REVIEW ARTICLE

DIFFERENTIAL DIAGNOSIS OF DELAYED AWAKENING FROM GENERAL ANESTHESIA: A REVIEW

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Abstract

With the general use of fast acting anesthetic agents, patients usually awaken quickly in the post operative period. However, sometimes recovery is protracted and the list of possible causes in long. Accurate diagnosis is key to institution of appropriate therapy.

Key Words: Anesthetic agents, delayed recovery, overdose, risk factors.

Definition

There is no single definition of what might constitute delayed awakening or emergence after general anesthesia. With the almost universal use of evanescent agents such as propofol and desflurane, patients generally awaken in a few minutes. Even after prolonged surgery and anesthesia a response to stimulation within 60-90 minutes should occur[1]. 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 (Table 1) 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 occur[2]. Other scores have been developed including the Aldrete Score (Table 2)[3] and the Postoperative Quality Recovery Scale (PQRS)[3]. Recognizing that recovery from anesthesia 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. In consists of 6 domains; physiologic, nociceptive, emotive, activities of daily living, cognitive and patient perspective[4]. Physiologic recovery was complete in 40% of patients by 40 minutes. In only 11% of patients was recovery complete in all domains by day 3. Thus the concept of awakening would seem to be more involved with far greater dimensions than assessing a patient as being "recovered" or "awakened" and judging the anesthetic effect as terminated. These added factors have been assessed in several studies by patient reported surveys addressing functional quality of recovery[5-9]. Patient reports are an important approach in assessing recovery, but other crucial aspects are in areas perhaps influenced by anesthesia that may not rise to the patient's consciousness. For example the topic of cognitive recovery especially after cardiac and even non cardiac surgery is rarely assessed. This questions as to whether recovery as a measure

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Table 1
Glasgow Coma Scale. A score of >12 indicates return of consciousness in most patients and <8 indicates coma. The scale is also used as a trend monitor.

Category		Best Response
Eye opening		
Spontaneous		4
To speech		3
To pain		2
None		1
Verbal	(Modified for Infants)	
Oriented	Babbles	5
Confused	Irritable	4
Inappropriate words	Cries to pain	3
Moans	Moans	2
None	None	1
Motor		
Follows commands		6
Localizes to pain		5
Withdraws to pain		4
Abnormal flexion		3
Abnormal extension		2
None		1
Glascow Coma Score		
Best possible score		15
Worst possible score		3
If tracheally intubated then verbal designated with "T"		
Best possible score while intubated		10T
Worst possible score while intubated		2T

of the quality of anesthesia care should be targeted for not only identification but also for improvement[10-16].

Incidence

In otherwise healthy patients who have undergone relatively short operative procedures the incidence of delayed awakening is practically zero and its occurrence usually relates to some underlying but undiagnosed condition or medical error.

Causes

Drug effect: Too much drug may have been given or the patient is very susceptible or drug interaction has occurred.

Duration and type of anesthetic. Speed of emergence is inversely related to blood gas solubility and directly related to alveolar ventilation. Other factors include total tissue uptake of the drug (depends on solubility), duration of anesthesia and average

Table 2
The commonly used Aldrete score is broad based. A value of 9 is required for discharge from the postanesthetic care unit (PACU).

Parameter	Description of patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respirations	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mm Hg > preanesthetic level	2
	Is 20 to 50 mm Hg > preanesthetic level	1
	Is 50 mm Hg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air	2
	Requires supplemental oxygen to maintain level >90%	1
	Has level <90% with oxygen supplementation	0

Maximum total score is 10; a score of ≥9 is required for discharge.

concentration.

Potentiation by other drugs: Premedication with other sedatives such as benzodiazepines or alcohol increases central nervous system depression.

Neuromuscular blockade: Although these patients may not be unconscious, prolonged muscle paralysis may be almost indistinguishable from delayed awakening.

Risk Factors

Risk factors for slower than normal return to consciousness are shown in Table 3.

