USE OF 4-AMINOPYRIDINE TO REVERSE MORPHINE-INDUCED RESPIRATORY DEPRESSION IN MAN

R. L. SIA AND D. F. ZANDSTRA

SUMMARY

4-Aminopyridine administered to patients antagonized respiratory depression by morphine 0.33 mg kg$^{-1}$. It is suggested that 4-AP may be useful in the treatment of morphine-induced respiratory depression.

Morphine, when used to supplement anaesthesia has minimal effects on the cardiovascular system (Hasbrouck, 1971; Wong et al., 1973). However, in high dosage it can cause respiratory depression and somnolence which may persist for several hours (Hasbrouck, 1970; Longnecker, Grazis and Eggers, 1973; Gairola, Gupta and Pandley, 1980). Although such depression of respiration may not be a problem during operation when ventilation is controlled, it may be dangerous in the period after operation. 4-Aminopyridine increases the extracellular concentration of acetylcholine centrally and peripherally by enhancing transmitter release (Lundh, 1978), and has been found to stimulate breathing in anaesthetized cats (Fastier and McDowall, 1958; Folgering, Rutten and Agoston, 1979). In man it was shown that 4-aminopyridine (4-AP) can reverse fentanyl-induced respiratory depression (Sia et al., 1979). The present study was designed to confirm this finding in patients receiving morphine.

PATIENTS AND METHODS

Twenty patients, 14 male and six female, aged between 18 and 54 yr (mean 34 yr) were admitted for elective ear, nose and throat operations. All gave their full informed consent, and were free from respiratory disease. The study was performed before the commencement of surgery. Premedication consisted of droperidol 0.05 mg kg$^{-1}$ and atropine 0.5 mg 1 h before operation. Anaesthesia was induced with thiopentone 5 mg kg$^{-1}$ and maintained with 67% nitrous oxide in oxygen. Suxamethonium 1 mg kg$^{-1}$ was administered to facilitate oro-tracheal intubation and ventilation was controlled until spontaneous respiration reappeared. No further neuromuscular blocking agent was used. Whenever the patient showed signs of wakening, thiopentone 25–50 mg was administered to maintain stable anaesthesia.

A radial artery cannula was inserted after the induction of anaesthesia to allow withdrawal of arterial blood for the measurement of blood-gas tensions. End-expiratory carbon dioxide concentration was monitored using a Godart infra-red capnograph. Respiratory flow, tidal volume and changes in the frequency of respiration were recorded by means of a No. 2 Fleisch flow transducer connected to the pneumotachograph. Tidal volume and respiratory rate were measured with a Wright respirometer. Occlusion pressures were read by digital display (Hewlett Packard ECG apparatus) and were measured by a Statham P23 ID pressure transducer as described by Kay (1979). Control values were measured over a 1 min period with the patient breathing 67% nitrous oxide in oxygen. A bolus dose of morphine sulphate 0.33 mg kg$^{-1}$ was injected i.v. over a period of 10 s. This resulted in a period of apnoea during which the lungs were ventilated manually at a rate sufficient to keep the end-tidal carbon dioxide concentration between 5% and 7%. As soon as depressed spontaneous breathing appeared, two consecutive series of measurements, 2 min apart, of respiratory flow, tidal volume, respiratory rate, occlusion pressure and arterial $P_{CO_2}$ and $P_{O_2}$ were made. A bolus of 4-AP 0.3 mg kg$^{-1}$ was injected over a period of 10 s and 2 min later the same two consecutive series of measurements, 2 min, apart were made. The same sequence of measurements was undertaken in a group of control patients to whom 4-AP 0.3 mg kg$^{-1}$ alone was given. No data
on the use of morphine alone are presented because prolonged respiratory depression is known to occur after substantial amounts of morphine (Longnecker, Grazis and Eggers, 1973; Johnstone, 1975). Statistical analysis of the results was by means of the paired one-tailed Student's t test.

RESULTS
All patients \( (n = 16) \) who received morphine became apnoeic, following which respiration was slow and shallow. After the administration of 4-AP, there was a statistically significant improvement in all the indices measured. The following changes were observed:

(1) Reversal of respiratory depression was evident 30 s after 4-AP as shown by the pneumotachograph (fig. 1).

(2) The tidal volume more than doubled and approached the control value (fig. 2B).

(3) There was a significant increase in respiratory frequency (fig. 2c).

(4) There was a significant increase in the occlusion pressure (fig. 2d).

(5) There was a decrease in \( P_{CO_2} \), whereas \( P_{O_2} \) remained greater than its physiological value (figs 2A, 2e).

