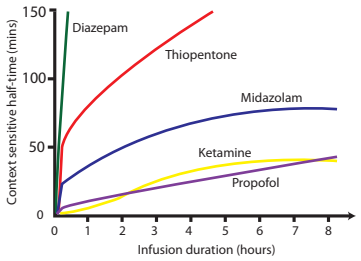
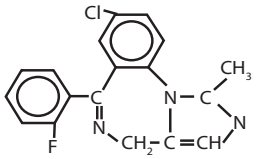
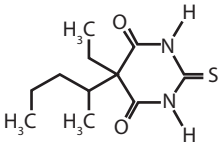
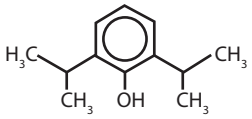
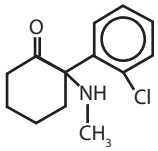
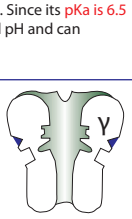
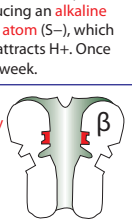
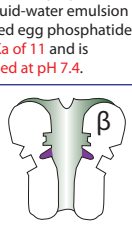
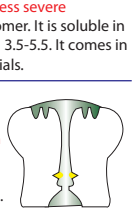
INTRAVENOUS ANAESTHETIC AGENTS

The ideal intravenous anaesthetic agent. May be described in terms of the pharmaceutical aspects, the pharmacokinetic and pharmacodynamic perspective. From a pharmaceutical perspective it should be soluble in water, stable in solution, not require reconstitution, stable in the presence of air, light and temperature, not support bacterial growth, be compatible with outer drugs and fluids, have no additives and be inexpensive. From a pharmacokinetic perspective it should have a rapid onset of action, high lipid solubility (needs to cross BBB), be non cumulative during infusion, have a rapid and predictable recovery, be completely metabolised to inactive metabolites, and be safe in renal or hepatic impairment without adjustment. From a pharmocodynamic perspective it shoul not cause pain on injection, and be safe if it extravasates, have no adverse drug reactions, have a smooth induction, demonstrate analgesic, antiemetic, antiepileptic properties, and muscle relaxation. It should not cause emergence phenomena, not modify cerebral blood flow, ICP or intra-occular pressure and decrease brain O2 requirements. It should have minimal cardiovascular or respiratory depression or stimulation. Be safe in paediatric, pregnant and elderly populations.

Factors which affect recovery from IV anaesthesia may be subdivided into surgery factors, patient factors and anaesthetic factors. The surgery factors relate to the type of procedure, , its duration, and the intraopertaive complications. whether it is planned or emergent. The patient factors relate both to pre-existing disease, body habitus, sex, age and current disease state which may complicate the common sequelae of GA recovery. Physiological changes accompanying emergence from general anesthesia can be profound. It is easiest to think of this in terms of systems. Cardiovascular issues are driven by the sympathetic nervous system regaining tone. Hypertension and tachycardia are common, which is enhanced by pain. Myocardial ischemia can appear or markedly worsen during emergence in patients with coronary artery disease. Neurologically, emergence excitement occurs in 5–30% of patients and is characterized by tachycardia, restlessness, crying, moaning and thrashing, and various neurological signs. This may be exacerbated in people with pre-exisiting behavioural disturbances and psychiatric conditions. Postanesthesia shivering occurs frequently because of core hypothermia or a delay in the return of central nervous system function compared to peripheral nervous system. Respiratory issues are significant and exacerbated significantly by prexisting disease such as COPD, restrictive lung disease or sleep apnoea. Airway obstruction may occur during the postoperative period because residual anaesthetic effects continue to partially obtund consciousness and reflexes. Strong inspiratory efforts against a closed glottis can lead to negative pressure pulmonary edema. Pulmonary function is reduced postoperatively following all types of anesthesia and surgery, and hypoxemia may occur. Respiratory suppression associated with opioids can be problematic among postoperative patients with a substantial residual anesthetic effect. Intevention factors relate both to the procedure performed and the agents employed to maintain the general anaesthesia.

