Depth of anesthesia: EEG findings

Advanced, Organ-Based and Clinical Sciences

A full 16-lead, 8-channel electroencephalogram (EEG) is a recording of the electrical activity/potentials occurring in the cerebral cortex and can be used to monitor depth of anesthesia. EEG activity occurs mostly at frequencies between 1-30 Hz and can be broadly categorized into 4 wave patterns: alpha, beta, theta, and delta. Alpha waves, with a frequency of 8-14 Hz, are found in a relaxed but alert patient (i.e. resting with eyes closed). Beta waves, with a frequency of 14-30 Hz, are found in a highly alert and focused patient. Theta waves, with a frequency of 4-8 Hz, are found in the first stage of sleep or during “light” anesthesia. Delta waves, with a frequency of 0.5-4 Hz, are found in a deep sleep or “deep” anesthesia.

A BIS monitor processes two-channel EEG signals and examines 4 components associated with the anesthetic state: high frequency beta activation found during light anesthesia, low frequency delta waves found during deep anesthesia, suppressed EEG waves, and burst suppression.

EEG and BIS findings (~with example reading) in different patient states are summarized below.

Awake : EEG shows very high frequency, very low amplitude beta > alpha waves. BIS reveals high beta ratio (~96).

Sedated : EEG shows high frequency, low amplitude alpha/theta > delta waves. BIS reveals low beta ratio (~78).

Unresponsive : EEG shows spindles, K complexes, and alpha/theta/delta waves. BIS reveals bispectral coherence (~52).

Surgically anesthetized : EEG shows slow delta wave predominance. BID reveals bispectral coherence (~42).

Deeply anesthetized : EEG shows burst suppression and isoelectricity. BIS reveals high burst suppression ratio (~8).

EEG: high dose opiates

Pharmacology, Physiology - Neurologic

Opioids produce a dose related decrease in the frequency and amplitude of the EEG.

Low dose opioids show a loss of beta waves and a slowing of alpha waves.

Moderate dose opioids show diffuse theta waves and some delta waves.

High dose opioids show delta waves (high amplitude, 0-4 Hz) . See [Delta Waves]https://en.wikipedia.org/wiki/Delta_wave on Wikipedia.

Unlike with volatile gases, barbituates, and propofol, **complete isoelectric EEG waves cannot be obtained, even with high dose opioids.**

Sources

Keys to the Cart: January 22, 2018; a 5-minute video review of ABA Keywords

Awareness: Equipment issues

Awareness results partly from the inability to accurately measure the depth of anesthesia. There is no monitor that can guarantee no intraoperative awareness/recall. It is primarily subjectively judged by observing trends in heart rate, blood pressure, lacrimation, and movement. Level of consciousness monitors (depth of anesthesia monitors) can also be helpful, especially in certain patients and when using certain anesthetic techniques (i.e. TIVA).

In general, there are four causes:

1. Individual variability in dose requirements for anesthetic drugs (genetics, drug habits: benzodiazepines, cocaine, EtOH)
2. Patient inability to tolerate full anesthesia due to low physiologic reserves (heart failure, hypovolemia)
3. Iatrogenic masking of physiologic responses that would indicate the need for an anesthetic dose change (use of beta-blockers or the presence of pacemaker)
4. Compromised delivery of anesthetic due to equipment malfunction or misuse (broken vaporizer, disconnected circuit/IV line/leak)

Patient risk factors contributing to increased likelihood of intraoperative awareness include age, limited cardiac reserve, drug resistance or substance abuse, history difficult intubation or previous episodes of intraoperative awareness.

Surgical procedures related to increased risk of intraoperative awareness: C-section, cardiac surgery, trauma surgery, and procedures for which muscle relaxants are used

3 categories of depth of anesthesia devices for awareness: measure EEG (BIS), auditory evoked potentials (BAEPs), scalp EMG activity. There is no empiric data to suggest that these monitors are superior to preventing awareness than simply keeping patient >0.7 MAC of end-tidal inhaled anesthetics during routine general anesthesia cases. Various styles of anesthetics or physiologic changes (cerebral

ischemia, hypoperfusion, NMBDs, ephedrine, elderly with low amplitude EEG) can also affect the sensitivity/specificity of readings on these monitors. These monitors probably have the most utility in cases where patients are at increased risk for intraoperative awareness