Patient Factors

Extremes of Age

Geriatric Patient:

Older patients have an exaggerated response to central nervous system (CNS)-active drugs due to an underlying age-related decline in CNS function as well as increased pharmacodynamic sensitivity towards the benzodiazepines, general anesthetics and opioids[18]. However, for opioids and local anesthetics used for CNS blockade, the pharmacodynamic involvement is not always clear[19]. However, other studies have shown that the demand for opioids is reduced by almost 50% and with total intravenous anesthesia the dosages of propofol and remifentanil and recovery times are more determined by patient age than by body weight[20]. A report by Fredman et al assessed the effect of different doses of midazolam (0.5mg-2mg) in geriatric patients undergoing brief urologic procedures and found that midazolam irrespective of the dose given significantly increased depressed mental function and delayed PACU discharge[21]. Anticholinergic agents (atropine, scopolamine) also add to postoperative somnolence, attributed to decreased brain cholinergic activity caused by anesthetics[22]. Muscle relaxants if given on a weight controlled basis both delay onset of action and prolonged duration of drug effects and must be considered with increasing age as these effects lead to respiratory depression and continued sedation[20]. Pharmacodynamic involvement appears to be nearly absent if neuromuscular agents are given in the reduced dosages required for this group of patients[19]. Close monitoring of depth of anesthesia and neuromuscular blockade and avoidance of benzodiazepines and substitution of non steroidal analgesic agents and peripheral blocks for opiates should all be considered as preventive of prolonged sedation in geriatric patients.

Neonates:

Several studies have demonstrated the adverse consequences of untreated pan and stress on brain development in preterm infants. Controversy still exists over the safety of benzodiazepines and opiates[23]. Predictive pharmacokinetic/pharmacodynamic models have been developed for fentanyl[24]. Because awareness has been raised that anesthesia is essential for newborns, the risk of overdose and hence over sedation becomes considerable. Recent information suggests that there may be an association between anesthetic exposure on a depth and time level to later

Table 3
Many factors may result in delayed awakening, roughly divided into 4 factors although clearly there is considerable overlap

Patient Factors	**Drug Factors**	**Surgical Factors**	**Metabolic factors**
Extremes of age	Dosage/hypoxia/hypotension	Long surgery and anesthesia	Hypo/hyper glycemia
Genetic variation	Absorption/distribution	Muscle relaxant use	Hypo/hyper natremia
Body habitus	Metabolism	Regional techniques with sedation	Hypothermia
Co-morbidities	Excretion	Decreased pain and stimulation	Hypothyroidism
Obstructive sleep apnea	Drug interactions	Intracranial surgery	Hepatic/renal failure
Cognitive dysfunction	Local anesthetic toxicity		Central anticholinergic syndrome
Seizures	Fluid overload		Acidosis
Stroke		Embolism	Coagulation defects

cognitive dysfunction[25,26] Two large-scale clinical studies are currently underway to explore these issues. The PANDA study is a large-scale, multisite, ambi-directional sibling-matched cohort study in the USA. The GAS study will compare the neurodevelopment outcome between sevoflurane anaesthesia and regional anaesthesia, in infants undergoing inguinal hernia repair. Results from these studies may not be known for 1-2 decades[27].

A common cause of delayed return to consciousness in children is hypothermia. Because of their relatively large body area compared to weight, heat loss is greater than in adults. Hence drug metabolism is delayed[28].

Genetic factors

Unexpected responses such as prolonged somnolence following the administration of specific anaesthetics are most commonly associated with a genetic defect of the metabolic pathway either of a given agent or its receptor. Most anesthetic agents are metabolized in the liver by the cytochrome P450 superfamily enzymes (CYPs) and phase II drug-metabolizing enzymes (glutathione S-transferases (GSTs), sulphotransferases (SULTs), UDP-glucuronosyltransferases (UGTs) and NAD (P) H: quinone oxidoreductase (NQO1))[28]. Polymorphic changes in GABRG 2 receptor can adversely affect the expected rapid reversal of propofol anesthesia[28]. Unanticipated drug reactions are a common and important complication of drug therapy both in adults and in children. It is becoming increasingly apparent that genetically controlled variations in drug disposition and response are important determinants of unexpected events for many important adverse events associated with drug therapy[29].

Pharmacogenetic differences appear to play major roles in predicting adverse effects, especially of opioids[30]. A subset of genes appears to modulate the proteins involved in pain perception pathways, metabolism of analgesics (pharmacokinetics), and transport and receptor signaling (pharmacodynamic). Adult genetic studies have limited direct applicability, as children's genetic predispositions to analgesic response are influenced by different factors and contain developmental and behavioral components as well as altered sensitivity to analgesics and variation in gene-expression patterns. While the entire science of pharmacogenetics is still in its infancy, it is growing rapidly. Undoubtedly in the not too distant future, it will be possible to plan a precise, tailored anesthetic.

