ANTAGONISM OF MORPHINE WITH NALOXONE IN DOGS: CARDIOVASCULAR EFFECTS WITH SPECIAL REFERENCE TO THE CORONARY CIRCULATION

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SUMMARY

The cardiovascular effects of naloxone 15 μg/kg following morphine 2.0 mg/kg were studied in closed-chest dogs during light nitrous oxide-halothane anaesthesia. The bolus injection of naloxone caused an increase in heart rate (73%), cardiac output (20%) and mean arterial pressure (20%). Total peripheral resistance was unaffected. LV dP/dr max and LV dP/dr max/IP increased by 25% and 14% respectively, but positive inotropic effects could not be shown when load data, heart rate and the decrease in left ventricular ejection fraction (22%) were taken into consideration. The cardiovascular stimulation resulted in an increase in myocardial oxygen demand (66%) which was met by an increase in coronary blood flow (59%). The data suggest that the antagonism of narcotics with high doses of naloxone may impair the myocardial oxygen supply in patients suffering from coronary insufficiency. It is concluded that naloxone should be titrated for each patient to ensure adequate reversal of respiratory depression and to avoid circulatory stress.

Recent studies by Lowenstein and others (1969), Wong and others (1973), Samuel and Dundee (1975) and Stoelting and others (1975) demonstrated that high doses of narcotics did not cause major cardiovascular depression in normal man. Therefore large doses of narcotic analgesics are used frequently as sole anaesthetic agents, especially for patients requiring open heart surgery, and are used increasingly as supplements to anaesthesia. Depending on the amount of narcotics used and the elapsed time from the last dose, this technique may result in a profound respiratory depression, generally necessitating mechanical ventilatory support until the narcotics are metabolized. Alternatively, a narcotic antagonist may be used.

Since the synthesis of naloxone in 1960 by Lewenstein and Fishman (Blumberg, Dayton and Morris, 1961), several investigators have studied its effect following narcotic-nitrous oxide anaesthesia for the purpose of antagonizing unwanted narcotic-induced respiratory depression (Hasbrouck, 1971; Longnecker, Grazis and Eggers, 1973; Heisterkamp and Cohen, 1974; Johnstone et al., 1974; Stephen, Cooper and Harvey, 1976). However, little attention has been focused upon the simultaneous cardiovascular response. Since there are some clinical observations of tachycardia and hypertension (Huse, Hartung and Nadjmabadi, 1974; Tanaka, 1974; Freye, 1975) the purpose of this experimental study was to evaluate the response of haemodynamics, myocardial inotropism, coronary blood flow and the metabolic demand of the heart to naloxone in antagonizing morphine-nitrous oxide anaesthesia in dogs.

METHODS

The experiments were performed in six healthy unpremedicated mongrel dogs of either sex ranging in weight from 26 to 32 kg. Anaesthesia was induced with piritramide 2.0 mg/kg (Dipidolor, Janssen) i.v. and, after endotracheal intubation, anaesthesia was maintained with halothane 0.5% in a mixture of oxygen in nitrous oxide with controlled ventilation using an Engström respirator set at a frequency of 12/min. The minute volume, and the inspired \( P_{O_2} \), were adjusted to maintain \( P_{aCO_2} \) at 5.3 kPa and \( P_{aO_2} \) at 13.3 kPa approximately. If metabolic acidosis developed during the preparation or blood-gas data deviated from the normal, sodium bicarbonate was administered or the respirator settings were altered as appropriate. The base deficit never exceeded 6 mmol/litre. Under fluoroscopic control, catheters were inserted into the right atrium, descending aorta, pulmonary artery and the left ventricle via the brachial and femoral vessels and then connected to pressure transducers (Statham P 23 Db), thus enabling us to
measure the matching pressure values. Left ventricular pressure was measured using a catheter-tip micro-manometer (Milar PC 350) which was passed from the femoral artery. The rate of increase (LV dP/dt) was obtained by differentiating the left ventricular pressure signal using a Statham SP 1400 amplifier and an RC differentiating circuit. Myocardial blood flow (CBF) was measured continuously by the pressure difference technique as described by Hensel and Bretschneider (1970). The reference pressure catheter was inserted into the right external jugular vein; its tip was advanced into the coronary sinus and fixed in position with a fluid-filled cuff. Oxymetry and the blood flow contours confirmed the position of the catheter in the coronary sinus.

