A consideration of prolonged succinylcholine paralysis with Innovar®: Is the cause droperidol or fentanyl?

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This article, based on a select clinical sampling and literary review, reveals that the droperidol component of Innovar® is responsible for prolonging succinylcholine paralysis. The author discusses the pharmacology of succinylcholine, fentanyl, and droperidol, and suggests some possible mechanisms of interaction.

The purpose of this article is to clarify a phenomenon demonstrated by Wehner in 1979 concerning prolonged succinylcholine paralysis in conjunction with the commonly used neuroleptanesia (NLA) drug Innovar.® This study demonstrates which component of Innovar,® that is, droperidol or fentanyl, contributes to the effect, and offers possible explanations for such an interaction.

Pharmacological considerations

To construct a pharmacological framework within which an understanding of possible NLA drug interactions can be placed, the following will be discussed: a contemporary model of receptors at the myoneural junction, the pharmacology of succinylcholine, and the pharmacologies of droperidol and fentanyl.

A contemporary model of the receptors for acetylcholine (ACh) at the myoneural junction has been elaborated upon by Bradshaw. He points out that the junction is composed of two alternate layers of receptors: R₂ receptors, then R₁ receptors. The R₁ receptors possess a negative charge which attracts the positively charged ACh molecule upon release from the presynaptic terminal and promotes depolarization of the sarcolemma. The R₂ receptors offer a site for attachment of ACh to acetylcholinesterase, thereby inactivating the ACh molecule. The R₂ receptors form an active barrier to the ACh molecules, which must be traversed to accomplish depolarization at the R₁ receptor-sites.

Lehmann offers a useful discussion of the physiologic functions of the enzymes acetylcholinesterase (AChE) and pseudocholinesterase (ChE). True cholinesterase or acetylcholinesterase, is found in red blood cells and nervous tissue. It is responsible for inactivating ACh during the process of neuromuscular transmission, reducing ACh to acetate and choline. Pseudocholinesterase (cholinesterase, butyl, or non specific cholinesterase) is synthesized in the liver and is found in most tissues and the plasma, but not in red blood cells. It hydrolyzes many choline esters including succinylcholine (SCh). The main physiological function of ChE is to inhibit the choline esters that react with AChE, including propionyl-choline and butyrylcholine, both produced by bacterial action along the gastrointestinal tract.

Lehmann also explains that in order for ACh to be inactivated, AChE combines with ACh at an anionic and an esteratic site (on the AChE molecule) to hydrolyze the ACh molecule. Similarly,
choline esters and succinylcholine combine with ChE at an anionic and esteratic site on the ChE molecule to promote hydrolysis and inactivation. For succinylcholine, the hydrolysis results in succinylmonocholine and choline. Both AChE and ChE hydrolyze succinylmonocholine into succinic acid and choline.

Bradshaw suggests that the mechanism of action for SCh activity is similar to that for ACh. That is, depolarization at the postsynaptic area of the myoneural junction by SCh is accomplished by the attraction of the positively charged SCh molecule to the negatively charged R1 receptor. Once the SCh molecule attaches to the receptor and promotes a brief period of depolarization (phase I neuromuscular blockade manifested by muscular fasciculation) a depolarized state is maintained, preventing repolarization.

Some R1 receptors eventually appear to become desensitized to the presence of the SCh molecules, allowing repolarization of those receptors, though paralysis continues. This phenomenon (phase II neuromuscular block) occurs when the receptor becomes less sensitive to the SCh molecule. The formation of a phase II block appears to be related not only to the dose of SCh, but also to the length of time that the myoneural junction remains depolarized.

Termination of the phase I block occurs with redistribution of SCh away from the affected end-plate into other tissues, especially into the plasma. Hydrolysis of SCh in the plasma by ChE promotes a concentration gradient of the drug between the nervous tissue and the plasma, leading to redistribution. The termination of a phase II block appears to be time-related to the redistribution of the SCh molecule away from the end-plate.

Another type of prolonged response to SCh is related to low levels of ChE or abnormal genetic variants of ChE. Low levels of ChE are often found among women, and especially among pregnant women. The genetically atypical form of ChE, both the homozygous and the heterozygous, occurs in about 4% of the total United States population.

The pharmacology of Innovar® is best discussed by considering its components separately. In general, fentanyl is a synthetic narcotic that is chemically and pharmacologically related to the phenylpiperidines, with analgesic potency about 80-100 times greater than morphine. Fentanyl demonstrates a rapid onset and a relatively short duration of action. The short duration appears to be related to a rapid redistribution into body fluid compartments. The drug seems to be active at the thalamic level, the hypothalamic level, and the reticular and gamma systems in the central nervous system.

Fentanyl elicits some autonomic responses associated with vagomimetic properties: bradycardia, increased gastrointestinal motility, and contraction of the sphincter of Oddi. There is little effect on bronchial tone. The autonomic effects can be attenuated by pretreatment with atropine. The drug is a powerful respiratory depressant, decreasing respiratory rate, minute volume, and tidal volume. Fentanyl has been associated with neuromuscular rigidity following rapid intravenous (IV) administration, possibly due to increased intrinsic muscle tone following fentanyl-induced spinal cord depression. The drug is metabolized in the liver and excreted through the urinary tract. An average induction dose of fentanyl, for anesthesia, is about 5.0 mcg/kg or about 1 ml/10 kg IV.

