On the suitability of Innovar, a neuroleptic analgesic, for cardiovascular experiments

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The effects of 0.2 and 0.5 mL/kg Innovar (a neuroleptic analgesic) on cardiovascular functions and reflexes in rabbits were measured. We recorded the effects of Innovar on arterial pressure, heart rate, respiration rate, ventricular contractility, and arterial oxygen tension, as well as the drug's effects on the bradycardia and vasoconstrictor response to cigarette smoke stimulation of the nose (the so-called "nasopharyngeal reflex").

In animals given 0.2 mL/kg Innovar, all steady state cardiovascular variables had returned to pre-Innovar levels in 45 min, as had the efficacy of the nasopharyngeal reflex. In animals given 0.5 mL/kg Innovar, all steady state cardiovascular variables, except Pa_{O_2}, were slightly but significantly depressed for up to 135 min after injection. The nasopharyngeal reflex returned to normal within 90 min.

Because of the calmative and analgesic effects of Innovar, and its only moderate effects on cardiovascular functions and reflexes, we feel it is a suitable neuroleptic analgesic agent for cardiovascular experiments where neither fully conscious nor surgically anesthetized animals can be used.

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On a évalué les effets de 0.2 et de 0.5 mL/kg d'Innovar (un analgésique neuroleptique) sur les fonctions et les réflexes cardiovasculaires du lapin. Nous avons enregistré les effets de l'Innovar sur la pression artérielle, le débit cardiaque, la fréquence respiratoire, la contractilité ventriculaire et la tension d'oxygène artériel. Nous avons aussi enregistré les effets de la drogue sur la bradycardie et la réponse vasoconstrictrice à la stimulation de la fumée de cigarette expirée par le nez (le soit-disant "réflexe nasopharyngien").

Chez les animaux ayant reçu 0.2 mL/kg d'Innovar, toutes les variables cardiovasculaires et le réflexe nasopharyngien retrouvèrent leur état précédant l'injection d'Innovar et ce, en 45 min. Chez tous les animaux ayant reçu 0.5 mL/kg d'Innovar, la valeur de toutes les variables cardiovasculaires, sauf le Pa_{O_2}, fut réduite légèrement, mais néanmoins significativement et ce jusqu'à 135 min après l'injection. Le réflexe nasopharygien redevint normal en 90 min.

À cause des effets calmants et analgésiques de l'Innovar, et de ses effets modérés sur les fonctions et réflexes cardiovasculaires, nous croyons que c'est un analgésique neuroleptique valable pour les expériences cardiovasculaires lorsque l'animal n'a pas à être totalement conscient ou sous anesthésie chirurgicale.

[Traduit par le journal]

Introduction

A growing body of evidence shows that the commonly used anesthetics not only affect steady state cardiovascular and respiratory variables (Cox 1972*a*, 1972*b*; Samar and Coleman 1978; Vatner 1978; Younes and Youssef 1978) but, more important, they quantitatively and qualitatively change the integrated response to circulatory perturbations, hypoxia, and other physiological stimuli (Korner *et al.* 1968; Vatner 1978; Cox and Bagshaw 1979). Therefore, experiments designed to elucidate cardiovascular functions and reflexes should properly use conscious animals to avoid the compromising effects of anesthesia. Yet, working with fully conscious animals is extremely difficult. Extraordinary care is required to ensure the animal's comfort, and only docile domestic species can be used as experimental subjects without requiring complex restraining systems.

To help circumvent these problems, a calmative and analgesic agent is required that only minimally compromises cardiovascular and respiratory functions and reflexes. Although morphine with atropine has been used for these purposes (Cox and Bagshaw 1979), we decided to test the suitability of the neuroleptic analgesic Innovar (McNeil Laboratories Limited, Stouffville, Ont.) for use in conscious animals during cardiovascular experiments. We chose Innovar because the clinical literature describes it as having minimal steady state cardiovascular effects (Dixon *et al.* 1970; Tarhan *et al.* 1971; Moran *et al.* 1972; Faulkner *et al.* 1974). Innovar is a mixture of fentanyl citrate, a narcotic analgesic, and droperidol, a neuroleptic agent which induces general quiescence and reduced responsiveness to environmental stimuli.

