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Thiopental to desflurane - an anaesthetic journey. Where are we going next?

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Abstract/summary

Development targets in anaesthetic pharmacology have evolved from minimising harm caused by unwanted effects through an era in which rapid onset and offset of drug effect were prioritised. Today's anaesthetists have access to a library of effective drugs whose characteristics offer controllable hypnosis, analgesia and paralysis with manageable off-target effects. The availability of these agents at generic prices inhibits commercial interest and this is reflected in the limited number of current anaesthetic drug development projects.

Recently, questions around neonatal neurotoxicity, delirium and post-operative cognitive dysfunction have stimulated research to characterise these phenomena and explain them in mechanistic terms. Emergent basic science from these enquiries together with exploration of possible effects of anaesthetic drug choice on patient outcomes from cancer surgery may yield new targets for drug discovery.

The past 40 years have seen extraordinary developments in anaesthetic pharmacology culminating in a limited but versatile set of hypnotics, analgesics and muscle relaxants adaptable to every clinical situation. The successful evolution of shorter acting compounds with relatively favourable safety profiles now inhibits further development against previously established criteria.[1] Current commercial developments target the opportunity to develop non-anaesthetist sedation.[2] Future opportunities have been suggested against paediatric neurotoxicity, emergence

delirium, cancer outcomes and post-operative cognitive dysfunction however until the basic science of these phenomena is unravelled we lack credible biological targets to address with innovative pharmacology.[3]

Drivers for development of inhaled anaesthetics

Systematic development of novel inhalational agents arguably began with the first human use of halothane in 1956.[4] It progressively replaced trichloroethylene, cyclopropane and diethyl ether which had been in use since the 1940s, the 1920s and the 19th-century respectively. Advantages of halothane included a lack of flammability, tolerability for inhaled induction and swift emergence. A propensity to arrhythmia, haemodynamic depression[5] and rarely to liver problems[6] and malignant hyperthermia ultimately led to its replacement although its modest cost sustains continued use in some low income environments.

Rational development of subsequent agents required robust underpinning science and methodology, much of which was developed by Prof Eger and his collaborators at the University of California, San Francisco. A unifying scale of anaesthetic dose was established by the development of the MAC concept.[7]

"In any comparative study, there must be an index of comparison. We define this common index as the minimal anaesthetic concentration in the alveolus required to keep a dog from responding by gross movement to a painful stimulus such as tail clamping or varying electrical current supplied to sensitive mucous membranes. This alveolar concentration was abbreviated as M AC 1.0. Anaesthetic depth was then expressed as a ratio of alveolar concentration of anaesthetic to their M AC 1.0."[7]

Subsequent to halothane, methoxyflurane (with analgesic properties) and enflurane (earlier emergence) came and went giving way to isoflurane, sevoflurane and desflurane which remain in widespread use today. Table 1.

TABLE 1 NEAR HERE

Sevoflurane undergoes a complex interaction with soda lime with subsequent temperature increases and the production of several breakdown compounds.[11] The generation of these compounds, their toxicology and the adverse effects of the parent molecule sevoflurane were exhaustively explored by Prof Eger, a paid consultant for Baxter the manufacturer of the rival anaesthetic desflurane. Despite these endeavours described in around 60 papers between 1987 and 2005 sevoflurane remains widely used. Aspects of this sustained exploration through high quality scientific investigation of the adverse aspects of a commercial competitors drug attracted editorial criticism[12, 13] and a robust defence.[14]

Volatile anaesthetics can be presented for injection by incorporation into an intravenous emulsion. Both sevoflurane and isoflurane have been explored in this format. When used to maintain anaesthesia following midazolam/propofol induction, isoflurane emulsion gave a faster recovery than inhaled isoflurane[15], possibly because of a “lipid-sink” effect whereby the volatile agent is partially trapped by lipid. Whether these formulations have acceptably low rates of pain on injection and thrombophlebitis requires evaluation.