All pressure values, LV dP/dt, coronary blood flow and e.g. derived from standard limb leads were recorded continuously on a multichannel recorder (Hellige EK 21).

Cardiac output was measured using the thermodilution technique (Slama and Piiper, 1964). The thermodilution curves were recorded and integrated with the cardiac output computer BN 6560 (Fischer, Göttingen). Arterial and coronary vein blood was sampled intermittently to determine the oxygen saturation and the haemoglobin content using a CO-Oxymeter (Instrument-Laboratories, model 182).

Calculations

From the recorded variables the following data were derived: TPR = (MAP - CVP) : CO

where

\[ TPR = \text{total peripheral resistance} \]
\[ (\text{mm Hg. ml}^{-1}. \text{min. kg}^{-1}) \]
\[ MAP = \text{mean aortic pressure (mm Hg)} \]
\[ CVP = \text{central venous pressure (mm Hg)} \]
\[ CO = \text{cardiac index (ml.min}^{-1}. \text{kg}^{-1}) \]

CVR = (MDAP - CVP) : CBF

where

\[ CVR = \text{coronary vascular resistance} \]
\[ (\text{mm Hg.ml}^{-1}. \text{min per 100 g tissue}) \]
\[ MDAP = \text{mean diastolic aortic pressure (mm Hg)} \]
\[ CBF = \text{coronary blood flow} \]
\[ (\text{ml.min}^{-1} \text{ per 100 g tissue}) \]

The end-systolic volume per 100 g of the left ventricle (ESV) was calculated using the formula for approximation (Bretschneider et al., 1972):

\[ ESV = (\text{SAP} \times 11) : \sqrt{\text{LV dP/dt max}} \]

where

\[ SAP = \text{systolic aortic pressure (mm Hg)} \]

Stroke volume was calculated as the ratio of cardiac output and heart rate. Assuming that the blood flow in the coronary sinus represents only 75% of the left ventricular perfusion (Heiss et al., 1973), the measured coronary sinus blood flow was calculated for 100%. This value was related to 100 g of the left ventricle, the weight of which was determined after sacrifice of the animals following completion of the study. The myocardial oxygen consumption (LV Vo2) was derived from the product of coronary blood flow and the arterio-coronary venous oxygen content difference, the latter being calculated from oxygen saturation differences of the arterial and coronary venous blood and the haemoglobin concentration using the value 1.34 ml/g for the oxygen-combining capacity of haemoglobin. The preload independent index of myocardial contractility LV dP/dt max/IP (Veragut and Krayenbuehl, 1965; Prys-Roberts et al., 1972) was obtained by dividing LV dP/dt max by the pressure developed instantaneously in the left ventricle (IP). IP was calculated by subtracting left ventricular end-diastolic pressure (LVEDP) from the left ventricular pressure existing at the time dP/dt max occurred:

\[ EF = \frac{SV}{100 \text{ g}} : (\frac{SV}{100 \text{ g}} + \text{ESV}) \]

where

\[ EF = \text{ejection fraction of the left ventricle} \]
\[ (\%) \]

\[ SV/100 \text{ g} = \text{stroke volume per 100 g of left ventricle (ml/100 g)} \]

Experimental procedure

After the induction of anaesthesia, approximately 2 h elapsed for surgical preparation and the catheterization of the vessels. Under light halothane anaesthesia with controlled ventilation the experimental animals received morphine 2.0 mg/kg i.v. and were then allowed to achieve a steady cardiovascular state over a period of 45 min. After control measurements were commenced naloxone (Narcan) 15.0 g/kg was given as an i.v. bolus. The haemodynamic responses to naloxone were followed for 10 min. Statistical comparisons were made using Student's t test for paired observations. Statistical significance was defined as P equal to or less than 0.05. The control values are presented as mean ± SEM.
RESULTS

A tracing from a typical experiment illustrates the cardiovascular response to naloxone in antagonizing morphine anaesthesia (fig. 1). There was an increase in heart rate, systemic arterial pressure, coronary blood flow, cardiac output and peak LV $dP/dt$. The onset of action started immediately after the i.v. injection of naloxone and the maximum effect (1st min) was still apparent 5 min later. A return to the control values did not occur over the period of observation (10 min).

