Etomidate and Other Non-Barbiturates

C. Vanlersberghe(✉) and F. Camu

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 ($GABA_A$) 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 $GABA_A$ 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 $GABA_A$ receptor as the key target for etomidate and aminosteroids.

C. Vanlersberghe
Department of Anesthesiology, University of Brussels V.U.B. Medical Center,
Laarbeeklaan 101, 1090 Brussels, Belgium
anesvec@uzbrussel.be

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1 Etomidate

Etomidate [R(+)-ethyl-1-(α-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 methohexital). 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 pK_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 methohexital 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-β-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).

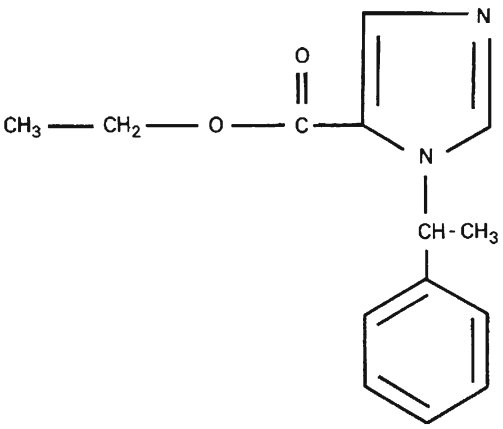

Fig. 1 Chemical structure of etomidate

1.1 Pharmacokinetics

In initial studies by Heykants et al. (1973) in man, the plasma concentration of etomidate after intravenous injection decayed in a biphasic manner with elimination half-life of 75 min. The plasma concentration of the metabolites increased over the first 30 min after administration, and then decreased with a slower half-life of 160 min. The distribution of both stereoisomers of etomidate (R(+) and S(−)) does not differ substantially in blood, brain, or liver. However, the S(−) form has considerably less hypnotic effect, suggesting stereospecificity of the receptor area in the brain.

Later kinetic studies in humans under general anesthesia showed wide variations in the clearance of etomidate after single doses and continuous infusions. In the investigations of Van Hamme et al. (1978), the plasma concentrations of etomidate following a single dose were consistent with a three-compartment distribution model, with individual plasma half-lives of 2.6 min, 28.7 min, and 275.4 min, respectively. The apparent volume of distribution (V_{dss}) was 4.51 l/kg and the systemic or plasma clearance rate 11.7 ml/kg per minute. Data from infusion studies were best fitted to a two-compartment model with mean elimination half-lives ranging from 1.13 to 2.9 h, mean apparent volumes of distribution of 154 to 310 l, and mean systemic clearance varying between 1,175 and 2,550 ml/min (Schüttler et al. 1980; De Ruiter et al. 1981; Hebron et al. 1983; Schüttler et al. 1985). In the presence of a steady-state concentration of fentanyl (10 ng/ml) the clearance of etomidate was reduced from about 1,600 to 400 ml/min, with little alteration of the elimination half-life. However, the initial volume of distribution (V_c) decreased from 21 l to 5 l and V_{dss} from 160 l to about 40 l. The exact nature of this kinetic drug interaction is not known, but may possibly involve saturation of the enzymes responsible for the metabolism of etomidate (Schüttler et al. 1983).

The relationship between concentration and drug effect is well established. Etomidate penetrates the brain rapidly. Anesthesia was associated with concentrations between 300 and 500 ng/ml, with burst suppression of the electroencephalogram (EEG) found at concentrations greater than 1.0 μg/ml. The mean half-time for blood/brain equilibration ($t_{1/2}\ k_{e0}$), which represents the speed of equilibration between concentrations in plasma and effect compartment or biophase, was 1.6 min. Brain sensitivity expressed as the magnitude of the maximal slowing of the EEG spectral edge (E_{max}) was 7.2 Hz and the mean plasma drug concentration that caused 50% of the maximal EEG slowing (IC_{50}) was 0.39 μg/ml (Arden et al. 1986). Studies in volunteers using EEG median frequency as surrogate for hypnotic effect and pharmacokinetic/-dynamic modeling established a mean IC_{50} value (which is the plasma concentration of etomidate necessary to cause half of the possible EEG depressant effect) of 0.32 μg/ml. Of the greatest possible EEG-depressant effect, 90% was achieved at mean plasma concentration of 0.56 μg/ml (Schwilden et al. 1985). Based on the concentration response curves from these studies and the IC_{50} values, the relative potency ratio for pure hypnotic effect of etomidate versus thiopental was 50:1.

