

Delayed recovery of consciousness after anaesthesia

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Key points

Delayed recovery from anaesthesia is often multifactorial.

Consider drug interactions with neuromuscular blocking agents.

Metabolic abnormalities will not present with the usual signs and symptoms in the anaesthetized patient.

Organic causes of prolonged unconsciousness may have important sequelae that should be managed appropriately.

Rarely, disassociative states may present with episodes of unconsciousness with no other identifiable cause.

A conscious individual, as defined in the Oxford English Dictionary, is 'awake and aware of their surroundings and identity'. However, consciousness represents a continuum with varying depths of consciousness. Coma is derived from the Greek 'koma' meaning a state of sleep; more specifically, it is defined medically as 'a state of unresponsiveness from which the patient cannot be aroused'.

By convention we use the Glasgow coma scale (GCS) to provide a rapid, reproducible quantification of depth of unconsciousness. Although the GCS was developed for assessment and prediction of outcome in traumatic brain injury, it remains a useful tool to assess conscious state regardless of the causative factor. The GCS scores verbal, movement and visual responses to stimulation; a GCS <8 defines coma.

Causes of prolonged unconsciousness after anaesthesia

The causes of prolonged unconsciousness after anaesthesia are summarized in Table 1. 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 facilitates 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, dose-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-dependant 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, neuromuscular 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; these are outlined in Table 2.¹ The majority of drug interactions with non-depolarizing neuromuscular blocking agents prolong blockade by interfering with calcium, the second messenger involved in acetylcholine

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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	Utilisation of regional techniques,
Metabolism		Degree of pain/stimulation
Excretion		
Context-sensitive half-life		
Pharmacodynamic interactions (summation, potentiation, synergism)		
Pharmacokinetic interactions (distribution, metabolism, excretion)		
Respiratory Failure		
Central drive		
Muscular/ventilatory disorders		
Pulmonary pathology		
Neurological Causes		
Intracerebral event		
Seizures		
Central hypoxia		
Central ischaemia		
Local anaesthetic toxicity		
Metabolic Causes		
Hypoglycaemia		
Hyperglycaemia		
Hyponatraemia		
Hypernatraemia		
Hypothermia		
Central anticholinergic syndrome		
Hypothyroidism		
Hepatic or renal failure (uraemia)		
Sepsis		

release. Electrolyte disturbances cause cell wall hyperpolarization 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 prolonged. 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. Typically,

Table 2 Interactions with neuromuscular antagonists.

Interactions with non-depolarising muscle relaxants	
Drug Interactions	Volatile anaesthetic agents Aminoglycosides Lithium Diuretics Calcium channel antagonists
Metabolic Causes	Hypothermia Acidosis Hypokalaemia Hypermagnesaemia Myasthenia gravis Eaton Lambert/Myasthenic syndrome
Genetic	
Interactions with depolarising muscle relaxants	
Genetic	Succinylcholine apnoea Myotonic Dystrophy
Acquired acetylcholinesterase deficiency	Pregnancy Liver Disease Renal failure Cardiac failure Thyrotoxicosis Drugs (ecothiopate, ketamine, oral contraceptive pill (OCP), lidocaine, neostigmine, ester local anaesthetics)

a reduction of 80% in the effect-site concentration is required for emergence. For example, the time to emergence from a 2-h propofol-only anaesthetic can be modelled and shows non-linear context-sensitive half-lives. An 80% decrease in effect-site concentration after 2 h will take 36 min; if the dose of propofol is doubled, the emergence time becomes 105 min, and if it is halved (sedation), the time decreases to 10 min.²

Thus, 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 MAC_{awake} (the end-tidal concentration associated with eye-opening to verbal command). MAC_{awake} is consistently and approximately 30% of MAC . (MAC_{awake} : 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. sevoflurane 7 min; isoflurane 11.5 min). Alveolar hypoventilation lengthens the time taken to exhale the anaesthetic and delays recovery. Time to emergence increases with increasing duration of anaesthesia (i.e. context-sensitive half-life increases), but does not change MAC_{awake} . 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 receives them, what point in time relative to cessation of general anaesthesia they occur, and what other agents have been administered.

Metabolic causes

Hypoglycaemia

Hypoglycaemia is diagnosed by confirmation of a venous blood glucose concentration of $<2.2 \text{ mmol litre}^{-1}$. 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 behaviour, seizures and coma. In the elderly population, lateralizing neurological signs are commonly seen. Postoperative hypoglycaemia 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 hypoglycaemia are listed in Table 3.

Hyperglycaemia

Severe hyperglycaemia can prolong unconsciousness after anaesthesia. A venous blood glucose $>14 \text{ mmol litre}^{-1}$ causes an osmotic diuresis and dehydration in the untreated patient. The effects of dehydration range from drowsiness to acidosis. Furthermore, blood hyperosmolality 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

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 $<120 \text{ mmol litre}^{-1}$ will cause confusion and irritability. Serum sodium concentration $<110 \text{ mmol litre}^{-1}$ 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. Inappropriate anti-diuretic hormone secretion (SIADH) can result from brain trauma, subarachnoid haemorrhage 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-urethral resection of the prostate (TURP), that is TURP syndrome. Glycine is a hypotonic solution ($220 \text{ mmol litre}^{-1}$). The result is hyponatraemia, pulmonary oedema and cerebral oedema causing variable cerebral signs, including coma. Intensive resuscitation and management is required.

Hypernatraemia

Extreme hypernatraemia 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 ($<35^\circ\text{C}$), unconsciousness ($<30^\circ\text{C}$), apnoea ($<24^\circ\text{C}$), absent cerebral activity ($<18^\circ\text{C}$). 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.