We chose to investigate the effect of Innovar on the cardiovascular reflexes induced by smoke stimulation

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of the nose in the conscious rabbit, the so-called "nasopharyngeal reflex" (White and McRitchie 1973). Stimulating the trigeminal afferents in the conscious rabbit with smoke, benzene, ammonia, or other noxious vapours causes immediate apnea in the expiratory position, bradycardia (with heart rate falling to 30% of prestimulus rate), and a 40% fall in cardiac output. Arterial pressure is maintained in spite of such severely depressed cardiac output by extensive arterial vasoconstriction (White *et al.* 1974). Because the nasopharyngeal reflex involves complex cardiovascular integration and is obliterated in anesthetized rabbits (White *et al.* 1974), we decided it would be an ideal response to test the hypothesis that Innovar is a suitable adjunct to cardiovascular experiments in mammals where neither fully conscious nor surgically anesthetized animals can be used.

Materials and methods

Ten New Zealand white rabbits of both sexes, ranging in weight from 2.5 to 4.7 kg, were used. All surgical procedures were performed under Halothane anesthesia, and all incisions were heavily infused with local anesthetic (2% xylocaine).

We exposed the trachea, carotid arteries, and maxillary vein with a longitudinal incision in the throat. The carotid artery was freed from surrounding tissue and was cannulated with polyethylene tubing (PE 190, 1.19 mm inside diameter (ID)) connected to a Biotech BT 70 pressure transducer. The cannula was advanced from the point of insertion into the left ventricle to record ventricular pressure. The shortest possible length of tubing was used (generally 15 cm or less) and the system was filled with deoxygenated saline to ensure maximum frequency response (> 70 Hz).

The maxillary vein was cannulated with polyethylene tubing (PE 90, 0.86 mm ID) for drug injection. The ventral surface of the trachea was exposed, and a portion of a 20-guage hypodermic needle (with the last 1–2 mm bent at a right angle) was inserted and held in place with a small amount of tissue glue. The needle was connected to a Statham pressure transducer with PE 90 tubing. This system was used to record tracheal pressure (i.e., respiratory movements).

The femoral artery was exposed in the right leg, freed from surrounding tissue, and cannulated with PE 90 tubing connected to a Statham pressure transducer. This cannula was also used to take blood samples for blood gas analysis. Heart rate was obtained from this arterial pressure recording using an instantaneous rate meter.

After all the incisions had been closed with surgical wound clips, the animal was taken off Halothane, lightly restrained in a prone position on a padded operating table and given 2 h to become fully conscious.

Nasopharyngeal reflexes were induced by gently blowing cigarette smoke at the rabbit's nose either from a mechanical pump or from the mouth of the experimenter. Two smoke stimuli were presented 45 min apart. Forty-five minutes after the second smoke stimulus, 0.2 or 0.5 mL/kg Innovar (0.05 mg fentanyl and 2.5 mg droperidol per millilitre) was administered via the maxillary vein. Smoke stimuli were presented again at 5, 45, 90, and (for rabbits given 0.5 mL/kg Innovar) 135 min after Innovar injection.

Arterial pressure, ventricular pressure, the rate of ventricular pressure development (dP/dt), respiration (tracheal pressure), and heart rate were simultaneously recorded on a six-channel pen recorder (Watanabe, Tokyo), writing on rectilinear coordinates. Arterial blood samples were taken immediately before every smoke stimulus and immediately before the Innovar injection. Arterial P_{O_2} (Pa_{O_2}) was determined polarographically with a temperature-controlled O_2 electrode (Radiometer Acid-base Analyser, Copenhagen) calibrated with water vapour saturated O_2–CO_2–N_2 and CO_2–N_2 gas mixtures.

Mean values of all data were analysed statistically using the paired sample *t*-test and 5% was considered as the fiducial limit of significance for the difference between pairs of means.

