EDITORIAL

Eltanolone: 50 years on and still looking for steroid hypnotic agents!

The knowledge that steroids can induce and maintain anaesthesia is not new; in 1927, Cashin and Moravek caused hypnosis in cats by using a colloidal suspension of cholesterol [1]. However, present-day interest in these molecules stems from the systematic review of the hypnotic properties of steroids (mainly belonging to the pregnane and androstane groups) by Selye in 1941 [2]. There was no apparent relation between hypnotic (anaesthetic) and hormonal properties in any of the screened steroids; the most potent anaesthetic steroid, pregnane-3,20-dione (pregnanedione), was virtually devoid of endocrinological activity.

However, one of the major problems with these steroidal agents was their poor water solubility, and little further work was conducted until Laubach and colleagues synthesized hydroxydione [3]. This was the 21-hydroxy derivative of pregnanedione, which was made water soluble by esterification at the C21 po-sition as the sodium hemisuccinate. Hydroxydione had a high therapeutic index, and few adverse effects in cats and dogs [4].

In clinical practice, hydroxydione produced minimal changes in cardiorespiratory function, good muscle relaxation, a low incidence of coughing and pleasant recovery, with a very low incidence of vomiting [5,6]. However, induction took several minutes. As there was early obtunding of the pharyngeal and laryngeal reflexes, it was possible to achieve airway intubation. The respiratory rate increased with an accompanying decrease in tidal volume and with a resulting increase in minute volume. Marked respiratory depression and apnoea were not usually seen. Cardiac output and arterial blood pressure also fell. However, there were several unwanted side effects: pain on injection; and a high incidence of post-anaesthetic irritation at the site of intravenous (i.v.) administration and along the associated vein.
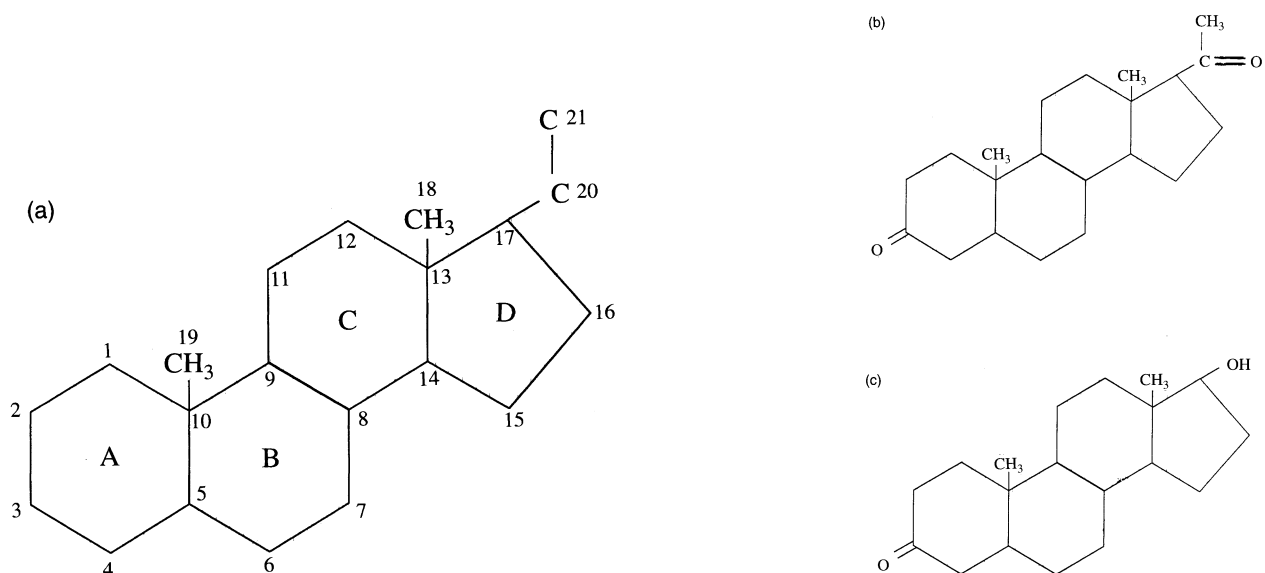
Fig. 1. (a) Notation of the steroid four ringed nucleus, and structure of pregnane and androstane steroids, as typified by (b) progesterone and (c) testosterone.

