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The Effects of High-Dose Fentanyl on Cerebral Circulation and Metabolism in Rats

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There is considerable controversy with respect to the effects of narcotics on the cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMR_{O_2}). The present study examined the effects of high doses of intravenous fentanyl (25–400 μg/kg) on the CBF and CMR_{O_2} in rats. Cerebral cortical blood flow and metabolism were measured using the ^{133}Xenon modification of the Kety-Schmidt technique. Fentanyl produced a dose-related decrease in both the CBF and the CMR_{O_2}. CBF and CMR_{O_2} were maximally depressed by 50 and 35%, respectively, in rats given fentanyl 100 μg/kg compared with nitrous oxide–oxygen ventilated controls. The values for CBF and CMR_{O_2} were 168 ± 15 ml · 100 g^{-1} · min^{-1} and 10.3 ± 0.7 ml · 100 g^{-1} · min^{-1}, respectively in the nitrous oxide controls compared with 85 ± 3 ml · 100 g^{-1} · min^{-1} and 7.1 ± 0.1 ml · 100 g^{-1} · min^{-1} in animals receiving fentanyl 100 μg/kg. Higher doses of fentanyl did not further decrease either CBF or CMR_{O_2} (108 ± 12 ml · 100 g^{-1} · min^{-1} and 7.0 ± 0.4 ml · 100 g^{-1} · min^{-1}, respectively for fentanyl 400 μg/kg); however, seizure activity was noticed in about 25% of the rats receiving either 200 or 400 μg/kg fentanyl. The seizures seemed to be related to the narcotic in that they could be abolished by injections of naloxone. The seizure activity appeared to increase the CMR_{O_2} relative to animals who received the same dose of fentanyl but did not have seizures. The CBF was not affected. The results confirm that narcotics in high enough doses may depress the CBF and CMR_{O_2}. (Key words: Analgesics: fentanyl. Anesthetics, intravenous: fentanyl. Brain: blood-brain barrier; blood flow; convulsions; electroencephalography; metabolism.)

THE DEPRESSANT EFFECTS of anesthetic doses of barbiturates and related compounds on cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMR_{O_2}) are well-delineated.[1,2] The effects of narcotics on these same functions is less clear. Several investigators found no effect with morphine on CBF and CMR_{O_2} in humans.[3,4] This was true even for relatively large doses of 3 mg/kg.[4] However, in one study in awake, healthy volunteers, 1 mg/kg morphine sulfate produced a significant reduction in CMR_{O_2} which was partially reversed by nallorphine, but the same study showed no significant change in CBF.[5] In dogs, 2 mg/kg morphine sulfate, together with nitrous oxide, 70%, and halothane, 0.1% in oxygen, decreased the CBF and CMR_{O_2} by 50% and 17%, respectively.[6] Studies of meperidine in dogs receiving halothane, 1%, showed a small (13%), but significant fall in CMR_{O_2}, but no fall in CBF.[7] With fentanyl, the results are more equivocal. Freeman and Ingvar[8] found no significant change in CBF in cats receiving 5 to 20 μg/kg fentanyl. With doses of 40 to 80 μg/kg fentanyl, they noticed seizure activity on EEG which was accompanied by increases in CBF. In dogs receiving 70% nitrous oxide in oxygen, fentanyl (6 μg/kg) produced a 50% fall in CBF and an 18% fall in CMR_{O_2}.[9] In humans, fentanyl (10 μg/kg) together with diazepam and nitrous oxide produced a 34% decrease in both CBF and CMR_{O_2}.[10] The above studies suggest that in the appropriate species at a high enough dose, narcotics will probably depress CBF and CMR_{O_2}. However, the quantitative range of these changes, particularly of narcotics alone, is not known.

This question is relevant for fentanyl which has been used recently in high doses (50 to 100 μg/kg) for single-agent anesthesia.[11,12] Studies of the effects of fentanyl on CBF and CMR_{O_2} in these dosages are not available, nor have studies been done using fentanyl alone, without nitrous oxide, halothane, or diazepam. In the following study we have examined the effects of intravenous fentanyl in doses of 25 to 400 μg/kg on the CBF, CMR_{O_2}, and EEG in rats. The results suggest some similarities to barbiturates, but also demonstrate the possibility of central nervous system excitation with increasing doses of potent narcotics such as fentanyl.

Materials and Methods

Male Wistar rats, weighing 275–340 g, were used for this study. All animals had free access to commercial rat pellets and tap water until the experiments began. The

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study consisted of four parts which will be described separately.

