**Prolonged unconsciousness after anaesthesia**

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**Introduction**

Consciousness implies “awake and aware of surroundings and identity” according to the Oxford English Dictionary. But consciousness is a continuum with varying depths. Coma, from the Greek, means a state of sleep and is defined medically as “a state of unresponsiveness from which the patient cannot be aroused”. Although the Glasgow Coma Scale was originally developed as a means to assess prognosis after head trauma, it has also been used to trend the level of consciousness although inconsistencies may occur1. Other scores have been developed including the Aldrete Score and the Postoperative Quality Recovery Scale (PQRS)2. Recognizing that recovery from anaesthesia and possible long term effects of the perioperative experience are complex issues, this latter scale tracks multiple domains of recovery from immediate to long-term periods in patients of different ages, languages and cultures.

The causes of prolonged unconsciousness after anaesthesia are summarized in Table I. The time taken to emerge to full consciousness is affected by patient factors, anaesthetic factors, duration of surgery and painful stimulation. Non-pharmacological causes may have serious sequelae; thus, recognizing these organic conditions is important.

**Pharmacological**

The residual effects of a drug (after administration has ceased) are influenced by a number of factors, as outlined in Table 1. With so many variables, it is not surprising that administration of an ideal dose to one patient can have a very different effect on an apparently similar patient.

**Benzodiazepines**

Benzodiazepines are used for anxiolysis and pre-medication; co-induction facilities the hypnotic and sedative properties of other agents. Used alone, benzodiazepines are unlikely to cause prolonged unconsciousness except in susceptible, elderly patients or when given in overdose. However, central nervous system (CNS) depression can prolong the effects of other anaesthetic agents. Benzodiazepines combined with high-dose opioids can have a pronounced effect on respiratory depression, producing hypercapnia and coma. Midazolam is metabolized by the same P450 iso-enzyme as alfentanil, such that co-administration prolongs the actions of both drugs.

**Opioids**

Opioids produce analgesia, sedation and respiratory depression; the intensity of each action varies between subjects and can be difficult to predict. As noted previously, dos**e**-response is affected by co-administered sedatives and analgesia and by patient factors. There are two major mechanisms resulting in coma; respiratory depression and direct sedation via opioid receptors. The sensitivity of the brainstem chemoreceptors to carbon dioxide is reduced by opioids with consequent dose-dependent respiratory depression and resultant hypercapnia. This may affect clearance of volatile agents and carbon dioxide; both can cause unconsciousness. The direct opioid receptor effect varies with drug potency, half-life, metabolism and patient sensitivity. Active metabolites of morphine and meperidine (pethidine) prolong the duration of action, especially in the presence of renal failure.

**Neuromuscular block**

Neuromuscular block in the conscious patient can mimic unconsciousness. In addition, neurosmuscular blockers may result in prolonged unconsciousness after operation if a residual block causes hypoventilation. A large number of pharmacological interactions with neuromuscular blocking agents prolong neuromuscular block. The majority of drug interactions with non-depolarzing neuromuscular blocking agents prolong blockade by interfering with calcium, the second messenger involved in acetylcholine

Table 1: Causes of prolonged unconsciousness after anaesthesia

|  |  |  |
| --- | --- | --- |
| Pharmacological Effects | | |
| **Drug Factors** | **Patient Factors** | **Surgical Factors** |
| Dose | Age (especially extremes) | Requirement for muscle relaxation. |
| Absorption | Genetic variations | Duration of surgery |
| Distribution | Disease processes; renal, hepatic failure | Utilization of regional techniques |
| Metabolism |  | Degree of pain / stimulation |
| Excretion |  |  |
| Context-sensitive half-life |  |  |
| Pharmacodynmic interactions (summation, potentiation, synergism) |  |  |
| Pharmacokinetic interactions (distribution, metabolism, excretion) |  |  |
| Respiratory Failure |  |  |
| Central drive |  |  |
| Muscular / ventilator disorders |  |  |
| Pulmonary pathology |  |  |
| Neurological Causes |  |  |
| Intracerbral event |  |  |
| Seizures |  |  |
| Central Hypoxia |  |  |
| Central ischaemia |  |  |
| Local anaesthetic toxicity |  |  |
| Metabolic Causes |  |  |
| Hypoglycaemia |  |  |
| Hyperglycaemia |  |  |
| Hyponatraemia |  |  |
| Hypernatraemia |  |  |
| Hypothermia |  |  |
| Central anticholinergic syndrome |  |  |
| Hyperthyroidism |  |  |
| Hepatic or renal failure (Uraemia) |  |  |
| Sepsis |  |  |

release. Electrolyte disturbances cause cell wall hyper polarization and prolonged block. Hypothermia decreases metabolism and acidosis donates protons to tertiary amines, increasing receptor affinity.