Progress with intravenous anaesthetics

The need to improve on the characteristics of thiopental was championed by Prof John Dundee who, in 1985 identified development targets which remain valid today.[16]

"Ideally one would like a water-soluble, non-irritant, rapidly-acting, smooth induction agent, with no antanalgesic action. Cardiovascular and respiratory depression should be minimal with normal dosage…. A slight delay in onset would not be a major obstacle, provided this is predictable, but the prime need is for a rapidly acting less toxic alternative to thiopentone." [16]

Major obstacles in developing novel intravenous hypnotics have been their propensity to central nervous system excitation and pharmaceutical difficulties in solubilising the active ingredients. Table 2. All commercially available intravenous anaesthetics since thiopental have been associated with some degree of excitation although its degree varies from occasional small peripheral movements during induction with propofol to significant myoclonus with etomidate.[17] Excitation was frequently reported in experimental anaesthetics which never reached general clinical use and may be present to some degree in the experimental short-acting etomidate derivative ABP-700 which is currently under development.[18] The genesis of anaesthesia induced excitation and seizures remains obscure. [17, 19]

TABLE 2 NEAR HERE

No reliable preclinical model exists to predict excitation (or the lack of it) by hypnotics. Excitation seems especially prevalent in compounds with steroid derived structures including minaxolone, eltanolone and other experimental anaesthetics including ORG21465 and ABP-700.[18, 20-23]

Death by attrition-why old drugs fade away.

The thalidomide disaster precipitated a new era in medicines regulation. At the time the 1968 Medicines Act was introduced, product licences of right were issued to all drugs which were currently on the market. During the 1990s these drugs were reviewed then either fully licensed or withdrawn from use. In some cases, the maintenance of a licence would have required additional laboratory or clinical trial evidence which was not a commercially attractive prospect for the original manufacturer of these agents which were by now generic and therefore very inexpensive.

Recent developments regarding licensed hypnotics

Nitrous oxide

Nitrous oxide is our longest serving anaesthetic, globally available and still widely used. Inexpensive and effective, it has a pharmacodynamic profile similar to desflurane. Concerns about potential for cardiovascular morbidity and mortality due to interference with homocysteine metabolism[24] have been allayed by the ENIGMA2 trial which showed no difference in mortality between groups of high risk patients randomised to receive general anaesthesia with or without nitrous oxide.[25, 26] Further, the propensity to excess nausea and vomiting associated with nitrous oxide anaesthesia can be allayed by the use of antiemetics.[27] A sub-study of the ENIGMA1 trial[28] suggested that patients receiving general anaesthesia including nitrous oxide were less likely to develop chronic postsurgical pain[29] however this was not confirmed in a larger investigation using ENIGMA2 patients.[30] The possibility that an

effect may exist in genetically distinct groups of patients requires further investigation.[30] Recently, nitrous oxide has emerged as a candidate therapy for treatment-resistant major depression.[31, 32]

Fospropofol

This water soluble propofol pro-drug[33] was developed to reduce the frequency of pain on injection during induction of anaesthesia/sedation and to offer a sustained period of hypnotic effect as the prodrug is progressively converted to propofol and formaldehyde. Regulatory insistence that its use be confined to those with anaesthesia competencies and an unfavourable adverse events profile including a proportion of patients experiencing burning perineal pain during administration undermined its attractiveness to the clinical community[2] and it has now fallen out of use. An alternative to fospropofol, HX0969w is metabolised to propofol and gamma-hydroxybutyric acid.[34] No human studies of HX0969w have so far been reported.

Ketamine

In addition to its traditional role as a general anaesthetic agent for use in the operating room, ketamine remains popular for prehospital care and in the emergency department for both adults and children with safe use by non-anaesthetists.[35] The traditional view that ketamine may increasing intracranial pressure has been challenged although the evidence base remains weak.[36] Evidence that ketamine is an effective prophylactic against chronic postsurgical pain remains elusive[37] although it may have some role in established intractable chronic pain.[38] Ketamine has show promise as an experimental therapy for treatment resistand depression, possibly through non-NMDA receptor effects..[39-41]

Esketamine or S(+)-ketamine is one of the two optical isomers that comprise racemic ketamine. Esketamine is twice as potent as racemic ketamine[42] and may demonstrate modestly different recovery characteristics.[43] A nasal spray of esketamine is under development for the treatment of depression.[44]

Dexmedetomidine

Alpha-2 adrenoreceptor agonists are established anaesthetics in animals. By contrast, in man clonidine is used as an anaesthetic adjunct or component of an analgesic scheme. Dexmedetomidine is extensively used as a sedative and as an anaesthetic adjunct[45] and is under evaluation in combination with remifentanil as a general anaesthetic in human infants (ClinicalTrials.gov Identifier: NCT02799589).