The Effect of Intravenous Fentanyl on the Pain Response

Ten animals were used to evaluate the dose of intravenous fentanyl which was required to depress or abolish the response to pain. Initially, the animals were anesthetized with halothane (1–2% inspired) in 70% nitrous oxide and oxygen. Catheters were then inserted into a tail artery and external jugular vein. At the completion of surgery the anesthesia was discontinued and the animals placed in a cage (thus they were not restrained during the experiments). The arterial catheter was connected to a transducer and polygraph for continuous blood pressure recording. This catheter was also used for anaerobic sampling of blood gases and *p*H. Rectal temperature was measured via a thermistor probe. Thirty to sixty minutes after discontinuing the anesthetic, the animals were given 5, 10, 20, or 50 μg/kg fentanyl intravenously, and their reaction to tail or nose clamping was tested every minute for 15 min. Any withdrawal or change in blood pressure in response to the clamping was noted. The least analgesic dose was defined as the dose of fentanyl for which no pain reaction could be observed either by withdrawal or change in blood pressure.

The Effect of Fentanyl on CBF and CMR_{O_2}

Forty-two animals were prepared for study of CBF and CMR_{O_2}. During the surgical preparation, the animals were anesthetized with halothane (1–2% inspired) in 70% nitrous oxide and oxygen. Following tracheotomy, the animals were connected to a small animal ventilator and then paralyzed with curare (0.5 mg/kg). Bilateral femoral artery and vein catheters were inserted for anaerobic sampling of blood, blood pressure recording, drug infusion, and blood infusion, respectively. The animals were then placed prone, their heads fixed in a steriotaxic apparatus, and a small burr hole was made over the distal part of the superior sagittal sinus for sampling of cerebral venous blood. Bilateral frontooccipital EEG was recorded in all animals, using wire leads inserted into the connective tissue of the scalp.

After completion of surgery the halothane was discontinued and the animals were ventilated with nitrous oxide (70%) in oxygen. Thirty minutes after the completion of surgery, fentanyl (25, 50, 100, 200, or 400 μg/kg) was injected intravenously over a 5-min period. The injection was followed by a slow continuous infusion at the rate of twice the initial dose per hour. Our studies on "response to pain" suggested that the effects of fentanyl began to decrease 15–20 min after a single injection. The infusion rate we used appeared to maintain a more constant level of narcosis as judged by the blood pressure and EEG. When the injection of fentanyl was started, the nitrous oxide was discontinued and the animals were ventilated with nitrogen (70%) in oxygen. Temperature was recorded with a rectal temperature probe and maintained at 37° C with a heat lamp servomechanism. About 20–25 min following the discontinuation of the nitrous oxide, in fentanyl-treated animals, and the equivalent period in the controls, CBF was measured using a modification of the Kety-Schmidt technique.[13,14] Briefly, approximately 10 mCi of radioactive gas (^{133}Xe) was added to the inspiratory gases for 15–20 min in order to saturate the brain with the tracer. At the end of the saturation period, capillary samples were taken from the femoral artery and superior sagittal sinus. Equal levels of radioactivity in arterial and cerebral venous samples at the end of the saturation period indicated full saturation of brain tissue. The ^{133}Xe source was disconnected from the inspiratory gases and then repeated capillary samples were obtained from the femoral artery and sagittal sinus over a 15-min period. Blood from a donor rat was transfused as needed to maintain the blood pressure above 120 mmHg. The samples were analyzed for radioactivity using a gamma counter and the two wash out curves were analyzed graphically for CBF using the trapezoid rule.[13] Separate capillary samples were taken for measurement of total oxygen content in both the artery and cerebral sinus just before and during the CBF measurement. The oxygen content was measured with a polarographic technique.[15] The results of an experiment were discarded if the two calculated arteriovenous differences varied by more than 10%. The arteriovenous difference in oxygen content (AVD_{O_2}) was multiplied by the CBF to obtain the CMR_{O_2}.

The Effects of Fentanyl on Seizure Activity

During the studies which evaluated CBF and CMR_{O_2}, seizure activity was recorded in the EEG of some animals receiving the highest doses of fentanyl. The following four investigations were undertaken to define further the nature of this seizure activity.

One set of three animals was prepared with tail artery and vein catheters. EEG was also recorded in these rats. One hour after recovery from anesthesia, 400 μg/kg fentanyl was administered intravenously. Ventilation with 70% nitrogen in oxygen was maintained with a ventilator by using a specially designed face mask. These animals were apneic, but unparalyzed so that changes in EEG activity could be correlated with muscle activity. Adequacy of ventilation was monitored by measuring arterial blood gases.