Etomidate is metabolized by enzymes present in plasma, but mainly in the liver by ether hydrolysis to pharmacologically inactive metabolites. The main metabolite in man is the corresponding carboxylic acid of etomidate. In man, approximately 75% of the dose administered is excreted in the urine during the first 24 h after administration, mainly as inert metabolites, with only 2% of the etomidate excreted unchanged (Heykants et al. 1975).

In vitro protein binding of etomidate has been studied by equilibrium dialysis using radiolabeled etomidate. Human serum albumin was found to bind 78.5% etomidate, while human γ-globulin bound not more than 3% etomidate. Total plasma protein binding of etomidate was 76.5% in man, with distribution percentages for blood cells, plasma proteins, and plasma water being 37.7%, 47.6%, and 14.7%, respectively.

1.2 Pharmacological Organ Effects

Etomidate induces a hypnotic effect within one arm–brain circulation time, with no detectable histamine release, minimal cardiovascular and respiratory depressive effects, and a reduction in cerebral metabolism, cerebral blood flow (CBF), and intracranial pressure, and with a rapid recovery of consciousness and orientation to time, space, and person.

1.2.1 The Cardiovascular System

Animal Data

In animals, therapeutic doses had no depressant effect on atrial muscle function or conduction, while high doses (1.25–2.5 mg/kg) induced a slight decrease of arterial pressure. Etomidate had little effect on myocardial contractility of isolated normal and cardiomyopathic rat papillary muscle, presumably by maintaining the availability of intracellular Ca^{2+} for contractile activation in vitro (Komai et al. 1985; Riou et al. 1993; Gelissen et al. 1996). Etomidate also caused little or no myocardial depression in dogs, as evaluated with isovolumetric and ejection-phase indexes of contractility (Kissin et al. 1983; De Hert et al. 1990). However, the actions of etomidate on load-independent measures of contractile state and on diastolic function have not been specifically addressed.

The effects of etomidate on vascular smooth muscle cells have been widely investigated. In rat aortic vascular smooth muscle cells, etomidate (5×10^{-5} M–5×10^{-4} M) moderately inhibited the angiotensin II-induced calcium influx. Etomidate also produced a significant rightward shift in the dose–response curves of acetylcholine (receptor-mediated endothelium-dependent agonist), phenylephrine, and 5-hydroxytryptamine, and potassium chloride-induced contraction in rat aorta. The underlying mechanism was an inhibitory effect on the calcium influx

by blocking the L-type calcium channels. Indeed, these effects of etomidate were absent in aorta rings pretreated with verapamil (Pili-Floury et al. 2004; Shin et al. 2005). These data indicate that etomidate may alter the vascular response to endogenous and exogenous vasoactive agents. However, these effects of etomidate occurred at concentrations exceeding the clinically relevant concentration, and thus the effect of etomidate on blood pressure regulatory systems in clinical conditions is limited.

Etomidate, however, may affect blood pressure in a different way. Bovine adrenal chromaffin cells, which express functional γ-aminobutyric acid type A ($GABA_A$) receptors, were excited by etomidate at clinically relevant concentrations, thereby stimulating catecholamine release. Etomidate directly activated $GABA_A$ receptors found in chromaffin cells and increased intracellular Ca^{2+} concentrations. This depolarized chromaffin cells, thus activating voltage-dependent Ca^{2+} channels and stimulating catecholamine release (Xie et al. 2004). Etomidate also showed agonist effects at α2-adrenoceptors in mice lacking individual α2-adrenoceptor subtypes (α2-KO). In membranes from HEK293 cells transfected with α2-receptors, etomidate inhibited binding of the α2-antagonist [3H]RX821002. In α2B-receptor-expressing HEK293 cells, etomidate rapidly increased phosphorylation of the extracellular signal-related kinases (ERK)1/2. (Paris et al. 2003). Thus, the interaction of etomidate with α2B-adrenoceptors could in vivo primarily increase blood pressure and may contribute to the cardiovascular stability observed in patients after induction of anesthesia with etomidate.