Aging: Volatile agents & EEG changes

Advanced, Basic Sciences, Statistics

EEG changes with volatile anesthetics

Use of EEG in preventing Post-Operative Delirium

A question-based tutorial on EEG findings under general anesthesia can be found here:

http://www.openanesthesia.org/learn-about-eeg-for-anesthesia-and-earn-cme/

A very complete series of lectures on EEG and anesthesia can be found here:

http://icetap.org

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[PubMed: 25928189]

Barbiturate enzyme induction

Barbiturates (except for the less-soluble phenobarbital) are mainly metabolized by the liver into inactive, water-soluble compounds by oxidation and then are renally excreted or conjugated to glucuronic acid and excreted in bile. The most significant aspect of the metabolism of barbiturates (e.g., phenobarbital, thiopental, methohexital) is their effect on the hepatic microsomal enzyme system (cytochrome P450 (CYP) enzymes). These effects are dependent on the duration of exposure to the barbiturate. Acutely, barbiturates interact with various CYPs and inhibit the biotransformation of other CYP substrates; likewise, other substrates (e.g., other drugs or endogenous substrates) can inhibit the barbiturate metabolism. Chronic use of barbiturates will cause upregulation, or induction, of the microsomal enzymes (CYPs 1A2, 2C9, 2C19, and 3A4), increasing the metabolism of drugs metabolized by these enzymes. This can lead to patients requiring larger dosages of medication to achieve therapeutic effect and/or increased clearance. This enzyme induction also causes barbiturate tolerance due increased barbiturate metabolism. In addition, barbiturates induce other enzymes, notably δ-aminolevulinic acid (ALA) synthetase. ALA synthetase is involved in the porphyrin production pathway, and therefore barbiturates are contraindicated in patients with acute intermittent porphyria (AIP) or variegate porphyria because they may precipitate an attack, manifested by severe

abdominal pain, nausea, vomiting, psychiatric disorders, and neurologic abnormalities.

Sources

Goodman & Gilman's the Pharmacological Basis of Therapeutics. 12th ed.

Miller's Anesthesia, 7th ed.

Barbiturates: PK in the elderly

Advanced, Clinical Subspecialties

Pharmacokinetics – or what the body does with a drug – involves drug absorption, volume of distribution, metabolism (and half-life), and clearance. Phenobarbital is rapidly absorbed orally, is metabolized in the liver by oxidation primarily via CYP2C9, and is ultimately excreted primarily in the urine and minimally in the feces. Regarding the pharmacokinetics of phenobarbital in the elderly, a study published in 2005 examined clearance values in 224 patients aged 65-90 years old and found that serum levels of phenobarbital were equivocal in the elderly vs. non-elderly patients (aged 20-50 years old); however, the clearance to bioavailability (CL/F) values were on average 22% lower in the elderly patient group. Thus compared to the non-elderly, elderly patients require lower doses of phenobarbital to achieve a similar serum concentration.

Of note, this study demonstrated some variability between individuals, and thus certain data did not reach statistical significance. Interestingly, the coadministration of other antiepileptic drugs (specifically carbamazepine and phenytoin) also plays a significant role in reducing phenobarbital clearance in the elderly. Overall the likely explanation for reduction in clearance in the elderly is a physiologic decrease in GFR – and thus decreased excretion of both metabolized and unchanged drug – as well as decreased hepatic metabolism by CYP2C9.

Sources

Epilepsia;2005 Mar;46(3):372-7

Hypoglycemia: Glucagon

Physiology - Endocrine/Metabolic

Background : Glucagon was originally thought to be a "contaminant" that caused hyperglycemia found in pancreatic extracts in studies from 1923. Looking for the

hyperglycemic mechanism of this “contaminant” led to the nobel prize-winning discovery of cyclic adenosine monophosphate (c-AMP) in the 1960s. Full understanding of this hormone did not come until the 1970s, when somatostatin was discovered and found to inhibit the action of Glucagon.

Glucagon is a peptide hormone, synthesized and secreted by Alpha cells of the pancreas. Its main action is to stimulate glycogenolysis, i.e. release of stored glucose (glycogen) from the liver. It also inhibits glycogen synthesis thus averting further storage of glucose in the liver, and increases gluconeogenesis in the liver from protein and fat. Other actions include transiently paralyzing the smooth muscles of the intestines. After a 12-16 hour fast, arterial and venous concentrations range between 25 and 150 pg/ mL and, the normal human pancreas contains approximately 700- 1000 micrograms of glucagons.

