Abstract  It is today generally accepted that anesthetics act by binding directly to sensitive target proteins. For certain intravenous anesthetics, such as propofol, barbiturates, and etomidate, the major target for anesthetic effect has been identified as the γ-aminobutyric acid type A (GABAA) receptor, with particular subunits playing a crucial role. Etomidate, an intravenous imidazole general anesthetic, is thought to produce anesthesia by modulating or activating ionotropic Cl−-permeable GABAA receptors. For the less potent steroid anesthetic agents the picture is less clear, although a relatively small number of targets have been identified as being the most likely candidates. In this review, we summarize the most relevant clinical and experimental pharmacological properties of these intravenous anesthetics, the molecular targets mediating other endpoints of the anesthetic state in vivo, and the work that led to the identification of the GABAA receptor as the key target for etomidate and aminosteroids.
1 Etomidate

Etomidate \([\text{R}(+)\text{-ethyl-1-(\alpha\text{-methyl-benzyl})-1H-imidazole-5-carboxylate, MW 342.4}]\) is a short-acting anesthetic agent, unstable in water, and is currently marketed as a preparation containing 2 mg/ml solubilized in either propylene glycol (pH solution 5.1, 4,965 mOsmol/kg) or a lipid emulsion (pH solution 7.6, 400 mOsmol/kg). Etomidate has a very high therapeutic index in animals (26.4 compared to 9.5 for methohexitol). The drug is optically active and exists in two mirror-image enantiomeric forms. Only the dextro isomer is active as a hypnotic. The salt is water soluble, but the base is soluble in ethanol, propylene glycol, and chloroform. The p\(K_a\) of etomidate is 4.24. The imidazole ring renders etomidate water soluble at acidic pH and lipid soluble at physiological pH, with almost 99% of the drug unionized in the blood (Fig. 1).

The drug is used as hypnotic component for the induction of anesthesia. It is considered by many to be the ideal agent for induction of anesthesia in cardiac-compromised or hypovolemic patients. The recommended dose in humans is 0.3 mg/kg, which produces an equal duration of sleep to methohexitol 1.5 mg/kg (Kay 1976). The duration of sleep is dose-dependent and there is little evidence of accumulation of the drug even with repeated dosing. The speed of onset and short duration of action is the result of rapid uptake and elimination by the brain and a fast redistribution of the drug from the plasma to other tissues. Minor side effects (pain on injection, thrombophlebitis, involuntary muscle movements, coughing, and hiccups) may accompany the injection of etomidate. The occurrence of thrombophlebitis has been attributed to the solvent propylene glycol. Both the emulsion formulation and the use of 2-hydroxypropyl-\(\beta\)-cyclodextrin as solvent significantly reduce the incidence of pain on injection, thrombophlebitis, and red cell hemolysis without affecting the pharmacokinetics and -dynamics of etomidate (Doenicke et al. 1994).

![Chemical structure of etomidate](image)

**Fig. 1** Chemical structure of etomidate