ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different?

The first demonstration of the anaesthetic properties of steroid molecules was in 1927 when Cashin and Moravek produced hypnosis in cats using a colloidal suspension of cholesterol. But it was not until the 1940s that a systematic review was undertaken by Selye into the hypnotic properties of steroids (mainly belonging to the pregnane and androstane groups). Of the screened steroids, there was no apparent relationship between hypnotic (anaesthetic) and hormonal properties; indeed Selye found the most potent anaesthetic steroid to be 5\(\beta\)-pregnane-3,20-dione (pregnanedione), a metabolite of progesterone, that had little endocrinological activity.

Most steroid molecules are poorly water soluble, and little further development was seen until Laubach, P'An and Rudel synthesized hydroxydione in 1955 (fig. 1A). This was the 21-hydroxy derivative of 5\(\beta\)-pregnanedione, and was solubilized by esterification at the C\(_{21}\) position as the sodium hemisuccinate to give a somewhat unstable solution for i.v. injection. Studies in mice showed that hydroxydione had a high therapeutic index (17.3) and few adverse effects in cats and dogs.

In clinical practice hydroxydione produced minimal changes in cardiorespiratory function, good neuromuscular block, a low incidence of coughing and pleasant recovery, with a very low incidence of vomiting. However, induction took several minutes. As there was early obtunding of the pharyngeal and laryngeal reflexes, it was possible to achieve airway intubation without the use of neuromuscular blocking agents. Hydroxydione was also a respiratory stimulant; the rate increasing with an accompanying decrease in tidal volume, leading to an increase in minute volume. Marked respiratory depression and apnoea were not usually seen. Cardiac output and systemic arterial pressure also decreased. There were, however, several unwanted side effects: pain on injection, high incidence of postanaesthetic irritation at the site of i.v. administration and along the associated vein.

Studies by Robertson and Williams described the use of hydroxydione by continuous infusion. Although they tried several approaches to overcome the thrombophlebitis (dilution of drug solution, pre-mixing with blood, use of large veins), none achieved their goal. In their discussion, the authors surmised that some of the metabolites of hydroxydione might be responsible for part of its anaesthetic activity, particularly molecules with hydroxyl groups at the C\(_3\) position (in place of the ketone) and at the C\(_{21}\) position (in place of the attached succinate moiety). This would, of course, have provided an explanation for the delayed onset of action of the steroid, and has been borne out by the more recent studies of Mok, Herschkowitz and Krieger in the mouse.

Despite the limitations of hydroxydione, there has been a determined effort to seek other water-soluble steroid induction agents. Figdor and colleagues demonstrated anaesthetic properties of a series of water-soluble amino-esters based on 21-hydroxy-pregnanedione. Further studies by Hewett and colleagues investigated the animal pharmacology of several androstanes or pregnanes with amino-radicals attached at C\(_{2}\), C\(_6\) or C\(_{16}\). The most potent in causing loss of righting reflex was 3\(\alpha\)-hydroxy, 2\(\beta\)-morpholino, 5\(\alpha\)-pregnan-20-one, which had a therapeutic index of 4.7. However, the compound had several disadvantages—long threshold time to onset of anaesthesia and a prolonged duration of effect. Introduction of an 11-keto group shortened the duration of the ED\(_{50}\) dose (30 to 17 min) but had little effect on potency.

A second line of investigation was undertaken by Phillips and colleagues who examined a range of steroids where basic side chains were added at
the C11 position. Compounds with 11α or 11β- dialkylaminoacyloxy (or dialkylamino) substituents formed water soluble salts (usually the citrate) which showed anaesthetic activity in mice. Minaxolone citrate was one such steroid, where 11α-dimethyl amino and 2β-ethoxy groups were introduced into the pregnane ring, and the C3 hydroxyl group was in the α-configuration (fig. 1A). Introduction of the 2β-ethoxy group led to increased potency compared with alphaxalone, while the dimethyl amino group at the C11 position in the C ring (in place of the dione group) conferred water solubility. In mice, cats and dogs, minaxolone had a high therapeutic index (>5) and was 2–3 times as potent as Althesin, and eight times as potent as thiopentone. The properties of minaxolone and Althesin appeared similar—less respiratory depression and more rapid recovery than that seen after thiopentone, although there was greater incidence of excitatory movements during anaesthesia in dogs.