Manufacturing : Synthetic Glucagon is manufactured by genetically engineering E. coli. It is prepared as a powder and freeze-dried.

Route : IV, IM, SQ

Preparation : It is administered by mixing with 1mL of glycerin.

Dosage : [Children < 44 pounds] 0.03-0.1 mg/kg/dose IV/IM q20min prn; not to exceed 0.5 mg/dose; not to be administered at concentrations >1 mg/mL. [Adults & Children >44 pounds] 1mg (1unit). After mixing, the solution should appear clear and without floating particles and should not be discolored. Metabolism: Kidney (23-39%) > Liver. ↓ catabolism of Glucagon seen in renal failure and starvation. No changes seen in diabetics or liver disease.

Major Stimulation of Glucagon Secretion : Hypoglycemia, exercise, trauma, infection, and other stress. Hypoglycemia both directly (stimulates Alpha cells) and indirectly (↓ insulin secretion which otherwise tonically inhibits Glucagon) increases Glucagon release. Other contributions come from: NorEpi (autonomic adrenergic), acetylcholine (cholinergic), and peptidergic neural & epinephrine (adrenomedullary signals). ***In Diabetics (type 1&2), alpha cells can become dysfunctional and not secrete Glucagon in response to hypoglycemia, predisposing diabetics to severe hypoglycemia. Similar problems occur in chronic pancreatitis and in pts s/p pancreatectomy.

Interactions : Effects of anticoagulants may be enhanced by glucagon (although onset may be delayed); monitor prothrombin activity and for signs of bleeding in patients receiving anticoagulants; adjust dose accordingly.

Pregnancy : B- no studies in pregnant women, some risk seen in animals.

Side effect : N/V

Contraindications : Not to be administered to patients with little to no glycogen stores: starvation (including chronic alcoholics), adrenal insufficiency, pheochromocytomas or chronic hypoglycemia.

Mechanisms of Action : [figure needed]

Effects : Glucagon dose, in appropriate patients, will produce maximal glucose effects 5-20min (IV) and approximately 30 min for IM/ SQ.

TPN discontinuation complications

Definition

TPN is usually slowed or discontinued prior to anesthesia, primarily to avoid complications from excessive (hyperosmolarity) or rapid decrease (hypoglycemia) in infusion rates in the busy operative arena. That said, because **abrupt discontinuance may lead to severe hypoglycemia, TPN must be turned down gradually.**

According to Miller (Chapter 35), Dr. Michael F. Roizen has adopted the following: “Infusion of TPN or enteral nutrition is reduced beginning the night before surgery, and a 5% or 10% dextrose solution is substituted preoperatively. If serum glucose, phosphate, and potassium concentrations (measured preoperatively) are abnormal, they are restored to within normal limits. Strict asepsis is maintained. Conversely, one should continue infusing the TPN solution by using a pump system or enteral nutrition while strictly maintaining its normal rate and asepsis, administering all fluids through a different intravenous site, and performing a rapid-sequence induction of anesthesia (for those who received enteral nutrition).”

Similar Keyword: TPN discontinuation — hypoglycemia

Subspecialty

Critical Care and Trauma

Related Media

TPN: Respiratory quotient

Definition

Respiratory quotient is the ratio of VCO_2 and VO_2 (carbon dioxide production). In other words: RQ = CO_2 eliminated/O_2 consumed. It is used in calculations of basal metabolic rate (BMR). Under typical metabolic conditions with stable respiratory function, the range of RQ in human metabolism is approximately 0.7 to 1.0. A value of 1.0 is consistent with pure carbohydrate oxidation, whereas a value of 0.7 is consistent with pure fat oxidation. Measurement of RQ in patients on TPN is important for two reasons: prevention of fat accumulation in the liver and alleviation of potential respiratory distress secondary to excess glucose. So the key is to keep the RQ somewhere between those two values.

TPN: metabolic effects

Definition

Phosphorus

Hypophosphatemia (defined as phosphate <2.5mg/dL) is **reported in 17-28% of critically ill patients**. It can result from increased renal excretion of phosphate, decreased absorption by the

GI tract, or **most commonly, an increase in intracellular movement of phosphate**. Phosphate < 1.0 mg/dL may also lead to hemolytic anemia, heart failure, tachypnea, CNS symptoms (including seizures), and death.