Drivers for developing new hypnotics

To date, the principles set out by Dundee[16] and the pursuit of rapid onset/offset inhalational agents have determined commercial interest in hypnotic development. On this basis standard general anaesthesia is dominated by propofol, isoflurane, sevoflurane and desflurane with some continued use of nitrous oxide. Thiopental, and methohexital are seldom used or restricted to special circumstances. Etomidate use has greatly declined following concerns about adrenocortical depression and the realisation that most patients can be safely managed with propofol provided it is administered cautiously.[46] Recently the potential for etomidate induced harm has been challenged.[47-50]

New hypnotics in the endoscopy suite

The two novel hypnotic compounds have recently been progressed into advanced clinical development, remimazolam[51] and ABP-700[18] were both targeted in the first

instance at sedation for gastrointestinal endoscopy. The business opportunity is to replace propofol sedation with a short-acting safe hypnotic suitable for use by non-anaesthetists whilst achieving an improved recovery profile in comparison to midazolam. Whether these opportunities translate into general use will be determined by safety considerations, quality of experience for both patients and endoscopists and of course cost.

Remimazolam

The esterase hydrolysed sedative remimazolam performs as a typical benzodiazepine which appears to have a swifter onset and a better recovery profile than midazolam.[51, 52] Remimazolam effects are achieved by binding to the standard benzodiazepine site on the $GABA_A$ receptor.[53] Non-specific tissue esterases rapidly hydrolysed remimazolam to an inactive carboxylic acid metabolite, Figure 1, which then undergoes further oxidation or glucuronidation.[54] Remimazolam is currently in Phase 3 clinical trials. Whether the use of remimazolam and its inevitable additional cost can sustain higher turnover in busy clinics will probably determine its commercial success. Several other opportunities including induction and maintenance of anaesthesia and intensive care sedation have been identified[55] however these alone are probably insufficient to provide a return on the cost of development.

FIGURE 1 NEAR HERE

ABP-700

The short acting etomidate analogue ABP-700 is a true general anaesthetic with an anaesthetised state similar to that achieved by etomidate of which it is an ester derivative.[56] ABP-700 and other etomidate analogues bind to sites within the transmembrane domain of the $GABA_A$ receptor, away from the main benzodiazepine binding site.[53] Etomidate has been associated with a high incidence of post-operative nausea and vomiting however the relevance of this to a rapidly broken down analogue like ABP-700 is unclear. Volunteer (Phase 1) and early clinical trial experience with ABP-700 showed dose-related excitatory effects similar to the parent molecule etomidate.[18] The presence of excitatory effects during human testing prompted additional pre-clinical investigation which demonstrated seizures in some dogs anaesthetised with ABP-700. Seizures had not been observed in humans and these dog findings may be species-specific. Nevertheless, the compound was withdrawn from development in August 2017..

FIGURE 2 NEAR HERE

To be administered by non-anaesthetists for sedation during endoscopy, a true general anaesthetic like ABP-700 would have needed satisfactory clinical trial experience and regulatory approval. The requirement to demonstrate safety and efficacy in a heterogenous patient population with the safety profile sufficiently robust to avoid explicit “Anaesthetist only” labelling is a high barrier to progress for drug candidates in this area. Nevertheless, trained nurse sedationists managing selected

patients using a well-defined protocol can safely administer low-dose propofol sedation to patients undergoing endoscopy[57] and arguments have been made to liberalise non-anaesthetist access to propofol[58, 59] and ketamine[35] provided appropriate controls are in place. However safe it may or may not be, and despite the existence of a well defined training strategy[60], non-anaesthetist use of propofol is highly controversial.[61]

Defining the boundaries of "soft" pharmacology

in 2009 Egan welcomed the progression of "soft" pharmacology in anaesthesia,[62] and defined it as "… a strategy wherein novel active compounds are specifically designed to be vulnerable to rapid biotransformation into inactive metabolites…."

Ester hydrolysed compounds to control heart rate (esmolol), provide analgesia (remifentanil) and muscle relaxation (mivacurium) were about to be joined by one or more "soft" hypnotics providing an apparently complete portfolio of titrateable infusions to establish and maintain anaesthesia and sedation.

