simplified example, context sensitive half-time and C₅₀ could give a good approximation as to how long recovery should take. The true situation is more complicated. C₅₀ might be greatly decreased in the elderly patient, while delta might be smaller, consistent with the wide variability of response that can be seen in this group. For example, C₅₀ for propofol is 47% lower in elderly patients compared to young adults, in conjunction with a lower value for delta.⁷² Similarly, it has been demonstrated that elderly patients require approximately 40% less propofol to maintain a constant predetermined EEG endpoint.⁷³ Thus, the selected dose may be inappropriately large, such that recovery might not occur until plasma concentration falls by 90%. In this situation the context sensitive half-time is not clinically significant. A more accurate predictor in this situation would be the 90% decrement time in the context of the length of drug infusion.⁷⁴

Recovery from inhaled anesthetics may be used as an illustrative example, in that context sensitive half-time has been used to describe the pharmacokinetics of these agents.⁷⁵ In addition, at least in the steady state, the measured alveolar concentration provides a readily measured estimate of the effect compartment concentration.

The minimal alveolar concentration of potent inhalational agents at which 50% of patients do not respond to surgical stimulation (MAC) decreases roughly 6.7% per decade from the MAC value of 40 year old adults. The concentration required to attain a given EEG endpoint is similarly decreased.⁷⁶ MAC-Awake, the alveolar concentration at which patients obey commands, also decreases with age, although the ratio of MAC-Awake to MAC seems to remain the same throughout different age groups. MAC-Awake, on average is approximately one-third of MAC (Figure 5).⁷⁷ Clearly in a situation where the inspired or end-tidal concentration of inhaled anesthetic is set for 1 MAC, as displayed by most anesthesia machines (not age-adjusted), a decrement of 50% predicted by the context-sensitive half-time has little relevance to the expected time for awakening. In this situation, the 90% decrement time, the time for the anesthetic concentration to fall by 90%, would be a

more appropriate predictor. It should be noted however, that the effect of context, i.e. length of drug administration has a greater effect on the 90% decrement time than it does for the context-sensitive half-time. Although the context-sensitive half-time is small and relatively unchanged throughout a wide range of exposure times for all inhalational agents as seen in figure 6 the changes in 90% decrement time are quite remarkable⁷⁵. Even with the “shorter acting” agent, sevoflurane, where there is little change in decrement times during the first 90 minutes of exposure, additional exposure results in a marked increase in 90% decrement times. As a result, awakening times in excess of one hour may occur after a 6 hour exposure.

Hence, the combined effects of pharmacokinetic and pharmacodynamic changes in elderly patients may variably and unpredictably prolong arousal time.

Algorithm for Approaching A Patient with Delayed Arousal

The work-up for delayed arousal must address the multiple possible causative factors: functional abnormalities that occur naturally with aging, structural abnormalities such as focal lesions in specific areas of the brain or diffuse cortical problems such as multi-focal injuries, and metabolic disturbances of common electrolytes or pharmacological agents. These metabolic problems may be due to toxic effects or to changes in pharmaco-kinetic or -dynamic issues. Work-up of each of these problems requires a different solution.

Determining the etiology of “delayed arousal” will require clinical, chemical and structural tests. We are using the term “structural” to refer to physical processes such as hemorrhage either subarachnoid or epidural, or ischemia or infarction. In this section we shall review the tools to diagnose the cause of delayed arousal.

In general, focal or multi-focal lesions can be identified by instruments that define structural abnormalities. Therefore computerized tomography (CT), or magnetic resonance imaging (MRI), or derivatives of MRI such as diffusion weighted imaging (DWI) are useful to define the area of injury, since ischemia can be detected within 5–10 minutes.

Computerized tomography

Computed tomography (CT) is a medical imaging method employing X-ray radiation and tomography. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.

A CT scan of the head without contrast can be useful to determine whether the patient has had an intra-cranial hemorrhage. Unfortunately, cerebral ischemia is poorly visualized by CT scan with contrast because it takes 5–7 days to become manifest.

Magnetic resonance image

MRI scans can determine old and new focal infarcts and even ischemia within minutes using DWI^{78,79}. A negative CT scan or MRI image may rule out a large mass lesion produced by intra-cerebral hemorrhage or areas of ischemia when viewed by DWI. Should there be evidence of cerebral ischemia, then it may be necessary to perform a cerebral angiogram to re-establish cerebral perfusion.