Body Habitus

Males with a higher percentage of fat have a tendency to delayed awakening after propofol anesthesia, an effect that is not seen in women[31] With the exception of neuromuscular antagonists, lean body weight is the optimal dosing scale for most drugs used in anaesthesia especially opioids and anaesthetic induction agents[32]. A diagnosis of obstructive sleep apnea with an increased incidence of fat deposits in the pharynx and chest wall coupled with increased oxygen utilization and carbon dioxide production places the morbidly obese patient at risk for adverse respiratory events secondary to anesthetic agents, thus altering the pharmacodynamic properties of these drugs.

Cardiac output increases with obesity and thus these individuals require administration of higher drug doses to attain the same peak-plasma concentration than would be required for a standard-size person. Lean body weight (LBW) correlates highly with increased cardiac output, more so than fat mass[33]. Clearance for most drugs increases nonlinearly with total body weight but linearly with LBW. Thus morbid obesity, which implies mainly increased fat mass, has no clinically significant impact on the uptake of the inhalation anesthetics isoflurane, sevoflurane, and desflurane in routine clinical practice. Total body weight dosing of neuromuscular blocking agents may result in a prolonged effect although other studies have found different results[32,33]. However, in a study of 56 obese patients undergoing craniotomy Bilotta et al found desflurane-based anesthesia allowed earlier postoperative cognitive recovery and reversal to normocapnia and normal pH[34].

Propofol and remifentanil infusions have been used for spinal fusion, especially in obese individuals, when evoked potential monitoring was required. However, this combination has been shown to delay

awakening. Addition of dexmedetomidine reduces the dose requirements of propofol and remifentanil allowing faster wake up[35].

Co-morbidities

Preexisting cardiac and pulmonary disease require adjustments in anesthetic dosages to prevent overdose and postoperative somnolence. Significant lung disease decreases the ability to wash out inhaled agents as the speed of emergence relates directly to alveolar ventilation. Similarly, congestive cardiac failure and decreased cardiac output prolong somnolence.

Both hyper and hypo glycemia may induce coma[36]. Patients with hyperglycemia have usually been diagnosed as type ll diabetics. A sugar infusion may have been inadvertently given or the patient may have recently eaten a carbohydrate meal. Dexamethasone and long duration of surgery (stress response) can also significantly increase hyperglycemia. Hypoglycemic patients are more likely to be juvenile or insulin dependent diabetics. Postoperative hypoglycemia most frequently results from starvation, or excessive insulin, especially in patients with end stage renal disease. Causes of hyper/hypoglycemia are shown in Table 4.

Table 4
Several causes of either hyperglycemia or hypoglycemia may be identified as contributing to delayed return to consciousness in the PACU (Adapted from ref 36, RCF Sinclair and RJ Faleiro)

HYPERGLYCEMIA	HYPOGLYCEMIA
Ketoacidosis/pancreatitis	Starvation
Hyperosmolar non ketotic coma	Sepsis
Gestational diabetes	Liver failure
Failure to take antiglycemic medications	Children
Steroids	Hypoadrenalism
Insulin resistance (Cushing, acromegaly)	Endocrine tumors

Obstructive sleep apnea (OSA)

Patients with OSA have several anatomical and functional factors that contribute to airway compromise. Obesity, body mass index (BMI) ≥ 30 kg/m^2, with enlarged neck circumference (males $\geq$ 17inches; females $\geq$ 16 inches) are often present. Other anatomical abnormalities include nasal polyps, septal deviation, lingual tonsils, large adenoids, retrognathia, or tumors of the naso-oro-hypo-pharynx.

Following anesthesia and surgery and for several days thereafter, sleep architecture is largely disturbed in most patients but more so in patients with OSA who already have altered architecture sleep patterns as a consequence of the disease[37,38]. Most patients do not experience the deeper planes of non rapid eye movement (NREM) sleep or REM sleep for the first three postoperative days. “REM rebound” then follows as a “catch-up” on missed REM sleep phase. During REM rebound, nightmares may trigger a sympathetic surge, causing dysrhythmias, and myocardial ischemia. Also, during REM sleep, the increase in upper airway resistance, coupled with generalized atonia and airway obstruction, may lead to severe hypoxemia. The residual effects of anesthetic agents and neuromuscular blocking agents that tend to have a more profound effect on the upper airway muscles than on ventilatory muscles, further contribute to respiratory obstruction. Benzodiazepines as well as opioids (especially methadone) may cause central followed by obstructive apneic events. Thus, profound/prolonged upper airway muscle weakness may be present despite adequate spontaneous ventilation by the patient. Thus patients with OSA are at considerable risk of cardiorespiratory complications after surgery and during a period when analgesia may be maintained principally with opiates[37,38].

