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Reversal of narcotic depression in the neonate by naloxone

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Summary

Naloxone 40 µg was administered intravenously one minute after birth to 20 out of 44 neonates whose mothers had been given pethidine in labour. These neonates were compared with 20 others whose mothers had had only lumbar epidural block. Alveolar P_{CO_2} , alveolar ventilation, and ventilatory rate were measured 10 and 30 minutes after birth. The untreated neonates of mothers who had had pethidine showed significant ventilatory depression compared with infants in the epidural and naloxone-treated groups. The naloxone-treated neonates were comparable with the epidural group, although the effects of naloxone were diminishing at 30 minutes. Naloxone is an effective narcotic antagonist which should be considered to be the drug of choice for treating narcotic depression in the neonate.

Introduction

Narcotic analgesics, which are widely used during labour, may depress neonatal ventilatory function.¹ Nalorphine and levallorphan are unsatisfactory antagonists because they have substantial agonist activity and may therefore cause ventilatory depression. Naloxone, an effective antagonist free of agonist activity,^{2,3} should be more appropriate in treating the neonate suffering

from narcotic depression, but no evidence exists of the effectiveness of naloxone in the newborn.

Method

Maternal consent for the investigation was obtained. Mature healthy neonates (38-42 weeks) delivered spontaneously or by easy forceps delivery whose mothers received pethidine during labour were randomly allocated to receive either naloxone (pethidine-naloxone group) or no treatment (pethidine group). Naloxone, 40 µg in 1.3 ml of water, was injected into the umbilical vein one minute after birth; this dose was based on adult doses. These neonates were compared with those whose mothers had had analgesia only by continuous lumbar epidural block using bupivacaine hydrochloride 0.5% without adrenaline (epidural group).

The time to first breath, the time of onset of sustained ventilation, and the Apgar score at one and five minutes were recorded. Ten and 30 minutes after birth the alveolar P_{CO_2} was measured by rapid infrared analysis of the expired gas, continuously sampled through a nasal catheter. Carbon dioxide excretion was measured by entraining expired gas in a steady air flow drawn through a gently applied face-mask. The carbon dioxide concentration of the gas flow was continuously measured by an infrared carbon dioxide analyser; the output signal of the analyser was electronically integrated to provide a measure of carbon dioxide excretion. Alveolar ventilation was calculated, after appropriate corrections, from the alveolar P_{CO_2} and the rate of carbon dioxide excretion.⁴ Alveolar P_{CO_2} and carbon dioxide excretion were measured sequentially in 30-second periods. Ventilatory rate was recorded.

The plasma pethidine concentration of umbilical venous blood was measured by gas chromatography.

Statistical analysis was performed using Student's *t* test or, when appropriate, the Mann-Whitney U test.⁵

Results

Sixty-four neonates were studied. Forty-four were delivered to mothers who had received pethidine, and 20 of these received naloxone. The mean (SD) dose of pethidine administered to the mothers was

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173 (75) mg. The mean plasma pethidine concentration of umbilical venous blood was 1.04 (0.44) $\mu\text{mol/l}$ (25.7 (10.9) $\mu\text{g}/100\text{ ml}$) in the pethidine-naloxone group and 0.84 (0.48) $\mu\text{mol/l}$ (20.8 (11.9) $\mu\text{g}/100\text{ ml}$) in the pethidine group.

The mean weights of neonates in the pethidine-naloxone, pethidine, and epidural groups were similar: 3.25 (0.45) kg, 3.32 (0.54) kg, and 3.36 (0.39) kg respectively.

At one minute the mean Apgar score in the pethidine-naloxone group was similar to that in the pethidine group and lower than that in the epidural group ($P=0.02$) (table I). The difference between the pethidine and epidural groups was not statistically significant ($P=0.12$). At five minutes the Apgar scores were similar in the three groups.

TABLE I—Mean Apgar scores, time to first breath, and time to onset of sustained ventilation of neonates in the three groups of neonates

	Group		
	Pethidine-naloxone (n=20)	Pethidine (n=24)	Epidural (n=20)
Apgar score at 1 minute	7.3	7.8	8.5
Apgar score at 5 minutes	9.9	9.7	9.9
Time to first breath (s)	32.4	28.6	21.6
Time to onset of sustained ventilation (s)	80.3	70.0	46.1

The times to first breath of the pethidine-naloxone and pethidine groups were similar but both were longer than that in the epidural group ($P=0.02$). The times to the onset of sustained ventilation of the

Mean ($\pm$ SE) alveolar PCO_2 10 and 30 minutes after birth in the three groups of neonates. --- = Pethidine group. — = Pethidine - naloxone group = Epidural group.

TABLE II—Mean (SD) alveolar PCO_2 , alveolar ventilation, and ventilation rate 10 and 30 minutes after birth in the three groups of neonates

Time after birth:						10 minutes	30 minutes
						Alveolar PCO_2 (kPa)	
Pethidine-naloxone	..	..	..	..	..	5.30 (0.58)	4.98 (0.58)
Pethidine	..	..	..	..	..	5.91 (0.82)	5.53 (0.82)
Epidural	..	..	..	..	..	5.0 (0.76)	4.53 (0.64)
						Alveolar ventilation (l/min/kg)	
Pethidine-naloxone	..	..	..	..	..	0.169 (0.57)	0.166 (0.61)
Pethidine	..	..	..	..	..	0.156 (0.41)	0.143 (0.39)
Epidural	..	..	..	..	..	0.176 (0.70)	0.183 (0.68)
						Ventilatory rate (per min)	
Pethidine-naloxone	..	..	..	..	..	42.7 (12.9)	44.7 (14.4)
Pethidine	..	..	..	..	..	39.2 (10.1)	40.9 (11.6)
Epidural	..	..	..	..	..	43.7 (9.5)	44.6 (10.9)

Conversion: SI to traditional units—1 kPa $\approx$ 7.5 mm Hg.

pethidine-naloxone and pethidine groups were similar and were longer than that in the epidural group ($P=0.002$ and $P=0.04$ respectively). Initially, therefore, ventilation in both pethidine groups was similarly depressed compared with that in the epidural group.