Anaesthetic factors relate to the anaesthesia strategy employed, in particular the type of anaesthesia employed (volatile, mixed or TIVA). The focus here is on the IV agents. Most of the IV GA agents are characterised by rapid emergence from GA when given as a bolus, this is due to generally to their redistribution (they are lipophilic to ensure good penetrate to the CNS) and metabolism. When given as an infusion however context sensitive half times become more important and this varies considerably between agents. After prolonged infusions, drug half-lives and durations of action are dependent on a complex interaction between the rate of redistribution of the drug, the amount of drug accumulated in fat, and the drug's metabolic rate. This phenomenon has been termed the context-sensitive half-time; that is, the half-time of a drug can be estimated only if one knows the context—the total dose and over what time period it has been given. Propofol is rapidly metabolised and has a clearance which exceeds hepatic blood flow suggesting extrahepatic metabolism. Although clearing the central compartment rapidly, it has a prolonged terminal half life, probably due to slow release from fat. In prolonged infusions the terminal half life may stretch out to 60 hours but the context sensitive half time does not increase significantly and therefore waking may remain relatively rapid. Thiopentone is also rapidly distributed to other tissues and this explains the rapid recovery from a single dose (rather than metabolism). When given as an infusion however compartments are rapidly saturated and the duration of action becomes dependent on the terminal half life and the clearance of the liver which is slow for thio (and may become saturated - therefore zero order) leading to an increased context sensitive half time. Midazolam is metabolised to metabolites which are cleared quickly in contrast to diazepam and this accounts for the marked difference in their context sensitive half times (following bolus the recovery profile is similar). Ketamine, like the other drugs discussed here is rapidly distributed to tissues. It is metabolised hepatically to an active metabolite but it does not have a significantly increased context sensitive half time. Indeed it may induced hepatic enzymes which leads to tolerance with repeated dosing. Of note in terms of recovery is the marked neurological emergence issues associated with ketamine.