The maximum changes in haemodynamic variables following the administration of naloxone are presented in figures 2, 3 and 4. In the group of six animals the heart rate increased by an average of 73% ($P<0.005$) of the control value of 96 ± 6 beat/min, in parallel with an increase in cardiac index (control: 94.7 ± 9.6 ml.min$^{-1}$.kg$^{-1}$) and in mean aortic pressure (control: 122 ± 4 mm Hg) of approximately 20% ($P<0.01$). The mean stroke volume index (control: 1.0 ± 0.1 ml/kg) decreased by 29% ($P<0.005$), while total peripheral resistance did not change significantly from the control value of 1.3 ± 0.1 mm Hg.ml$^{-1}$.min.kg$^{-1}$ (fig. 2).

While the central venous pressure decreased by an average of 44% ($P<0.005$) of the control value of 2.3 ± 0.7 mm Hg, no statistically significant differences were present in the pulmonary artery pressure (control: 16.7 ± 1.2 mm Hg) and in the left ventricular end-diastolic pressure (control: 8.3 ± 0.5 mm Hg). Total increases of 25% ($P<0.01$) in LV $dP/dt$ max and of 14% ($P<0.005$) in LV $dP/dt$ max/IP above the control values (1740 ± 140 mm Hg. s$^{-1}$ and 28.5 ± 2.0 s$^{-1}$ respectively) were observed. The ejection fraction of the left ventricle decreased by 22% ($P<0.005$) from the control value of 33.7 ± 2.7% (fig. 3).

The antagonism of morphine anaesthesia with naloxone was associated with a significant increase in

![Fig. 1. The effect of naloxone 15 μg/kg on heart rate (e.c.g.), aortic pressure ($P_{aorta}$), cardiac output (CO), coronary blood flow (CBF), pulmonary arterial pressure ($P_{PA}$), central venous pressure (CVP), pressure in the left ventricle ($P_{LV}$) and its rate of increase ($dP/dt$), and left ventricular end-diastolic pressure ($P_{LVED}$) in a dog narcotized with morphine 2.0 mg/kg. Tracing from a typical experiment.](https://academic.oup.com/bja/article-abstract/49/6/525/323578)
FIG. 2. The effect of naloxone 15 μg/kg on heart rate (HR), cardiac index (CO), stroke volume index (SV), mean aortic pressure ($P_{aorta}$) and total peripheral resistance (TPR) in dogs ($n = 6$) receiving morphine 2.0 mg/kg.

FIG. 3. The effect of naloxone 15 μg/kg on central venous pressure (CVP), mean pulmonary arterial pressure ($\bar{P}_{PA}$), left ventricular end-diastolic pressure ($P_{LVED}$) and left ventricular max $dP/dt$, $dP/dt$ max/IP and ejection fraction (EF) in dogs ($n = 6$) receiving morphine 2.0 mg/kg.
FIG. 4. The effect of naloxone 15 μg/kg on coronary blood flow (CBF), coronary vascular resistance (CVR), coronary arterio-venous oxygen difference (AVDO$_2^{cor}$) and left ventricular oxygen consumption (LV $\dot{V}$O$_2$) in dogs (n = 6) receiving morphine 2.0 mg/kg.

coronary blood flow (control: 58 ± 6 ml. min$^{-1}$ per 100 g) by 59% ($P<0.01$), in arterio-venous oxygen content difference of the heart (control: 15.4 ± 0.8 vol%) by 4% ($P<0.005$), and in myocardial oxygen consumption (control: 8.7 ± 0.7 ml.min$^{-1}$ per 100 g) by 66% ($P<0.01$). The coronary vascular resistance decreased by an average of 23% ($P<0.005$) of the control value of 2.1 ± 0.2 mmHg.ml$^{-1}$ per 100 g (fig. 4).