(6) In the control group of patients \( (n = 4) \) who received 4-AP alone, no significant changes were seen in tidal volume, respiratory rate, \( P_{O_2} \), or \( P_{CO_2} \) (fig. 3).

DISCUSSION
The administration of 4-AP 0.3 mg kg\(^{-1}\) to patients with morphine-induced respiratory depression significantly improved tidal volume, respiratory rate, \( P_{CO_2} \) and occlusion pressure. The occlusion pressure \( (p^o_{MAX}) \) has been found to be a reliable index of respiratory drive in anaesthetized patients.
4-AP REVERSAL OF RESPIRATORY DEPRESSION

FIG. 2. Effect of 4-AP 0.3 mg kg⁻¹ on respiration in patients breathing spontaneously 67% nitrous oxide in oxygen before surgery. Open histograms represent mean control values obtained after 1 min of spontaneous respiration. Dotted histograms represent mean values obtained after injection of morphine at 2-min intervals. Closed histograms represent mean values obtained at 2-min intervals after 4-AP. Vertical lines are SEM. *P < 0.01; paired Student's t test. n = 16.

FIG. 3. Effect of 4-AP 0.3 mg kg⁻¹ alone in the absence of morphine in patients breathing spontaneously 67% nitrous oxide in oxygen before surgery. Detailed description of the histogram is given in legend to figure 2. No changes were statistically significant (Student's t test). n = 4.

man (Derenne et al., 1976). During the period of depressed respiration following the administration of morphine, $p_{\text{max}}^o$ was extremely low and reflected probably the inhibition of respiratory drive. The significant increase in $p_{\text{max}}^o$ which occurred after 4-AP may indicate that 4-AP only stimulates respiratory centre activity when this is depressed markedly. In the group of patients who received 4-AP alone, the drug did not appear to produce any significant changes.

Recent investigations suggest that calcium plays an important role in the interaction of opiates with neuronal tissue. The acute administration of morphine was found to decrease the concentration of calcium in the brain, in particular in nerve endings (Yamamoto et al., 1978). An *in vitro* study on longitudinal muscle strips of guineapig ileum showed that an increase in calcium concentration completely reversed the effects of morphine (Opmeer and van Ree, 1979). Since 4-AP blocks the potassium channels and increases the influx of calcium into the nerve terminals (Lundh, 1978), it appears that one of the possible mechanisms of action of 4-AP in the reversal of morphine-induced respiratory depression may be by increasing calcium concentrations in the brain. 4-AP 0.3 mg kg⁻¹ given i.v. to conscious volunteers caused aching pain around the site of injection lasting for about 20 min and perioral paresthesia lasting for about 5 min. It seems that 0.3–0.35 mg kg⁻¹ is a safe and effective dose to antagonize morphine-induced respiratory depression in man without producing side-effects such as
restlessness and convulsive activity (Spyker et al., 1980).

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to Professor Dr. P. E. Hoeksema and Dr. E. Th. Edens (Department of Ear, Nose and Throat Surgery) for giving access to their patients and for their co-operation and encouragement in the conduct of these investigations.

REFERENCES


USAGE DE LA 4-AMINOPYRIDINE POUR INVERSER LES DEPRESSIONS RESPIRATOIRES PROVOQUÉES CHEZ L'HOMME PAR LA MORPHINE

RESUME

L'administration de 4-aminopyridine a contrarié la depression respiratoire caused par 0,33 mg kg⁻¹ de morphine. On suggère dans cet article que 4-AP pourrait être utile pour le traitement de toute depression respiratoire provoquée par la morphine.

VERWENDUNG VON 4-AMINOPYRIDIN ZUR AUFHEBUNG VON MORPHIUMBEDINGTER RESPIRATORISCHER DEPRESSION BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Verabreichung von 4-Aminopyridin führte zur Aufhebung einer durch 0,33 mg kg Morphium bedingten respiratorischen Dämpfung, woraus geschlossen wird, dass diese Droge 4-AP zu diesem Zweck auf nutzbringende Weise eingesetzt werden kann.

USO DE 4-AMINOPIRIDINA PARA INVERTIR LA DEPRESIÓN RESPIRATORIA INDUCIDA MEDIANTE MORFINA EN EL HOMBRE

SUMARIO

La 4-aminopiridina administrada a pacientes invirtió la depresión respiratoria inducida por 0,33 mg kg⁻¹ de morfina. Se sugiere que la 4-AP puede usarse provechosamente en el tratamiento de la depresión respiratoria inducida por la morfina.