PREVENTION OF LATE FENTANYL-INDUCED RESPIRATORY DEPRESSION AFTER THE INJECTION OF OPIATE ANTAGONISTS NALTREXONE AND S-20682: COMPARISON WITH NALOXONE

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SUMMARY

Compared with naloxone, two opiate antagonists (naltrexone and S-20682) were tested in the intact dog in order to reverse respiratory depression, induced by fentanyl 50 μg kg⁻¹ i.v. Respiratory rate and arterial blood-gases were measured at 5, 30, 60, 120, 180 and 240 min after the additional i.v. injection of the antagonist (1 μg kg⁻¹). Only S-20682, but not naloxone or naltrexone, prevented late (240 min) fentanyl-induced depression of respiratory drive. A late respiratory depression coincided with an increase in amplitudes and a reduction of frequency in electrical cortical activity (EEG). Naltrexone exhibited an antagonist effect of duration twice (60 min) that of naloxone.

Four of the present “pure” opiate antagonists, naloxone, naltrexone, nalbuphine and nalmexone all have in common the feature of a hydroxyl-group in the position 14 (Blumberg and Dayton, 1974). Thus the OH-group seems to be responsible for the pure antagonistic effect and for the absence of dysphoria, which often is noted after the administration of other opiate antagonists such as nalorphine and cyclazocine (Lasagna and Beecher, 1954; Houde and Wallenstein, 1955; Keats and Telford, 1957).

All four oxymorphone-derivatives, however, are characterized by a short duration of action. Fentanyl, which accumulates in the so-called silent receptor sites—the proteins of the blood, the lung, the liver, the heart, the muscle mass, the skin and the fat-tissue (Hess, Herz and Friedel, 1971)—may be released into the blood stream in the period late after operation (redistribution). Thus any increase in plasma fentanyl concentration induces a rapid transfer of the opiate through the blood–brain barrier occupying opiate receptor sites in the area postrema (Pert and Snyder, 1973), followed by respiratory depression.

For example 60 min after the injection of an initial dose of fentanyl 0.5 mg in man, 65% of the dose may be found in the silent receptor sites (Heykants, 1977). From this depot (the peripheral compart-

METHODS

Trained animals were divided in three groups each group yielding six experiments. Each animal received fentanyl 50 μg kg⁻¹ in a bolus injection. Five minutes thereafter the antagonist was administered. Either naloxone, naltrexone (EN-1639, Endo Laboratories USA) or S-20682 (Shionogi Company Japan) were given in a dose of 1 μg kg⁻¹ i.v. The following were measured before and after fentanyl,
and 5, 30, 60, 120, 180 and 240 min after the injection of the antagonist:

(1) **Respiratory rate**, as measured by a change of impedance over the thoracic cage during respiratory movement of the animal (American Optical respiratory rate monitor).

(2) **Arterial blood-gases** ($P_{CO_2}, P_{O_2}$) measured from blood samples drawn from an exteriorized common carotid loop artery (Instrumentation Laboratory System 1303 Lexington, USA).

Since any change in respiration is often accompanied by a change in the level of consciousness when opiates have been given, the EEG bipolar frontal activity (position C2-C3) was detected, by silver/silver chloride stick-on electrodes, and amplified by an EEG-Schwarzer recorder (time constant 0.3, cut off frequency 30 Hz).

The values of each group were compared with the control as the percent change of each variable. For a given time the groups were compared among each other, calculating the statistical significance (Wilcoxon Rank, two-tailed probability). Significance was defined as $P$ equal to or less than 0.05.

**RESULTS**

Figure 2 shows the change in respiratory rate after the administration of fentanyl, followed by the three different opiate antagonists. Compared with the awake control with a respiratory rate of 49 ± 2 (mean ± SEM) b.p.m., fentanyl induces a decrease to 6 ± 1 b.p.m. (−85%). This depression was rapidly reversed by the opiate antagonist naloxone and by naltrexone, resulting in an overshoot reaction with a rate of 93 ± 22 and 88 ± 23 b.p.m. respectively. This antagonistic effect, however, was of short duration; 60 min after injection, the naloxone-group had a reduced respiratory rate of 14 ± 3 b.p.m. (70% depression), an effect which was most obvious for naloxone and for naltrexone at 240 min (8 ± 1 and 12 ± 8 b.p.m. respectively).