DISCUSSION

Narcotic antagonists have been employed clinically for a variety of purposes: the treatment of known or suspected opiate poisoning (Evans, 1973; Waldron, 1973), the diagnosis of narcotic addiction (Fraser, 1957) and the management of respiratory depression induced by narcotics (Eckenhoff and Oesch, 1960). Since the narcotic antagonists used previously, levallorphan and nalorphine, possess also dose-dependent agonist properties, there was a pressing need for a new narcotic antagonist free from undesirable side-effects. Naloxone, being 10-20 times more active than nalorphine and 3-6 times more active than levallorphan (Jasinski, Martin and Haertzen, 1967) in therapeutic doses, does not cause respiratory depression or exhibit any other agonist action. Therefore, it is considered to be the specific narcotic antagonist of choice for clinical use.

The reversal of respiratory depression after the clinical administration of naloxone has been studied on several occasions (Hasbrouck, 1971; Longnecker, Grazis and Eggers, 1973; Johnstone et al., 1974). Only a few reports, however, have described the cardiovascular response to naloxone. In a study of 40 surgical patients who were not premedicated with narcotics, Foldes, Duncalf and Kuwabara (1969) observed that 5 μg/kg of naloxone had only insignificant effects on the circulation. When administered to non-narcotized conscious dogs or anaesthetized dogs, this narcotic antagonist was found to cause no circulatory change (Freye, 1974). However, there is one report of a paradoxical hypertensive episode following its administration (Tanaka, 1974). In a more detailed study Huse, Hartung and Nadjamabadi (1974) demonstrated that, in neurosurgical patients receiving neuroleptanalgesia, a single dose of naloxone 0.4 mg produced an increase in heart rate of 38%, in
cardiac output of 44% and in arterial pressure of 35%. Freye (1974) investigated the haemodynamic response to naloxone 0.4 mg/kg given following increasing doses of fentanyl 0.0025–0.16 mg/kg in dogs and observed increases in heart rate, arterial pressure, LV \( \frac{dP}{dt} \) and in myocardial oxygen consumption up to 100% as compared with control values. However, these experiments were performed on dogs in whom thoracotomy had been performed and whose coronary sinus blood flow has been exteriorized through a 14-gauge catheter of relatively high flow resistance permitting only intermittent readings. No cardiac output measurements were made. Furthermore, the dose of naloxone used seems to be excessive.

In our experiments the cardiovascular response to naloxone in antagonizing morphine was studied in closed-chest dogs. The pressure difference technique allowed continuous readings of the coronary blood flow and the cardiac output was determined frequently. The following reports led us to choose a dose of 15 \( \mu \)g/kg of naloxone for an i.v. bolus injection following an administration of morphine 2.0 mg/kg; formerly the manufacturer recommended a dose of 0.4–0.8 mg of naloxone to be given initially (this has been changed recently to 0.1–0.2 mg); Longnecker, Grazis and Eggers (1973) showed antagonism of morphine 1.4 mg/kg with naloxone 15 \( \mu \)g/kg (5 \( \mu \)g/kg i.v. plus 10 \( \mu \)g/kg i.m.); and Johnstone and others (1974) reported that the Wong team (1973) recommended an average of 40 \( \mu \)g/kg of naloxone in divided doses to antagonize morphine 2.0 mg/kg. The dose of 2.0 mg/kg of morphine is frequently used as the sole anaesthetic agent for high risk patients undergoing cardiac surgery (Lowenstein et al., 1969) and has been used for cardiovascular studies on human volunteers (Wong et al., 1973).

The data of the present study demonstrated that the dose of naloxone investigated led to a stimulation of the cardiovascular system. In spite of the decrease in stroke volume (29%) the increase in heart rate by 73%, resulted in an increase in cardiac output and, consequently, moderate hypertension, indicating that the systemic vascular resistance remained unaffected. Although the increase in the inotropic parameter, peak LV \( \frac{dP}{dt} \), and the preload independent index of myocardial contractility, LV \( \frac{dP}{dt} \) max/IP, by 25% and 14% respectively could suggest positive inotropic effects, the increase in arterial pressure (20%) and cardiac output (20%) was not attributable to improved myocardial contractility. Taking load data and heart rate into consideration, the changes in LV \( \frac{dP}{dt} \) max and LV \( \frac{dP}{dt} \) max/IP were mainly the consequence of tachycardia and of increases in preload and afterload (Wallace, Skinner and Mitchell, 1963). The reduction of left ventricular ejection fraction suggests even slight myocardial depression. Since halothane is generally thought to impair cardiac performance (Prys-Roberts et al., 1972), the low control values of LV \( \frac{dP}{dt} \) max, LV \( \frac{dP}{dt} \) max/IP and of EF were probably a result of the halothane anaesthesia.

