THE ABSENCE OF ANTAGONISM BY NALOXONE DURING HALOTHANE/NITROUS OXIDE ANAESTHESIA IN MAN

B.A. MACLEOD, F.C. PING AND L.C. JENKINS

ABSTRACT

Sixteen patients were studied to determine if naloxone could be shown to affect general anaesthesia with halothane and oxygen or nitrous oxide and oxygen with halothane. Changes in blood pressure, pulse rate, electroencephalogram and evidence of physical response were observed. The end-tidal halothane and carbon dioxide were controlled. The temperature and blood gases were held constant, as was the degree of neuromuscular blockade. Naloxone 1.2 mg was administered during general anaesthesia with either halothane in oxygen or halothane with nitrous oxide to 16 patients who were premedicated without a narcotic. No significant responses were recorded.

The discovery of endogenous opiate-like substances (enkephalins) and specific opiate receptors in the brain^{1,4} has led to interesting speculation concerning their role in the production of analgesia.⁵ Naloxone, a specific narcotic antagonist, has been shown to enhance clinical pain⁵ as well as to decrease analgesia associated with acupuncture and electrical stimulation of the periaqueductal grey areas in the brain.^{6,7} In mice analgesia produced by nitrous oxide has been decreased by naloxone, and its administration in the rat during general anaesthesia with halothane, cyclopropane and enflurane resulted in increased somatic response to painful stimulus.^{8,9}

In view of these findings it was decided to investigate the effect of naloxone on patients anaesthetized with halothane, and with halothane and nitrous oxide mixture.

METHOD

Sixteen female patients with ages ranging from 24 to 57 years were studied. All were A.S.A. Class I, scheduled for abdominal hysterectomy. Informed consent was obtained preoperatively. None were in pain preoperatively nor were they receiving preoperative analgesia.

The first eight patients were given halothane-oxygen anaesthesia, the next eight patients received halothane, oxygen and 60 per cent nitrous oxide.

B.A. MacLeod, M.D., F.R.C.P.(C), F.C. Ping, M.B., B.Ch., B.A.O., L.C. Jenkins, M.D., C.M., F.R.C.P.(C). Department of Anaesthesia, Vancouver General Hospital.

Premedication consisted of pentobarbitone 200 mg orally two hours before operation.

Before induction of anaesthesia an electroencephalogram was recorded from four quadrants on a Beckman Superacutrace. Monitoring was by means of a sphygmomanometer, electrocardioscope, oral temperature probe and a peripheral nerve stimulator over the ulnar nerve. End-tidal halothane and carbon dioxide concentrations were monitored continuously on a Beckman infrared analyzer.

Induction was with thiopentone 5 mg · kg⁻¹ and tracheal intubation was facilitated by succinylcholine 1 mg · kg⁻¹.

When the blood pressure, heart rate, end-tidal halothane and carbon dioxide concentrations had remained unchanged for 15 minutes and there was no response to surgical stimulus, a ten-minute control period was started. The end-tidal halothane concentrations at which the study was done were those which obtunded response to surgical stimuli of each individual patient. During this time the end-tidal halothane and carbon dioxide were held constant. The blood pressure and heart rate were recorded every two minutes. The electroencephalogram was recorded and the ulnar nerve was stimulated by a two-second tetanic burst at maximum voltage setting. The temperature was noted and the absence of evidence of inadequate anaesthesia such as sweating or grimacing was noted.

At the end of this ten-minute control period naloxone 1.2 mg was injected rapidly intravenously. Over the next ten minutes the end tidal halothane and carbon dioxide levels were monitored continuously and again held constant. Temperature, electroencephalogram and re-

TABLE I
MEAN BLOOD PRESSURE AND PULSE RATE BEFORE AND AFTER NALOXONE
(GROUP DATA)

	Mean blood pressure pre-naloxone	Mean blood pressure post-naloxone	Mean pulse rate pre-naloxone	Mean pulse rate post-naloxone
Group I (O ₂ /halothane)	87 No significant change	90 No significant change	77 No significant change	78 No significant change
Group II (O ₂ /N ₂ O/halothane)	98 No significant change	94 No significant change	83 No significant change	81 No significant change

sponse to nerve stimulation were again noted. Blood pressure and pulse rate were again checked every two minutes. The patient was observed for signs of light anaesthesia.

