INTRODUCTION TO SEDATIVE DRUG PHARMACOKINETICS

When using a sedative agent, you should think of…

USE

Sedative agents induce loss of consciousness, loss of response to noxious stimuli and inhibition of memory. Many sedative agents are also used as drugs to induce anaesthesia. Some are used in other situations, for example to treat seizures. All sedative drugs act by depressing central nervous system function.

SITE OF ACTION

Sedative agents act in various parts of the brain, such as the thalamus, the limbic system (associated with memory) and certain cortical areas. The exact mechanism and key sites of action is incompletely understood for many agents, although the receptors at which drugs work are known.

METHOD OF ACTION

For drugs to work they have to reach a sufficient **concentration** at their **site of action**. This means they have to penetrate the central nervous system and enter brain cells. A number of steps are required to achieve this, including entering the blood, circulation to the brain, crossing the blood-brain barrier, and penetrating the target brain cells. The rate at which this occurs depends on a range of factors. Key factors are the properties of the drugs, the diffusion gradient "driving" drugs into brain cells, and the rate at which each drug can cross cell membranes.

FACTORS DETERMINING THE RATE OF ONSET OF A SEDATIVE OR ANALGESIC DRUG

A range of factors determine the rate of onset of a sedative or analgesic drug. These are generally all properties that affect how quickly the drug reaches the concentration necessary within the target brain cells to produce a reduction in conscious level.

Molecule size

Smaller molecules are generally able to cross cell membranes more rapidly. Sedative drugs tend to be small molecules.

Concentration Gradient

*Movement of sedative drugs across cells and membranes is dependent on **passive diffusion**. This means the drug molecules move from an area of high concentration to one of low concentration without consuming energy. Rates of passive diffusion depend on the **concentration gradient** across the membrane. Factors such as the dose of drug given, its water and lipid solubility, and cardiac output will all determine the concentration gradient determining movement of a sedative to its site of action in the brain.*

Ionization

Many drugs are weak acids or bases. This means that in the body they can exist in both unionised (no net charge) or ionised (positively or negatively charged) forms, depending on the pH. Sedative drugs cross cell membranes by diffusion when they are unionised and have no positive or negative charge. Drugs that easily exist in unionised forms within the body tend to act more quickly because they rapidly enter cells.

Lipid Solubility

The lipid solubility of a drug influences its rate of onset and duration of action in several ways. More lipid soluble drugs cross cell membranes quicker, because the membranes themselves are lipid bilayers. This tends to increase the rate of onset of the drug if it is present in high concentrations in the brain. However, more lipid soluble drugs tend to be taken up by tissues in other parts of the body with high lipid content, such as adipose tissue. Rapid uptake by these tissues may reduce the amount of drug reaching the brain, which will decrease the amount of drug in the brain available to cause sedation. The lipid solubility of a drug also influences how long the drug has clinical effects in the body.

Plasma Protein Binding

Most drugs exist in the blood in two forms: bound and unbound to plasma proteins. The amount of a drug that is protein bound depends on its individual properties. It is the unbound proportion of the drug that is easily available to enter the brain. This is also the drug that is most actively metabolised and excreted. In general less protein bound drugs have more rapid onset, because the drug reaches high concentrations in the brain more quickly as less is taken up by proteins.

The blood proteins that bind drugs include albumin, lipoproteins, glycoproteins and globulins. The levels of all of these proteins can be affected by critical illness, which may affect the metabolism and duration of action of sedative and other drugs. In practice this is difficult to predict, but may partly explain why the clinical effects of some sedatives are greater than expected in sick patients.

WHERE DO SEDATIVE DRUGS ACT?

Sedative drugs act via several receptor types in the brain.

GABA RECEPTORS: *gamma*-aminobutyric acid (GABA) is an important neurotransmitter in the brain. It is the main inhibitory transmitter and acts via GABA receptors. GABA receptors do not mediate analgesia. Sedative drugs which act on GABA receptors include benzodiazepines (midazolam, lorazepam, diazepam), propofol, and barbiturates (thiopentone, phenobarbital). Ethanol also acts on GABA receptors.

α2-RECEPTORS: α receptors are part of the adrenergic/sympathetic system. α1 receptors mediate vasoconstriction of arterioles and are the receptors that norepinephrine acts on to increase blood pressure. α2 receptors are present in the central and peripheral nervous system. Peripheral nervous system α2 receptors mediate many effects, but importantly inhibit norepinephrine release and can cause bradycardia and hypotension. Central nervous system α2 receptors mediate sedation and analgesia. Sedative drugs which act on α2 receptors (α2 agonists) include dexmedetomidine and clonidine. These have both sedative and analgesic effects.