Results

Effect of Innovar on steady state cardio-respiratory variables

Values for mean arterial pressure ($\overline{AP}$; diastolic + $\frac{1}{3}$ pulse pressure), ventricular contractility (dP/dt max; maximum rate of ventricular pressure development), respiration rate (Rf), and heart rate (HR) were measured directly from the chart records before each of the two initial (i.e., pre-Innovar) smoke stimulations. The values from each rabbit were averaged and the grand means (± 95% confidence intervals) for all animals in the groups given 0.2 and 0.5 mL/kg are shown in Table 1. Values for pre-Innovar cardio-respiratory variables are similar to those found by other investigators working with unanesthetized rabbits (McRitchie and White 1974; White *et al.* 1974).

All variables were also measured before smoke stimuli presentation in those tests performed after Innovar was administered. The effects of both dose levels of Innovar are also shown in Table 1. The relatively large 95% confidence intervals are mostly due to variability between animals. To help circumvent this problem, the data were also analysed so that each rabbit served as its own control (i.e., self-paired samples). In this study, the values of the cardio-respiratory variables measured after Innovar was injected are expressed as a percentage of the mean pre-Innovar measurement. These results are shown in Figs. 1 and 2. In both figures, 100% signifies that mean pre- and post-Innovar values were identical.

Rabbits given 0.2 mL/kg Innovar (Fig. 1) showed reductions in heart rate, mean arterial pressure, and contractility 5 min after injection of the drug. Respiration rate was reduced to approximately 50% of its pre-Innovar level, although arterial P_{O_2} was not significantly affected. After 45 min, all variables except mean arterial pressure were not significantly different from pre-Innovar values. Mean arterial pressure remained

TABLE 1. Acute effects of 0.2 and 0.5 mL/kg intravenous injection of Innovar on cardio-respiratory variables in rabbits

(*a*) Rabbits given 0.2 mL/kg Innovar

Condition	HR, beats/min	$\overline{AP}$, kPa	d*P*/d*t* max, kPa/s	Rf, breaths/min	Pa_{O_2}, kPa
Pre-Innovar	226± 6.3	12.3 ±0.7	1049±133	72.6± 9.1	12.2±0.6
5 min after injection	183±19.8	9.78±1.6	828±55	33.0±12.7	11.0±1.6
45 min after injection	224± 7.5	11.0 ±2.0	987±239	70.8±25.6	12.0±0.8
90 min after injection	220±10.8	11.5 ±1.3	1188±206	73.4±18.5	12.1±1.8

(*b*) Rabbits given 0.5 mL/kg Innovar

Condition	HR, beats/min	$\overline{AP}$, kPa	d*P*/d*t* max, kPa/s	Rf, breaths/min	Pa_{O_2}, kPa
Pre-Innovar	240±13.2	12.9±1.1	1478±445	95.1±32.1	12.2±0.5
5 min after injection	171±18.4	12.4±2.3	856±406	19.7± 5.3	9.7±0.9
45 min after injection	214±14.6	10.7±0.7	1026±405	80.2±68.1	13.1±1.3
90 min after injection	228±14.8	11.4±1.1	1122±529	87.9±67.3	13.0±1.8
135 min after injection	221±12.3	11.9±1.2	1204±470	84.0±68.6	12.4±2.1

NOTE: Data are means ± 95% confidence intervals. Abbreviations: HR, heart rate; $\overline{AP}$, mean arterial pressure; d*P*/d*t* max, ventricular contractility; Rf, respiratory frequency; Pa_{O_2}, arterial oxygen tension.

