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Steroid Anesthesia Revisited: Again

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Neurosteroids are interesting molecules. Endogenous and exogenous progesterone, androstane and deoxycorticosterone compounds bind to gamma-aminobutyric acid receptor class A (GABA_A) receptors and allosterically modulate their function.¹ Low (nM) concentrations of neurosteroids increase the probability of the GABA_A-gated ion channel being in the open state, modulate chloride ion transport, and inhibit neurotransmission. Endogenous neurosteroids are thought to be responsible for the analgesia and reduced minimum alveolar concentration associated with pregnancy. Exogenous neurosteroids with sedative-hypnotic properties have been developed into general anesthetics.² Consistent with an action on GABA_A receptors, neurosteroid anesthetics possess anxiolytic, anticonvulsant, analgesic, sedative, and anesthetic activity.

Few practitioners active today will recall the “neurosteroid era” in anesthesiology.³ Neurosteroids investigated or used clinically include hydroxydione, alphaxalone, eltanolone, minaxolone, and others. None remain. The major problem was the formulation of these highly lipid soluble (and hence water insoluble) compounds for IV administration. Nevertheless, neurosteroids possess many characteristics of the “ideal” anesthetic.

The most successful neurosteroid was Althesin®, a mixture of alphaxalone (3 α -hydroxy-5 α -pregnane-11,20-dione) and alphadolone acetate dissolved in a 20% solution of polyoxyethylated castor oil surfactant (Cremophor® EL). Both steroids showed anesthetic

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effects, but the potency of alphadolone was half that of alphaxalone, and was added only to increase the solubility of alphaxalone. From 1972 to 1984 Althesin® was widely used, with the exception of the United States, for induction and maintenance of anesthesia. The attraction was its rapid onset, short duration of effect, a large therapeutic index, and minimal cardiovascular and respiratory depression.^{2, 3} At Althesin® induction doses up to twice the median effective dose (ED50), cardiovascular depression was minimal. As an IV infusion, the cardiovascular depression from of Althesin® was less than observed with volatile anesthetic drugs.

Unfortunately, Althesin® and other drugs containing Cremophor EL were associated with an untoward incidence of adverse reactions, typically anaphylactoid. In patients, anaphylactoid reactions to Althesin® were reported following a single exposure.⁴ Repeat administration was associated with much more common and severe hypersensitivity reactions, attributed to complement activation.⁵ Althesin® was withdrawn from the market in the 1980s. Similarly, 2,6-diisopropylphenol (disoprofol, later renamed propofol in a reformulation) was also initially formulated in Cremophor. Development of the Cremophor formulation was terminated, due to concerns about potential adverse effects of the solubilizing agent, including anaphylaxis. Propofol was subsequently reformulated as an emulsion in soybean oil (Intralipid) and introduced as Diprivan.⁶

This edition of *Anesthesia & Analgesia* includes a re-examination by Goodchild et al. of alphaxalone, reformulated with a cyclodextrin as the solubilizing agent.⁷ Cyclodextrins are ring structures composed of 6, 7, or 8 sugar molecules, and widely used in the food and pharmaceutical industries. Notably, cyclodextrins form inclusion complexes with hydrophobic molecules to render them water soluble. Cyclodextrins have been used to increase the aqueous solubility of etomidate, alphaxalone and propofol.⁸ Unfortunately, the particular cyclodextrin which successfully solubilized these drugs, and enabled formulations for veterinary use, was toxic in humans.

Goodchild and colleagues reformulated alphaxalone in 7-sulfobutylether β -cyclodextrin, which had previously been used to solubilize etomidate and propofol, and they evaluated the pharmacology of this novel formulation in rats. Alphaxalone (in cyclodextrin) was compared with alphaxalone (together with alphadolone in Cremophor EL, as in the original formulation) and propofol. The results are encouraging. Both alphaxalone (in cyclodextrin) and alphaxalone (in Cremophor) produced anesthesia with fast and similar onset, rapid and similar recovery, and with equal potency. The cardiovascular effects of the two alphaxalone formulations were also similar, with comparable changes in heart rate and blood pressure.

Aside from the novelty of the alphaxalone-cyclodextrin formulation, and its fortuitous similarity to the traditional formulation in hypnotic and cardiovascular effects, the study includes an interesting and somewhat unexpected safety profile of the alphaxalone-cyclodextrin formulation. First, depression of systolic and diastolic blood pressure by alphaxalone-cyclodextrin was significantly less than that by propofol. Second, and more surprisingly, the therapeutic index (median lethal dose (LD50) divided by the ED50) of alphaxalone-cyclodextrin (30) was significantly greater than that of alphaxalone-Cremophor (15) and that of propofol (6). Whereas 52 mg/kg alphaxalone-Cremophor caused death in all

10 rats, the same dose of alphaxalone-cyclodextrin caused no lethality. This is a striking difference. The authors attributed the effect to the 7-sulfobutylether β -cyclodextrin vehicle, because (in a second experiment) the lethality of alphaxalone-Cremophor was 80% in rats pretreated with saline, but only 20% in rats pretreated with 7-sulfobutylether β -cyclodextrin. The mechanism of this protective effect, without a corresponding influence on sedative-hypnotic effects, was not apparent from the experiments presented, nor specifically evaluated. It remains a curiosity, but may be the most interesting finding in the report.

Clearly, excipients used in drug formulations, such as those to aid in solubilization, may not just be innocent bystanders. Some excipients are pharmacologically active themselves. Others may not be active from the perspective of a direct pharmacologic effect, but influences the pharmacologic effects of the active compound of interest. There is much precedent for this. For example, in animals, formulation did not affect the sedative-hypnotic and most side effects of 2,6-diisopropylphenol. No significant differences were found between the Cremophor and lipid emulsion formulations in pharmacokinetics, concentration effect-site relationship, effect-site half-life ($T_{1/2k_{E0}}$), sleeping and recovery times, ED50, therapeutic index (LD50/ED50), or effects on heart rate, cardiac output, blood pressure, and respiratory rate.^{6, 9} In contrast, the Cremophor but not the emulsion formulation caused marked increases in plasma histamine concentration.⁶

The search for an ideal anesthetic continues. Based on the results of the initial experiments by Goodchild et al., it appears that alphaxalone-cyclodextrin may be a better alphaxalone than alphaxalone-Cremophor. The more interesting question is whether alphaxalone-cyclodextrin will be a better anesthetic than propofol.

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