MRI does not use x-ray radiation. Rather, MRI is based on the aligning the proton of the hydrogen ion in water in the presence of a strong magnetic field. A second magnetic field is used to perturb this orientation and energy is released as a photon when the field is turned off. Gradient fields are turned on and off and complicated sequences can be performed to reveal structural and chemical properties of areas of the brain. The basic parameters of

image acquisition are produced by varying particular values of the *echo time* (TE) and the *repetition time* (TR), which can take on the property of T2-weighting. On a T2-weighted scan, water- and fluid-containing tissues are bright and fat-containing tissues are dark. The reverse is true for T1-weighted images. With an additional radio frequency pulse and additional manipulation of the magnetic gradients, a T2-weighted sequence can be converted to a FLAIR sequence, in which free water is now dark, but edematous tissues remain bright.

There are also specialized MRI scans. Diffusion MRI produces images in which the contrast between tissues is dependent on differences in microscopic water diffusion. In free space, water diffuses at random by Brownian motion. But in biological tissue, it is restricted in its free motion. In the brain, water diffusion rates are lowest in white matter, higher in gray matter and highest in CSF. White matter also shows prominent diffusion anisotropy, with more rapid diffusion parallel to the orientation of axons along white matter tracts. In pathological tissue, the lowest diffusion rates are seen in acute infarction (restricted intracellular diffusion), with higher rates in chronic infarcts and reactive interstitial edema such as that associated with tumors, infection or trauma (more freely diffusing extracellular water), and highest rates in CSF-filled cystic collections such as surgical cavities or arachnoid cysts (unrestricted diffusion in unstructured water). These different water diffusion properties are depicted in two ways. The directly acquired diffusion-weighted images (DWI) show low diffusion rates as high signal and high diffusion rates as low signal. After processing these images, quantitative apparent diffusion coefficient (ADC) maps are created which show low diffusion rates as low signal and high diffusion rates as high signal

80.

Seizures

Status epilepticus may impair consciousness. Elderly patients have increased probability of having previous cerebral infarcts which may not even be evident to the patient, or new ischemic events arising intra-operatively. These may predispose them to have either seizures which may be focal with secondary generalization, or seizures that are generalized in nature. Some of these seizures may not have a motor component (non-convulsive) and therefore are manifest solely as impaired consciousness. These seizures can be precipitated by metabolic abnormalities that lower seizure threshold and predispose patients to status epilepticus.

Electroencephalography

Functional tests such as electroencephalography can determine rhythms such as burst suppression consistent with persistent sedative-hypnotic medication, or cerebral rhythms associated with hepatic encephalopathy that may narrow the differential diagnosis.

The electroencephalogram can also be used to evaluate altered states of consciousness⁸¹⁻⁸³. However, this evaluation should be performed by a trained electroencephalographer using a full EEG montage because many artifacts including muscle action potentials, which are on the order of a thousand fold larger in amplitude than cortical activity recorded from the scalp, can confuse interpretation of the electrophysiological signal. Diffuse slowing of background rhythms and the presence of triphasic waves suggest metabolic dysfunction particularly hepatic (Figure 7) or renal; spindle coma patterns are believed to indicate dysfunction at the brainstem level⁸³. Generalized fast activity may be seen with drug intoxication. And, most significantly, non-convulsive status epilepticus can be diagnosed under conditions when it is least expected. There are a number of electroencephalographic patterns for non-convulsive status epilepticus (Figures 8-9)⁸¹. Many of these patterns are controversial: periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs (BIPLDs) (Figure 8), periodic epileptiform discharges (PEDs) which can be focal or generalized, and generalized triphasic waves. Unfortunately, most of these patterns are

not specific for a single etiology. For example, both hypoxia and our commonly used sedative-hypnotic medications such as propofol, etomidate or thiopental can produce burst-suppression⁸¹.