OPIOID RECEPTORS: Opioid receptors are distributed widely in the central and peripheral nervous system, and found in other parts of the body. There are many sub-types of receptors, including μ-, κ-, and δ-receptors each of which have sub-types. All opioid receptors mediate analgesia, but they can also cause sedation and a wide range of other effects including nausea, respiratory depression, dysphoria, cardiovascular effects (bradycardia and hypotension), itch, and constipation. The effect of individual opioid agonists (opiate drugs) will depend on the effects on individual receptors. Opiates include morphine, fentanyl, alfentanil, remifentanil, and methadone.

FACTORS DETERMINING THE DURATION OF ACTION OF A SEDATIVE DRUG

Several factors determine how long a drug lasts following a specific dose. These all relate to how quickly the concentration of the drug in the brain decreases. Drugs tend to leave the brain by diffusion back into the plasma and transport to other parts of the body. The gradient "driving" the drug out of the brain is important, which is effectively the reverse of the factors determining the rate of onset of the sedative effect.

Important factors that decrease the plasma concentration quickly, leading to the drug leaving the brain are:

METABOLISM: As the drug is metabolised into breakdown products and excreted from the body the plasma concentration falls and the drug effect wears off. Most drugs are metabolised in the liver and kidneys. In general drugs and their metabolites that are water, and therefore plasma, soluble tend to be excreted primarily in urine but some are excreted in bile. Drugs and metabolites that are not water soluble tend to rely on hepatic metabolism and excretion. Impaired liver and renal function will alter the metabolism of sedative, and other, drugs and may prolong the duration of sedation from a given dose.

REDISTRIBUTION: If the drug is redistributed rapidly into other parts of the body the plasma concentration will decrease quickly, the drug will leave the brain down its concentration gradient, and the sedative effect will wear off. Drugs that are very lipid soluble tend to redistribute quickly because the drug is taken up by lipids in adipose and other tissues.

ACTIVE METABOLITES: The metabolites of some sedatives and analgesics still have sedative, analgesic, or other effects. These active metabolites can prolong the duration of action of the drug, especially if the active metabolite is not excreted from the body normally because of impaired liver or kidney function. For example, morphine is partly metabolised into Morphine-6-glucuronide. This is normally excreted quickly by the kidney but can accumulate in renal failure. Midazolam is excreted from the body quickly in healthy individuals, but its active metabolite, alpha1-hydroxymidazolam, can accumulate in patients with liver and renal failure.

PATIENT SENSITIVITY: Factors such as age and chronic ill health may increase the sensitivity of a patient to sedative or analgesic drugs. In addition, the acute illness may affect brain function, for example by causing coma or delirium, which will increase sensitivity to sedative effects.

DRUG INTERACTIONS: Some drugs interact to have additive or synergistic sedative and/or analgesic effects. Synergy means the effects of the drugs are greater than expected from their individual doses added together, as is the case for midazolam and Propofol. Drug interactions are also possible from other drugs used in the ICU, especially those that affect drug metabolism.

THE IDEAL INTRAVENOUS SEDATIVE AGENT

The following table highlights some properties of the ideal sedative and analgesic drug for use in the ICU:

THE IDEAL INTRAVENOUS SEDATIVE AGENT			
RECEPTOR TYPE	GABA Receptors	α2-Receptors	Opioid Receptors
Receptor type			
ONSET	Rapid (< 1 minute)	Intermediate (1-3 minutes)	Slow (> 3 minutes)
Rate of Onset	✓		
Rate of Offset	PREDICTABLE RATE OF OFFSET		
EFFECT	Strong	Weak	None
Sedative effect	✓		
Amnesic effect	DEPENDS ON CLINICAL SITUATION		
Analgesic effect	✓		
RISKS	None	Lower Risk	Higher Risk
Cardiovascular effects	✓		
Respiratory depression	✓		
Potential to cause delirium	✓		
Active metabolites and/or accumulation	✓		
Potential toxic effects	✓		
COST	Low	Intermediate	High
Cost	✓		

COMMON INTRAVENOUS SEDATIVE AND ANALGESIC AGENTS

The following pages are a quiz to highlight the important properties of the commonly used sedative and analgesic drugs in the ICU. Tick the boxes that correspond to the best description for each drug.

