Guidelines for sedation, analgesia and neuromuscular blockade in the Intensive Care Unit

Introduction

Sedatives and analgesics are the most commonly administered medication in both surgical and medical ICU accounting for 10-15% of the total drug costs. Despite JCAHO mandates and available guidelines, inadequate or excessive sedation and analgesia still is common in intensive care units. Failure to meet goals of proper sedation and analgesia have deleterious sequele that are associated with an increase in adverse events, poor outcomes, longer ICU stays and economic effects. Recent studies have shown better outcomes and cost savings using protocol driven sedation and analgesia guidelines. Patients who were woken up on a regular basis during their ICU stays had lesser days on ventilators. Use of tools such as the Ramsay sedation scale as well as the Visual Analog Scale(VAS) and the FACES scale for pain have made titration of drugs more precise and cost effective
In an attempt to improve sedation and analgesia in our ICU patients, thereby improving patient outcome and costs the following guidelines have been created. These guidelines are based on recommendations developed by the Society of Critical Care Medicine (January 2002) combined with data on the pharmacodynamics and pharmacokinetics of the drugs in the critically ill
We will use the Ramsay sedation scale or the Richmond Agitation Sedation Scale (RASS) and the VAS and FACES scale for pain assessment

Ramsay Scale

Sedation level	Description
1	Anxious and agitated
2	Cooperative, tranquil, oriented
3	Responds only to verbal commands
4	Asleep with brisk response to light stimulation
5	Asleep without response to light stimulation
6	Non responsive

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation

Visual Analog Scale (VAS)

no pain 0——————————————————10 worst pain

FACES Scale

ANXIOLYTICS AND SEDATIVES

Lorazepam is a benzodiazepine of intermediate duration of action and may be administered as an infusion or by intermittent bolus injection. Like other benzodiazepines, it has anticonvulsant properties. Given its terminal elimination half-life (10-20 hr), it is the benzodiazepine of choice for prolonged sedation. An advantage is no change in elimination half-life in renal disease. It is still prudent to decrease lorazepam doses in the patient with liver disease. Recent studies have however shown a prolonged duration of sedation in critically ill patients on long term lorazepam infusion as compared to a midazolam infusion. Hence lorazepam may be the sedative of choice only when liver or renal dysfunction is present

Midazolam is a short-acting, hydrophilic benzodiazepine that becomes a lipophilic compound in the blood. It is metabolized in the liver to alpha-hydroxymidazolam which has some sedative activity. Accumulation of the parent drug and its metabolite can produce a longer than expected duration, particularly in critical illness or hepatorenal dysfunction.

Propofol is an alkylphenol which is formulated in 10% Intralipid®. It is properly classified as an anesthetic, as it does not possess the ceiling effect of the above sedatives. Therefore, it is more appropriately used to sedate intubated, mechanically ventilated patients. In those patients who are ready to do so, it allows more rapid weaning from the mechanical ventilator than benzodiazepines due to its short duration of action and lack of accumulation. For the same reasons, of all currently used sedatives it can most easily be titrated to a desired level of consciousness. At anesthetic doses, it can cause hypotension secondary to vasodilation and, to a lesser degree, direct myocardial depression. Although a cerebral vasodilator, propofol reduces intracranial pressure and has anticonvulsant properties; it may provide cerebral protection in the head-injured patient providing hypotension is avoided. Its formulation in Intralipid® mandates that intravenous tubing be changed every day, that strict aseptic technique be adhered to in handling the drug, that preferably a dedicated infusion port be utilized and that total parenteral nutrition be adjusted for lipid content.

Dexmedetomidine (Precedex) is a selective alpha-2 receptor agonist that has sedative, analgesic and anesthetic properties when given as a slow infusion. It undergoes rapid distribution, the distribution half life being only 6 minutes. It is indicated for short term sedation in the ICU. It has no respiratory depression and so can be used for hemodynamically unstable patients, or for patients who need sedation for a short period but cannot afford to have respiratory depression. A bolus of 1mcg/kg is given over 10 minutes followed by an infusion of 0.1-0.8 mcg/kg/hr.