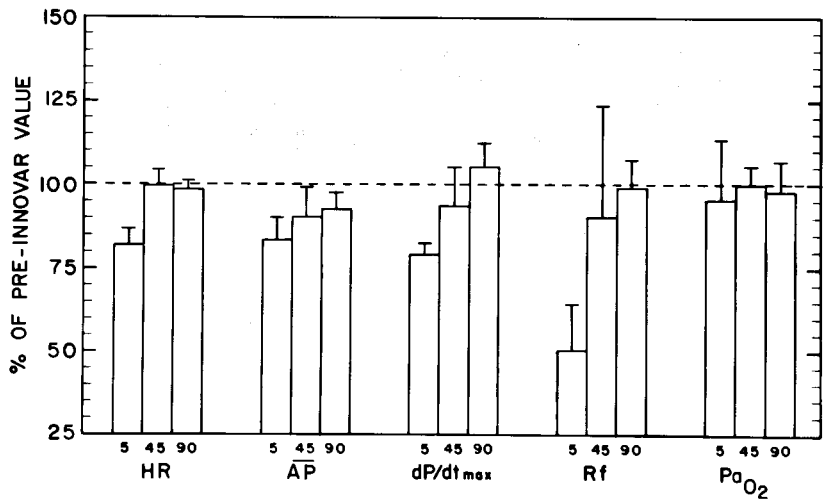

FIG. 1. Relative effects of a 0.2 mL/kg intravenous injection of Innovar on steady state cardio-respiratory variables 5, 45, and 90 min after the drug was administered. The data are represented so that each rabbit served as its own control (i.e., self-paired samples). Therefore the bars indicate the average magnitude (± 95% confidence intervals) of each cardio-respiratory variable expressed as a percentage of its mean pre-Innovar magnitude. The 100% line indicates identical pre- and post-Innovar values. (HR, heart rate; $\overline{AP}$, mean arterial pressure; d*P*/d*t* max, ventricular contractility; Rf, respiratory frequency; Pa_{O_2}, arterial oxygen tension.)

slightly depressed (approximately 5–15% below pre-Innovar levels) for at least 90 min. Rabbits given 0.5 mL/kg Innovar (Fig. 2) showed significantly larger reductions in heart and respiration rates 5 min after the drug was administered. Mean arterial pressure was unchanged, confirming that hypoxia, induced by

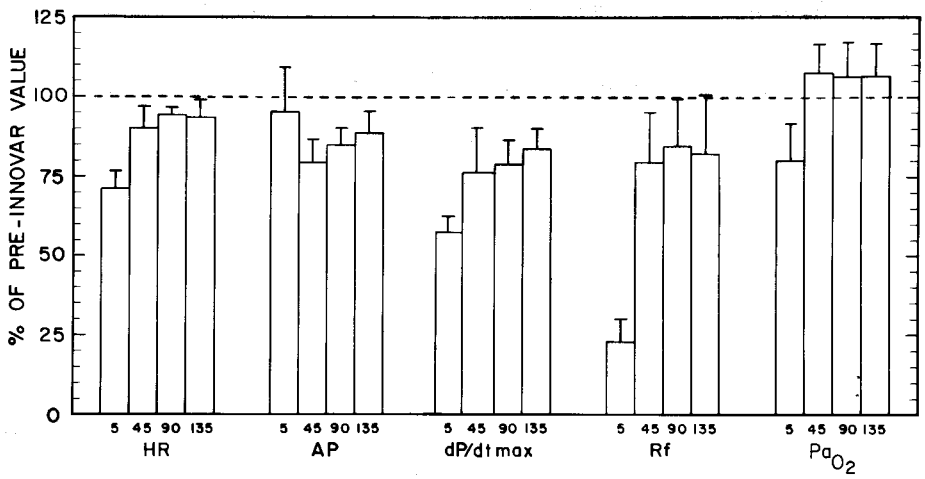

FIG. 2. Relative effects of a 0.5 mL/kg intravenous injection of Innovar on steady state cardio-respiratory variables 5, 45, 90, and 135 min after the drug was administered. The data are represented so that each animal served as its own control. The bars indicate the average magnitude (± 95% confidence intervals) of each cardio-respiratory variable expressed as a percentage of its man pre-Innovar magnitude. (HR, heart rate; AP, mean arterial pressure; d*P*/d*t* max, ventricular contractility; Rf, respiratory frequency; Pa_{O_2}, arterial oxygen tension.)

anaesthesia, causes hypertension (Cox and Bagshaw 1979). Heart rate, mean arterial pressure, contractility, and respiration rate all remained slightly, but significantly, depressed for up to 135 min. Arterial P_{O_2} however, returned to pre-Innovar levels within 45 min.