Deficiencies of plasma cholinesterase prolong block produced by succinylcholine; therapeutic plasma concentrations persist because of decreased metabolism. Extension of the block is variable and depends upon the genotype.

**I.V. Anaesthetic Agents**

The termination of action of i.v. agents given as a bolus for induction is predominantly determined by redistribution and should not delay recovery. Propofol has a large volume of distribution at steady-state and a relatively long elimination half-life. The effect of propofol after total i.v. anaesthesia (TIVA) is prolonged3. The context-sensitive half-life is the time taken for the effect-site concentration of drug to reduce to 50%, and is dependent upon the duration of infusion (i.e. the context). A set of context-sensitive half-life curves can be constructed for each drug allowing prediction of offset time.

The, duration of unconsciousness is affected by context-sensitive half-life, amount of drug, co-administration with other drugs, and patient factors.

**Volatile anaesthetic agents**

Emergence from volatile agent anaesthesia depends upon pulmonary elimination of the drug and MACawake (the end –tidal concentration associated with eye-opening to verbal command). MACawake is consistently and approximately 30% of MAC. (MACawake; isoflurane 0.39%; desflurane 2.17%; sevoflurane 0.61%). Pulmonary elimination is determined by alveolar ventilation, blood-gas partition co-efficient and dose (MAC-hours). Using an agent with low blood-gas solubility results in a quicker emergence (e.g. sevoflurne 7 min; isoflurane 1.5 min). Alveolar hypoventilation lengthens the time taken to exhale the anaesthetic and delay recovery. Time to emergence increases with increasing duration of anaesthesia (i.e. context-sensitive half-life increases), but does not change MACawake. Practically, once a patient has emerged from anaesthesia any remaining volatile agent leaching from the body stores is unlikely to cause an effect-site concentration that would cause unconsciousness.

It is important to remember that drug overdoses are relative; they depend upon who received them, what point in time relative to cessation of general anaesthesia they occur, and what other agents have been administered.

**Metabolic causes**

**Hypoglycaemia**

The glucose level that defines hypoglycemia is variable. In people with diabetes levels below 3.9 [mmol/L](https://en.wikipedia.org/wiki/Reference_ranges_for_blood_tests" \o "Reference ranges for blood tests) (70 mg/dL) is diagnostic.4 In adults without diabetes, symptoms related to low blood sugar, low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis. Otherwise a level below 2.8 mmol/L (50 mg/dL) after not eating or following exercise may be used. In newborns a level below 2.2 mmol/L (40 mg/dL) or less than 3.3 mmol/L (60 mg/dL) if symptoms are present indicates hypoglycemia.5,6 Other tests that may be useful in determining the cause include insulin and [C peptide](https://en.wikipedia.org/wiki/C_peptide) levels in the blood. . The brain is totally dependent upon glucose as its energy source. The effects of hypoglycaemia can be divided into those resulting from the sympathetic (catecholamine) response and those caused by neuroglycopenia. Neuroglycopenia manifests as confusion, abnormal behavior, seizures and coma. In the elderly population, lateralizing neurological signs are commonly seen. Postoperative hypoglycacmia most often results from poorly controlled diabetes, starvation and alcohol consumption. Alcohol impairs gluconeogenesis, and will exacerbate hypoglycaemia in starved patients or those with minimal energy reserves. Other causes of hypoglycacmia are listed in Table.