ANTIDELERIUM DRUGS

Haloperidol is a useful drug for the treatment of delirium. Agitation in the ICU is frequently a manifestation of delirium and may respond well to haloperidol. Thus, haloperidol should be used as a first line agent when agitation is thought unrelated to pain or anxiety. It is particularly safe in non-intubated patients because it rarely causes respiratory depression. It may cause exacerbation of parkinsonism and should be used with caution when combined with other centrally acting antidopaminergics, including metoclopramide. Haloperidol causes QT prolongation, which may be exacerbated in the presence of class III antiarrhythmics, hypocalcemia and intracranial hypertension. It is a mild alpha-adrenergic antagonist. Its safety has been questioned in acute head injury, as animal studies suggest worsening of secondary brain injury by the central antidopaminergic effect.

ANALGESICS

Morphine is suitable when given by infusion or patient-controlled intravenous analgesia. It is particularly appropriate when administered by infusion over several days, because of its relatively low volume of distribution and rapid hepatic clearance. However, caution is exercised in the patient with renal insuffiency. as its water-soluble metabolites (morphine 3- and 6-glucuronide) have analgesic efficacy and are dependent on renal elimination.

Fentanyl possesses one-hundred times the potency of morphine, but has similar efficacy. Because of its high lipophilicity, it is rapidly acting and widely distributed. It has high accumulative potential secondary to both its high volume of distribution and slow hepatic clearance. As a result, its half-life increases progressively from 30 minutes to 9-16 hrs with continuous infusion, and care must be taken to adjust infusion rate with time. Fentanyl is suitable for patients with morphine allergy and established renal insufficiency. Unlike morphine, it does not cause histamine release and is purported to afford greater hemodynamic stability as a result. However, all sedatives and analgesics cause hypotension usually by sympatholysis, and must be used with caution in those patients with hypovolemia, cardiac failure and cardiac tamponade.

PHARMACOLOGY OF NEUROMUSCULAR-RECEPTOR BLOCKERS

Pancuronium. Pancuronium, one of the original NMBAs used in ICUs, is a long-acting, nondepolarizing compound that is effective after an intravenous bolus dose of 0.06–0.1 mg/kg for up to 90 minutes.Though it is commonly given as an i.v. bolus, it can be used as a continuous infusion by adjusting the dose to the degree of neuromuscular blockade that is desired . Pancuronium is vagolytic (more than 90% of ICU patients will have an increase in heart rate of 10beats/min), which limits its use in patients who cannot tolerate an increase in heart rate. In patients with renal failure or cirrhosis, pancuronium's neuromuscular blocking effects are prolonged because of its increased elimination half-life and the decreased clearance of its 3-hydroxypancuronium metabolite that has one-third to one-half the activity of pancuronium.

Vecuronium. Vecuronium is an intermediate-acting NMBA that is a structural analogue of pancuronium and is not vagolytic. An i.v. bolus dose of vecuronium 0.08 – 0.1 mg/kg, produces blockade within 60–90 seconds that typically lasts 25–30 minutes. After an i.v. bolus dose, vecuronium is given as a 0.8–1.2 mcg/kg/min continuous infusion, adjusting the rate to the degree of blockade desired. Because up to 35% of a dose is renally excreted, patients with renal failure will have decreased drug requirements. Similarly, because up to 50% of an injected dose is excreted in bile, patients with hepatic drug requirements to maintain adequate blockade. The 3-desacetyl vecuronium metabolite has 50% of the pharmacologic activity of the parent compound, so patients with organ dysfunction may have increased plasma concentrations of both the parent compound and the active metabolite, which contributes to the prolongation of blockade if the dose is not adjusted.

Cisatracurium. Cisatracurium, an isomer of atracurium, is an intermediate acting benzylisoquinolinium NMBA that is increasingly used in lieu of atracurium. It produces few, if any, cardiovascular effects and has a lesser tendency to produce mast cell degranulation than atracurium.
Bolus doses of 0.1–0.2 mg/kg result in paralysis in an average of 2.5 minutes, and recovery begins at approximately 25 minutes; maintenance infusions should be started at 2.5–3 mcg/kg/min. Cisatracurium is also metabolized by ester hydrolysis and Hofmann elimination, so the duration of blockade should not be affected by renal or hepatic dysfunction. Prolonged weakness has been reported following the use of cisatracurium.