Human Data

Investigations in normal patients (Gooding and Corssen 1977; Patschke et al. 1977; Criado et al. 1980) and those with cardiovascular disease (Colvin et al. 1979; Gooding et al. 1979) have repeatedly demonstrated that etomidate produced little change in hemodynamics.

In humans, etomidate did not affect heart contractility or mean aortic pressure. During infusion of etomidate, coronary blood flow slightly increased and coronary resistance decreased to the same extent, leaving a constant coronary perfusion pressure. Myocardial oxygen consumption was unaltered and cardiac work diminished in proportion to any decrease in mean arterial pressure (MAP) (Kettler et al. 1974). Only at high infusion rates did etomidate decrease cardiac output and liver blood flow, causing greater plasma drug concentrations than might otherwise have been predicted (Van Lambalgan et al. 1982; Thomson et al. 1984).

Patients with severe coronary artery disease showed no major alterations in cardiac function or hemodynamics. Patients with aortic or mitral valve disease responded to etomidate with a 19% fall in MAP, which was associated with decreased systemic vascular resistance and left ventricular stroke work index. Cardiac index and pulmonary artery pressures decreased slightly, and central venous pressure and heart rate remained unchanged (Colvin et al. 1979).

As with other anesthetic agents, etomidate induced modest decreases in MAP, presumably resulting from depressed neural control of the peripheral vasculature by depression of central generation of neural tone, which may contribute to attenuated activity of the central sympathetic nervous system. No direct effect of etomidate has been established concerning receptor organ function or afferent transmission when reflexes are involved, or on the synaptic transmission at the level of the autonomic ganglion or at the vascular smooth muscle neuromuscular junction (Prakash et al. 1981).

1.2.2 The Brain

Etomidate decreased CBF, the cerebral metabolic rate for oxygen ($CMRO_2$), and intracranial pressure in humans, while blood pressure was well maintained (Van Aken and Rolly 1976; Moss et al. 1979). In dogs receiving continuous infusions, etomidate decreased CBF and cerebral metabolic oxygen requirements by 35%–45%, with marked increases in cerebrovascular resistance (Milde et al. 1985). The decrease in CBF was independent of changes in cerebral metabolic rate of oxygen ($CMRO_2$), as $CMRO_2$ decreased more slowly than CBF. At increasing doses of etomidate after suppression of EEG activity, a minimal $CMRO_2$ was established and maintained (2.6 ml/min/100 g). Normal levels of ATP and phosphocreatine and a normal energy charge of the brain tissue indicated, despite small increases in lactate, that energy production remained adequate to supply the energy requirements of the brain.

Because of these properties, etomidate was considered a neuroprotective agent and has often been used to attenuate the effects of cerebral ischemia in neurovascular surgical procedures that require temporary cerebral arterial occlusion. The neuroprotective effects of etomidate have been investigated in several animal models of cerebral ischemia, neurodegenerative diseases, and spinal cord trauma. Ates et al. (2006) investigated the effects of high-dose etomidate (2 mg/kg) on oxidative stress in streptozotocin-induced (STZ-induced) hyperglycemia in the rat brain and spinal cord. Malondialdehyde (MDA), total nitrite, and xanthine oxidase activity were used as markers. Etomidate treatment partly prevented the elevation of MDA, xanthine oxidase, and nitrite levels in the hippocampus, cortex, cerebellum, brain stem, and spinal cord of the rats. These data suggested a neuroprotective effect on the neuronal tissue against diabetic oxidative damage. A similar neuroprotective effect was demonstrated in experimental spinal cord injury in rats with etomidate (2 mg/kg), methylprednisolone, and the combination of both drugs. When administered immediately after spinal cord injury etomidate offered similar neuroprotection to methylprednisolone. However, the combined treatment with methylprednisolone and etomidate did not provide better protection than that obtained with each drug given separately (Cayli et al. 2006).