Cognitive Dysfunction

Structural disorders of cerebral nervous system such as increase in intracranial pressure, brain ischemia, and psychological disorders may all cause postoperative somnolence For example, patients with Parkinson’s disease are more prone to postoperative confusion and hallucinations[39]. Inhalational anaesthetic agents have complex effects on brain dopamine concentrations, inhibiting synaptic reuptake of dopamine, thereby increasing the extracellular concentration and affecting both spontaneous and depolarization-evoked

dopamine release[40-2], changes that occur at clinically relevant concentrations. Hypotension is a concern due to hypovolemia, norepinephrine depletion, autonomic dysfunction and the co-administration of other medications. Patients taking bromocriptine or pergolide are prone to excessive vasodilation further exacerbating hypotension.

Patients who are depressed and taking monoamine oxidase inhibitors (MAO) or selective serotonin reuptake inhibitors (SSRI) may experience severe drug interactions with intravenous agents that can result in hyper/hypotension and postoperative coma, up to a full blown serotinergic syndrome. Other agents that can result in drug interactions include St John's Wort, ginseng, lithium, ondansetron, metoclopramide, codeine, fentanyl, oxycodone among many others. Severe symptoms include tachycardia and shock. Temperature may rise to above 41.1 °C (106.0 °F) in life-threatening cases. Other abnormalities include metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation; these effects usually arising as a consequence of hyperthermia[43].

Patients with Down syndrome or mental retardation may be particularly susceptible to delayed awakening. Risk factors included age <21 years, males and those given > 0.032mg/kg midazolam especially when administered together with propofol[44]. Intravenous sedation for dental patients with disabilities, particularly those with cerebral palsy increases the risk of hypoxia and delayed recovery of > 60 minutes is expected.

Seizures

Seizures are not uncommon after brain injury, including after surgical intervention. A post ictal state may well mimic unconsciousness. Anti epileptic drugs are well known to reduce neuromuscular blocking agent responsiveness when given chronically but not acutely[45-47]. Sahoo et al reported on a case of a patient with a long term seizure history who was not currently taking any antiseizure medication and was paralyzed for over 3 hours following rocuronium 40mg and a loading dose of phenytoin 20mg.kg[47].

Stroke

Stroke is not common after anesthesia although several risk factors such as hypertension, smoking, diabetes, obesity among others increase susceptibility. Stroke may occur following carotid endarterectomy when an atheromatous plaque has been dislodged of after cardiac surgery due to the embolization of small clots or air. Occasionally this complication can be detected intraoperatively by cerebral oximetry. However, usually the first sign is a delayed return to cognitive function. Diagnosis depends on signs and radiologic studies. Neurologic consult should be sought immediately and an interventionalist consulted if time allows for intravenous administration of recombinant tissue plasminogen activator (usually within 4-6 hours of the event). Occasionally in patients who have had a stroke in the past but recovered, paralysis of the previously affected limb may appear. This complication usually reverses within a few hours.

Drug Factors

The most common cause of delayed return to consciousness relates to residual drug effects Due to the many patient variables as noted above, it is not surprising that a drug given at one dose may be satisfactory for one patient but not for another.

Overdose

The dose may have been excessive or the patient elderly or of small size. If vaporizers are not calibrated correctly, higher dose than believed of inhaled agents may be delivered, especially if end tidal drug concentrations are not measured. Drug metabolism is delayed by renal or hepatic failure and in hypothermic patients. Sensitivity to some drugs is recognized, for example in patients with myasthenia gravis non-depolarizing muscle relaxants have a long duration of action. Preoperative oral midazolam while it may cause delayed awakening in geriatric patients was not predictive of delayed emergence in adolescents or preadolescents unless there was detectable preoperative sedation[48].

Inhaled Agents

The speed of emergence from inhaled agents directly relates to alveolar ventilation and hypoventilation may delay emergence. The less soluble the agent, the more rapid the elimination. Thus awakening is fastest with desflurane and nitrous oxide. After prolonged surgery and anesthetic administration, tissue uptake, which relates to drug solubility becomes a factor[49].