Sedation and Analgesia for mechanically ventilated patients in the ICU- pharmacokinetic and pharmacodynamic model

For patients requiring sedation for prolonged periods, the use of continuous infusions, is associated with easier and quicker attainment of target sedation scores. Besides this is cost effective too Based on pharmacokinetics and pharmacodynamics of these drugs in the critically ill, the following guidelines have been formulated. The infusion rates depend on the age of the person, concomitant analgesic use as well as whether they have been anesthetized and have a residual effect due to the anesthetic drugs. Midazolam is the recommended drug for short infusions less than 72 hours. Beyond this the pharmacokinetic and pharmacodynamics are less predictable especially in patients with hepatic and renal compromise. The SCCM recommends lorazepam for long term infusion. Though the half life of lorazepam is significantly increased in the critically ill it is more predictable than midazolam. However lorazepam has propylene glycol (PG) as a solvent. PG has been implicated in acute tubular necrosis lactic acidosis and hyperosmolar states when dosages of >18 mg/hr have been given for weeks or >25 mg/hr have been given for hours to days.

DOSING MIDAZOLAM

ICU patients - to achieve Ramsay 3 or a RASS of between 0 and -1

hour	0		1	2	4	6	8	12	24	48	72	96
dose in mg/hr (<60 years)	2mg bolus	6	6	5	4	4	4	4	4	4	4	4
dose (>60 years)	2mg bolus	3	3	3	2	2	2	2	2	2	2	2
Emergence (hrs)								15	15	15	15	15

Post op patients to ICU still under influence of anesthesia - to achieve Ramsay 3 or a RASS of between 0 and -1

hour	0	0	1	2	4	6	8	12	24	48	72	96
dose in mg/hr (<60 years)	no bolus	1	1	1	2	4	4	4	4	4	4	4
dose in mg/hr (>60 years)	no bolus	1	1	1	1	2	2	2	2	2	2	2
Emergence							15		15		10-15	10-15

note- increase or decrease dose by 50 % every 1 hour if inadequate or over sedation

DOSING LORAZEPAM

ICU patients - to achieve Ramsay 3 or a RASS of between 0 and -1

hour	**0** bolus	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**
dose mg/hr (age<60)	2	3	2	1	1	1	1	1	1	1	1	1
dose mg/hr (age >60)	1	2	1	1	1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1
emergence (hr)				22	25	27	28	28	30	30	31	31

Post op patients to ICU still under influence of anesthesia - to achieve Ramsay 3 or a RASS of between 0 and -1

hour	**0** bolus	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**
dose mg/hr (age<60)	0	.5	.5	1	1	1	1	1	1	1	1	1
dose mg/hr (age >60)	0	0	0.5	0.5	0.5	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1
emergence					10	10-15	10-15	15-20	15-20	20-30	20-30	20-30

note- increase or decrease dose by 50 % every one hour if inadequate or over sedation

DOSING PROPOFOL

ICU patients - to achieve Ramsay 3 or a RASS of between 0 and -1

hour	bolus mg/kg	**0**	**3**	**6**	**12**	**24**	**48**	**72**	**168 (7 d)**	**336 (14d)**	
mcg/kg/min	.28	**40**	**35**	**35**	**30**	**30**	**25**	**22**	**20**	**20**	
emergence time (hours)		**0**	**0.12**	**0.13**	**0.17**	**0.22**	**0.32**	**0.57**	**3.30**	**3.38**	

note- increase or decrease dose by 25 % every 10-20 minutes if inadequate or over sedation

ICU patients - to achieve deep sedation or for use in refractory ICP management

hour	bolus mg/kg	**0**	**3**	**6**	**12**	**24**	**48**	**72**	**96**	**120**
mcg/kg/min	1	50-100	100	100	100	85	75	75	50-75	50-75
emergence time (hours)			.4	2	9	24	48	58	60-70	>70