TABLE 1. Mean Arterial Blood Pressure (MABP), Arterial Blood Gases, and *p*H after Measuring CBF and CMR_{O_2} in Rats that Had Received Various Doses of Fentanyl

Experimental Groups	n	MABP (mmHg)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	*p*H
Control (nitrous oxide, 70%, in oxygen)	12	129 ± 12*	130 ± 6	39 ± 2	7.35 ± 0.02
Fentanyl (μg/kg, iv)					
25	6	137 ± 3	124 ± 12	42 ± 1	7.32 ± 0.02
50	6	128 ± 5	134 ± 5	41 ± 1	7.32 ± 0.01
100	6	138 ± 4	139 ± 5	42 ± 1	7.29 ± 0.01
200	6	141 ± 7	133 ± 4	40 ± 2	7.31 ± 0.02
400	6	158 ± 3†	126 ± 9	39 ± 2	7.27 ± 0.02†

* Mean ± SEM.

† $P < 0.05$ (compared to control).

The other three investigations were performed following tracheotomy in animals that were paralyzed and mechanically ventilated with halothane 1%, in nitrous oxide (70%) in oxygen. Femoral artery and vein catheters were inserted and EEG electrodes were placed. After completion of surgery, the halothane was discontinued for at least 30 min prior to the onset of the experiment. Nitrous oxide was replaced by nitrogen after the injection of fentanyl.

In one set of four animals, Evans blue (5 mg/kg) was given intravenously five minutes before the fentanyl injection (400 μg/kg). Thirty minutes later, the animals were killed, and the brains removed and sliced into 2-mm sections. The slices were examined grossly and by microscope for extravasation of dye which would indicate a disruption of the blood-brain barrier.[16]

In another set of four rats, serum sodium and osmolality were determined before and five minutes after injection of fentanyl (400 μg/kg). Since this large dose of fentanyl necessitated injection of a significant fluid load (15 ml/kg), the possibility of water intoxication as a source of seizures needed to be ruled out. Sodium was measured on whole blood using a sodium-specific electrode, and osmolality was measured on serum using vapor pressure depression.

The last set of four animals was prepared as above and received the same dose of fentanyl. During the seizures, naloxone (0.2 mg) was given intravenously and the effects of it on EEG were followed for 30 min.

STATISTICS

Statistical significance was determined using analysis of variance or Student's *t* test.

Results

THE EFFECT OF INTRAVENOUS FENTANYL ON THE PAIN RESPONSE

Fentanyl (5 μg/kg) provided no pain relief as judged by clamping the tail or nose. These animals had an increase in blood pressure and attempted to withdraw from the painful stimuli. When 10 μg/kg fentanyl was given, the animals did not move with stimulation; however, there was a slight increase in blood pressure. With 25 μg/kg there was no withdrawal response, nor was there a change in blood pressure. The abolition of these responses lasted about 10 min. These doses of fentanyl did not depress respiration; the Pa_{O_2} remained above 90 mmHg, and the Pa_{CO_2} remained below 50 mmHg. When 50 μg/kg fentanyl was given, the animals became apneic.

THE EFFECT OF FENTANYL ON CBF AND CMR_{O_2}

Table 1 shows the blood pressure, arterial blood gases, and *p*H obtained just after measuring the CBF and CMR_{O_2}. In animals receiving 400 μg/kg fentanyl, the arterial blood pressure was significantly higher and the *p*H was lower than the controls. However, the degree of change would not be expected to alter the CBF and CMR_{O_2}. Rectal temperature was 37° C in all animals.

The values of CBF and CMR_{O_2} are shown in figures 1 and 2. The CBF showed a progressive depression with increasing doses of fentanyl. The maximal depression of CBF was 50% of control and was seen with 100 μg/kg fentanyl. Increasing the dose of fentanyl to 200 or 400 μg/kg did not decrease the CBF further. The CMR_{O_2} also showed a dose-related depression which reached a maximum of 35% of the control value at 100 μg/kg fentanyl.

Four of the 16 animals that received 200 or 400 μg/kg fentanyl showed seizure activity on EEG (bottom trace, fig. 3). Their values for CBF and CMR_{O_2} are plotted separately in figures 1 and 2 (open triangles). The CMR_{O_2} of these animals was equal to or greater than control, while the CBF was not comparably increased. Mean blood pressure and arterial blood gases in these animals were no different from those with no seizure activity; however, a marked increase in the arteriovenous oxygen difference was noticed in the ani-