VENTILATORY MEASUREMENTS

At 10 minutes the mean alveolar PCO_2 was lowest in the epidural group and highest in the pethidine group ($P=0.008$) (fig 1). The alveolar PCO_2 of the pethidine-naloxone group was close to that of the epidural group and also significantly less than that of the pethidine group ($P=0.03$).

At 30 minutes the alveolar PCO_2 of all three groups had fallen significantly ($P<0.01$ for the three groups). The alveolar PCO_2 of the pethidine-naloxone group was still lower than that of the pethidine group ($P=0.07$) but higher than that of the epidural group ($P=0.03$). The values in the pethidine and epidural groups were also significantly different ($P=0.005$).

At 10 and 30 minutes the alveolar ventilation was highest in the epidural group and lowest in the pethidine group; at 30 minutes this difference was significant ($P=0.04$). The alveolar ventilation of the pethidine-naloxone group was intermediate. The ventilatory rate reflected these changes but none of the differences reached statistical significance.

Discussion

Although the influence of maternal analgesia on Apgar scores and onset of ventilation has been studied, the influence of analgesia on early neonatal ventilation has not been examined in detail. Ten and 30 minutes after birth the untreated neonates whose mothers received pethidine during labour had a higher alveolar PCO_2 , a lower alveolar ventilation, and a lower ventilatory rate than the neonates of the mothers who received no narcotics.

The neonates in both pethidine groups had comparable umbilical pethidine concentrations, Apgar scores, and times of onset of ventilation. Indeed, the pethidine-naloxone group was at a slight disadvantage. Nevertheless, the intravenous administration of 40 μg naloxone to the neonate one minute after birth produced a substantial difference in ventilatory function, the most obvious change being a lower alveolar PCO_2 . Clearly naloxone is an effective narcotic antagonist, reversing the ventilatory depressant effects of maternally administered pethidine. Only healthy neonates were studied so that ventilatory change could not be ascribed to intrapartum hypoxia or unfavourable delivery. Since naloxone has no agonist activity, unlike nalorphine or levallorphan, it can be safely given to any neonate believed to be suffering from narcotic-induced depression.

A single intravenous dose of naloxone has a short duration of action in the adult.² Thirty minutes after birth there was some indication that the effect of naloxone was diminishing. The depressed neonate who has been treated with intravenous naloxone should therefore be kept under careful observation in

case ventilatory depression returns. The use of a larger dose of naloxone, given either intravenously or intramuscularly, is being investigated to determine whether the action of naloxone can be usefully prolonged.

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Streptokinase in acute myocardial infarction: a controlled multicentre study in the United Kingdom

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Summary

In a multicentre trial of streptokinase in acute myocardial infarction 302 patients received an intravenous infusion of 2 500 000 IU of streptokinase over 24 hours, while 293 patients served as controls. Neither group received anticoagulants unless indicated by thromboembolic complications. No significant difference in mortality was evident during inpatient treatment nor at six-week or six-month follow-up. The inpatient death rate was 12.6% in the streptokinase group and 13.7% among controls.

There was no significant difference in the peak levels or pattern of enzyme increase. The incidence of cardiac failure and reinfarction was similar in the two groups, but major arrhythmias were less common in those on streptokinase ($P < 0.05$). In the streptokinase group there were 36 minor and six more serious haemorrhagic com-

plications. Gastrointestinal haemorrhage may have contributed to the death of one patient in each group. There were 18 thromboembolic complications in the streptokinase group and 38 among the controls. Pathological examination of the hearts of 25 patients who had taken streptokinase and 24 controls showed no striking differences between the groups, but haemorrhagic infarcts were found in three patients who had received streptokinase.

An infusion of streptokinase within 24 hours of the onset of acute myocardial infarction does not significantly affect the mortality or course of the illness up to six months.

Introduction

Since the introduction of streptokinase into clinical practice 17 years ago^{1,2} the therapeutic value of thrombolytic agents in acute myocardial infarction has remained in doubt. Only recently have a series of major controlled trials been undertaken (table I).³⁻⁷ No conclusive result in favour of streptokinase has emerged from these studies, in which the initial thrombolytic treatment followed by anticoagulation was compared with anticoagulant treatment alone. The trial reported here was started in the United Kingdom in August 1971 and ended in June 1974. Its object was to determine whether thrombolytic treatment influenced early or late mortality, the incidence of complications, and the pathological findings in the hearts of patients who died. Preliminary results have been briefly reported⁸; we present here the final results, concluding the study at six months' follow-up.

Design of trial

Criteria for admission—The trial was conducted in coronary care units in five different hospitals, the only requisite for entry being a diagnosis of myocardial infarction within the previous 24 hours. At the time of entry into the trial this rested necessarily on the clinical picture and the initial electrocardiogram (ECG). The ECG criteria for infarction used were those of the World Health Organisation,⁹ the diagnosis of acute infarction was not accepted unless there was a significant increase in either serum aspartate aminotransferase (SGOT) or lactate dehydrogenase (LDH) concentrations, or both. Both sexes were accepted and no upper age limit was prescribed.

Statistical design—The statistical design, described by Armitage,¹⁰ tested the null hypothesis that the death rates in the streptokinase and control groups were the same against a two-sided alternative

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