In models of cerebral mitochondrial dysfunction after temporary middle cerebral artery occlusion in rats, however, etomidate showed an adverse effect on ischemic

injury. Prior inhibition of nitric oxide synthase (NOS) with l-NAME did not influence the volume of cerebral injury. Administration of a large dose of l-arginine, a NO donor, prevented the adverse effect of etomidate. These data suggest that etomidate impaired mitochondrial function by inhibition of NOS early in the setting of temporary focal cerebral ischemia (Drummond et al. 2005).

In humans, the effects of etomidate and temporary cerebral arterial occlusion on brain tissue oxygen pressure (PO_2), carbon dioxide pressure (PCO_2), and pH were evaluated during intracranial aneurysm surgery. Etomidate was administered to produce EEG burst suppression before temporary cerebral arterial occlusion. This resulted in cerebral deoxygenation as brain tissue PO_2 decreased 30% compared with before etomidate administration. Overall, supplemental oxygen therapy returned brain oxygen tensions to pre-etomidate baseline values, but subsequent temporary cerebral artery occlusion decreased tissue PO_2 again (32% below preclip values), while tissue PCO_2 increased (23%) and acidosis set in (pH decrease 0.1-unit). Thus, brain tissue PO_2 decreased during cerebral aneurysm surgery despite etomidate administration (Edelman et al. 1997). In patients who had middle cerebral artery occlusion for 30 min after craniotomy, tissue PO_2 decreased with etomidate with significant tissue acidosis (7.09 to 6.63) (Hoffman et al. 1998). These results suggest that tissue hypoxia and acidosis were often observed during etomidate treatment in the setting of cerebral ischemia and that etomidate enhanced hypoxic risk during middle cerebral artery occlusion.

Etomidate may activate seizure foci manifesting as fast activity on the EEG and has been observed to augment the amplitude of somatosensory evoked potentials. Myoclonus is frequently observed and may resemble seizures, but it is not associated with epileptiform discharges on the EEG. Etomidate-induced myoclonus could be related to disinhibition of subcortical structures that normally suppress extrapyramidal motor activity (Laughlin and Newberg 1985).

1.2.3 The Respiratory System

Etomidate depressed the medullar centers that modify the ventilatory drive in response to changing CO_2 tensions, but this effect was less marked than that of the barbiturates (Choi et al. 1985). Induced reductions in tidal volume were offset by compensatory increases in breathing frequency, and these effects on ventilation were transient, lasting only a few minutes.

The ability of etomidate to prevent airway constriction or bronchospasm under normal and pathological conditions was explored in vitro. General anesthetics modify airway responsiveness via, at least partially, a direct inhibitory effect on calcium signaling in airway smooth muscle cells. Contraction experiments were done in human airway rings that were either normal or passively sensitized with asthmatic serum. The lowest effective concentration of etomidate that altered the intracellular Ca^{2+} response was 10^{-4} M. Etomidate reduced histamine-induced contraction in human isolated airway smooth muscles that were either not sensitized or passively sensitized with asthmatic serum. In rat isolated tracheal

myocytes, etomidate (10^{-4} M) altered the intracellular Ca^{2+} signal in response to the depolarizing agent potassium chloride and acetylcholine (Ouedraogo et al. 1998). Another model evaluated the ability of etomidate to relax and prevent agonist-induced contraction in tracheal rings isolated from chronically hypoxic rats and precontracted with the muscarinic agonist carbachol (CCh) and the depolarizing agent KCl. Etomidate (10^{-4} M) inhibited chronic hypoxic tracheal ring contraction in response to cumulative concentrations of CCh and KCl (Ouedraogo et al. 2003).