Effect of Innovar on the nasopharyngeal reflex

In this study, the efficacy of the nasopharyngeal reflex was measured as the animal's ability to maintain arterial pressure in the face of large reductions in heart rate. Heart rate and arterial pressure were measured, as described above, before the smoke stimulus was presented and 20 and 30 s after the onset of smoke-induced apnea. Values measured before smoke stimulation were averaged, as were those measured after.

Mean arterial pressure and heart rate during the smoke stimulus, expressed as a percent of the mean values of these variables measured immediately before the stimulus, are shown in Figs. 3 and 4. In those tests performed before Innovar was administered, there was no significant change in arterial pressure in spite of the heart rate falling to approximately 30% of prestimulus values in some animals. The bradycardic response was, however, significantly reduced 5 min after 0.2 mL/kg Innovar (the heart rate fell to approximately 54% of its prestimulus value) (Fig. 3). In those rabbits given 0.5 mL/kg Innovar, the bradycardic response was drastically reduced 5 min after the drug was administered and remained reduced up to 45 min. With both 0.2 and 0.5 mL/kg Innovar, mean arterial pressure was maintained during the smoke stimulus, in spite of the large changes in heart rate.

Discussion

Effects of Innovar on steady state cardiovascular variables

At a dose level of 0.2 mL/kg, only the mean arterial pressure was significantly affected by Innovar 45 min after the drug was administered. Our results therefore agree with those of Yelonsky and Gardocki (1964) and Dixon *et al.* (1970), who used similar Innovar dosage levels. Unfortunately, their data are compromised because they used animals under general anesthesia (pentobarbital, and allobarbital plus urethane, respectively). The effects of 0.5 mL/kg Innovar on heart rate, respiration rate, ventricular contractility and arterial P_{O_2} were striking 5 min after injection. All variables were considerably depressed from control values. By 45 min, arterial oxygen levels had returned to normal, but all other cardiovascular variables remained somewhat depressed for up to 135 min. In general, the effects of this higher level of Innovar are less than, or at least no worse than, the acute cardiovascular changes caused by surgical doses of pentobarbital or halothane (Samar and Coleman 1978; Vatner 1978).

Innovar's effect on the nasopharyngeal reflex

The nasopharyngeal reflex was quantitatively unaffected by Innovar as little as 45 min after the highest dose given. Even after 5 min, at both dose levels, the response was present, although the extent of bradycardia was reduced.

Innovar is therefore a more suitable adjunct to cardiovascular experiments involving the nasopharyngeal

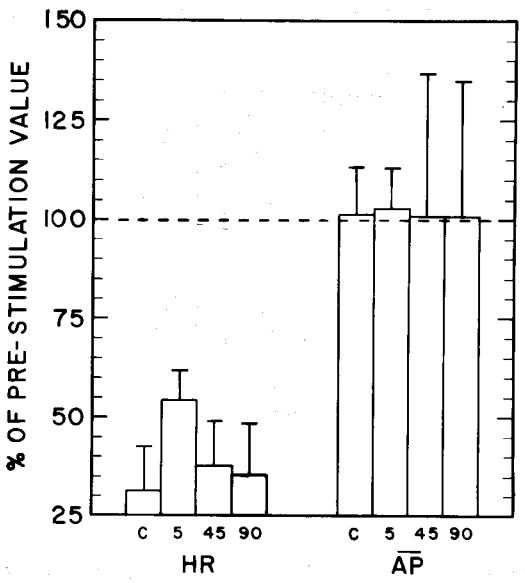

FIG. 3. Relative effects of a 0.2 mL/kg intravenous injection of Innovar on the cardiovascular response to nasal receptor stimulation by cigarette smoke in the rabbit (the so-called "nasopharyngeal reflex"). The data are represented so that each animal served as its own control. C indicates the average fractional change (± 95% confidence interval) in heart rate (HR) and mean arterial pressure ($\overline{AP}$) during smoke stimulation before Innovar was administered. The remaining bars indicate relative changes in HR and $\overline{AP}$, due to smoke stimulation, 5, 45, and 90 min after Innovar was injected intravenously.