Heart rate, arterial systolic pressure, ejection time and velocity of myocardial contraction are the main determinants of the metabolic demands of the heart (Sonnenblick, Ross and Braunwald, 1968; Braunwald, 1971; Bretschneider, 1971). Therefore tachycardia, hypertension and the increase in LV \( \frac{dP}{dt} \) max following the administration of naloxone led to an increase in myocardial oxygen consumption (66%) in parallel with an increase in coronary blood flow (59%). Although the widening of the coronary arterio-venous oxygen content difference was statistically significant, indicating that the metabolic demand of the heart was not met adequately by the increase in coronary blood flow and that additional oxygen utilization was necessary, the change in coronary arterio-venous oxygen difference of 4% is believed to be clinically insignificant if similar changes occur in man.

There is presumptive evidence that cardiovascular stimulation occurs also following the antagonism of other narcotics. Circulatory effects similar to those described above were found under identical experimental conditions in dogs narcotized with fentanyl 0.03 mg/kg (fig. 5).

The possible mechanism for these haemodynamic responses is not clear. Freye (1974) believes that naloxone in the presence of high doses of narcotics competes for identical receptor sites in the central nervous system and thus the “low dose effect” of narcotics becomes apparent. The author postulates that narcotics at low doses increase adrenergic activity as a result of catecholamine release from the adrenal medulla (Vassalle, 1961; Klingman and Maynert, 1962; Fennessy and Rattray, 1971), while high doses are not associated with this response. Since the cardiovascular effects reported above were similar to those seen after the abrupt withdrawal of narcotics, a more likely interpretation is an “overshoot reaction” associated with an acute abstinence syndrome (Wikler, Fraser and Isabell, 1953; Martin, 1967).

Therefore, the data of the present study suggest that the dose of 15 \( \mu \)g/kg of naloxone given as a single
injection was in excess. Although naloxone in inappropriate doses can reduce the analgesic effect of narcotics, the haemodynamic reaction seen in our experiments was probably not mediated reflexly by stress or pain, as the experimental animals were anaesthetized with nitrous oxide and halothane.

The following conclusions could be drawn from the present study: A single i.v. bolus injection of naloxone for the complete or partial antagonism of narcotic depression after operation should not be administered, since excessive doses of naloxone may initially antagonize analgesia and may result in discomfort and also in circulatory stress. Although such cardiovascular stimulation may be tolerated in patients with normal myocardial and coronary vascular function, in those who suffer from coronary insufficiency a careful titration with increments of naloxone should be employed to avoid an unbalanced ratio between myocardial oxygen demand and supply. In these patients the intrinsic autoregulatory mechanisms of the coronary blood flow are impaired and the coronary blood flow depends mainly on a linear pressure-flow relationship. Since our experiments demonstrated that the increase in metabolic requirements of the heart exceeded the increase in coronary perfusion pressure three-fold, a tissue metabolic-perfusion mismatching and, consequently, anaerobic glycolysis may occur.

REFERENCES


**ANTAGONISME DE LA MORPHINE ET DU NALOXONE CHEZ LES CHIENS: EFFETS CARDIOVASCULAIRES AVEC REFERENCE SPECIALE A LA CIRCULATION CORONAIRE**