ANALGESIA

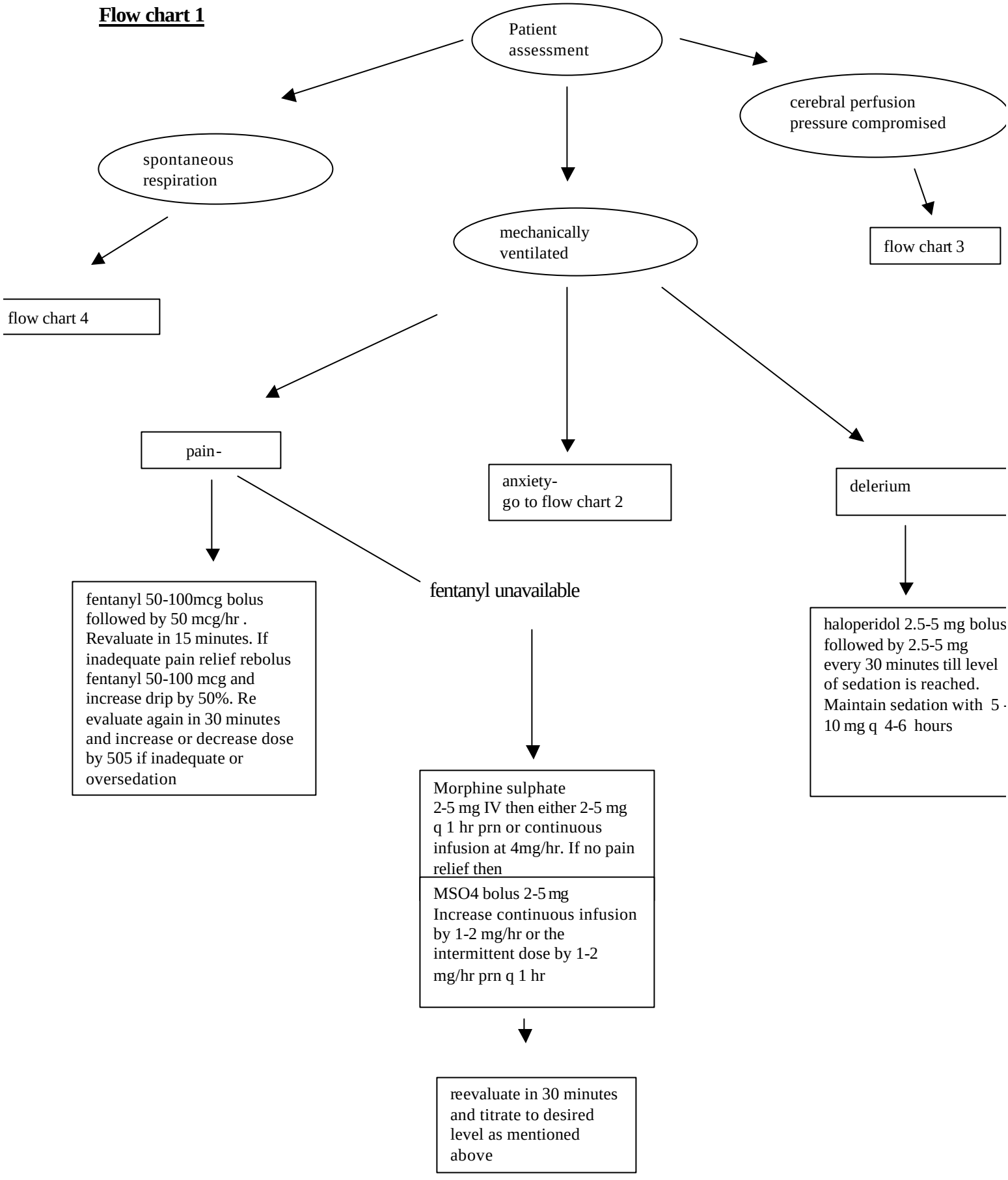
Hemodynamically stable patient

MSO4 bolus 2-5 mg, followed by 5mg/hr infusion. Reassess after 30 minutes. If inadequate pain relief, re-bolus MSO4 2-5 mg and increase drip by 50%. Re evaluate again in 30 minutes and increase or decrease dose by 25 % if inadequate or over sedation. However fentanyl is probably the drug of choice in this patient population too