One of the significant features of steroid anaesthesia derived from these early studies has been the clear evidence of definite structure–activity relations. Large numbers of pregnane and androstane steroids have subsequently been screened for hypnotic activity, either in animals [7] or, more recently, using $GABA_A$ receptors in bovine chromaffin cells of receptors expressed in Xenopus oocytes [8,9].

The basic steroid structure is that of four joined rings (A, B, C and D) (Fig. 1a). Hypnotic efficacy requires molecules with an oxygen function (either hydroxy or ketone) at each end of the steroid (in the C3 position, and the C20 position of pregnanes or the C17 position of androstanes) (Fig. 1b, c). Any substitutions into the steroid structure, such as extra hydroxy groups, reduce anaesthetic activity and occasionally introduce convulsant properties (e.g. 11β-hydroxy compounds). Both 5α-and 5β-isomers are hypnotically active, and the hydroxyl group attached to the C3 carbon can be in either the α or β position. In general, 3α-hydroxy-5α- or 3α-hydroxy-5β-pregnanes show the greatest activity, followed by 3β-hydroxy-5β- and 3β-hydroxy-5α-compounds, while 3-keto substituents have little or no hypnotic activity. Similarly, in general, esters of hydroxy compounds are less active and more slowly acting than the parent alcohols. Introduction of a single double bond in the A or B rings does not significantly affect anaesthetic activity, but two or more double bonds in these rings, or a single double bond in the D ring are associated with the molecule having no hypnotic activity. Conversely, the presence of a C_5 hydrogen atom which is 'cis' to the C_{10} methyl group is associated with increased hypnotic potency.

On the basis of these observations, other steroid hypnotic agents have been evaluated over the last 30 years [5β-pregnane-3α-ol, 11, 20 dione 3 phosphate disodium (GR 2/146); alphaxalone-alphadolone acetate (Althesin); minaxolone citrate; and more recently, 5β-pregnanolone (eltanolone), as well as ORG 20599 and ORG 21465]. Unfortunately, many of these drugs have had significant adverse effect profiles, including: delayed onset anaesthesia in animals and man, and paraesthesia in arm and neck after i.v. dosing (GR 2/146) [10]; allergic reactions to the solvent (Cremophor EL) and/or the constituent steroids (Althesin) [11–14]; and slow onset of action and delayed recovery, with a high incidence of excitatory movements and hypertonus, and possible oncogenic effect in rats (minazolone citrate) [15, 16]. However, all of these induction agents had the advantage of high therapeutic indices—an important safety feature.

Following the observations by Gyermek of the high potency and high therapeutic index of pregnanolone in animals [17], and the successful formulation of the 5β-isomer of pregnanolone (eltanolone) in Intralipid, initial pre-clinical evaluation suggested a drug profile similar to that of propofol and Althesin [18,19]. However, when assessed in clinical practice, the recovery profile of eltanolone differed from that of propofol [20]. Why?

In the recent study by Whyte *et al.* [21], eltanolone was given by incremental dosing to supplement fentanyl-nitrous oxide anaesthesia for minor gynaecological surgery and compared with propofol. Early indices of recovery were achieved faster in the propofol group, but there were no differences in the quality of intermediate recovery when measured using the Digit Symbol Substitution Test and Maddox Wing Test. However, did these authors really compare like with like in this study?

The *one* important requirement of a drug used in this way to provide stable anaesthetic conditions is that a change in plasma drug concentration results in a rapid change in dynamic response. In turn, this will depend on the speed of equilibration of the drug between the blood and the effector site ($=$biophase). In the case of eltanolone, Hering and colleagues have reported a half time of equilibration ($t_{1/2}k_{eo}$) of 8 min, showing there to be significant hysteresis between change in drug concentration and change in response [22]. Corresponding values for other frequently used hypnotic agents are: 1.5 min for thiopentone and 3 min for propofol; there is no evidence of any hysteresis for etomidate and ketamine [23–26].