Risk of hypophosphatemia is one of the reasons why parenteral regimens are advanced slowly for the first few days. **ALWAYS replete PO4, K, Mg prior to starting TPN.**

Other Electrolytes

All electrolytes should be assessed with some frequency in these patients (especially magnesium and potassium).

Glucose

Glucose loading, as occurs with administration of TPN, results in intracellular glucose movement. As TPN is instituted, glucose transport and oxidative phosphorylation acutely increase, resulting in increased demand for intracellular phosphate to support the formation of ATP.

Refeeding Syndrome

Refeeding syndrome results from rapid changes in fluids and electrolytes when initiating nutrition in previously malnourished patients. As mentioned above, patients who suffer from refeeding syndrome are usually *hypophosphatemic*, as well as *hypomagnesemic* and *hypokalemic*. TPN can exacerbate these conditions, especially secondary to glucose loading (leading to hypophosphatemia, as described above, as well as insulin release and worsened hypokalemia). It is primarily the result of hypophosphatemia and can lead to impaired myocardial contractility and cardiovascular collapse, as well as respiratory failure, rhabdomyolysis, seizures, delirium, and death.

In patients with marginal extracellular phosphate levels, hypophosphatemia can rapidly develop. Hypophosphatemia may be responsible for the progressive weakness and inanition that characterizes “refeeding syndrome.” Many of these patients will develop **glucose intolerance and hyperglycemia**.

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Peripheral TPN complications

Definition

Solutions: Many solutions are commonly used. Electrolytes can be added to meet the patient’s needs. Patients who have renal insufficiency and are not receiving dialysis or who have liver failure require solutions with reduced protein content and a high percentage of essential amino acids.

- For patients with heart or kidney failure, volume (liquid) intake must be limited
- For patients with respiratory failure, a lipid emulsion must provide most of non-protein calories to minimize CO2 production by carbohydrate metabolism.
- Neonates require lower dextrose concentrations (17 to 18%).

Beginning TPN administration: Require CVP line Solution is started slowly at 50% of the calculated requirements, using 5% dextrose to make up the balance of fluid. Energy and nitrogen should be given simultaneously. The amount of regular insulin given (added directly to the TPN solution) depends on the blood glucose level; if the level is normal and the final solution contains the usual 25% dextrose concentration, the usual starting dose is 5 to 10 units of regular insulin

Complications: With close monitoring by a nutrition team, the complication rate may be < 5%..

1.Glucose abnormalities are common. a. Hyperglycemia can be avoided by monitoring blood glucose b. Hypoglycemia can be precipitated by suddenly discontinuing constant concentrated dextrose infusions. Treatment, depending on the degree of hypoglycemia, may consist of 50% dextrose IV or infusion of 5 or 10% dextrose for 24 h before resuming TPN via the central venous catheter.

2.Abnormalities of serum electrolytes and minerals Elevated BUN may reflect dehydration, which can be corrected by giving free water as 5% dextrose via a peripheral vein.

3. Volume overload

4. Metabolic bone disease, or bone demineralization (osteoporosis or osteomalacia), develops in some patients receiving TPN for > 3 mo. The mechanism is unknown

5. Adverse reactions to lipid emulsions (eg, dyspnea, cutaneous allergic reactions, nausea, headache, back pain, sweating, dizziness)

- are uncommon
- can occur if lipids are given at > 1.0 kcal/ kg/h.

6. Hepatic complications – liver dysfunction, painful hepatomegaly, and hyperammonemia. – Contributing factors probably include cholestasis and inflammation. Progressive fibrosis occasionally develops. Reducing protein delivery may help. Painful hepatomegaly suggests fat accumulation; carbohydrate delivery should be reduced. Hyperammonemia can develop in infants. Signs include lethargy, twitching, and generalized seizures. Correction consists of arginine

7.Gallbladder complications include cholelithiasis, gallbladder sludge, and cholecystitis. These complications can be caused or worsened by prolonged gallbladder stasis. Stimulating contraction by providing about 20 to 30% of calories as fat and stopping glucose infusion several hours a day is helpful. Oral or enteral intake also helps. Treatment with metronidazole

Periop Insulin – Effects

Definition

Surgery and anesthesia lead to a metabolic stress response that causes alterations in the homeostatic mechanisms involved in glucose control. This is particularly true in patients with baseline alterations in glucose management. The stress response includes the release of epinephrine, norepinephrine, cortisol, glucagon, and growth hormone along with inhibition of insulin secretion and action. There is also a negative effect on pancreatic b-cell function causing plasma insulin levels to fall and impairment of insulin secretion in response to glucose. Both the anabolic and anti-catabolic effects of insulin may be attenuated or reversed shifting toward perioperative hypercatabolism.