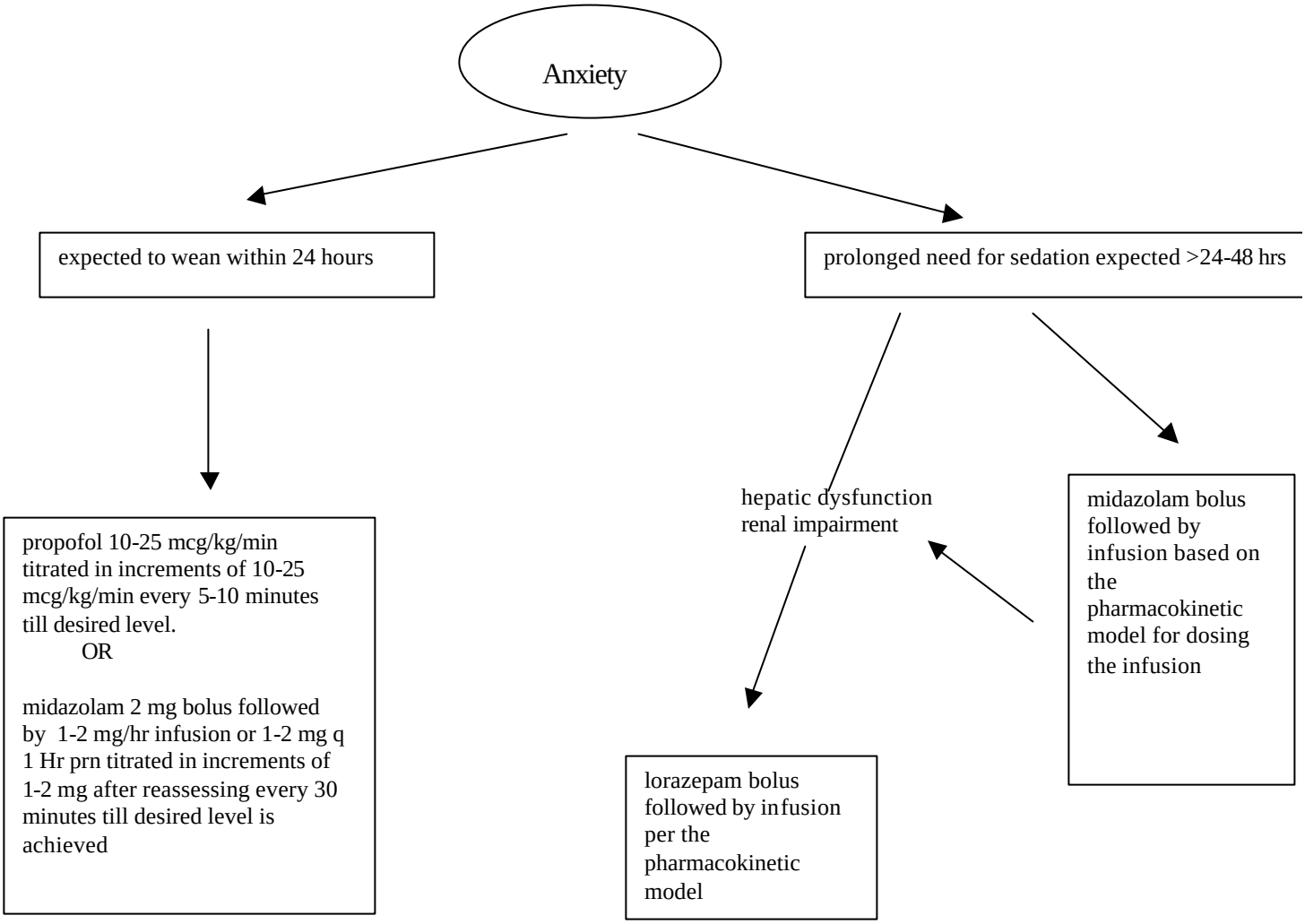
Hemodynamically unstable patient

Use fentanyl 50-100 mcg followed by an infusion at 50 mcg/hr. Revaluate in 15 minutes. If inadequate pain relief, re-bolus fentanyl 50- 100 mcg and increase drip by 50%. Re evaluate again in 30 minutes and increase or decrease dose by 50% if inadequate or over sedation.

Flow chart 1


Patient assessment
spontaneous respiration
mechanically ventilated
cerebral perfusion pressure compromised
flow chart 3
flow chart 4
pain-
anxiety- go to flow chart 2
delerium
fentanyl 50-100mcg bolus followed by 50 mcg/hr . Revaluate in 15 minutes. If inadequate pain relief rebolus fentanyl 50-100 mcg and increase drip by 50%. Re evaluate again in 30 minutes and increase or decrease dose by 505 if inadequate or oversedation
fentanyl unavailable
haloperidol 2.5-5 mg bolus followed by 2.5-5 mg every 30 minutes till level of sedation is reached. Maintain sedation with 5 - 10 mg q 4-6 hours
Morphine sulphate 2-5 mg IV then either 2-5 mg q 1 hr prn or continuous infusion at 4mg/hr. If no pain relief then
MSO4 bolus 2-5 mg Increase continuous infusion by 1-2 mg/hr or the intermittent dose by 1-2 mg/hr prn q 1 hr
reevaluate in 30 minutes and titrate to desired level as mentioned above