This salute to the new pharmacology may have been premature. For any ultra-short compound certain truths cannot be escaped. Specifically, as an infusion progresses, substantial amounts of one or more metabolites will be produced and the pharmacology of the metabolite therefore becomes proportionately more important. Sustained infusion of remifentanil in the intensive care environment produces concentrations of remifentanil acid 10-100 times greater than the parent in patients with impaired renal function[63] (a commonplace on the ICU). The hydrolysed able etomidate analogue methoxycarbonyl etomidate has a metabolite with some hypnotic effect whose accumulation impairs EEG recovery after a period of infusion[64] and this prevented further development of that molecule. If a constant infusion is to

be used then the ratio of injectate volume between a single bolus dose and a steady state infusion becomes problematic. Thus if remifentanil is diluted to 100 mcg.ml^{-1} then the bolus dose becomes a fraction of a millilitre. More dilute preparations of remifentanil give manageable bolus volumes but increase the frequency with which syringes must be changed during maintenance infusion. Sustained infusions of rapidly hydrolysed molecules implies the administration of the substantial mass of drug when infusion is sustained. Thus AZD3043 (an analogue of propanidid) required an infusion rate of 30mg.kg.hr^{-1} to maintain anaesthesia in humans.[65] The mass of drug has substantial implications for cost and makes the assumed potential for a flexible compound usable for everything from bolus dose to sustained infusion unrealistic. Finally, clinicians and their managers are cost conscious and the emergence of an expensive soft drug may tempt clinicians use a cheaper longer acting agent for the bulk of the required period with an economical switch to the soft compound for a wind-down phase thereby achieving swift emergence with greatly reduced cost whilst maintaining the majority of the recovery benefit. This has been demonstrated for alfentanil and remifentanil in neurosurgical procedures.[66]

New directions

Beyond endoscopy lie the current controversies associated with general anaesthetics . One important question is whether we can separate the hypnotic effects of drugs from their side effects (eg. water insolubility; excitation following induction; cardiovascular and respiratory depression) by minor changes to drug structure

Intravenous anaesthesia is now almost monopolised by propofol which is widely available, inexpensive and generally safe. Characteristics of the current oil in water

emulsion propofol formulations that are considered problematic include: pain on injection, cardiorespiratory depression, susceptibility to contamination and subsequent bacterial growth. Pain on injection is manageable (but not preventable) by lidocaine admixture[67], and choice of injection site. Hypotension induced by propofol can be moderated by slow administration[68], modest dosing and coadministration of fluid. Bacterial contamination can be minimised by meticulous technique when transferring propofol into syringes and its subsequent timely administration. Adjustments to formulation have attempted to address these issues by varying the lipid emulsion to reduce pain on injection and adding a preservative to inhibit bacterial growth.[69] PF0713, a structural variant of propofol with demonstrably superior haemodynamic characteristics in volunteers was unable to attract funding for clinical development.[70, 71] A presentation of alfaxolone[72] in lipid emulsion which does not cause pain on injection and offers rapid onset, rapid offset anaesthesia with minimal haemodynamic disturbance compared to propofol has so far only been described in volunteers and it is unclear whether it will command the necessary investment for full commercial moment.[73]

Four new questions concerning the current library of licensed anaesthetics have emerged. Specifically: are anaesthetics neurotoxic in human infants; can emergence delirium be avoided; does choice of anaesthetic influence outcome from cancer and can anaesthetic drugs precipitate cognitive impairment or dementia? In each case the question is more or less defined but clear answers are elusive. Any one of these if true immediately provides a powerful motivator for development.[3] First however we need to understand the cell chemistry and molecular biology at work and this understanding may lead us to opportunities for rational drug design.

Anaesthetic neurotoxicity

Anaesthetic neurotoxicity has been demonstrated in cell, tissue or small animal models for every currently licenced general anaesthetic. Human data is sparse, retrospective and with a single exception non-experimental. Epidemiological studies of children and infants exploring correlates between early exposure to general anaesthesia with subsequent impaired neuropsychological status offer a mixed and confusing picture. Briefly, some reports associate early exposure to anaesthesia with impaired outcomes (autism, lower test performance etc) however publication bias, methodological issues and underlying confounding leave the matter unresolved. Two prospective trials have made some progress in exploring this uncertainty. The GAS study randomised infants to general or regional anaesthesia with a primary outcome measure based on intelligence testing at five years. The final outcome is awaited, a planned interim analysis found no difference in neurodevelopmental outcome at two years.[74] The Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) trial compared anaesthetised infants with sibling controls and found no difference in neurocognitive function and behaviour at three years.[75] The strengths and weaknesses of the GAS and PANDA studies have been reviewed in detail.[76] Whilst opining that “there is no significant neurocognitive deficit for short anesthetic exposure early in life” the authors nevertheless hedge their bets by suggesting that elective surgery be delayed as long as possible. Regulators have responded to this uncertainty with a revised US Food and Drug Administration warning highlighting unfavourable pre-clinical data and advising that anaesthetics and sedatives “may negatively affect brain development in children younger than 3 years”. Professional bodies have issued guidance to anaesthetists and the public attempting to reconcile the need for transparency and openness with the uncertain knowledge base and understandable parental anxiety.