Compared with the two oxymorphone-derivatives, S-20682 had a maximum action at 20–30 min, with a respiratory rate of 43 ± 8 b.p.m. and no overshoot. At 240 min the respiratory rate in the S-20682-group was 28 ± 5, 40% less than control, while both the naloxone and the naltrexone-group exhibited a depression by 85% and 78% respectively. The differences in the latter groups are statistically significant when compared with the S-20682 group.

This difference of action of the three antagonists is even more obvious when the increase in $P_{CO_2}$ is compared in the three groups (fig. 3). Hypercapnia with a mean value of 6.6 ± 0.3 kPa shortly after fentanyl (+30%) are rapidly reversed by naloxone and naltrexone. However, 60 min after antagonist injection, $P_{CO_2}$ increased significantly in the naloxone group (+11%) and in the naltrexone-group.
FIG. 2. Percent change of respiratory rate in fentanyl-pretreated dogs. EN-1639 = naltrexone; F50 = fentanyl 50 µg kg⁻¹.

FIG. 3. Percent change of $P_{\text{aCO}_2}$ in fentanyl-pretreated dogs. EN-1639 = naltrexone; F50 = fentanyl 50 µg kg⁻¹.
(+17%). This effect increased at 180 and 240 min after injection.

At about 240 min the naloxone group showed an increase in PCO₂ (+33%) while the naltrexone group showed an increase (28%). Compared with these two compounds, S-20682 exhibited no immediate reversal of the fentanyl-induced hypercapnia. The maximum effect of S-20682 was at about 25–30 min when compared with control Paco₂ (+3%). At 240 min PaCO₂ did not exceed 5.2 kPa, significantly less when compared with the PCO₂ values in the naloxone and naltrexone groups (6.8 and 6.1 kPa respectively).

In respect of changes in PacO₂, naltrexone had a longer duration than did naloxone, the former inducing an antagonistic effect up to 60 min after injection (fig. 4). This effect decreased at 180 min when PO₂ was less than 11.9 ± 0.5 kPa. Only S-20682 demonstrated a long-lasting effect (fig. 4).

Figure 5 shows that, compared with the awake state with a dominant e.e.g. pattern in the beta band (high frequency of at least 18 Hz and low amplitudes), fentanyl induced a sleep-like pattern in the delta band, showing a low frequency with 0.5–2 Hz and high amplitudes. Such a pattern was reversed by all three antagonists. At 240 min the cortical activity of animals receiving S-20682 reveals a pattern similar to the awake state—activity with a maximum in the low alpha band (13–15 Hz). The other two groups present dominant low frequency, high amplitude waves again.

**DISCUSSION**

Redistribution of fentanyl causes a late (240 min) respiratory depression (McQuay et al, 1979; Stoeckel, Hengstmann and Schüttler, 1979). Naloxone has a short duration of action which results in remorphization and secondary respiratory depression up to 3 h after injection. Similar effects of remorphization accompanied by respiratory depression have been observed in man (Longnecker, Pia Grazis and Eggers, 1973; Evans et al., 1974; Heisterkamp and Cohen, 1974).

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**Fig. 4.** Percent change of PacO₂ in fentanyl-pretreated dogs. EN-1639 = naltrexone; F50 = fentanyl 50 μg kg⁻¹.

**Fig. 5.** Time-related effect of naloxone (top panel) and S-20682 (bottom panel) on fentanyl-induced EEG changes.
NALOXONE  Control

Fentanyl 50 μg kg⁻¹ i.v.

Fentanyl plus naloxone (25 min)

Fentanyl plus naloxone (35 min)

Fentanyl plus naloxone (120 min)

Fentanyl plus naloxone (240 min)

S-20682  Control

Fentanyl 50 μg kg⁻¹ i.v.

