EFFECT OF A NEW ANALEPTIC DRUG, ALMITRINE, ON FENTANYL-INDUCED RESPIRATORY DEPRESSION AND ANALGESIA IN MAN

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SUMMARY
Five female patients received fentanyl 0.0066 mg kg⁻¹ i.v. (group A); five other female patients received the same dose of fentanyl, followed immediately by almitrine 0.5 mg kg⁻¹ i.v. (group B) and 20 minor gynaecological operations were performed under a combination of almitrine 0.5 mg kg⁻¹ and fentanyl 0.0066 mg kg⁻¹ (group C). In group A, fentanyl produced a marked and significant respiratory depression (P < 0.001). In group B and C, almitrine antagonized the fentanyl-induced respiratory depression. Analgesia did not seem to be affected.

Opiates and opioid drugs are used widely during anaesthesia and after operation for the relief of pain. The major disadvantage of such drugs is respiratory depression and, unfortunately, this side-effect cannot be dissociated from their analgesic activity. If such narcotic-induced depression of ventilation could be antagonized without affecting the analgesia, this would be of value in clinical practice. Naloxone is a specific opiate antagonist which is capable of reversing the ventilatory depressant effect, but it also antagonizes much of the analgesia. Furthermore, a rebound action has been reported (Dauthier, Gaudy and Willer, 1980). At the present time, doxapram hydrochloride seems to be the only analeptic agent which can antagonize, to some degree, the depression of ventilation induced by narcotics, without reversing the analgesic effect significantly (Gairola, Gupta and Pandley, 1980).

Almitrine (bis- (allylamino)-4,6-{(bis (fluoro-4-phenyl) methyl-4-piperazinyl)} 2 triazine, bis-methane sulfonate), is a new respiratory stimulant, recently developed in France. Its stimulant action on respiration was established in animals (rat, rabbit, cat and dog) (Laubie and Diot, 1972). In these species, the administration of almitrine 0.1–3 mg kg⁻¹ i.v. induced an immediate stimulation of ventilation even at the lowest dose (0.1 mg/kg body weight). The effect of the drug was still noticeable 45 min after administration. In man a dose of almitrine 0.5 mg kg⁻¹ i.v. over 20–60 s induced, within a few seconds, hyperventilation which persisted for more than 1 h (Bromet, 1980). In patients with chronic obstructive pulmonary disease (COPD), the effects of 3 mg kg⁻¹ by mouth were noticeable within 30 min and lasted for up to 15 h (Bromet, 1980).

Almitrine stimulates the arterial chemoreceptors located at the arch of the aorta and the carotid bodies; the drug does not seem to have any central respiratory stimulant action (Laubie and Diot, 1972). This characteristic may explain the lack of cortical stimulation and the absence of convulsions. Almitrine has been recommended for treating patients with COPD (Neukirch et al., 1974; Schrijen and Romero-Colomer, 1978; Sergysels et al., 1978) and recent studies have confirmed that, besides its action as a respiratory stimulant, almitrine is able to modify pulmonary shunting (du Cailar et al., 1980).

In 1972, Courtois and colleagues demonstrated that, in the rat and rabbit, almitrine antagonized the depressant effects induced by morphine, without affecting the analgesia. In the anaesthetized dog, fentanyl-induced ventilatory depression was inhibited by almitrine, with only minimal changes in the analgesic effect (Dauthier, Gaudy and Willer, 1980). The scope of the present study was to investigate evidence of its effectiveness in man. Two series of investigations have been carried out: first, the potency of almitrine as an antagonist of fentanyl-induced ventilatory depression was determined and second, the effects of almitrine, when used in association with fentanyl in minor surgical operations, were delineated with a particular regard to adequacy of ventilation and analgesia.

PATIENTS AND METHODS
The study was carried out on young healthy female
patients (20–30 yr) who were selected from a series of patients admitted either for termination of pregnancy (TOP) or for minor gynaecological procedures. Explanations were given as to the purpose and procedure, and 30 patients were chosen with their consent. A preliminary assessment based on clinical history, physical examination, routine chest radiograph and e.g., was performed and established that the patients were free from cardiopulmonary disease. No premedicant was administered before anaesthesia. A forearm vein was cannulated and a solution of 5% dextrose infused slowly.

Initially, the ventilatory effects of fentanyl alone were studied and then those produced by the combination of fentanyl and almitrine. Five patients received fentanyl 0.0066 mg kg\(^{-1}\) i.v. in 20 s (group A). Five other patients received the same dose of fentanyl, immediately followed by almitrine 0.5 mg kg\(^{-1}\) i.v. in approximately 60 s (group B). Ventilation was measured using a Fleisch pneumotachograph (No. 2) fitted with a plastic transparent mask in the 5 min preceding, during and immediately after the administration of the drug(s). The mask was carefully adjusted on the face of the patient, who was allowed to breathe room air. Before and after each study the pneumotachograph was calibrated with a 646-ml syringe.