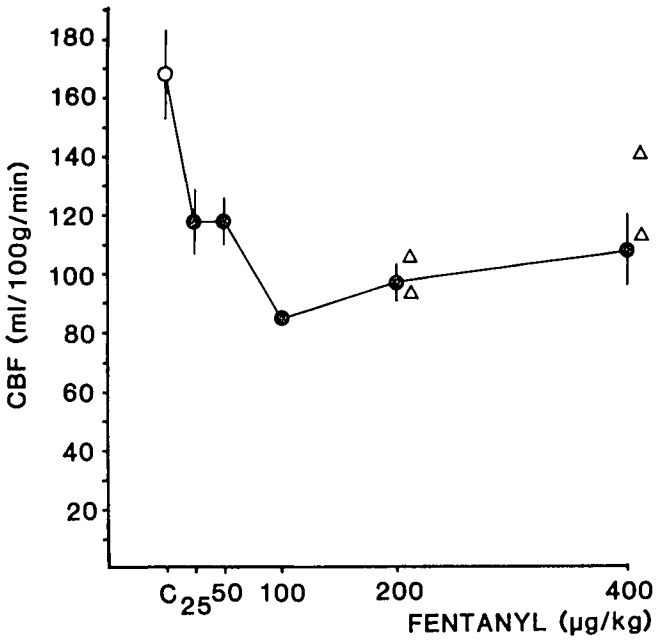

FIG. 1. Effects of various doses of intravenous fentanyl on CBF. Each circle represents the mean ± 1 SEM from 12 nitrous oxide–oxygen ventilated controls (C) or six rats who received a given dose of fentanyl. Triangles represent CBF from individual rats which showed epileptic changes on EEG. Solid circles represent flows which are significantly less than the control ($P < 0.05$).

mals with seizure activity when compared with those without seizures, suggesting that a markedly increased oxygen extraction accounted for the increase in CMR_{O_2} in this group (table 2).

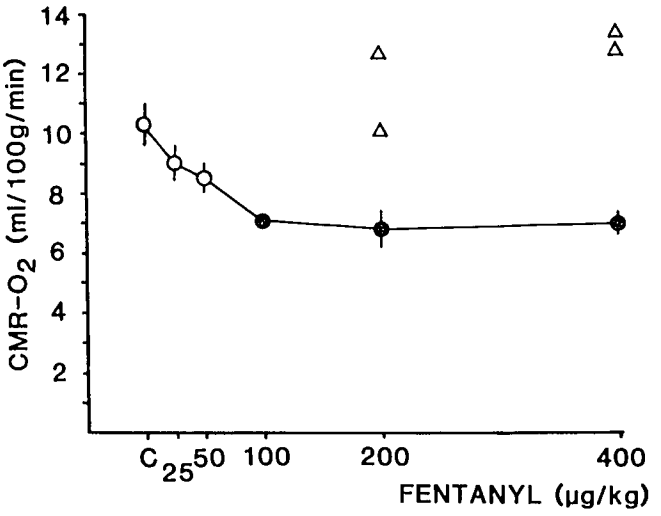

FIG. 2. Effects of various doses of fentanyl on CMR_{O_2}. Each circle represents the mean ± 1 SEM from 12 nitrous oxide–oxygen ventilated controls (C) or six rats who received a given dose of fentanyl. Triangles represent CMR_{O_2} from individual rats who showed epileptic changes on EEG. Solid circles represent metabolic rates which are significantly less than control ($P < 0.05$).

THE EFFECT OF FENTANYL ON EEG AND ON SEIZURES

Figure 3 shows the effects of the various doses of fentanyl on the EEG in different groups of animals compared with a nitrous oxide–oxygen ventilated control. At 25 μg/kg of fentanyl there was marked slowing of the EEG which was characterized by increased amplitude and decreased frequency. The degree of slowing increased with increasing doses of fentanyl. However, with 200 or 400 μg/kg fentanyl, about 25% of the animals developed sudden episodes of sharp waves with an epileptic pattern (bottom trace of fig. 3). The duration of this seizure activity ranged from seconds to minutes; the episodes of seizures were often repeated, separated by periods characterized by a virtually isoelectric EEG pattern.

In a series using three unparalyzed rats, 400 μg/kg fentanyl was given and the animals were then ventilated via face mask. During a 10-min period this ventilation maintained a Pa_{O_2} greater than 90 mmHg, and despite chest wall rigidity, ventilation was sufficient to produce a Pa_{CO_2} between 40 and 52 mmHg. All three animals initially showed EEG findings of low-frequency, high-amplitude activity. In two of the three animals there was a sudden change in the EEG with sharp waves and spikes similar to epileptic activity. This began about two minutes following the fentanyl injection. Coincident with the EEG changes the animals had generalized tonic-clonic motor activity characteristic of grand-mal seizures.