Intravenous Agents

Recovery is determined chiefly by redistribution from blood and brain into muscle and fat. Awakening after propofol is fast because of rapid hepatic metabolism and no accumulation. Pentothal is redistributed quickly but elimination by oxidative metabolism in the liver is slow and the drug has a long elimination half life of 3.4 to 22 hours. Up to 30% of the dose may remain in the body for up to 24 hours if repeat doses have been given or it is administered as an infusion[49]. Advanced age or renal or hepatic disease can prolong drug action of agents dependent on hepatic metabolism or renal excretion. One report notes miscalculation combined with advanced age and cardiac disease as a cause of continued somnolence in an 86 year old patient receiving an intravenous lidocaine infusion for dysrythmia[50].

Neuromuscular Blocking Agents

Residual paralysis is not delayed awakening but unresponsiveness may be perceived as such.

Causes include, overdose, incomplete reversal, syringe swap when additional dosing may have been given rather than the reversal agents, infiltration of the intravenous cannula or in patients following succinylcholine administration who may have plasma cholinesterase deficiency[51]. Repeated doses of succinylcholine may result in dual block. Causes of succinylcholine apnea are listed in table 4. Mivacurium is also metabolized by plasma cholinesterase and can have prolonged effects in susceptible individuals.

Table 4
Several factors may contribute to prolonged apnea after succinylcholine administration.

Genetic	**Acquired**
Plasma cholinesterase deficiency	Hepatorenal disease
Myotonic dystrophy	Pregnancy
(Malignant hyperthermia)	Thyrotoxicosis
Mitochondrial myopathies	Cardiac failure
	Drug interactions(ecothiopate, neostigmine, fertilizers)

Potentiation by other drugs

Prior ingestion of sedative premedication such as benzodiazepines, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and some herbal preparations like St Johns Wort or alcohol potentiates the central nervous system depressant effects of anesthetic and analgesic drugs and may delay emergence from anesthesia. The effects of non depolarizing muscle relaxants may be increased by drugs such as amino glycosides, lithium, calcium channel antagonists, and diuretics[36].

Local Anesthetic Toxicity

Repeated dose of local anesthetic agents especially into very vascular areas may result in toxicity that may manifest from somnolence to seizures to cardiac arrest. Management requires cardiopulmonary support and lipid emulsion infusion[52-4].

Fluid Overload

Crystalloids migrate from the vascular space quickly after infusion to dependent and soft tissue spaces such as the airway, gut wall and lungs. Pulmonary edema after lung surgery correlates with large fluid administration (12-15% incidence)[55]. Ten% of patients receiving >6l fluid over 24 hours had respiratory failure. Hypoxia and hypercarbia are common due to cardiac failure.

Surgical Factors

As noted above long surgery is associated with

delayed return to consciousness.

Procedures most likely to be associated with postoperative somnolence are neurosurgical interventions. Comparison of patients undergoing spinal or intracranial surgery indicated that those who underwent craniotomy for removal of large mass lesions awoke more slowly than patients who had spinal procedures or only small lesion[56]. Incidental rupture of an arteriovenous malformation may cause intracerebral hemorrhage and delay awakening[57]. Acute intracranial hemorrhage has also been described after ventriculo-peritoneal shunt placement[58].

Patients with dystonia undergoing deep brain stimulation may have an almost 70% incidence of delayed emergence, related to excessive anesthetic potentiation of the low output pallidal state in dystonia which may depress the pallido-thalamo-cortical-circuitry or depression of the ventral pallidal inputs to the septo-hippocampal system[59].

The beach chair position has been associated with decreased cerebral perfusion and cerebral ischemia[60]. Recommendations are that blood pressure should be measured at the level of the auricle and some form of cerebral monitoring be used such as entropy or cerebral oximetry.

Metabolic Factors

Many of these factors are already mentioned above as also being part of patient characteristics.

Other causes include:

1. Epileptic drugs reduce neuroblocking agents responsiveness when given chronically but not acutely[47].
2. Hypo- hyperglycemia, electrolyte, acid-base disorders and hypothermia may cause delayed emergence from anesthesia. Hypokalemia is induced by low potassium intake, excessive excretion from gastrointestinal (GI) and kidneys (diuretics).
3. Hypothyroidism may be diagnosed for the first time by delayed awakening[61].