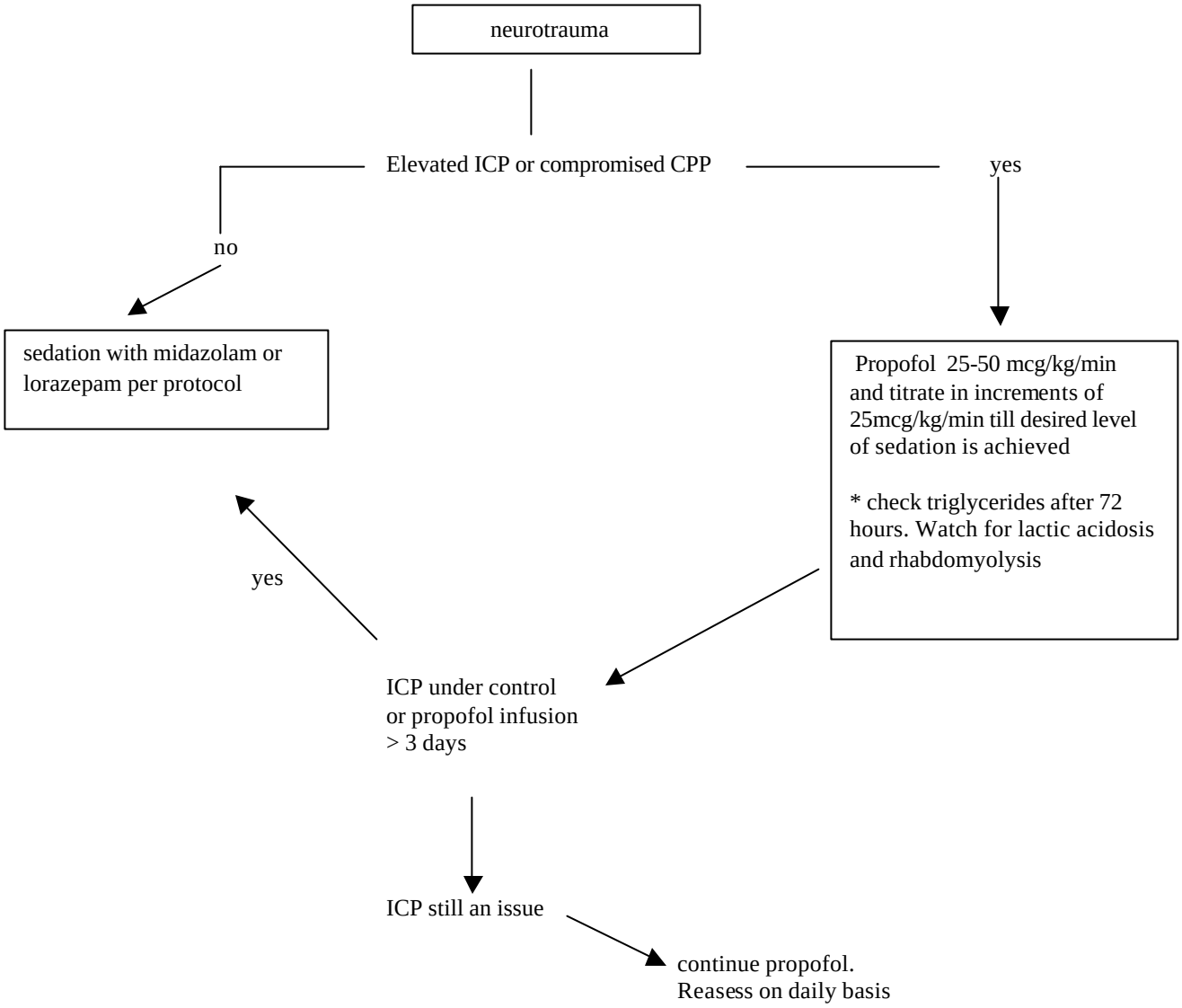
Flow chart 2



***once adequate level of sedation and analgesia are achieved, the patient is to be evaluated every 4 hours. If depth of sedation is more than desired, decrease anxiolytics by 25% and analgesic by 25%**

Flow chart 3- Guidelines for sedating patients with cerebral injury and at risk for cerebral compromise