MIDAZOLAM

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset		√	
Rate of offset			√
EFFECT	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)			√
Amnesic effect			√
Analgesic effect	√		

RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure		√	
Respiratory Depression		√	
Potential to cause delirium			√
Active metabolites and/or accumulation			√
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST	√		

Key point: Midazolam is a short acting benzodiazepine (GABA receptors) with hypnotic, anxiolytic, and amnesic properties but NO analgesic properties. It causes little or mild cardiovascular and respiratory depression in appropriate doses. It has a short duration of action but has potential to accumulate in sick patients with renal and hepatic failure due to delayed metabolism and accumulation of active metabolites. Midazolam can promote delirium, but is a potent anticonvulsant for use in seizures.

LORAZEPAM

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset			√
Rate of offset			√
EFFECT	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)			√
Amnesic effect			√
Analgesic effect	√		
RISKS	NONE	LOWER RISK	HIGHER RISK

Cardiovascular effects (low pulse and/or blood pressure		√	
Respiratory Depression		√	
Potential to cause delirium			√
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST	√		

Key points

Lorazepam is a longer acting benzodiazepine (GABA receptors) with hypnotic and anxiolytic properties but no analgesic properties. It is a particularly potent amnesic drug. It causes little or mild cardiovascular and respiratory depression in appropriate doses. It has no active metabolites and its metabolism is little affected by organ dysfunction, but it has a long half-life (10-20 hours). It is usually given by intermittent bolus injection. Lorazepam can promote delirium, but is a potent anticonvulsant for use in seizures.

PROPOFOL

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset	√		
Rate of offset		√	
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)			√
Amnesic effect			√
Analgesic effect	√		
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure			√

Respiratory Depression			√
Potential to cause delirium		√	
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST		√	

Key points

Propofol acts via GABA receptors and has hypnotic, anxiolytic, and amnesic properties but no analgesic properties. It can cause cardiovascular and respiratory depression in sick patients, so bolus doses should be used cautiously. It has no active metabolites and its metabolism is little affected by organ dysfunction,. Propofol probably has lower tendency to cause delirium than benzodiazepines. In high doses propofol can cause a serious complication, the “propofol infusion syndrome (PRIS)”

PROPOFOL INFUSION SYNDROME (PRIS)

The PRIS is a rare complication associated with high dose infusion of propofol. Clinical features include bradycardia, metabolic acidosis, rhabdomyolysis, hyperlipidaemia, and liver enlargement. PRIS has most commonly been reported at doses higher than 4 mg/kg/h for greater than 24-48 h duration and is more common in children than adults. It is more common in patients receiving catecholamines and corticosteroids. Early cardiac signs include right bundle branch block and ST elevation in ECG leads V1 to V3 (similar to those seen in a specific cardiac syndrome - Brugada syndrome). It may occur in genetically "at risk" patients due to abnormalities of mitochondrial function, but this is uncertain. There should be a high index of suspicion in patients receiving high

doses of propofol, for example head injury, who develop some or all of the signs. Mortality from PRIS is high (up to 33%) and may occur even after discontinuing the infusion. The treatment is withdrawal of propofol and multi-organ support.

DEXMEDETOMIDINE

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset			√
Rate of offset			√
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)			√
Amnesic effect		√	
Analgesic effect			√
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure		√	
Respiratory Depression	√		
Potential to cause delirium		√	
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST			√

Key points

Dexmedetomidine is a centrally acting $\alpha 2$ agonist with hypnotic, anxiolytic, and analgesic properties. It has less amnesic effects than benzodiazepines. It's onset of action is relatively slow (10-15 minutes). Importantly it causes virtually no respiratory depression and can be continued safely in extubated patients. However, it commonly causes bradycardia. It has a short duration of action which wears off quickly, and is not thought to accumulate in hepatic and renal failure. Dexmedetomidine is currently an expensive sedative agent usually restricted to "difficult" sedation problems and/or drug withdrawal. It probably reduces the prevalence of delirium significantly compared with benzodiazepines.

A similar α2 agonist is clonidine

Clonidine is an "older" α2 agonist with lower selection for central nervous system receptors. It has less potent sedative properties, and causes more bradycardia and hypotension than the more centrally selective dexmedetomidine. Clonidine is therefore less suitable as a "first line" agent for sedation in the ICU, but its effects on the sympathetic nervous system mean it is effective during drug withdrawal syndromes where tachycardia and hypertension are prominent features. It is also sometimes used as an adjunct to sedation in patients with difficult sedation and agitation.