Emergence delirium

Delirium after anaesthesia can occur at any age and is distressing for patients and those caring for them. Whether delirium is a signal of adverse outcomes is unclear.[77]. Intravenous anaesthesia has been reported to decrease delirium in children[78] and BIS guided anaesthesia may be an effective delirium reduction strategy in adults.[79] However, the diversity of anaesthesia techniques and deficiencies in trial methodology mean that the topic is poorly understood and requires further study.[80]

Anaesthesia and cancer

Surgery and anaesthesia present an inflammatory and immunomodulatory challenge to the patient. Pre-clinical data suggest that the behaviour of malignant cell lines and tumours is altered by therapeutic concentrations of anaesthetic agents and several retrospective analyses of cancer outcomes after surgery suggest that the anaesthetists choice of drugs and regional anaesthesia techniques may alter patient outcomes, potentially with substantial effect sizes.[81] However, the retrospective data can only be hypothesis generating and the outcomes of randomised controlled trials are awaited.[82]

Cognitive impairment, dementia and anaesthesia

Post-operative cognitive dysfunction, POCD has been described after surgery[83] and may be part of a broader spectrum ranging from brief delirium to longer lasting or even permanent cognitive impairment. Confusingly, nomenclature is inconsistent and not well aligned with the broader literature on psychiatry, dementia and geriatric medicine.[84] In children, delirium occurs more frequently after volatile agents than when propofol is used.[85] In adults, especially the elderly, POCD may be determined

by pre-operative cognitive impairments[86] and vascular disease[87]. Unpicking the links, if any, between anaesthesia and subsequent impaired brain function is important given the immense personal, social and economic impact of dementia.

Noble gases xenon and argon

In addition to understanding these phenomena we can hope to improve on existing pharmacology. Thus xenon is potentially useful for resuscitation of birth asphyxiated babies although it may be no more effective than induced hypothermia[88], and is under investigation for paediatric and adult anaesthesia however as a rare and expensive gas its widespread deployment will be limited by supply and the great complexity of equipment to administer it. Xenon provides effective general anaesthesia with cardiovascular stability and rapid clear-headed recovery balanced by a propensity to post-operative nausea and vomiting. [89] Argon is not anaesthetic but has overlapping properties with xenon including neuroprotection[90-93] and potential for protecting other organs.[94, 95] In contrast to xenon, argon is readily and cheaply available from the fractional distillation of liquid air. Argon's lack of hypnotic effect might actually be advantageous if the target is neuro protection as interpretation of neurological status and management of the patient will not be compromised by sedation/anaesthesia. If we can understand how these atoms achieve their apparently beneficial effects then perhaps we can design injectable small molecules to do the same thing with reduced complexity.

Mode of action

In the absence of a rational basis for finding new hypnotics we are left with existing methodology. Our belief that the mechanism of general anaesthetic action was in some simple way related to blood oil solubility was shattered by the demonstration

that the activity of firefly luciferase (a protein based system) is reproducibly impaired by the current hierarchy of anaesthetic drugs pointed anaesthetic pharmacologists towards sites within cell membrane proteins.[96] Subsequently mutations in fruit flies[97] and mice[98] have been demonstrated to have some (but not very much) effect on susceptibility to anaesthesia/anaesthetic drug effects. In addition, photo-ligand experiments[99, 100] and computationally intense modelling have supported credible sites within proteins where drug effect takes place. This understanding offers opportunities to characterise drug -like molecules through high throughput screening[101] but in the absence of mechanistic dissection of the controversies outlined above is unlikely that we will get anaesthetics which are much different from the ones that we have already.

The observation that the solubility of certain cyclic compounds with anaesthetic potential was subject to a threshold in effect[102, 103] has generated patents[104, 105] proposing a wide range of potential new molecular structures for anaesthetics but does not help us choose which ones to pursue.