RESULTS

No patient receiving either halothane or halothane-nitrous oxide showed any evidence of a decreased anaesthetic level following naloxone.

Table I shows mean values for blood pressure and pulse rate before and after naloxone administration. These were arrived at by averaging the blood pressure and pulse rate over the 10-minute pre-naloxone control period and for 10 minutes after naloxone.

A paired t-test revealed no significant difference between the pre- and post-naloxone values.

An example of an electroencephalogram recorded before a surgical anaesthetic level was reached is shown in Figure 1. The shift to a higher frequency and lower voltage upon electrical stimulation of the ulnar nerve are consistent with light anaesthesia.¹⁰ This was not seen in any of the patients during the control or post-naloxone periods.

Figures 2 and 3 represent typical electroencephalogram tracings. Both tracings show spindling patterns unchanged by the administration of naloxone. None of the patients revealed a change in the electroencephalogram.

No lacrimation, eye movements, sweating, or grimacing were noted in either the control or post-naloxone periods.

The temperature, end-tidal halothane and end-tidal oxygen concentrations also remained constant for the control and post-naloxone periods.

DISCUSSION

No evidence of changing depth in halothane, or halothane/nitrous oxide general anaesthesia was

FIGURE 1 Electroencephalographic evidence of lighter anaesthesia.

found in our patients after they had received naloxone 1.2 mg intravenously. The end-tidal concentration for each patient was held at the minimal level sufficient to obtund response to surgical stimulus. The use of a fixed MAC concentration of halothane (a population concept), is inappropriate to this study since at this concentration one-half of the patients would be responding to surgical stimulation.

This lack of effect contrasts with experiments in which an increased response to tail squeeze was reported in rats anaesthetized with halothane, cyclopropane and enflurane, as well as experiments in mice which indicated reversal of nitrous oxide analgesia when naloxone was given.^{8,9} In man, naloxone has been shown in some studies not to alter pain thresholds.¹¹ However, in a recent study of dental patients,

FIGURE 2 Representative electroencephalogram before, during, and after naloxone during halothane anaesthesia.

FIGURE 3 Representative electrocardiogram before, during, and after naloxone during halothane/nitrous oxide anaesthesia.

naloxone has been shown to enhance clinical pain.⁵ Furthermore, naloxone has been shown to decrease acupuncture produced analgesia as well as analgesia produced by direct brain stimulation.^{6,7}

Many possible reasons exist for the apparent variation in experimental results. First, the majority of the previous studies have measured changes occurring in the degree of analgesia, but the state of general anaesthesia is very different. The dosage used in animal experiments is much higher than that used in this study. It is difficult to extrapolate dosage from rat to man; however, corresponding doses of naloxone for reduction of analgesia induced by direct electrical stimulation of the brain are $1 \text{ mg} \cdot \text{kg}^{-1}$ in the rat and a total of 0.2 mg in man.^{7,12} Also, the respiratory cardiovascular and central nervous system depression induced by morphine in a dosage of $1.5 \text{ mg} \cdot \text{kg}^{-1}$ in man, has been shown to be reversed by a dosage of naloxone of $5 \mu\text{g} \cdot \text{kg}^{-1}$.¹³ Additionally, 0.8 mg of naloxone has been shown to decrease acupuncture-induced analgesia in man.⁶ For these reasons the dose recommended as a maximum in the treatment of respiratory depression, or a total of 1.2 mg was felt to be adequate to reveal any major role enkephalins might play in halothane and halothane-nitrous oxide anaesthesia.

The depth of anaesthesia chosen was surgical anaesthesia. An inverse relationship between mean arterial pressure and increasing MAC levels of both halothane and halothane-nitrous oxide anaesthesia has been demonstrated to occur during the first hour of anaesthesia, a period in which our measurements were made.¹⁴

The electroencephalogram patterns were consistent with light surgical anaesthesia¹⁰ during all periods of control and naloxone administration.