MORPHINE

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset			√
Rate of offset			√
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)		√	
Amnesic effect	√		
Analgesic effect			√
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure		√	
Respiratory Depression			√
Potential to cause delirium		√	
Active metabolites and/or accumulation			√
Potential toxic effects			√
COST	LOW	INTERMEDIATE	HIGH
COST	√		

Key points

Morphine is a potent analgesic acting on central and peripheral opioid receptors. Morphine has a wide range of potential side effects including respiratory depression, hypotension, nausea, itch, constipation, dysphoria, histamine release (causing urticarial and bronchospasm), and urinary retention. The onset of analgesia from morphine is relatively slow (5-10 minutes), but its effects

last 2-4 hours. Morphine is metabolized in the liver into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The majority of morphine is excreted via bile as M3G, but about 10% is converted to M6G which is excreted by the kidneys. M6G is a potent analgesic which explains why toxic opioid effects can occur in renal failure. In critically ill patients with renal failure morphine should be avoided.

FENTANYL

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset		√	
Rate of offset			√
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)		√	
Amnesic effect	√		
Analgesic effect			√
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure	√		
Respiratory Depression			√
Potential to cause delirium		√	
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST		√	

Key points

Fentanyl is a potent synthetic opioid drug (x100 morphine). The onset of analgesia from fentanyl is relatively rapid (1-3 minutes) and lasts for 30-60 minutes. An advantage of fentanyl is greater cardiovascular stability and lack of histamine release following injection; which results in part from a selective action on μ-receptors rather than all opioid receptors. These properties mean it can be used in high dose with safety in sick patients when analgesia and sedation are required, or for anaesthesia. Fentanyl is metabolised in the liver and has no active metabolites so is unlikely to

accumulate except when used in large doses. Fentanyl is very lipid soluble which explain how it can be used as fentanyl patches and lozenges for use in pain treatment.

ALFENTANIL

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset	√		
Rate of offset		√	
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)		√	
Amnesic effect	√		
Analgesic effect			√
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure		√	
Respiratory Depression			√
Potential to cause delirium	√		
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST		√	

Key points

The main differences between fentanyl and Alfentanil are lower potency (about 25% of fentanyl) more rapid onset of action (within 1 minute) and shorter duration of action (5-10 minutes). It is therefore well-suited to administration by continuous infusion, because it has no active metabolites and low risk of accumulation. As for fentanyl, there is a risk of respiratory depression.

REMIFENTANIL

ONSET	Rapid (< 1minute)	Intermediate (1-3 minutes)	Slow (>3 minutes)
Rate of onset	√		
Rate of offset		√	
EFFECTS	NONE	WEAK	STRONG
Sedative effect (hypnosis and anxiolysis)			√
Amnesic effect	√		
Analgesic effect			√
RISKS	NONE	LOWER RISK	HIGHER RISK
Cardiovascular effects (low pulse and/or blood pressure			√
Respiratory Depression			√
Potential to cause delirium	√		
Active metabolites and/or accumulation	√		
Potential toxic effects		√	
COST	LOW	INTERMEDIATE	HIGH
COST		√	

Key points

Remifentanil is an ultra-short acting synthetic opioid drug with onset and offset within 1-2 minutes. This occurs because it is metabolised by highly active esterase enzymes in the plasma, and does not require liver or renal function for metabolism. These properties mean it is administered by continuous infusion and is ideal for titrating analgesia and sedation in the ICU; this approach using a single agent has been called analgo-sedation. Remifentanil can cause significant hypotension as well as respiratory depression, especially in high dose. Its analgesic effect wears off very rapidly so dose reduction should be carried out with caution in patients anticipated to experience significant pain.

SUMMARY

The properties of sedative and analgesic drugs depend on a range of factors that influence the rate at which they reach a clinically effective concentration in the brain.

In general:

- Drugs acting on **GABA receptors** (benzodiazepines; propofol; barbiturates) cause sedation, anxiolysis and amnesia, but are not analgesic.
- Drugs acting on **α2 receptors** (dexmedetomidine; clonidine) have sedative and analgesic properties.
- Drugs acting on **opioid receptors** (morphine; fentanyl; alfentanyl; remifentanil) have powerful analgesic properties and milder sedative effects.

The individual properties of the drugs influence their rates of onset, duration of action, chance of accumulation during critical illness, and side effects.

Considering the sedation and analgesia needs of an individual patient and risks of side effects, clinicians should determine the choice of drug used according to local protocols and practices.