1.3 Effects on Adrenal and Gonadal Steroidogenesis

Etomidate inhibits stress- and drug-induced corticosteroid production in the adrenal gland, as well as the adrenocorticotropic hormone (ACTH)-induced stress response, in a dose-related and reversible fashion. Studies in vivo and with rat adrenal mitochondrial fractions and isolated rat adrenal cells indicated that there are four different sites of enzyme inhibition with apparent dose dependence: 11β hydroxylase, 17α hydroxylase, 18 hydroxylase, and probably the cholesterol side chain cleavage enzyme (20, 22 lyase) (de Jong et al. 1984; Fry and Griffiths 1984; Wagner et al. 1984; de Coster et al. 1985; Moore et al. 1985; Allolio et al. 1985). The main hormonal effects of etomidate are therefore to decrease cortisol and aldosterone synthesis and secretion, and increase the plasma concentrations of their precursors, 11-deoxycortisol and 18-deoxycorticosterone. The effect of etomidate on 11β hydroxylation is concentration-related. Crozier et al. (1988) found a sigmoid relationship between the relative inhibition of cortisol in response to ACTH stimulation and the log of the plasma etomidate concentration. The ED_{50} etomidate concentration was 110 nM, with suppression negligible at concentrations below 40 nM. On the basis of these data and the known kinetics of the drug, the expected duration of inhibition in humans will be about 4–8 h after administration.

Etomidate had no significant effect on microsomal enzymes in the glucocorticoid pathway (Wagner et al. 1984).

1.4 Effects on Other Microsomal Enzymes

Studies using antipyrine indicated that etomidate inhibited hepatic cytochrome oxidase P450-dependent drug metabolism in a concentration-dependent manner with IC_{50} concentrations in the order of 10 μM (Horai et al. 1985; Atiba et al. 1988). The minimal degree of in vivo inhibition of hepatic metabolism may delay elimination of low clearance drugs (diazepam, propranolol, carbamazepine, phenytoin), but is unlikely to affect drugs with high hepatic clearance, such as opioids and ketamine.

1.5 Effects on Central Nervous System Receptors

Central nervous system depression may reflect a $GABA_A$-like effect of etomidate. Indeed, etomidate is a selective modulator of this receptor and has, at clinically relevant concentrations, no effect on other ligand-gated ion channels. Etomidate acts by binding to and enhancing the function of $GABA_A$ receptors, which mediate inhibitory neurotransmission in the brain. The EC_{50} concentrations for general anesthesia in animals for the R(+) and S(−) isomers were 3.4 μM and 57 μM, respectively. The R(+) isomer was also much more effective than the S(−) isomer at potentiating GABA-induced currents (Tomlin et al. 1998). Etomidate is more potent than barbiturates in activating $GABA_A$ receptor channels, with potency comparable to that of GABA (Robertson 1989). In cortical homogenates, etomidate, like alphaxalone and pentobarbital, enhanced GABA or muscimol binding, apparently by increasing the number of binding sites (Thyagarajan et al. 1983). Etomidate also potentiated benzodiazepine binding by increasing the affinity of the benzodiazepine-binding site, an effect shown to be dose dependent, stereospecific, and antagonized by bicuculline or picrotoxin. It is noteworthy that in the presence of more than one anesthetic agent (e.g., pentobarbital plus etomidate) the enhancement in GABA and muscimol binding was additive. These results suggest that binding sites for different classes of intravenous anesthetic agents are distinct from each other as well as from benzodiazepine binding sites.