Early head injury protocol

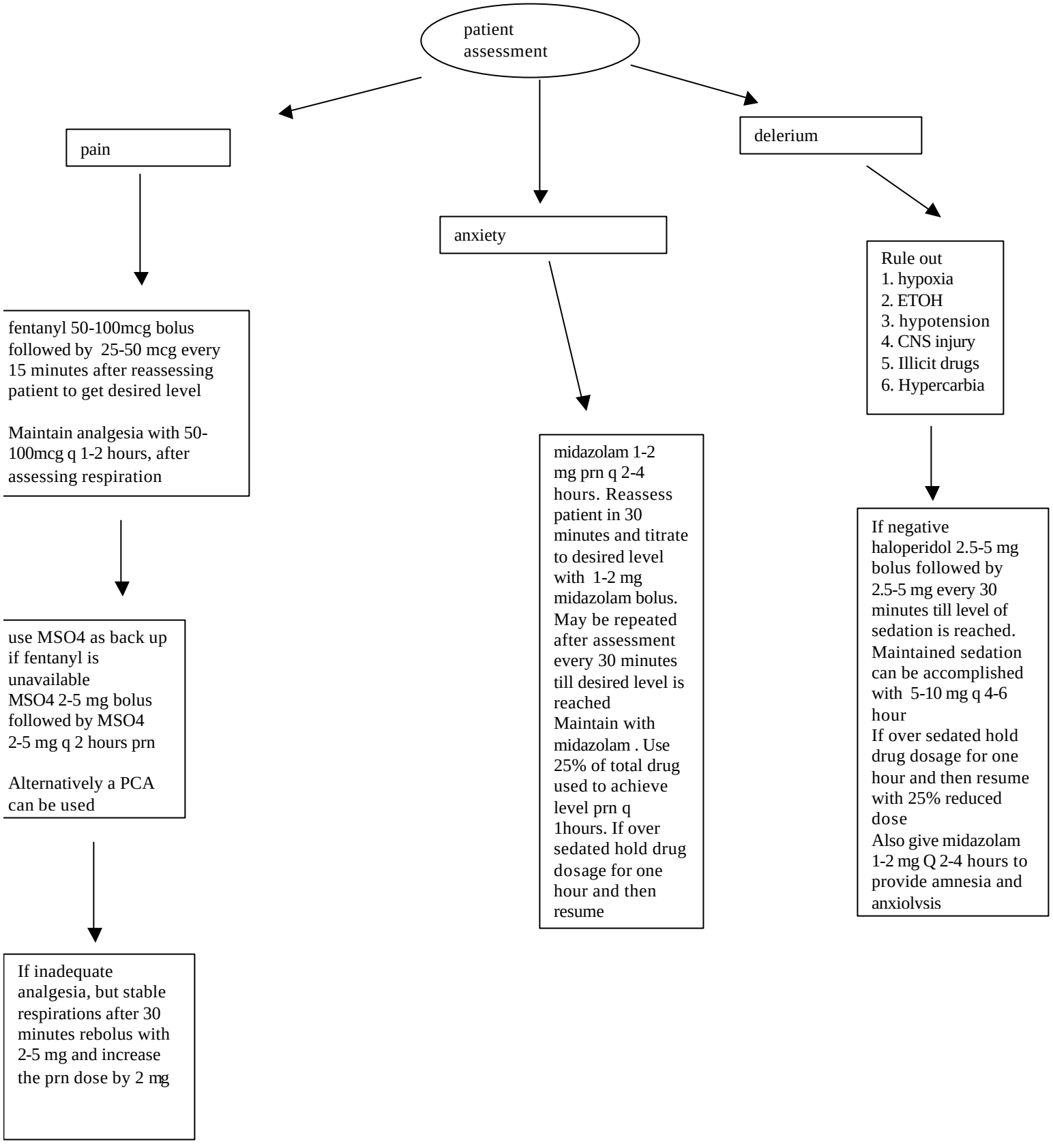


Late head injury protocol

Rule out causes of agitation such as
1. hypoxia
2. ETOH
3. hypotension
4. CNS injury
5. Illicit drugs
6. Hypercarbia