Clinical evaluation of minaxolone was carried out in 1251 patients between October 1978 and September 1979. Compared with Althesin, minaxolone had a slower onset of action and a more prolonged recovery. The ED50 induction dose was 0.52 mg kg−1. When given by incremental dosing to supplement nitrous oxide, the incidence of excitatory movements and hypertonus were greater in patients receiving minaxolone than in the comparator group. The cardiovascular and ventilatory effects of an induction dose of minaxolone 0.5 mg kg−1 were similar in magnitude to those after equipotent doses of Althesin. Both steroids were associated with a low incidence of postoperative nausea and vomiting. When given by continuous infusion, minaxolone infusion rates of 10–15 μg kg−1 min−1 were needed to supplement 67% nitrous oxide in oxygen anaesthesia. Comparison of the cardiovascular and respiratory effects with those of infusions of Althesin, propofol or methohexitone showed little difference between the four drugs.

Unfortunately, delayed recovery after minaxolone was not its only adverse property. There was also a high incidence of excitatory side effects during induction, increased muscle tone during operation and involuntary movements during recovery, with an overall incidence of approximately 27%, but with a range of 18–45% depending on the premedication prescribed. The incidence of haemodynamic depression was low (3.9% overall), while comparative studies reported a lower incidence of ventilatory side effects than after other i.v. hypnotic agents with the possible exception of etomidate.

Minaxolone also caused two more serious side effects—convulsions during recovery in three patients and abnormal liver function tests after prolonged infusion. In a subgroup of nine patients receiving minaxolone to supplement nitrous oxide for vascular surgery, there were no significant effects on hepatic function in seven of the subjects. However, the other two developed signs of postoperative obstructive jaundice (increases in alkaline phosphatase and serum bilirubin) in the first month after surgery. The aetiology is uncertain, but the jaundice resolved spontaneously in both patients. In September 1979, minaxolone was withdrawn from clinical studies not for clinical reasons but because administration of large doses of the steroid (approximately 100 mg kg−1) to a small number of rats was associated with CNS tumours. This was not supported subsequently by a larger toxicity study involving more than 600 animals.

More recently, two other water-soluble steroid hypnotic agents have been evaluated by Organon Ltd. In 1993, Gemmell and colleagues described the anaesthetic properties in the mouse, rat and dog of a water-soluble 2-morpholino substituted amino- steroid (ORG 20599) (fig. 1C). In laboratory animals, this had an efficacy similar to that of Althesin, a high therapeutic index of 13 and was associated with an hypnotic effect of short duration. However, gross excitatory movements in animals, and problems relating to the stability and solubility of the methane sulphonate salt have prevented its evaluation in humans.

Another water-soluble aminosteroid has now been evaluated in both animals and humans (fig. 1D). ORG 21465 (as the base) showed a high therapeutic index of 13.8 compared with values of 4–5 for propofol and thiopentone. In the monkey, ORG 21465 was compared with propofol in doses of 4 and 3 mg kg−1, respectively. Both showed rapid onset of hypnosis, but duration of sleep and recovery was slower with the aminosteroid, while in the dog the effective hypnotic induction dose of ORG 21465 was 3 mg kg−1, and maintenance doses were 2.8 μmol kg−1 min−1, giving a potency ratio of 1:8 with respect to propofol. The early clinical data from human volunteers are presented in an article in this issue of the British Journal of Anaesthesia.

Doses in excess of 1 mg kg−1 caused loss of consciousness within 1 min in unpremedicated male subjects, and the duration of effect was dose-dependent over the range 1.0–1.8 mg kg−1. Preliminary kinetic data indicate rapid clearance from the blood (as we have reported previously for other steroids), but there has been little evaluation of the kinetic–dynamic behaviour of the drug. As with other water-soluble steroids, the authors report a high incidence of excitatory side effects, although there was no accompanying EEG spike activity. Further clinical assessment of ORG 21465 in humans seems unlikely, and we are therefore left to wonder whether it is likely that any steroid anaesthetic agent will have a pharmacological profile superior to other i.v. induction agents presently available.

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References


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