The second component of Innovar, droperidol, is derived from the general class of tranquillizers, the butyrophenones. The following discussion of some of the pharmacological characteristics of the butyrophenones, and some of their similarities to the phenothiazines will help in obtaining perspective about droperidol.

The butyrophenones are similar chemically to the phenothiazines, but the butyrophenones are more potent. Both groups are based chemically on the tertiary aromatic amines (methyl ethylamine) with an "S" shaped propylene chain linked to at least one aromatic ring. Although the butyrophenones are slightly different in chemical structure from the phenothiazines, their pharmacologic action is similar and they probably share similar mechanisms of action.

Haloperidol is the prototype of the butyrophenones and is related structurally to droperidol. Its mechanisms of action are a peripheral blockade of catecholamine receptors, and the central inhibition of neurohumoral amine uptake in the midbrain. The central effects of droperidol result in a strong antidopaminergic response with a reduction in affective behavior and a weak anticholinergic response with antiemesis.

Droperidol has a similar mechanism of action to that of haloperidol. At the cellular level in the central nervous system, droperidol reduces the permeability of cell membranes by forming a monolayered lipid-water interface with reduced surface tension, resulting in the inhibition of structures excited by dopamine, noradrenaline, and 5-hydroxytryptamine. The effect is decreased synaptic transmission and an inhibition of amine re-uptake in the central nervous system, resulting
in sedation, inhibition of operant behavior, and inhibition of chemoreceptor trigger zone-mediated vomiting.\textsuperscript{9}

In the cardiovascular system, droperidol produces a significant decrease in total peripheral resistance (attributed to an increased capacity in the peripheral vascular bed) without altering cardiac stroke volume.\textsuperscript{11} A likely explanation for this effect is a subtotal alpha-adrenergic blockade; droperidol attenuates the cardiovascular response to sympathomimetic amides and produces vasodilatation with a tendency toward moderate hypotension.\textsuperscript{10}

Muldoon proposes that the mechanism of action for the alpha adrenergic blockade produced by droperidol at the cellular level is similar to the mechanism of action cited for the amide local anesthetics.\textsuperscript{12} Increased deamination within the adrenergic neurons, caused by the agent, decreases neuronal sensitivity to electrical stimulation. Unlike the amide local anesthetics, droperidol produces a selective and incomplete suppression of responses to nervous stimulation, hence, alpha blockade.

Droperidol has been associated with other interesting properties. In man, droperidol has demonstrated atropinic effects, especially inhibition of increased bronchial tone, and a significant decrease in serum cholinesterase levels.\textsuperscript{13} Among animals, droperidol antagonizes ACh, inhibiting skeletal neuromuscular transmission; it possesses antihistaminic activity; it has been described as being equipotent with lidocaine in local anesthetic activity;\textsuperscript{14} and it has been shown to produce a decrease in uterine contraction, reversible with oxytocin.\textsuperscript{15}

Droperidol is metabolized in the liver and excreted in feces.\textsuperscript{10} The extent that droperidol is distributed in the body is not known, although the drug crosses the placental barrier and is distributed in the spinal fluid.\textsuperscript{19}

A current, approximate anesthetic dose for droperidol is 0.15 mg/kg IV.\textsuperscript{5}

The study

The following considerations were made for patient selection and grouping in this study: thirty female patients, presenting for elective laparoscopic tubal cauterization, were randomly assigned to three treatment groups of ten patients each. Group B received thiopental and succinylcholine; Group A received fentanyl, thiopental, and succinylcholine; and Group C received Innovar\textsuperscript{®}, fentanyl, thiopental, and succinylcholine. The ages of the patients ranged from 19 to 34 years, and weights ranged from 50.9 to 81.8 kg (mean, 65 kg).

All of the patients were considered to be outpatients, desiring dismissal as early as possible the day of surgery. They received the following pre-anesthetic medications: meperidine 50-75 mg or Numorphan\textsuperscript{®} 1.0-1.25 mg IM; hydroxyzine 50 mg or promethazine 25 mg IM; and atropine 0.4 mg IM. These medications were given 45 min to 1 hr and 15 min prior to the induction of anesthesia.

All patients were monitored for cuff blood pressures and ECG, along with continuous auscultation of heart and breath sounds with a precordial stethoscope. An 18-gauge intercath IV was started peripherally, using D\textsubscript{5}O.25 normal saline 1000 ml prior to induction. A Burroughs-Wellcome\textsuperscript{™} peripheral nerve stimulator (PNS) was used to stimulate the ulnar nerve, to monitor the degree of phase I neuromuscular blockade.\textsuperscript{16}

The following acted as controls: procedural similarity and sex similarity across pseudocholineesterase levels. All patients demonstrated a negative disease history and a negative history for abnormal reactions to anesthesia. A negative family associated anesthetic history was demonstrated by patients having no personal anesthetic history.