The site of action of etomidate is at the β_3 subunit of the receptor, where amino acid residues have been identified that are essential for activation of the $GABA_A$ receptor function by etomidate. Within the ion channel pore, the amino acid Asp265 located in the membrane-spanning region TM2 of the β_3 subunits conferred anesthetic activity for etomidate, but not for pentobarbital, propofol, or steroid anesthetics (Tomlin et al. 1998; Belelli et al. 1997). However, recent studies using a photoreactive etomidate analog ([(3)H]azietomidate) yielded different results. R(+)azietomidate, a diazirine derivative of etomidate, retained the anesthetic potency of etomidate in vivo. Both agents equally enhanced $GABA_A$ receptor function in vitro. The enantioselectivity was comparable to etomidate's, with an approximate potency ratio of the enantiomers being R:S 1:10 (Husain et al. 2003). [(3)H]Azietomidate established photolabeling of two residues: one within the αTM1 transmembrane helix at α1Met-236 (and/or the homologous methionines in α2,3,5), not previously implicated in etomidate function, and one within the βTM3 transmembrane helix at β3Met-286 (and/or the homologous methionines in β1,2), an etomidate sensitivity determinant. The pharmacological specificity of labeling indicates that these methionines contribute to a single binding pocket for etomidate located in the transmembrane domain at the interface between β- and α-subunits, rather than in the β-subunit (Li et al. 2006).

These binding data have functional significance: under voltage-clamp conditions, etomidate potentiated GABA-induced chloride currents, which causes membrane hyperpolarization and a reduction in neuronal excitability (Proctor et al. 1986). But direct activation of chloride currents in the absence of GABA has also been observed with etomidate at concentrations slightly higher than those needed

for potentiation of GABA-evoked currents (Evans and Hill 1978). Etomidate thus differs from the benzodiazepines, which are unable to activate $GABA_A$ receptors.

Other studies indicate that there is distinct subunit dependence for different pharmacological actions of etomidate on the $GABA_A$ receptor. These studies used knockout mice or mice carrying point mutations in neurotransmitter receptor subunits to assess the contribution of the respective receptor subtype to the pharmacological actions of etomidate. It was recently shown, using β2 knockout mice to completely remove any contribution of the β2 subunit to the effects of etomidate, that the β2 subunit contributed to the sedative properties of etomidate (O'Meara et al. 2004). Etomidate was equally anesthetic in wildtype and knockout mice, indicating that the β3 subunit was responsible for its anesthetic properties.

Another study addressed the involvement of the β3 subunit in the respiratory, cardiovascular, hypothermic, and sedative actions of etomidate, using β3 knockin mice carrying etomidate-insensitive β3-containing $GABA_A$ receptors. The respiratory depressant action of etomidate, determined by blood gas analysis, was almost absent in β3 mice, but the cardiac depressant and hypothermic effects, and the sedative effect were still present. Thus, respiratory depression was mediated by β3-containing $GABA_A$ receptors, while the hypothermic, cardiac depressant, and sedative actions were largely independent of β3-containing $GABA_A$ receptors (Zeller et al. 2005).

Studies with hippocampus pyramidal neurons showed that deletion of the α5 subunit of the $GABA_A$ receptor reduced the amnestic but not the sedative-hypnotic properties of etomidate. Etomidate markedly increased the tonic inhibitory conductance generated by $GABA_A$ receptors and reduced long-term potentiation (LTP) of field excitatory postsynaptic potentials (EPSPs) in wildtype but not α5 null mutant ($\alpha5^{-/-}$) mice. The sedative-hypnotic effects were similar in wildtype and $\alpha5^{-/-}$ mice (Cheng et al. 2006).

1.6 Contraindications

The use of etomidate is contraindicated in patients with acute porphyria and with depressed adrenocortical activity, at least in the absence of any substitution therapy. Although allergic reactions to etomidate are very rare, caution is warranted in patients with history of atopy.

2 5β-Pregnanolone (Eltanolone)

This steroid with a 5β pregnane structure (5β-pregnan-3α-ol-20-one) has anesthetic properties with a high therapeutic index (<40). The drug is water insoluble and formulated in a 10% Intralipid (Fresenius Kabi, Badhomburg, Germany) emulsion. There is rapid hepatic metabolism to inactive glucuronide and sulfate conjugates, with excretion via the kidneys and the biliary tract.