The resulting spirogram (flow rate and integrated tidal volume) was displayed on a polygraph. The tidal volume (\(V_T\)) and the respiratory frequency (\(f\)) were measured and the minute ventilation (\(V_E\)) calculated as follows: \(V_E = V_T \times f\). E.g. (lead II) was continuously recorded and displayed on an oscillograph. Arterial pressure was measured at 2-min intervals by means of a sphygmomanometer.

In a subsequent part of the investigation the effects of almitrine in association with fentanyl were studied. Twenty patients admitted for TOP (suction curettage) (group C) were included. Almitrine 0.5 mg kg\(^{-1}\) was administered i.v. in approximately 1 min. Within 1 min of this first injection, when the first evidence of ventilatory stimulation appeared (essentially tachypnoea), fentanyl 0.0066 mg kg\(^{-1}\) was injected in 20 s. The surgical procedure started within the subsequent 2 min. In the 5 min preceding, during and for the 10 min following the administration of the drugs (i.e. the average duration of the surgical procedure) \(P_{CO_2}\) (Gould-Godart capnograph) and \(S_aO_2\) (Hewlett-Packard oximeter) were measured continuously. (Owing to unexpected circumstances, the capnograph and oximeter were not available simultaneously, and it was not possible to estimate the pulmonary ventilation by comparing the results obtained from the readings on the pneumotachograph and those expressed by using \(P_{CO_2}\) and \(S_aO_2\).) Arterial pressure was measured by means of a sphygmomanometer, before the first injection, within 1 min of the first injection, and at 5-min intervals thereafter. All patients were observed closely for 1 h after the end of the operation. Paired Student's \(t\) test was used to assess statistical probability.

**RESULTS**

**Ventilatory effects induced by fentanyl (group A) and by the combination of almitrine and fentanyl (group B)**

**Group A** (fig. 1). Fentanyl 0.0066 mg kg\(^{-1}\) i.v. induced marked hypoventilation. In the interval between the 1st and the 2nd min after the injection, ventilation (\(V_E\)) decreased significantly (\(P < 0.001\)), with decreases in both \(V_T\) (\(P < 0.001\)) and \(f\). (\(P < 0.02\)).

Bradypnoea occurred immediately after the 2nd min, and necessitated discontinuation of any further measurements. At this stage the patients were given oxygen and oral encouragement to stimulate ventilation. Thereafter, anaesthesia was induced in a routine manner.

The only side-effects that occurred were a sensa-
tion of itch and of warmth, predominantly on the face and the antero-superior part of the chest. A moderate bradycardia was noted also and could be prevented by atropine 0.25 mg i.v.

**Group B** (fig. 2). Almitrine 0.5 mg kg\(^{-1}\), administered after fentanyl 0.0066 mg kg\(^{-1}\) inhibited the hypoventilation. Decreases in \(VE, VT\) and \(f\) were small but significant. Five patients complained of pruritus and two of nausea. The injection of fentanyl induced a slight bradycardia, which disappeared after the administration of almitrine. The patients were observed for 5 min, before anaesthesia was induced as in group A.

![Graph](https://example.com/graph1.png)

**Fig. 2.** Group B Ventilatory effects of the combination of fentanyl 0.0066 mg kg\(^{-1}\) and almitrine 0.5 mg kg\(^{-1}\). \(VE\) = expired volume per minute (ml kg\(^{-1}\)); \(VT\) = tidal volume (ml kg\(^{-1}\)); \(RR\) = respiratory rate per minute. \(VE, VT, f\) are mean value ± SD

**Ventilatory and analgesic effects of a combination of almitrine and fentanyl in minor gynaecological operations**

**Group C** (fig. 3). The combination of almitrine and fentanyl was used in 20 patients undergoing suction termination of pregnancy. The average duration of the surgical procedure did not exceed 10 min. One minute after the administration of almitrine hyperventilation was observed, leading to a decrease in \(FE'CO_2\) and a slight tachycardia. After the administration of fentanyl, and during the 10 min required for the surgical procedure, \(FE'CO_2\) and \(Sao_2\) showed no significant variations, and the heart rate returned to normal. The major side-effects were pruritus and, in some patients, nausea.

The gynaecological operations were carried out as usual, although operation conditions were not ideal. In the 1 h following the operation, there were no changes in respiratory rate or arterial pressure. The patients remained sleepy for less than 2 h after the operation. Nevertheless, during this period they could be easily roused and were able to speak, cough, and swallow. Although they had no recall of anaesthesia or surgery, some of the patients had dreams (five patients) and others nightmares (two patients).