**Hyperglycaemia**

Severe hyperglycaemia can prolong unconsciousness after anaesthesia. A venous blood glucose> 250mg/dl causes an osmotic diuresis and dehydration in the untreated patient. The effects of dehydration range from drowsiness to acidosis. Furthermore, blood hyperosmolarity and hyperviscosity predispose to thrombosis and cerebral oedema. Intraoperative cerebrovascular accident may occur as a result of cerebral vascular occlusion, especially in diabetics with microvascular

Table 2 **Metabolic disturbances**

Endocrine disturbance Causes

Hypoglycaemia Diabetes

Starvation

Alcohol

Sepsis

Liver failure

Paediatrics

Sulphonylureas

Endocrine tumours

Hypoadrenalism

Hyperglycaemia Ketoacidosis

Hyperosmolar non ketotic acidosis (HONK)

Lactic acidosis

Gestational diabetes

Insulin resistance (acromegaly, Cushing’s syndrome)

Pancreatitis

Inherited syndromes

Hyponatraemia and water excess Na deficient I.v. fluids

TURP syndrome

Excessive drinking

SIADH

Drugs

Nephrotic syndrome

Hyponatraemia and dehydration Diuretics

Hypoadrenalism

Cerebral salt-wasting

Nephritis

Diarrhoea, vomiting

Pancreatitis

Renal tubular acidosis

and macrovascular disease. An anaesthetized patient will not display all the clinical signs of glucose abnormality.

**Hyponatraemia**

Mild hyponatraemia is usually asymptomatic, but serum sodium concentration <120 mmol litre-1 will cause confusion and irritability. Serum sodium concentration <110 mmol litre-1 causes seizures, coma and increased mortality. The causes of a hyponatraemia are multiple; however, those pertinent to anaesthesia are the conditions that may develop during operation. Inappropirate anti-diuretic hormone secretion (SIDAH) can result from brain trauma, subarachnoid heamorrhage and administration of drugs (e.g. opioids, haloperidol, vasopressin). Cerebral salt-wasting syndrome may also occur in the brain-injured patient, and infusion of mannitol can dehydrate. Cerebral salt-wasting syndrome describes sodium loss from the kidneys in association with intracranial pathology, thought to be mediated by atrial natriuretic peptide secretion. Cerebral oedema results in cerebral irritation and coma.

Fluid overload and hyponatraemia may occur when large volumes of irrigation fluid (glycine solution) are absorbed by open venous sinuses during trans-uretharal resection of the prostate (TURP), that is TURP syndrome. Glycine is a hypotonic solution (220 mmol litre-1). The result is hyponatraemia, pulmonary oedema and cerebral oedema causing variable cerebral signs, including coma. Intensive resuscitation and management is required.

Extreme hyponatraemia is less likely to occur in the post-operative environment; however, sodium excess results in a cellular dehydration including cerebral dehydration, ruptured vessels and intracranial haemorrhage. Symptoms include thirst, drowsiness, confusion and coma.

**Uraemia**

Uraemia results in dehydration and cerebral effects attributable to cellular damage and distortion. The clinical effects of uraemia are varied, but intracerebral changes may produce drowsiness confusion and coma.

**Hypothermia**

The effects of hypothermia are multiple and widespread throughout the body. Neurological and respiratory changes occur with decreasing temperature, e.g., confusion (<35°C), unconsciousness (<30°C), apnoea (<24°C), absent cerebral activity (<18°C). The direct hypothermic effects on brain tissue are compounded by cardiovascular and respiratory disturbance at less profound degrees of hypothermia. Cardiac output decreases with a decrease in temperature and arrhythmias occur. Low cardiac output affects circulation and drug pharmacokinetics, as well as tissue perfusion.

**Respiratory failure**

Postoperative respiratory failure causes hypoxaemia, hypercapnia, or both. The causes of respiratory failure are multiple and may be classified into neurological, pulmonary, and muscular. Central drive is lost during drug overdose, with intracranial pathology and in patients with chronic obstructive pulmonary disease or sleep apnoea. Ventilation is affected by primary muscle problems, metabolic imbalance, obesity and residual neuromuscular block. Pulmonary disease states result in various admixture, dead space, or both and include pulmonary embolism, atelectasis, obstruction, aspiration, consolidation, acute respiratory distress syndrome and transfusion-related acute lung injury. These varied problems may cause or exacerbate postoperative respiratory failure.

Hypoxaemia, through resulting cerebral hypoxia, will depress cerebral function, ultimately causing cell death. Cerebral damage results from lactic acid production, free radical accumulation, and release of intracellular metabolics. Hypoxaemia with continuing blood supply causes less damage than complete interruption of perfusion, because toxins are removed.