Why should this hysteresis occur? Wang and colleagues have shown that the potency of the 5α-isomer of pregnanolone solvented in an albumin solution was greater than one made up as an Intralipid formulation [27]. They suggested this may be the result of a delayed release of the active steroid from the lipid of the emulsion. However, all studies with eltanolone have shown that induction of anaesthesia can be satisfactorily achieved within 40–50 s from the start of drug administration by using a larger than necessary

dose. In many respects, this approach may be compared with the 'over-pressure' that is used during an inhalational induction of anaesthesia. Fortunately for eltanolone, large doses do not cause significant cardiovascular depression [28–30].

However, when we come to the maintenance of anaesthesia, we need a drug with a rapid response in order to maintain stable clinical anaesthetic conditions. In the case of eltanolone, the hysteresis effect will lead to a delayed response to a change in plasma drug concentration, while the steep concentration–effect relationship ($\gamma = 6.2$) will result in a sudden onset and offset of effect (in this case, clinical anaesthesia). If overpressure is again used during the maintenance phase (i.e. larger than needed incremental doses), recovery will be subsequently delayed! Thus, to compare propofol and eltanolone when given by similar dosing strategies would not be comparing like with like!

Another facet to the profiling new i.v. agents is the incidence of side effects. These can range from minor sequelae (e.g. pain on injection, hiccoughs and excess salivation) to more major ones (e.g. cardiovascular depression, laryngospasm and bronchospasm, rash, urticaria and true allergic reactions, and convulsions). Although there was a low incidence of excitatory involuntary muscle movements (<3%) in the study of Whyte and colleagues, this has been a significant feature in many other studies with eltanolone [28,29, 31]. However, the occurrence of urticarial reactions in two out of the 67 patients reported by Whyte (although these had none of the other systemic features which would suggest an allergic-type reaction) must be a cause for concern.

Reviewing the overall picture, the major side effects associated with use of eltanolone were involuntary muscle movements (with an incidence of between 5 and 10%), rash and urticaria (3% and 1%, respectively), and four reported cases of convulsions in a clinical trials programme of about 2100 patients and volunteers. In comparison, data for propofol (as cited in the US package insert) give incidences of 17.6% for pain on injection, 3–10% for involuntary movements, 1–3% and 3–10% for bradycardia and hypotension respectively, and 1–3% for rash. Hence, the safety profiles of both drugs show significant unwanted side-effects, but the advantage of propofol is the ability to titrate the drug more easily and reliably to noxious

Table 1. Properties of the ideal intravenous anaesthetic agent

Physical properties
 Water soluble
 Stable in solution
 Long shelf-life
 No pain on intravenous injection
 Non-irritant on subcutaneous injection
 Pain on arterial injection
 No sequelae from arterial injection of small doses
 Low incidence of venous thrombosis
 Small volume of an isotonic solution required for
  induction

Pharmacological properties
 Minimal cardiorespiratory depression
 Does not cause histamine release or predispose to
  hypersensitivity reactions
 Induction in one arm–brain circulation time
 Metabolism to pharmacologically inactive metabolites
 No myoneural blockade

stimuli, and apparent anti-nausea and anti-emetic effects in high-risk patient groups [32].

Thus, the profile of the ideal hypnotic agent first proposed by the late John Dundee in the 1970s has still to be attained (Table 1). The message to the pharmaceutical industry for future drug development seems clear. If we continue to seek the ideal, early kinetic-dynamic modelling in man *must* be undertaken to allow decisions made on the best strategies for drug administration and dosing. Otherwise, as in many of the studies with eltanolone, there will be failure to compare *like with like!*

J. W. Sear
Nuffield Department of Anaesthetics,
University of Oxford,
Oxford, UK

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