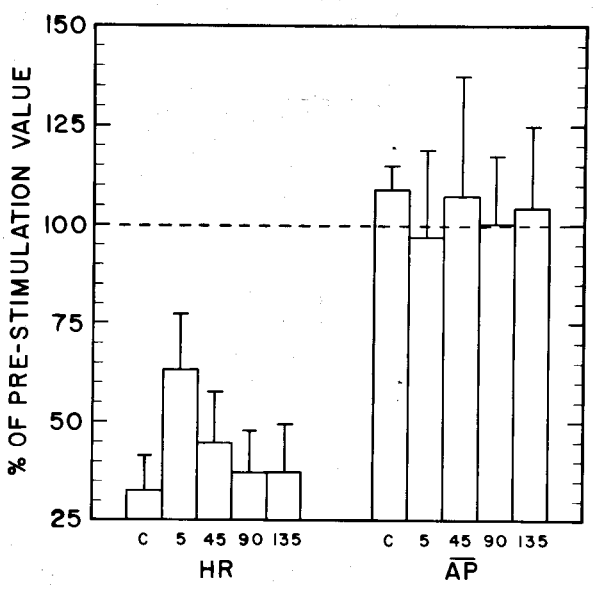

FIG. 4. Relative effects of a 0.5 mL/kg intravenous injection of Innovar on the cardiovascular response to nasal stimulation by cigarette smoke in the rabbit. The data are represented so that each animal served as its own control. C indicates the average fractional change (± 95% confidence interval) in heart rate (HR) and mean arterial pressure ($\overline{AP}$) due to smoke stimulation before Innovar was administered. The remaining bars indicate relative changes in HR and $\overline{AP}$ due to smoke stimulation 5, 45, 90, and 135 min after the drug was injected.

reflex than pentobarbital. In rabbits, seals, and dogs anaesthetized with the latter drug, the nasopharyngeal reflex is drastically (qualitatively as well as quantitatively) changed (Elsner *et al.* 1966; White and McRitchie 1973). Elsner *et al.* (1966) also have shown that even sedation with phenylcyclidine (Sernylan) eliminates the bradycardic and peripheral vasoconstrictive response of seals and dogs during face immersion in water.

On the suitability of Innovar as an adjunct during cardiovascular experiments

Even though we found Innovar produces a short-lived loss of responsiveness to pain (pinching the skin webbing the animal's toes), and loss of the blink and pupillary light responses, it is not considered a suitable surgical anaesthetic. No other attempt was made to quantify the analgesic properties of Innovar in this study. This has already been done by Yelonski and Gardocki (1964), who found the analgesic and calmative effects of Innovar significant but relatively short lived (30–60 min).

It is unlikely that there are any "ideal" anaesthetic or analgesic agents, i.e., those that have no effects on cardiovascular or respiratory functions or reflexes. Yet many experimental procedures require at least some degree of analgesia. As shown here, Innovar appears to have only moderate effects on steady state cardiorespiratory variables or responses. However, it should be emphasized that during any experiment the dose level of Innovar must be carefully selected to ensure a proper balance between the required analgesia and minimal cardiovascular effects. The analgesic and calmative effects of Innovar should minimize the animal's apprehension and discomfort and therefore permit more normal responses to experimental perturbations. Furthermore, use of Innovar should allow procedures to be performed which could not be done on fully conscious animals and procedures, such as the nasopharyngeal reflex, which cannot be done on fully anesthetized animals. Also, the need for complex restraining apparatus should be reduced when experiments involve other than docile domestic species.

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