Rare Causes of delayed return to consciousness

Hypokalemia

Rayazi et al reported 2 cases of delayed awakening associated with low potassium levels due perhaps to hyperventilation. They recommended serum potassium evaluation as part of determining the differential diagnosis[62].

Child Abuse

Ott et al reported a case of a child who underwent meatoplasty in what appeared to be a straight forward anesthetic. The child was very slow to recover and eventually died. Autopsy showed very high chlorpromazine levels, the drug apparently administered by her mother during the hospitalization[63].

Dandy Walker Malformation

De Santis et al described an incidental diagnosis of Dandy Walker malformation (DWM) in a 73 year old adult following coronary artery surgery complicated by delayed awakening. DWM is a rare posterior fossa malformation defined by hypoplasia and upward rotation of the cerebellar vermis. The patient remained intubated for 6 days[64].

Brainstem Paralysis

After local perioperative bupivacaine wound infiltration in 2 adolescent patients who underwent foramen magnum decompression for Arnold Chiari malformation delayed awakening was attributed to absent brainstem reflexes caused by the local anesthetic[65]. A similar case of absent brain stem reflexes due to a field block with bupivacaine was described by Fuzaylov et al in an infant[66].

Intravenous Infiltration

Infiltration of an intravenous infusion of remifentanil was noted shortly after induction in a 30 year old male[67]. A 2nd vein was cannulated and the anesthetic continued with remifentanil and sevoflurane for the short duration of the microlaryngoscopy. A

few minutes after extubation, the patient developed respiratory arrest, responsive to naloxone. He remained somnolent for the next 5 hours. No other abnormalities were detected and the cause was determined to be subcutaneous remifentanil accumulation.

Hunter Syndrome

Hunter syndrome, one of the mucopolysaccharide storage diseases, is known to complicate anesthetic and airway management. Following an apparently uneventful intraoperative course including isoflurane, nitrous oxide and fentanyl recovery was delayed in a patient with severe manifestations of the disorder for almost 2 hours until naloxone was given[68].

Diagnosis

As causes of delayed awakening are multifactorial, an accurate diagnosis must be made.

1. Past history should be reviewed, especially as regards drug ingestion, including herbal therapies such as St Johns Wort.
2. Ensure all agents are turned off.
3. The anesthetic record should be reviewed as regards concentration and dosages of drugs and duration.
4. Amount of fluid administration should be reviewed as excess fluid may gravitate to the lungs, causing decreased oxygen exchange and hypercarbia and hypoxia.
5. Vital signs should indicate cardiopulmonary stability.
6. Temperature should be close to normal.
7. Hypo and hyperventilation should be excluded by blood gas analyses.
8. Metabolic acidosis should be excluded.
9. Residual muscular paralysis should be excluded by train of four monitoring and head lift of >5 seconds.
10. Neurologic examination should include pupil examination, symmetric motor movements, presence of a gag or cough.
11. CT scan, neurologic/neurosurgical consultation is indicated if other causes have been excluded.
12. In difficult cases, there should be no delay in requesting help.

Treatment

Therapy depends on the cause. Nevertheless in the initial assessment of the patient who is not recovering as expected in the PACU, several steps must be followed:

1. Give oxygen to treat hypoxia.
2. Give naloxone and/or flumazenil to reverse an overdose of narcotics or benzodiazepines.
3. Reverse effects of non depolarizing muscle relaxants.
4. Give intravenous aminophylline to antagonize the effects of sedative and analgesic drugs, including propofol69.
5. Correct any airway difficulties including jaw life, insertion of an airway, reintubation, application of continuous positive airway pressure.
6. Establish blood pressure at appropriate levels for the patient with vasopressor if necessary.
7. Warm the patient to a temperature of 36-37 degrees.
8. Measure arterial blood gases, glucose and electrolytes and make corrections. Especially of acidosis.
9. Perform a complete blood count and give blood if indicated.
10. Obtain a 12 lead electrocardiogram and appropriate consults.
11. Order a CT scan and request a neurological consult.

Concluding Statement

The causes of delayed awakening after anesthesia are often multifactorial and governed by patient, drug, surgical and metabolic factors. Drug overdose and interactions, especially with neuromuscular blocking

agents, are among the most common causes. Metabolic abnormalities often do not present with the usual signs and symptoms in a patient who is anesthetized. Organic cause of unresponsiveness may have long lasting sequelae and thus early diagnosis and treatment are imperative. On rare occasions, dissociative states may present first as extended periods of unconsciousness without other identifiable causes.