Anabolic Action of Insulin

1. Stimulation of glucose uptake and glycogen storage in skeletal muscle
2. Stimulation of amino acid uptake and protein synthesis in skeletal muscle
3. Stimulation of fatty acid synthesis in the liver and storage in fat cells
4. Renal sodium absorption and intravascular volume preservation

Anti-catabolic Action

1. Inhibition of hepatic glycogen breakdown
2. Inhibition of gluconeogenesis

3. Inhibition of lipolysis
4. Inhibition of fatty acid oxidation and ketone body formation
5. Inhibition of preoteolysis and amino acid oxidation

Insulin deficiency: Phys effects

The effects of insulin, a hormone secreted by pancreatic islet beta-cells, are numerous, leading to biochemical changes in nearly every tissue in the body. Among its many functions, insulin induces glucose uptake by tissues and glycogen synthesis in the liver and muscles. By inhibiting lipase, insulin additionally limits free fatty acid release from adipose tissue and increases protein synthesis by inducing transport of amino acids into cells.

The widespread biochemical effects of insulin result in equally vast physiologic abnormalities when insulin is deficient. Reduced entry of glucose into peripheral tissues and increased release of glucose from the liver leads to **hyperglycemia**, which in turn leads to several physiologic consequences. Elevated blood glucose concentration leads to a filtered load of glucose that exceeds the kidney's reabsorptive capacity. Unreabsorbed glucose acts as an osmotic diuretic in the urine, leading to extracellular fluid volume contraction and resulting hypotension, as well as a decrease in total body sodium and potassium. A decreased insulin:glucagon ratio stimulates **catabolism of protein and fat**, which can lead to increased production and decreased clearance of VLDL leading to hypertriglyceridemia, as well as increase in the by-product acetyl CoA. Excess acetyl CoA in the body from breakdown of fats leads to formation of ketone bodies acetoacetate and b-hydroxybutyrate in the liver. The body is able to buffer some of the hydrogen ions in the setting of ketoacidosis, but metabolic acidosis still develops, leading to increased ventilation rate as a compensatory mechanism. Potassium shifts out of cells in the setting of hyperglycemia and acidosis, and thus normal or even increased serum potassium levels are often seen, despite total body depletion.

While insulin deficiency can lead to serious acute complications, there are chronic consequences as well, which are often seen in longtime diabetics. Increased levels of glucose lead to glycosylation of proteins and, consequently, advanced glycosylation end products (AGE) that bind to receptors present in endothelial cell macrophages. Chronic hyperglycemia can also lead to abnormal stimulation of signaling cascades, increased production of ROS, and abnormal activation of hemodynamic regulatory systems. Microvascular and macrovascular derangements result, leading to such complications as diabetic nephropathy, retinopathy, neuropathy, and atherosclerosis.

Stress response: Lipolysis

Surgical stress may lead to a catabolic state. One consequence of this is lipolysis or the hydrolysis of triglycerides into glyceride and free fatty acids. It is thought that lipolysis is largely a result of stimulating beta-2 adrenergic receptors. The beta-2 agonism results in an increase in

intracellular cAMP and downstream activation of triglyceride lipase by protein kinase A. Free fatty acids are then liberated and undergo beta-oxidation in the liver.

Of note, a process known as hypermetabolism may occur in the stress response. In this situation, insulin levels are actually normal to high (different from the fasting state) which leads to less ketone production. Therefore, glyceride from triglyceride breakdown enters into the gluconeogenesis cycle. However, due to insulin resistance (mediated by tumor necrosis factor alpha, IL-1, INF-alpha, and INF-gamma) there is concomitant fatty acid oxidation that which essentially results in opposing processes. Importantly, beta-oxidation is the major route of forming ATP in the stressed state. See diagrams from Miller's Anesthesia (1), which further illustrate the process of lipolysis and the futile metabolic cycles that arise in the stressed state.

An important component in understanding metabolism is the respiratory quotient (RQ), the ratio of CO2 elimination to O2 consumption. By definition, the RQ for carbohydrates is 1. Therefore, more calorically dense molecules such as fat (9 kcal/gram) will have a lower respiratory quotient (~0.7) as carbon dioxide production falls relative to oxygen consumption with the intake of more calorically dense foods.