Clinical investigations in humans indicated that the blood concentration needed to achieve hypnotic effect was 0.46 μg/ml. The drug is, therefore, as potent as etomidate (concentration for hypnotic effect 0.32 μg/ml) and five times more potent than propofol (concentration for hypnotic effect 2.3 μg/ml). Loss of consciousness is usually obtained with doses of 0.4–0.6 mg/kg eltanolone.

Investigations in volunteers have addressed the infusion pharmacokinetics of eltanolone and used EEG effect data for full pharmacodynamic modeling of a power spectral parameter of the EEG (median frequency) to the serum concentration using a sigmoid E_{max} model, including an effect compartment to minimize possible hysteresis. Population pharmacokinetics was analyzed using a three-compartment mammillary model with central elimination. Eltanolone showed a high total clearance (1.75 ± 0.22 l/min), small volumes of distribution ($V_c = 7.65 \pm 3.40$ l; $V_{dss} = 91.6 \pm 22$ l), and relatively short half-lives ($t_{1/2}\,\alpha = 1.5 \pm 0.6$ min; $t_{1/2}\,\beta = 27 \pm 5$ min; $t_{1/2}\,\gamma = 184 \pm 32$ min). With regard to the pharmacodynamic model parameters, eltanolone proved to be a potent hypnotic agent ($Cp_{50} = 0.46 \pm 0.09$ μg/ml). The equilibration half-time blood/brain is long (between 6 and 8 min, $k_{e0} = 0.087 \pm 0.013$ min^{-1}) compared with barbiturates or propofol (Hering et al. 1996a).

Such a long equilibration time between blood and the biophase makes eltanolone difficult to be administered by titration of dose to hypnotic effect. It also affects the context-sensitive times following infusions of eltanolone. Context-sensitive time is the time required for the plasma drug concentration to decline by 20%, 50%, or 80% after terminating the infusion, where context refers to infusion duration. Context-sensitive times were estimated for a 50% and 80% drop in the concentration of eltanolone after different infusion times. A 50% drop in concentration was estimated to occur after 8 min following a 3-h infusion and after 10 min for a 10-h infusion. Following a 1-h infusion, an 80% drop in concentration was estimated to occur after 55 min and this delay increased to 70–80 min following an infusion of 10 h (Parivar et al. 1996). During recovery, the corneal reflex reappeared on average 9.4 min after stopping infusion, with the first reactions to loud verbal commands being recorded after 24 min; full orientation was regained after an average of 35 min (Hering et al. 1996b). Concentration–effect relationships during recovery from a bolus dose and constant rate intravenous infusion in healthy male volunteers established Cp_{50} values for "eye opening" at 0.38 μg/ml after a bolus dose and 0.51 μg/ml after eltanolone infusions. Median time to eye opening was 16 min after a bolus dose and up to 49 min after eltanolone infusion (Wessen et al. 1996). Thus, the long time between the administration of the drug in the blood and the equilibration with the biophase implicates the potential disadvantage of drug accumulation, with prolonged recovery foreseen if larger-than-necessary doses are used to induce and maintain anesthesia.

The clinical effects on organ functions after i.v. administrations of eltanolone were generally mild. There was slight respiratory depression and a maximum reduction in arterial blood pressure of 31% compared to the resting level after a bolus dose of eltanolone. Diastolic arterial blood pressure decreased about 10%, while heart rate increased 24% (Hering et al. 1996b). In patients scheduled for coronary artery bypass grafting, systemic vascular resistance decreased significantly 2 min after

induction with eltanolone at all doses (0.5–1 mg/kg). Mean arterial pressure reduction induced by eltanolone was most likely the result of the combination of a decrease in cardiac contractility and peripheral vasodilatation (Tassani et al. 1996).

After a single dose of 0.6 mg/kg eltanolone, CBF decreased by 34%, with a comparable fall in cerebral oxygen consumption, thereby maintaining a coupling between metabolism and blood flow (Wolff et al. 1994).

Eltanolone administration may produce side effects such as skin rash, urticaria, short-lasting excitation, minor involuntary movements, and convulsions. Considering the lack of clinical advantages over existing anesthetic drugs, the drug has been withdrawn from clinical use.