	MIDAZOLAM	THIOPENTONE	PROPOFOL	KETAMINE
				
FORMULATION	Midazolam is presented as a clear solution at a pH of 3.5. At this pH is almost completely ionised and therefore water soluble. Since its pKa is 6.5 it is 89% un-ionised at physiological pH and can therefore cross lipid membranes.	The sodium salt is a pale yellowish-white powder with a bitter taste and an garlic-like odour. It readily dissolves in deionized water producing an alkaline solution due to its ionized sulphur atom (S–), which has strongly basic properties and attracts H+. Once reconstituted it is stable for ~ one week.	Propofol is a achrial. lipophilic, sterically hindered alkylated phenol. It is presented as a 1% preparation and appears a a white opaque liquid-water emulsion containing soya bean oil or purified egg phosphatide. It is a weak organic acid with a pKa of 11 and is therefore almost entirely un-ionised at pH 7.4.	Ketamine is presented as a racemic mixture or as the single S (+) enantiomer which is 2-3 times as potent, more quickly metabolised and has less severe side-effects than as the R (-) enantiomer. It is soluble in water forming an acidic solution pH 3.5-5.5. It comes in liquid solution, 100mg/mL in 2mL vials.
MECHANISM OF ACTION	$GABA_A$ RECEPTOR BINDING SITE Binds to the gamma subunit of the $GABA_A$ receptor, increasing the affinity of the receptor to GABA. 	$GABA_A$ RECEPTOR BINDING SITE Appears to exert its main action by facilitating $GABA_A$ mediated Cl influx. May also block Na^+, NMDA and Ca^{2+} channels. It is more promiscious in affecting multiple sites compared to Propofol. 	$GABA_A$ RECEPTOR BINDING SITE Potentiates and directly gates $GABA_A$ facilitating its action. May have some Na^+ and Ca^{2+} channels blocking action. 5HT has been implicated as the reason it has antiemetic properties. 	NMDA RECEPTOR BINDING SITE Distinct from the other IVGAs in that its primary action is NMDA non competitive antagonism. Has some opiod, nicotinic, monoamine oxidase, Na^+, and Ca^2 actions as well. 
CENTRAL NERVOUS SYSTEM EFFECTS	Midazolam, like all of the benzodiazepienes is a hypnotic, anxiolytic, anticonvulsant and amnesic agent. Benzodiazepienes reduce the cerebral metabolic rate of O_2 -$CMRO_2$, cerebral blood flow and suppress rapid eye movement - REM sleep.	Reduced neuronal activity is reflected in a dose-dependent depression of the EEG, progressing from an awake α pattern to high amplitude / low freq δ and θ activity to burst suppression and subsequently electrical silence. There is a corresponding decrease in cerebral blood flow and Thio may reduce ICP refractory to mannitol and hyperventilation. At maximal effect it may reduce cerebral metabolism by as much as 55%.	The nervous system effects of propofol are similar to those of thiopentone. It has several unique charateristics including antiemetic and antipruritic properties which may result from neuro actions at a subcortical level. Subhypnotic doses may provide some analgesia in contrast to thio which may be antalgesic. It has anticonvulsant properties. It exhibits pharmacological synergism with benzodiazepienes and opiods allowing reduction in doses.	In keeping with its distinct mechanism of action, the clinical effects are also distinct. The CNS effects are characterised by a dissociation between the thalamocortical and limbic systems, and the clinical result is intense analgesia, amnesia and a cataleptic like state of non responsiveness. Psychedelic effects and emergence reactions are a major issue. It is a potent cerebrovasodilator, increasing CBF, ICP and $CMRO_2$ and is relatively contraindicated in neuro sx.
CARDIOVASCULAR SYSTEM EFFECTS	Midazolam has minimal cardiovascular effects. Induction doses may cause modest haemodynamic effects, mostly attributable to a decrease of TPR.	Thio delivered by bolus causes a transient decrease in aterial pressure and CO, and increase in heart rate and no change in or a small increase in TPR. The decrease in BP is caused by venodilation and reduced preload. Higher doses reduce myocardial contractility but lower doses have little effect. The increase in HR is barorecepetor mediated. These effects are dangerous in pts with IHD, CCF, tamponade and valve disease.	Propofol decreases BP by 15-40%, reductions are generally greater than with similar doses of thio. There are significant reductions in TPR and preload with little effect on contractility. Propofol resets baroreceptor control of HR leading to unchanged HR despite a BP drop. It is not arrythmogenic nor does it sensitise to catecholamins. Haemodynamic effects are worse in elderly, hypovolaemic and LV dysfunction.	The cardiovascular effects of ketamine result primarily from inhibition of catecholamine reuptake and potentiation norad release from sympathetic ganglia. The direct action of ketamine is actually negatively iontropic and vasodilatory but indirect effects of catecholamines usually predominates. In patients with depleted catecholamine stores ketamine may result in profound hypotension.
RESPIRATORY SYSTEM EFFECTS	Benzodiazepienes alone cause minimal respiratory depression but they have marked synergistic interactions with other respiratory depressants, such as volatile anaesthetics and opoids.	Anaesthetic barbiturates are potent central respiratory depressants. They produce dose-dependent decreases in both minute volume and tidal volume. Medullary responses to hypercapnia and hypoxia are depressed. Induction doses do not inhibit airway reflexes, therefore laryngospasm and bronchospasm can occur.	Propofol is a potent respiratory depressant and may cause a 30-60 second period of apnoea at induction. There is greater depression of laryngeal reflexes when compared with thio, therefore reducing risk of laryngospasm. In contrast to thio it causes some bronchodilation.	Ketamine doesn't depress CO_2 responsiveness. RR may decrease during induction and rarely there is apnoea. Upper airway reflexes and muscle tone are maintained, the FRC is usually unchanged which differs from the other IVGAs. There is an ↑bronchial secretions (risk of cough/laryngospasm) but also bronchodilation.
PHARMACOKINETICS (also see drug cards)	Midazolam is metabolised hepatically into an active metabolite but cleared quickly and has a short context sensitive half time.	Following infusion develops zero order kinetics and subsequently slow context sensitive half time (doses should be calculated according to Vd steady state).	Unlike thio it has a much more rapid clearance in the central compartment, therefore despite a V_{dss} which is greater than thio it has a much more rapid recovery. Does adjustment is not required in renal or hepatic impairment.	Like all the IVGAs it demonstrates rapid distribution due to the lipophilicity. Ketamine has high hepatic clearance which approximates hepatic blood flow. There is an active metabolite norketamine. May demonstrate tolerance.

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