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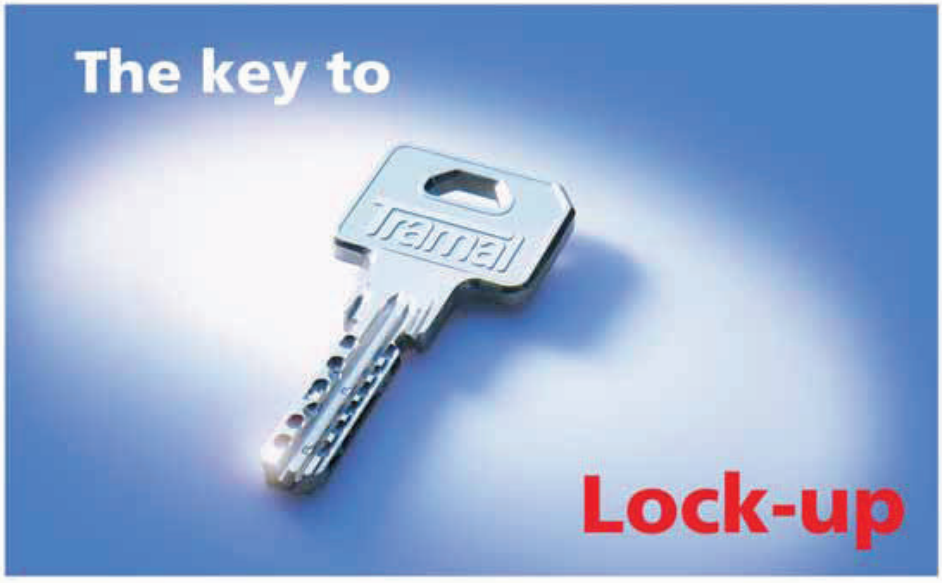

Postoperative Pain

STEP I

Initial bolus

Inject 1 ampoule Tramal® 100 mg i.v. or i.m. slowly over 2-3 minutes

STEP II

Ways of administration after initial bolus

Infusion[1]	PCA[2]	Injection[3]
Inject 2 ampoules Tramal®, each 100 mg, in 500ml of infusion solution. Infusion rate 12-24 mg Tramal®/h (10-20 drops/min or 30-60ml/h).	Subsequent increments of 20 mg with a lock-out time of 5 minutes.	Usual dose is 50 mg or 100 mg 4-6 hourly up to a total daily dose of 400 mg except in special clinical circumstances which might necessitate daily doses up to 600 mg. Further treatment with Tramal® boluses on demand.

If needed further doses of Tramal® 50 mg up to a total of 200 mg (including the initial bolus) within the first 60 min.

STEP III

Follow-up	50 mg	1-2 capsules	every 4-6 hours
	50 mg	20-40 drops	every 4-6 hours
	100 mg	1 suppository	every 4-6 hours
slow release	100 mg, 150 mg, 200 mg	1 tablet	every 12 hours

Intra-Operative	Post-Anaesthesia Care Unit
Loading Dose 2,5 - 3 mg/kg[2,3] at wound closure	If intra-operative dose not given then **BOLUS I.V.*** **100 mg over 2-3 mins**[4]
An intra-operative loading dose of Tramal® will reduce PONV rates[4]	*if needed further doses of 50 mg up to a total of 200mg (incl. the initial bolus) may be given within the first 60 min.