The molecular targets for eltanolone are also the $GABA_A$ receptor and the glycine receptor. Of the anesthetic isomers, 5α-pregnan-3α-ol-20-one and 5β-pregnan-3α-ol-20-one (eltanolone), only the latter has anesthetic effects. Both isomers enhanced $GABA_A$ receptor-mediated currents with similar potency and efficacy, but only 5α-pregnan-3α-ol-20-one enhanced glycine currents. On the other hand, eltanolone caused inhibition of the glycine currents (Weir et al. 2004). These data indicate that steroid modulation at the $GABA_A$ and glycine receptors differs.

3 ORG 21465 and ORG 20599

Two other 2-substituted aminosteroids, ORG 21465 and ORG 20599, have been evaluated in animals and humans. These agents are water-soluble. ORG 21465 (2β-3α-5α-3-hydroxy-2-(2,2-dimethylmorpholin-4-yl)-pregnan-11,20-dione) has a high therapeutic index in mice (13.8). The neuroactive aminosteroids differ in potency, but not in intrinsic efficacy at the $GABA_A$ receptor in vivo, as the estimates for the maximum activation of the receptor are similar (Visser et al. 2002).

In humans, ORG 21465 administration caused no cardiovascular or respiratory depression. Anesthetic effects were observed at doses of at least 1 mg/kg. However, as with other steroids, ORG 21465 produced a high incidence of excitatory side effects that was dose-related, but without accompanying EEG spike activity (Sneyd et al. 1997a).

With regard to pharmacokinetics following an i.v. dose, the decay of plasma concentrations supported a three-compartment model with compartmental volumes V_c, V_2, and V_3 of 4.31, 14.2, and 89.4 l, respectively. Clearance from the central compartment, V_c, was 1.55 l/min (Sneyd et al. 1997a). Using computer-controlled infusions of ORG 21465, a steady-state plasma concentration of 1.18 μg/ml depressed the EEG spectral edge frequency by 50%. The equilibration rate constant of the effect compartment was 0.112/min ($t_{1/2}$ k_{e0} 6.2 min) (Sneyd et al. 1997b).

ORG 20599 [(2β, 3α, 5α)-21-chloro-3-hydroxy-2-(4-morpholinyl)pregnan-20-one methanesulfonate], intravenously administered produced a rapid onset and short duration loss of the righting reflex in mice. The anesthetic potency of ORG 20599 exceeded that of propofol, thiopental, and pentobarbital. ORG 20599 produced a concentration-dependent and reversible potentiation of the peak amplitude

of GABA-evoked currents at human recombinant α1, β2, γ2L-subunit-containing $GABA_A$ receptors expressed in *Xenopus laevis* oocytes ($EC_{50} = 1.1$ μM), and for the $GABA_A$ receptors expressed by bovine adrenal chromaffin cells maintained in culture. At concentrations greater than those required for potentiation of GABA, ORG 20599 exhibited GABA-mimetic effects (Hill-Venning et al. 1996; Weir et al. 2004). The results suggest positive allosteric regulation of $GABA_A$ receptor function to be a plausible molecular mechanism of action for the drug.

The effect of ORG 20599 on strychnine-sensitive glycine receptors (the principal mediators of fast, inhibitory neurotransmission in the brain stem and spinal cord) were investigated at human recombinant α1, β2, γ2L-subunit-containing $GABA_A$ receptors and α1-glycine receptors expressed in *X. laevis* oocytes under voltage-clamp. ORG 20599 enhanced currents mediated by glycine receptors, although with higher EC_{50} values (22.9 μM) than for $GABA_A$ receptors (Weir et al. 2004).

The aminosteroids were also investigated for antinociceptive effects following intrathecal injection in rats. ORG 20599 had no antinociceptive properties as assessed by tail flick and electrical current nociceptive tests (Goodchild et al. 2000). These data suggest that the modulatory effects of the aminosteroids on the cerebral $GABA_A$ receptors cannot be transposed to the $GABA_A$ receptors of the spinal cord.

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