Recent work in rats¹⁵ and dogs¹⁶ has shown no evidence of naloxone reversal of general anaesthesia. Our study in man also found no evidence of naloxone reversal during general anaesthesia with halothane, or halothane and nitrous oxide.

REFERENCES

1. KUHAR, M.J., PERT, C.B. & SNYDER, S.H. Regional distribution of opiate receptor binding in monkey and human brain. *Nature* 245: 447-450 (1973).
2. GOLDSTEIN, A. Opiate receptors. *Life Sci.* 14: 615-623 (1974).
3. HUGHES, J., SMITH, T.W., KOSTERLITZ, H.W., FOTHERGILL, L.A., MORGAN, B.A. & MORRIS, H.R. Identification of two related pentapeptides

- from the brain with potent opiate agonist activity. *Nature* 258: 577-579 (1975).
4. PASTERNAK, G.W., GOODMAN, R. & SNYDER, S.H. An endogenous morphine-like factor on mammalian brain. *Life Sci.* 16: 1765-1769 (1975).
 5. LEVINE, J.D., GORDON, N.C., JONES, R.T. & FIELD, H.L. The narcotic antagonist naloxone enhances clinical pain. *Nature* 272 (1978).
 6. MAYER, D.J., PRICE, D.D. & RAFU, A. Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. *Brain Res.* 121: 368-373 (1977).
 7. AKIL, H., MAYER, D.J. & LIEBESKIND, J.C. Antagonism of stimulation produced analgesia by naloxone, a narcotic antagonist. *Science* 191: 961-962 (1976).
 8. BERKOWITZ, B.A., FINCK, A.D. & NGAI, S.H. Nitrous oxide analgesia and its reversal by narcotic antagonists. *Pharmacologist* 18: 177 (1976).
 9. FINCK, A.D., NGAI, S.H. & BERKOWITZ, B.A. Antagonism of general anaesthesia by naloxone in the rat. *Anesth.* 46: 221-245 (1977).
 10. FAULCONER, A. JR. & BICKFORD, R.G. *Electroencephalography in anesthesiology*. Springfield, Ill., Thomas (1960).
 11. EL-SOBKY, A., DOOTROVSKY, J.O. & WALL, P.D. Lack of effect of naloxone on pain perception in humans. *Nature* 263: 783-784 (1976).
 12. ADAMS, J.E. Naloxone reversal of analgesia produced by brain stimulations in the human. *Pain* 2: 161-166 (1976).
 13. LONGNECKER, D.E., GRAZIS, P.A. & EGGERS, G.W.N. Naloxone for antagonism of morphine-induced respiratory depression. *Anesth. & Analg.* 52: 447-452 (1973).
 14. BAHLMAN, S.H., EGER, E.E., SMITH, N.T., STEVENS, W.C., SHAKESPEARE, T.F., SAWYER, D.C., HALSEY, M.J. & CROMWELL, T.H. The cardiovascular effects of nitrous oxide halothane anaesthesia in man. *Anaesthesiol.* 35: 274-285 (1971).
 15. HARPER, M.H., WINTER, P.M., JOHNSON, B.H. & EGER, E.I. Naloxone does not antagonize general anesthesia in the rat. *Anesthesiol.* 49: 3-5 (1978).
 16. PACE, N.L. & WONG, K.C. Failure of naloxone and naltrexone to antagonize halothane anesthesia in the dog. *Anesth. Analg.* 58: 36-39 (1979).

RÉSUMÉ

L'objectif du travail était de déterminer l'effet du naloxone sur les niveaux d'anesthésie produits par les mélanges halothane-oxygène et protoxyde d'azote-halothane-oxygène. Seize patients volontaires ont été soumis à l'étude. On a observé les modifications de la pression artérielle, de la fréquence cardiaque, de l'électro-encéphalogramme ainsi que les manifestations physiques d'anesthésie légère, ceci après atteinte de conditions stables (halothane et CO₂ de fin d'expiration, température, gaz artériels et degré de relâchement musculaire). Une dose de 1.2 mg de naloxone était injectée à ce moment aux patients anesthésiés à l'halothane-oxygène et à ceux recevant le mélange protoxyde-oxygène. Aucune modification significative des paramètres étudiés n'a été observée.