Metabolic

A number of metabolic abnormalities impair consciousness. Most should be evident before surgery, but can be exacerbated during the course of surgery. By definition, these disorders are diffuse, however, some present with focal findings. One example is diabetes mellitus. Elderly patients are more likely to develop type 2 diabetes mellitus. A high percentage of patients with diabetes are poorly controlled^{80,84}. Patients who present out of control with high serum glucose concentrations may be in diabetic ketoacidosis. Some of these patients may develop focal neurologic findings via mechanisms that are not completely understood^{85,86}. On the other hand, since there is increasing use of insulin infusions to control serum glucose levels during surgery, it is likely more and more patients will become hypoglycemic during surgery. Hypoglycemia has become a bigger problem as treatment protocols for diabetes mellitus have attempted to control serum glucose levels closer to normal⁸⁷. Both of these extremes, hyper- and hypo-glycemia can impair consciousness.

Electrolytes

Resting membrane potential, action potentials and their generation are controlled by both extra- and intra-cellular electrolyte concentrations. Many medications have effects on electrolyte concentrations. For example, diuretics are considered first-line medications for treatment of hypertension⁸⁸⁻⁹¹, a condition common in the elderly. Chronic use of diuretics may lead to total body depletion of potassium. Since potassium is primarily an intra-cellular electrolyte, hypokalemia may be difficult to reverse acutely. Similarly divalent cations such as magnesium and manganese may have profound effects on the nervous system.

Workup

The work up has to be targeted to the likely cause of delayed arousal. A thorough knowledge of the patient's medical history, medications and nature of the surgical procedure is essential. The timeline of the work-up of delayed arousal is highly variable and depends on the clinical scenario in which we encounter the patient, as well as clinical judgment concerning the differential diagnosis. For example, in the patient who has undergone a carotid endarterectomy in which minimal medication was administered, the time threshold to explore a possible ischemic cause of delayed arousal is very short. In contrast, for the elderly patient with a prior history of organ dysfunction who has undergone a long procedure and has arrived at the recovery area at a low temperature after receiving a higher dose of medications, a longer time threshold is tolerated, as we consider a probable metabolic cause.

To the degree that it is possible, a neurological examination should be performed immediately including the cranial nerves, as well as the motor and sensory pathways. Frequently, little information can be derived.

The most common cause of delayed arousal is due to "overdose of a sedative-hypnotic" medication. A number of medications to reverse narcotic and benzodiazepine overdose are available and should be tried. However, should these fail, then a systematic review of other metabolic and structural possibilities needs to be performed (Figure 10).

Metabolic considerations can be immediately and some easily determined by an electrolyte panel including sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, and

glucose. Other electrolyte tests may take longer to be reported such as magnesium, manganese, lactate, elevated liver function tests, etc.

Based on the procedures that the patient had, and the clinical differential diagnosis, an evaluation of structural causes should be looked into that includes MRI with diffusion weighted imaging or CT scan. Based on the findings from this study, cerebral angiography may be necessary.

Because most of our anesthetics have context sensitive half-times, elimination of medications may be significantly prolonged. This fact alone makes it difficult to provide an exact time-line of which steps to take at which exact point in time. Instead, we have provided an algorithm to focus on the work-up of delayed arousal, with attention to the fact that the elderly population has a high variability in many different characteristics, including arousal.

Summary

Elderly patients have medical and psychological problems affecting all major organ systems. These problems may alter the pharmacokinetics and/or pharmacodynamics of medications, or expose previous neurological deficits simply due to sedation. Delayed arousal, therefore, may arise from structural problems that are pre-existent or new, or metabolic or functional disorders such as convulsive or non-convulsive seizures. Determining the etiology of “delayed arousal” may require clinical, chemical and structural tests. Structural problems which impair consciousness arise from a small number of focal lesions to very specific areas of the central nervous system, or from pathology affecting the cerebrum. In general, focal or multi-focal lesions can be identified by computerized tomography, or diffusion weighted imaging. An algorithm is presented that outlines an approach to working up an elderly patient with delayed arousal.

Acknowledgments

EJH was supported in part by Grant No. RO1-AG16404 from the National Institutes of Health.

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Figure 1.

The ascending arousal system in the brainstem consists of two branches: the first is an ascending pathway to the thalamus and cerebral cortex (yellow), and the second bypasses the thalamus, activating neurons in the lateral hypothalamic area and basal forebrain, and throughout the cerebral cortex (red).