The only variable sought in this study was duration of succinylcholine paralysis as it was influenced by the various agents.

All patients were pre-curarized with 3 mg of d-Tubocurarine (d-Tc) 3 min prior to SCh administration to prevent or lessen muscular fasciculation.\textsuperscript{16-18}

Anesthetic induction for the groups followed this procedure: Group C received Innovar\textsuperscript{®} 1 ml IV, then fentanyl 1 ml IV, followed by d-Tc 3 mg IV. Thiopental 3 mg/kg IV was given approximately 5 min following the previous drug combination. The PNS-tetanus followed the thiopental to test electrode placement and act as a control for later comparison. Succinylcholine 1 mg/kg IV was then administered, followed by tracheal intubation. The duration of paralysis was timed with a stop watch from the disappearance of twitch to the first return of visible twitch. This followed an example set by Coppage in 1972.\textsuperscript{16}

Group A received fentanyl 2 ml IV, and d-Tc 3 mg IV; Group B received d-Tc 3 mg IV. The timing and doses for thiopental and succinylcholine, as well as PNS technique, tracheal intubation, and measurement of the duration for SCh paralysis followed the format set for Group C.

Results

The mean duration of SCh paralysis and standard deviations from the mean for each group are illustrated in Figure 1. Prior to analysis of
variance, the data were analyzed for homogeneity of variance using the F max test. The significant F max for df=9 with k=3 was 5.34; the F max for the data was 1.06, demonstrating homogeneity of variance. Analysis of variance demonstrated a significant difference between the treatment groups (see Table I). A Tukey a-posteriori test was conducted to demonstrate critical differences between groups. It showed a significant difference between Group C, and Groups B and A, and a non-significant difference between Group A, and B (Table II).

Discussion

From the resulting data, we can observe that 2.5 mg of droperidol in 1 ml of Innovar® agonizes or prolongs Sch paralysis among the patients studied here. This result is generally similar to the results obtained by Wehner. However, the 1.5 min average prolongation, with the 2.5 mg dose, does not compare with the 4.62 min average found by Wehner. Wehner did not precurarize, and used a 5 mg dose of droperidol in his study.

Because of the methodological differences between the two studies, no correlation between the two studies should be inferred. The current research was constrained by two important conditions: no patient was given more than 1 ml of Innovar® and all patients were pre-treated with a non-depolarizing muscle relaxant.

The exact mechanism of the interaction between droperidol and SCh is not known at this point. We might speculate about some possible mechanisms based on some of the characteristics of droperidol and its pharmacological relatives, to stimulate thinking and possible future investigation.

We have seen that droperidol antagonizes ACh among animals, and that it has anti-pseudocholinesterase activity in man. A close look at the phenothiazines, which have been studied to a greater extent than the butyrophenones, may offer a plausible explanation for the phenomenon elicited here.

Burn reports that when chlorpromazine 3 mg/kg is used to treat prepared skeletal muscle, the muscle becomes unresponsive to direct stimulation and that chlorpromazine increases the duration of both depolarizing and non-depolarizing neuromuscular block. The local anesthetic action

| Table I |
|---|---|---|---|---|---|---|
| source | SS | df | ms | F | P |
| total | 58317.7 | 29 | - | - | - |
| treatment | 40099.5 | 2 | 20049.75 | 29.7 | 0.01 (critical value = 7.19) |
| within | 18218.2 | 27 | 674.75 | - | - |

| Table II |
|---|---|---|---|
| Tukey a posteriori test for critical differences. |
| A | B | C |
| (Fentanyl) A | 154.8 | 158.2 | 234 |
| (Thiopental) B | - | 79.2* |
| (Innovar®) C | - | 75.8* |
| (*=significant value, compared to critical value: 14.35 P 0.01) |

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of the chlorpromazine, its anti-acetylcholine activity, is the mechanism cited. Wylie mentions that the action of local anesthetic agents are that of membrane stabilization; local anesthetics inhibit membrane permeability to sodium in response to electrical stimulation.22

Wylie also mentions that local anesthetics block the release of calcium (calcium release precedes membrane depolarization) which acts as a membrane stabilizer. Droperidol is known to have local anesthetic properties, as well as anti-acetylcholine effects. If droperidol acts as a membrane stabilizer, in the manner of local anesthetics, then this could partially account for the agonism encountered with succinylcholine paralysis.

The phenothiazines also demonstrate some anti-pseudocholinesterase activity. Regan reports a case in which promazine (Sparine®), given for immediate postoperative sedation, induced apnea in a patient that had just received 550 mg of succinylcholine during the operative procedure.23 The mechanism that Regan cited was that the SCh-depressed pseudocholinesterase levels combined with the cholinesterase-depleting effect of the promazine, resulting in a phase II neuromuscular block, in the face of residual, circulating SCh. Thus if droperidol acts to deplete pseudocholinesterase in this manner, then this might also account for prolonged SCh paralysis.

REFERENCES


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