**RESUME**

Les effets cardiovasculaires du naloxone à raison de 15 μg/kg, après administration de morphine à raison de 2 mg/kg, ont été étudiés sur des chiens ayant la poitrine fermée pendant une légère anesthésie au protoxyde d’azote et à l’halothane. L’injection du bol de naloxone a provoqué une augmentation de la fréquence cardiaque (73%), du débit cardiaque (20%) et de la tension artérielle moyenne (20%). La résistance périphérique totale a été inafféctée. La fréquence maximale d’augmentation de la pression ventriculaire (LV dP/dt max) et le rapport LV dP/dt max/IP (IP = pression développée instantanément dans le ventricule gauche) ont respectivement augmenté de 25% et de 14%, mais on n’a pas pu voir les effets inotropes positifs lorsqu’on a pris en considération les données de charges, la fréquence cardiaque et la diminution de la fraction ventriculaire gauche d’éjection (22%). La stimulation cardiovasculaire a provoqué une augmentation de la demande myocardiale en oxygène (66%) qui a été suivie d’une augmentation du débit sanguin coronarien (59%). Les données laissent penser que l’antagonisme des narcotics avec de fortes doses de naloxone peut altérer l’alimentation myocardiale en oxygène sur les malades souffrant d’insuffisance coronarienne. On en conclut que le naloxone doit être titré pour chaque malade afin d’assurer un renversement approprié de la dépression respiratoire et pour éviter un effort circulatoire.
ZUSAMMENFASSUNG

Die kardiovaskulären Auswirkungen von 15 µg/kg Naloxon nach der Verabreichung von 2,0 mg/kg Morphium wurde bei Hunden ohne Brustaußerröffnung während einer leichten Narkose mit Stickoxyd und Halothan studiert. Die Bolus-Injektion von Naloxon verursachte einen Pulsanstieg (73%), einen Anstieg des Herzminutenvolumens (20%) und des mittleren arteriellen Druckes (20%). Der periphere Gesamtwiderstand wurde nicht beeinträchtigt. LV \( \frac{dP}{dt} \) max. (maximale Anstiegsrate des ventrikulären Druckes) und LV \( \frac{dP}{dr} \) max./IP (IP = sofort im linken Ventrikel entwickelter Druck) stiegen um 25% bzw. um 14%, aber positive inotropische Auswirkungen konnten nicht gezeigt werden, wenn Belastungsangaben, Pulszahl und die Verminderung des Ausstosswerts im linken Ventrikel (22%) in Betracht gezogen wurden. Die kardiovaskuläre Stimulierung führte zu einem Ansteigen des myokardialen Sauerstoffbedarfs (66%), dem durch einen Anstieg des Koronarblutflusses entsprochen wurde (59%). Diese Werte deuten an, dass durch die Gegenwirkung von Narkotika zusammen mit hohen Dosen von Naloxon die myokardiale Sauerstoffzufuhr bei Patienten beeinträchtigt werden kann, die an Koronarinsuffizienz leiden. Es wird empfohlen, Naloxon für solche Patienten zu titrieren um sicherzustellen, dass es zu einer adäquaten Umkehrung der respiratorischen Dämpfung und zu einer Vermeidung von Kreislauf-Überbeanspruchung kommt.

SUMARIO

Los efectos cardiovasculares de naloxona 15 µg/kg tras morfina 2,0 mg/kg fueron estudiados a tórax cerrado en los perros durante anestesia ligera con monóxido de nitrógeno-halotano. La inyección de bolo naloxona causó un aumento en la frecuencia cardíaca (73%), gasto cardíaco (20%) y presión arterial media (20%). La resistencia total periférica no se vio afectada. LV \( \frac{dP}{dt} \) max y LV \( \frac{dP}{dr} \) max/IP (IP = presión desarrollada instantáneamente en el ventrículo izquierdo) aumentaron en el 25% y 14% respectivamente, pero no pudieron demostrarse efectos inotrópicos positivos cuando se tomaron en consideración los datos de sobrecarga, frecuencia cardíaca y descenso de la fracción de eyeción ventricular izquierda (22%). La estimulación cardiovascular resultó en un aumento de la demanda de oxígeno miocárdico (66%) que fue satisfecha mediante un aumento del flujo hemático coronario (59%). Los datos sugieren que el antagonismo de los narcóticos con altas dosis de naloxona pudiera afectar el aporte de oxígeno miocárdico en pacientes aquejados de insuficiencia coronaria. Se concluye que la naloxona debiera ser titulada para cada paciente para asegurar una inversión adecuada de la depresión respiratoria y evitar el stress circulatorio.