Tramal® INVENTED BY GRUNENTHAL

1. Coetzee J.F. et al. Br.J. Aneasth 1998;81:737-741. **2.** Pang W. et al. Can. J. Anesth.2000; 47: 968-973.
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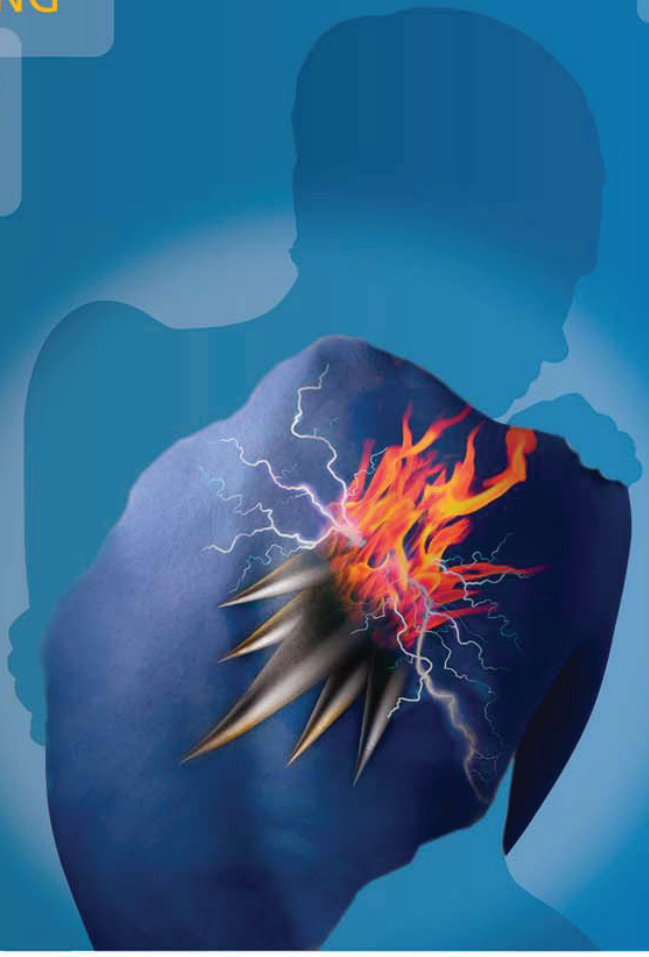

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BRIDION—for optimal neuromuscular blockade management and improved recovery

Predictable and complete reversal

- 98% of BRIDION patients recovered to a TOF* ratio of 0.9 from reappearance of T_2 ‡ within 5 minutes[2]
- 97% of BRIDION patients recovered to a TOF* ratio of 0.9 from 1 to 2 PTCs † within 5 minutes[3]

Rapid reversal

- BRIDION rapidly reversed patients from reappearance of T_2 ‡ in 1.4 minutes[2]
- BRIDION rapidly reversed patients from 1 to 2 PTCs † in 2.7 minutes[3]

BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade[1]

Important safety information

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.
BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the Intensive Care Unit (ICU) setting.
If neuromuscular blockade is required within 24 hours of BRIDION administration, a nonsteroidal neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or suckling on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (ie, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded. Volunteer studies have demonstrated a slight (17%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre existing or comorbid condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

* Train of four
† Post-tetanic counts
‡ Second twitch

REFERENCES: 1. BRIDION Summary of Product Characteristics (SPC). **2.** Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. [published online ahead of print July 30, 2010]. Eur J Anaesthesiol. doi:10.1097/EJA.0b013e32833c56b7.
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Please see summary of product characteristics for full prescribing information.

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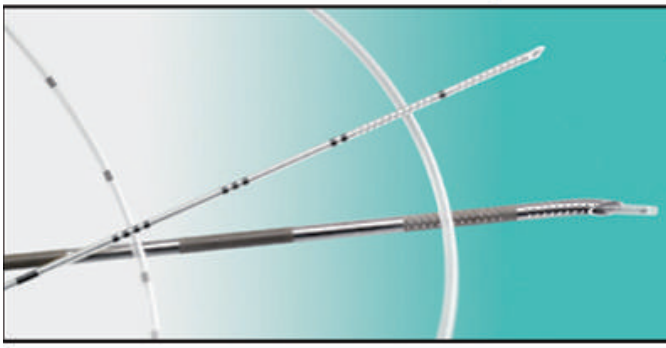

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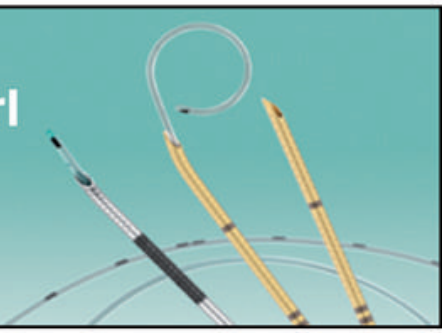

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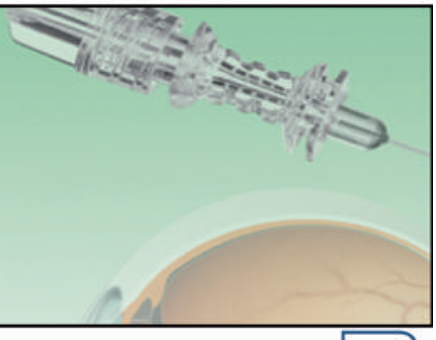

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