Conclusion

Development of new intravenous and inhaled general anaesthetics sits at a crossroad. Signals from the basic science around the NMDA receptor (ketamine, nitrous oxide and xenon), understanding of the systemic immunomodulatory effects of anaesthetics and their interaction with cancer, transplantation and inflammation may signpost exciting opportunities associated with anaesthesia that are not merely due to hypnotic effects. A convincing scientific rationale and the prospect of our meaningful impact on major patient outcomes would justify development of new molecules. However, the basic pharmacology required to keep patients safe and still

during surgery is now well established. The drugs that we have at the moment are effective, reasonably safe and excellent value for money with a few that are still on patent but likely to become generic in the near future. In the absence of a compelling narrative linking new structures to materially improved patient outcomes it's unlikely that we will see any more developed.

Agent	Introduced	Advantages	Problems
chloroform	1842		arrhythmias
nitrous oxide	1844	analgesia	
diethyl ether	1846		flammable
cyclopropane	1929		flammable
trichloroethylene	~1930		nausea, slow recovery
trifluoroethyl vinyl ether	1954		flammable, organ toxicity
halothane	1956	not flammable	hepatitis, malignant hyperpyrexia, cardiac depression arrhythmias
enflurane	1966		reduced seizure threshold
methoxyflurane	1962		nephrotoxic
isoflurane	1979		
sevoflurane	1990	rapid onset & offset	
desflurane	1990	rapid onset & offset	pungent

Table 1. Evolution of inhaled anaesthetics.

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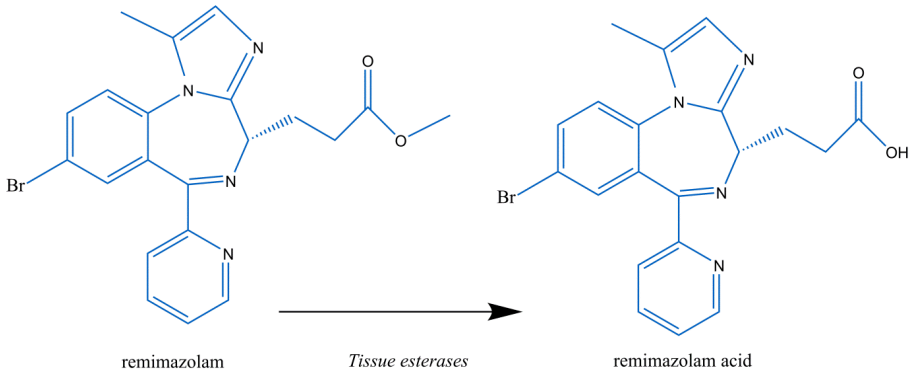
Agent	Introduced	Advantages	Problems
thiopental	1934		alkaline pH
methohexital	1961	short-acting	excitation,
ketamine	1970	cardiovascular stability minimal airway compromise	hallucinations
etomidate	1972	short-acting, dynamic stability	excitation, adrenocortical depression
propanidid	1963	short-acting, haemodynamic stability	excitation, anaphylaxis
midazolam	1976	water soluble, flumazenil reversal	
Althesin	1976	short-acting, haemodynamic stability	anaphylaxis
propofol	1980	rapid onset and offset, clearheaded emergence	pain on injection, lipid accumulation, bacterial contamination
fospropofol	2003	water soluble	prodrug, slow onset, variable peak concentration

Table 2. Evolution of intravenous anaesthetics.

Figure 1



Remimazolam is a benzodiazepine which is rapidly broken down by tissue esterase

Figure 2.

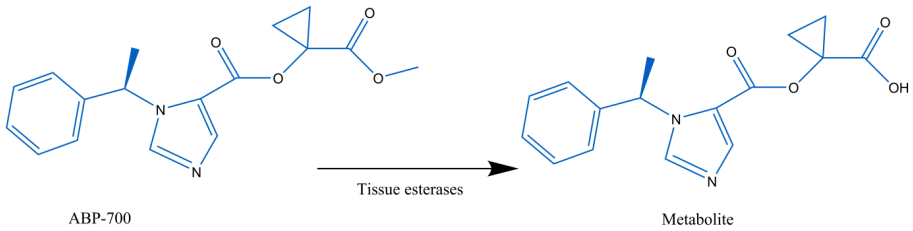


Figure 2. ABP-700 is an ester derivative of etomidate

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