**DISCUSSION**

Opioid drugs are used widely during anaesthesia and for the relief of pain after operation.

At the present time, newer and more potent analgesic drugs, such as fentanyl, have superseded the more conventional analgesic drugs, such as pethidine. Morphine is still frequently used, particularly in cardio-thoracic surgery and for the relief of pain. All these drugs are potent respiratory depressants and, unfortunately, analgesia and respiratory depression seem to be linked closely. Furthermore, the respiratory depression induced by opiates is potentiated by the anaesthetic drugs, including nitrous oxide, and numerous other drugs such as tranquilizers and neuroleptic agents. Respiratory depression occurring during the surgical operation can be managed by artificial ventilation. Respiratory depression in the period following surgery is a greater problem.

Many analeptic drugs have been used in an attempt to overcome this problem. The conventional analeptic drugs (strychnine, picrotoxin, pentylentetrazol) are no longer used on account of their
side-effects. They act mainly as central nervous system stimulants, thus inducing restlessness, disorientation, euphoria, optical hallucinations, dizziness, sweating, pyrexia, headache and convulsions and in very high doses, hypotension (Wang and Ward, 1981). Doxapram is used frequently. Although it has been demonstrated that doxapram could prevent narcotic-induced hypventilation, without impairing the analgesic effect (Gupta and Dundee, 1974a, b; Gairola, Gupta and Pandle, 1980), side-effects have been reported: prolonged pressor effect, tachycardia, extrasystoles, irregular heart rhythm (Wang and Ward, 1981).

Almitrine is a new analgetic drug which acts via the arterial chemoreceptors in the arch of the aorta and the carotid bodies. In animals (rat, rabbit, dog) the ventilatory depression induced by morphine or fentanyl was inhibited by almitrine without causing any major change in analgesia. The present study demonstrates the efficacy of almitrine in man as an antagonist to the respiratory depressant effect of fentanyl. In group A, fentanyl produced a marked decrease in ventilation. Almitrine 0.5 mg kg⁻¹ inhibit this respiratory depression. In addition, in group C, there was no evidence of respiratory depression either during operation or during the first hour following anaesthesia.

In group C, the efficacy of analgesia was more difficult to assess than the effects on ventilation. It should be emphasized that these surgical procedures carried out after the administration of almitrine in association with fentanyl were practically painless. While undergoing surgery none of the patients complained of pain or discomfort. Indeed, they all declared afterwards that they had no recollection of any pain. However, as tactile sensibility and hearing were unimpaired, the patients sometimes made involuntary muscle movements and these unwanted effects posed difficulties for the surgeon. Indeed, only an objective technique for the evaluation of pain might give a complete explanation of the mechanism of analgesia and whether pain relief was complete.

The dissociation between ventilation and analgesia is difficult to explain. Opiate iontophoresis on respiratory related units (RRU) (Denavit-Saubie, Champagnat and Zieglgansberger, 1978) or in the periaqueductal grey matter (Gent and Wolsencroft, 1976a, b) excites some neurons while inhibiting others.

Consequently, the lowering of spontaneous or induced firing of RRUs is related closely to the ventilatory effects produced by the opiates. Fentanyl acts on respiratory cells by impairing the transmitted synaptic impulse. The firing discharge is depressed selectively during the maximal frequency (inspiration) without impairing expiration (Denavit-Saubie, Champagnat and Zieglgansberger, 1978). Therefore almitrine may be capable of obtunding this effect without altering the mechanism of analgesia.

Although the results of the present study show that, in man, almitrine will antagonize respiratory depression induced by a morphinomimetic analgesic without abolishing the analgesic effect, a number of points deserve consideration. Since almitrine acts on peripheral arterial chemoreceptors, its action may be modified by certain anaesthetics, in particular those drugs that modify the response of these receptors to hypoxia (Weiskopf, Raymond and Severinghaus, 1974; Hirschman et al., 1975; 1977). The action of almitrine may also be modified by increasing oxygen concentrations (Guillerm and Radziszewski, 1974).

Since the threshold of clinical activity corresponds to a plasma concentration of 100 ng ml⁻¹, and since direct i.v. injection leads to greater plasma concentrations, infusion is the best route during the early period after operation (Bromet, 1980). Oral administration also produces adequate plasma concentrations, and might prove advantageous in the period after operation. The use of almitrine together with fentanyl, even for minor surgical procedures, is probably of a limited interest because of the possible side-effects and the poor operating conditions.

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REFERENCES


Denavit-Saubie, M., Champagnat, J., and Zieglgansberger, W.
ALMITRINE AND FENTANYL RESPIRATORY DEPRESSION