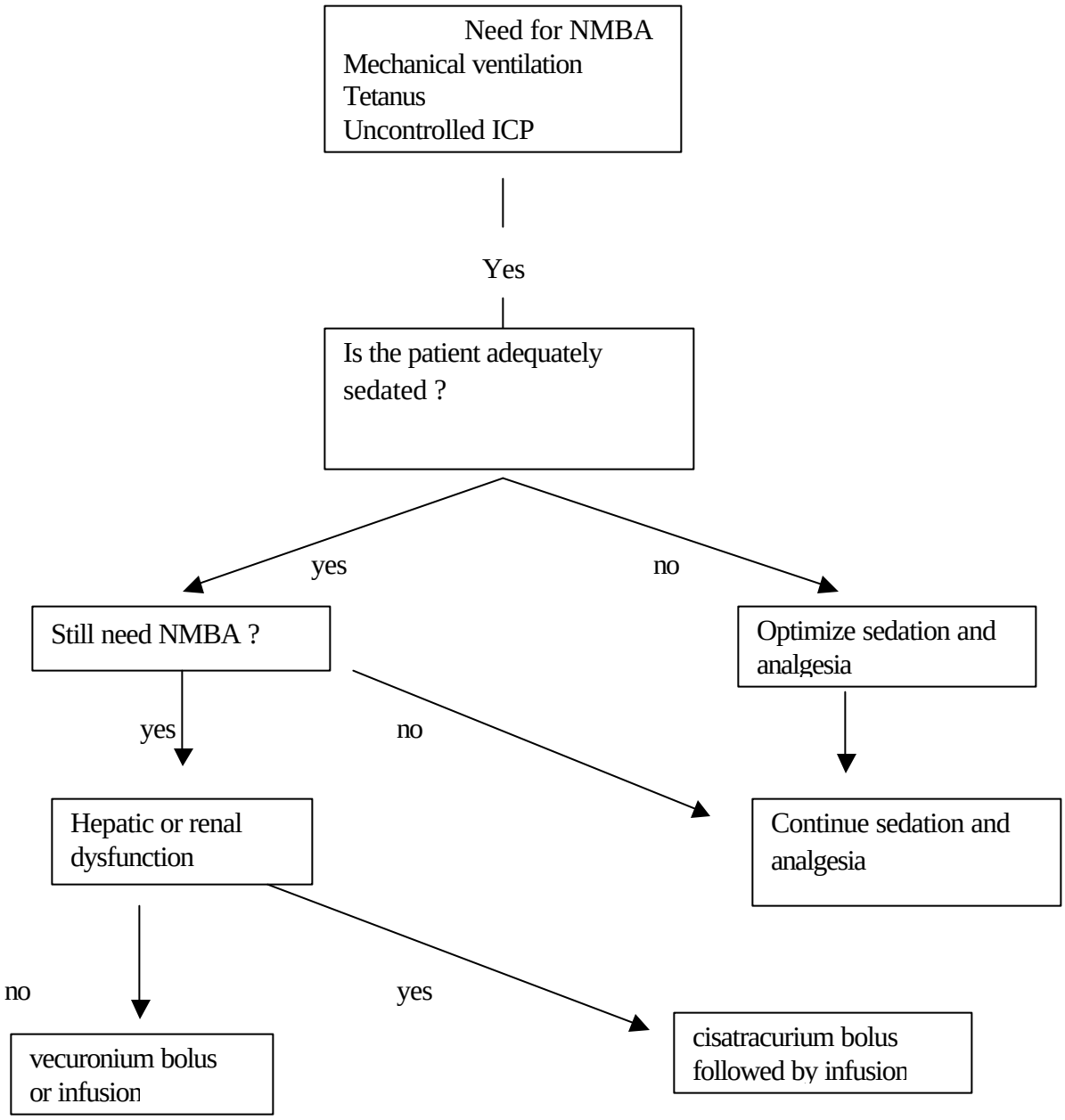
If negative haloperidol 2.5-5 mg bolus followed by 2.5-5 mg every 30 minutes till level of sedation is reached. Maintain sedation with 5 mg q 4-6 hours. If over sedated hold drug dosage for one hour and then resume with a 25% reduction in the dose. Also give midazolam 1-2 mg Q 2-4 hours to provide amnesia and anxiolysis since the long term effects of haloperidol on secondary brain injury is not

Flow chart 4- guidelines for sedation and analgesia in anxious, agitated, non intubated patients



Guidelines for sustained neuromuscular blockade in the critically ill

Neuromuscular blockade (NMBA) in the ICU, other than to facilitate endotracheal intubation, is utilized to facilitate mechanical ventilation, to allow different modes of ventilation and to manage patients with head trauma and tetanus. Independent of the reason for using NMBA, all other modalities to improve the clinical situation should be tried and NMBA used only as a last resort. A Task Force of the ACCM/ SCCM has recently put forth their recommendations. Though the task force still recommends Pancuronium as the drug of choice in patients with no known hepatic and renal function, it mentions the detrimental effects of the vagolysis in patients with compromised cardiovascular function or tachycardia. Since majority of our patients probably will not tolerate a 15% increase in the heart rate, the recommendations here, substitute vecuronium in place of pancuronium, maintaining the other recommendations of the SCCM. Nerve stimulation should be assessed during muscle relaxation.



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