Table 3 Endocrine disturbances

Endocrine disturbance	Causes
Hypoglycaemia	Diabetes
	Starvation
	Alcohol
	Sepsis
	Liver failure
	Paediatrics
	Sulphonylureas
	Endocrine tumours
	Hypoadrenalism
	Ketoacidosis
Hyperglycaemia	Hyperosmolar non ketotic acidosis (HONK)
	Lactic acidosis
	Gestational diabetes
	Insulin resistance (acromegally, Cushing's)
	Pancreatitis
	Inherited syndromes
	Na deficient i.v. fluids
Hyponatraemia and water excess	TURP syndrome
	Excessive drinking
	SIADH
	Drugs
	Nephrotic syndrome
Hyponatraemia and dehydration	Diuretics
	Hypoadrenalism
	Cerebral salt-wasting
	Nephritis
	Diarrhoea, vomiting
	Pancreatitis
	Renal tubular acidosis

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 venous 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 metabolites.

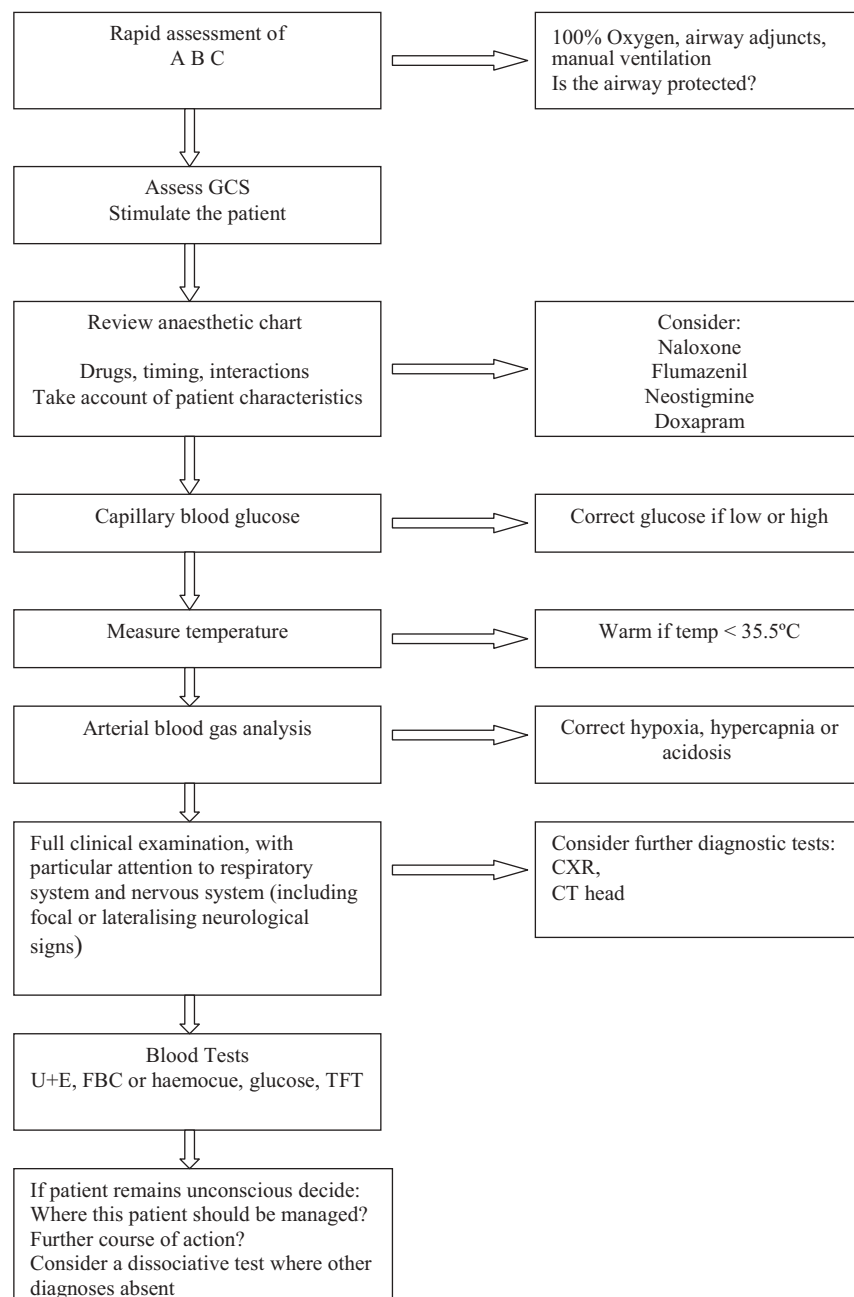


Fig. 1 A stepwise approach to the patient with prolonged unconsciousness.

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 impaired 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 impaired 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 masked by neuromuscular block, and from intraoperative air embolism. Finally, the spread of intracranial local anaesthetic can cause unconsciousness.

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 and urinary retention. The symptoms are rapidly reversed by physostigmine (an acetylcholinesterase inhibitor), but may recur when its effect terminates. Anti-Parkinsonian, antidepressant and antihistamine drugs can cause central anticholinergic syndrome.⁸

Disassociative coma

A number of authors report cases and hypothesize that, after exclusion of organic 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 phenomenon on three separate occasions after tracheal stenosis repairs.^{3–5, 9}

Ragaller and colleagues⁶ 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.⁸ 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 arrhythmia management as the result of a prescribing error.⁷ Valproate toxicity has been reported in eight postoperative neurosurgical patients who experienced prolonged unconsciousness, stupor or coma. 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 barrier in the pathological state.¹⁰

Clinical assessment

A stepwise approach to assessing and managing the unconscious patient is outlined in Figure 1. Clearly, it is important to assess each case individually.

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Please see multiple choice questions 17–19.