Hypercapnia, detected by central chemoreceptors, initially stimulates respiration but thereafter depresses the regulatory respiratory centres of the brain causing hypoventilation and apnoea. Respiratory acidosis results from hypoventilation rendering the patient acidaemic. Hypercapnia in a head-injured patient with impared cerebral autoregulation causes vasodilatation and a consequent increase in intracranial pressure which may result in secondary brain injury.

**Neurological causes**

Diverse pathologies can precipitate intraoperative cerebral insult, causing coma. The common mechanism is ischaemic brain destruction. Periods of hypoxaemia or ischaemia may occur during surgery; these are often a result of inadequate cerebral perfusion secondary to low mean arterial pressure (MAP). Cerebral autoregulation in the normal brain occurs between 60 and 160 mm Hg MAP. Carotid surgery and operations in a sitting position present a high risk of hypoperfusion. Intracranial haemorrhage, thrombosis or infarction can occur in association with intraoperative arrhythmias, hypo- or hypertension, or in patients with abnormal cerebral vasculature. The outcome from ischaemic events varies between discrete functional deficits, hemiparesis and coma. Secondary brain injury is prevented by impeccable monitoring and management of primary brain injuries. In the brain with impaires autoregulation, injury may be caused by hypercapnia, hypoxaemia, low MAP and increased metabolic rate. This may worsen preoperative neurological deficits. Cerebral hypoxaemia may result when epileptic seizures are marked by neuromuscular block, and from intraoperative air embolism. Finally, the spread of intracranial local anaesthetic can cause unconsciousness.

**A Stepwise approach to the patient with prolonged unconsciousness.**

100% Oxygen, airway adjuncts, manual ventilation.

Is the airway protected

Rapid assessment of

A B C

Assess GCS

Stimulate the patient

Consider:

Naloxone

Flumazenil

Neostigmine

Doxapram

Review anaesthetic chart

Drugs, timing, interactions

Take account of patient characteristics

Correct glucose if low or high

Capillary blood glucose

Warm if temp<35.5°C

Measure temperature

Correct hypoxia, hypercapnia or acidosis

Arterial Blood gas analysis

Consider further diagnosis tests;

CXR,

CT head

Full clinical examination, with particular attention to respiratory system and nervous system (including focal or lateralizing neurological signs)

Blood Tests

U+E, FBC or haemocue, glucose, TFT

If patient remains unconscious decide:

Where this patient should be managed?

Further course of action?

Consider a dissociative test where other diagnosis absent

**Uncommon causes**

**Central anticholinergic syndrome**

Historically, anticholinergic syndrome was a commonly encountered sequel to anaesthesia. Nowadays, less anticholinergic medications are used. Symptoms range from cerebral irritation with delirium and agitation to CNS depression with stupor and coma. These accompany peripheral anticholinergic effects that is tachycardia, blurred vision, dry mouth reversed by physostigmine (an acetylcholinesterase inhibitor), but may recur when its effect terminates. Anti-Parkinsonian, antidepressant and anti-histamine drugs can cause central anticholinergic syndrome.7

**Disassocative coma**

A number of authors report causes and hypothesize that, after exclusion of organs and pharmacological causes, coma may be attributed to a disassociative stupor. Reported delays in return to consciousness span time periods from 2 to 30 h, and longer periods of amnesia thereafter. There are four reports in the literature; each excluded other pathology with extensive examination, laboratory tests and radiological imaging. One individual experienced this phenomenton on three separate occasions after tracheal stenosis repairs.8-10

Ragaller and collagues11 describe a case of myxoedema coma presenting 24 h after operation with cardiac arrest and prolonged coma. This was successfully treated with thyroxine replacement. Thyroid failure should be considered as a possible cause of unconsciousness in the immediate postoperative period. Others have described the prolonged unconsciousness of an 86-yr old who received a postoperative lidocaine infusion for arrhythmias. The patient achieved three times the recommended blood concentration required for arrhythamia management as the result of a prescribing error. Valproate toxicity has been reported in eight postoperative neurosurgical patients who experienced prolonged unconsciousness, stupor or coma12. They demonstrated abnormal EEG patterns which returned to normal, as did the patients’ level of consciousness, after discontinuation of valproate. The mechanism was postulated to be attributable to the destruction of the blood-brain barier in the pathological state.13

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