Fentanyl plus S-20682 (60 min)

Fentanyl plus S-20682 (240 min)
Compared with naloxone the duration of action of the N-cyclo-propylmethyl analogue of oxymorphone, naltrexone, is twice as long in preventing fentanyl-induced respiratory depression. However, at 240 min after naltrexone, respiratory rate and $\text{Paco}_2$ reflect a reduction of respiratory drive. Only the 6-oxo analogue of oxilorphan, S-20682, was effective in minimizing the respiratory effects of fentanyl at 240 min. The cause for such a long duration of action may be the lack of an oxygen bridge, which makes the molecule less susceptible to biological degradation (Pachter, 1974). Additionally, S-20682 did not induce an “overshoot-reaction” — naloxone and even naltrexone were characterized by tachypnoea and hypocarbia.

A close interplay between cortical activity and respiratory function may be shown by the fact that respiratory depression was accompanied by slow and high amplitude waves in the EEG. This observation suggests that, in the case of opioid-induced respiratory depression, alertness is regularly depressed.

ACKNOWLEDGEMENT

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REFERENCES


PREVENTION DE LA DEPRESSION RESPIRATOIRE TARDIVE INDUITE PAR LE FENTANYL APRES L'INJECTION DE LA NALTREXONE ET DU S-20682, ANTAGONISTES DE LA MORPHINE: COMPARAISON AVEC LA NALOXONE

RESUME

Deux antagonistes des opiacés (la naltrexone et le S-20682) comparés à la naloxone, ont été testés chez le chien intact pour annuler la dépression respiratoire induite par 5 μg kg⁻¹ de fentanyl i.v. La fréquence respiratoire et les gaz du sang artériel ont été mesurés à 5, 30, 60, 120, 180 et 240 min après l'injection supplémentaire d'antagoniste (1 μg kg⁻¹). Cependant, seul le S-20682 et pas la naloxone ou la naltrexone prévient la dépression tardive (240 min) de la commande respiratoire induite par le fentanyl. La dépression respiratoire tardive coïncide avec une augmentation de l'amplitude et une diminution de la fréquence de l'activité électrique corticale (EEG). La naltrexone objectiva un effet antagoniste deux fois plus long (60 min) que la naloxone.
Vorbeugung der späten, durch Fentanyl induzierten Atemdepression nach Injektion des Opiat-Antagonisten Naltrexon und S-20682: Vergleich mit Naloxon

Zusammenfassung
Zwei Opiat-Antagonisten (Naltrexon und S-20682), wurden am gesunden Hund getestet und mit Naloxon verglichen, um die durch Fentanyl 50 µg kg⁻¹ hervorgerufene Atemdepression aufzuheben. Die Atemfrequenz und die arteriellen Blutgase wurden 5, 30, 60, 120, 180, und 240 min nach der zusätzlichen i.v. Gabe des Antagonisten (1 µg kg⁻¹) gemessen. Jedoch verhinderte nur S-20682, aber nicht Naloxon oder Naltrexon die späte Fentanyl-induzierte Atemdepression. Eine späte Atemdepression ging mit Zunahme der Amplitudengröße und Reduzierung der Frequenz der elektrokortikalen Aktivität einher (EEG). Naltrexon zeigte eine antagonistische Wirkung von doppelter Dauer (60 min) wie die von Naloxon.

Prevención de la depresión respiratoria tardía inducida por Fentanilo después de la inyección de agentes opiáceos antagonísticos, Naltrexona y S-20682: Comparación con Naloxona

Sumario
Se llevaron a cabo ensayos con dos agentes opiáceos antagonísticos (naltrexona y S-20682) comparados con la naloxona, en un perro intacto con el objeto de invertir la depresión respiratoria inducida por 50 µg kg⁻¹ de fentanilo i.v. Se hicieron mediciones de la frecuencia de respiración y de los gases-sangre arterial a los 5, 30, 60, 120, 180 y 240 min después de una inyección i.v. adicional de agente antagonístico (1 µg kg⁻¹). Sin embargo, sólo el S-20682, pero no así la naloxona ni tampoco la naltrexona, previno la depresión tardía (240 min) del impulso respiratorio, inducida por el fentanilo. Una depresión respiratoria tardía coincidió con un aumento de las amplitudes y una reducción de la frecuencia de la actividad cortical eléctrica (EEG). La naltrexona demostró tener un efecto antagonístico de una duración doble (60 min) de la del efecto de la naloxona.