Figure 2.

The regional effects of anesthetics on brain function are shown in humans who were given various anesthetic agents at doses that produced loss of consciousness. The data are a composite of results from different groups of investigators and encompass the study of eight different agents. All images show regional decreases in activity caused by anesthesia compared to the awake state, except the propofol correlation image, which shows where increasing anesthetic dose correlates with decreasing blood flow. The suppressive effects on the thalamus is a common anesthetic effect.

Figure 3.

The ventrolateral preoptic nucleus projects to the monoaminergic nuclei (red), including the tuberomammillary nucleus (TMN), the raphe cell groups and the locus coeruleus (LC). It also innervates neurons in the lateral hypothalamus (green), including the perifornical (PeF) orexin (ORX) neurons, and interneurons in the cholinergic (ACh) cell groups (yellow), the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT).

Figure 4.

The relationship between delta and the recovery from an infusion of fentanyl maintaining a constant concentration of 10 ng/ml for 60 minutes. Recovery in 50% of patients (C_{50}) is assumed to occur at concentration of 5 ng/ml. If $\delta = 10$, almost all patients recover at a concentration of 5 ng/ml at roughly the context-sensitive half-time (approximately 23 min.). However, when $\delta = 2$, the mean effect time, derived by integrating the probability of effect curve rises to 130 minutes, with approximately 10% of patients not recovering for 5 hours. From: Bailey JM: Technique for quantifying the duration of intravenous anesthetic effect. *Anesthesiology* 83:1095–1103, 1995

Figure 5.

Age related changes in MAC of inhalational anesthetics, normalized to MAC at 40 years of age. From: Eger EI, 2nd: Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. *Anesth Analg* 93:947–53, 2001

Figure 6. Context-sensitive 50%, 80% and 90% decrement times for inhalational anesthetics. Note that context-sensitive half-time is analogous to context-sensitive 50% decrement time. From: Bailey JM: Context-sensitive half-times and other decrement times of inhaled anesthetics. *Anesth Analg* 85:681–6, 1997

Figure 7.

Triphasic waves occurring in clusters are evident in the EEG of a patient with hepatic encephalopathy. Electrodes are placed in the 10–20 International electrode convention. All electrodes are referred to C_Z . The electrode positions are in pairs, left then right, from midline anterior to posterior in the upper 10 traces, and from lateral anterior to posterior in the lower 8 traces. Reprinted by permission from Brenner RP. EEG in Encephalopathy and Coma. *American Journal of Electroneurodiagnostic Technology* 2003;43(3):164–184.

Figure 8.

BIPLEDs are evident in the EEG in patient with prolonged hypoglycemia. Electrodes are placed in the 10–20 International electrode convention. The electrodes are arranged in a bipolar montage. The first and third set of 4 electrodes are on the left side of the head, and the second and fourth set of 4 electrodes are on the right side of the head. Within each set the electrodes are arranged anterior to posterior with the first and second sets representing midline electrodes, and the third and fourth sets representing lateral electrodes. The bottom 2 electrode pairs are F_z to C_z , and C_z to P_z . Reprinted by permission from Brenner RP. EEG in Encephalopathy and Coma. American Journal of Electroneurodiagnostic Technology 2003;43(3):164–184.

Figure 9.

Generalized non-convulsive status epilepticus in the EEG in patient following cerebral anoxia. Electrodes are placed in the 10–20 International electrode convention. Electrodes are placed in the 10–20 International electrode convention. The electrodes are arranged in a bipolar montage. The first and third set of 4 electrodes are on the left side of the head, and the second and fourth set of 4 electrodes are on the right side of the head. Within each set the electrodes are arranged anterior to posterior with the first and second sets representing midline electrodes, and the third and fourth sets representing lateral electrodes. The bottom 3 electrode pairs are F_z to C_z , and C_z to P_z with the bottom trace the electrocardiogram (ECG). Reprinted by permission from Brenner RP. EEG in Encephalopathy and Coma. American Journal of Electroneurodiagnostic Technology 2003;43(3):164–184.

Figure 10.

An algorithm to work-up a patient with delayed arousal. CT, computerized tomography; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; LFT, liver function tests; Mg, magnesium levels; Mn, manganese levels; and EEG, electroencephalogram.