In the four animals given Evans blue prior to 400 μg/kg fentanyl, no evidence of blood-brain barrier disruption was detected as indicated by the lack of tissue extravasation of the dye. Moreover, the seizures episodes did not seem to be caused by water intoxication, as the serum sodium was 138 ± 1.3 mEq/L before and 137 ± 1.6 mEq/L after the fentanyl, while the serum osmolality was 289 ± 2.7 mosm/kg before and 289 ± 3.8 mosm/kg after fentanyl. When naloxone was injected intravenously during a seizure, the EEG immediately reverted to a control pattern which remained stable over a 30-min observation period.

Discussion

We believe our findings resolve the issue as to whether or not narcotics affect CBF and CMR_{O_2}. In animals without halothane for one hour and without N_2O for 20–30 min, fentanyl produced significant dose-related decreases in both the CBF and CMR_{O_2}. Thus, our findings corroborate in the rat those of Michenfelder and Theye[9] in dogs and of Vernheit *et al.*[10] in humans. Our animals required a much higher dose of fentanyl to achieve the same degree of CBF depression

TABLE 2. Mean Arterial Blood Pressure (MABP), Arterial Blood Gases, CBF, Arteriovenous O_2 Difference (AVD_{O_2}) and CMR_{O_2} in Animals with Epileptic EEG Activity after Fentanyl Compared with Non-convulsing Animals

Groups	n	MABP (mmHg)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	CBF (ml · 100 g^{-1} · min^{-1})	AVD_{O_2} (ml/100 ml)	CMR_{O_2} (ml · 100 g^{-1} · min^{-1})
Fentanyl							
200 μg/kg							
No seizures	6	141 ± 7*	133 ± 4	40 ± 2	97 ± 9	7.2 ± 0.7	6.8 ± 0.6
With seizures		140	142	41	106	11.9	12.6
		125	103	37	94	10.6	10.0
400 μg/kg							
No seizures	6	158 ± 3	126 ± 9	39 ± 2	108 ± 12	6.8 ± 0.7	7.0 ± 0.4
With seizures		150	112	45	110	11.5	12.7
		175	90	36	140	9.5	13.3

* Value for non-convulsing animals are mean ± 1 SEM. The individual values for animals with convulsions are shown.

as was found by Michenfelder and Theye.[9] However, their experimental animals were all receiving 70% nitrous oxide in oxygen. The nitrous oxide may have produced a lower CBF for each given dose of fentanyl as has been shown for the combination of diazepam and nitrous oxide in the rat.[17] In addition, their method allowed them to measure CBF at the peak fentanyl effect, which we may not have done in our experiments.

It should be noted that our control values for CBF are higher than reported from some other laboratories.[18] However, this current value for the controls is similar to what we have found previously,[19] and may be accounted for by differences in sensitivity to stress[20] or the strain of the animals.[14] Even if this control value is elevated, the fact that CBF is significantly decreased ($P < 0.05$) in the 100 μg/kg animals compared with the 25 μg/kg rats substantiates our findings of narcotic-related depression of CBF.

The appropriateness of a nitrous oxide–oxygen control group also needs to be addressed. It is clear that no analgesia or sedation in paralyzed recently operated rats would be inhumane and might also produce marked elevations in CBF.[20] Though there is some controversy as to the effect of N_2O on CBF and CMR_{O_2},[21] in the rat at least, N_2O analgesia gives values for CBF that are similar to awake animals having adrenalectomy or treatment with propranolol (measures which blunt the stress response).[22]

Twenty-five per cent of the rats receiving the highest doses of fentanyl exhibited changes compatible with seizure activity. Seizures after narcotics are well-known and appear to be related to the dose, the species of animal, and the potency of the narcotic. Cats, for example appear quite sensitive to the epileptogenic effects of fentanyl, and seizures have been reported in doses of 20–80 μg/kg.[8] In dogs, fentanyl doses greater than 1,250 μg/kg are required to produce seizure activity.[23] Our findings suggest that the rat is somewhere between the cat and dog with respect to sensitivity to the epileptogenic effects of fentanyl. Though we are unaware of previous reports of seizures following fentanyl injected in rats, these findings are consistent with the report of seizures in rats after morphine administration.[24] The fact that naloxone abolished the seizure activity is further evidence that the seizures were related to the effects of fentanyl.[25]

Seizures after fentanyl injection have not been reported in humans. Sebel *et al.*[26] noted some sharp waves in patients receiving up to 70 μg/kg fentanyl, but no frank seizure activity. However, these patients also received lorazepam and N_2O, which may have modified the epileptic response to fentanyl. Also, the doses of fentanyl used by Sebel *et al.*[26] were lower than doses

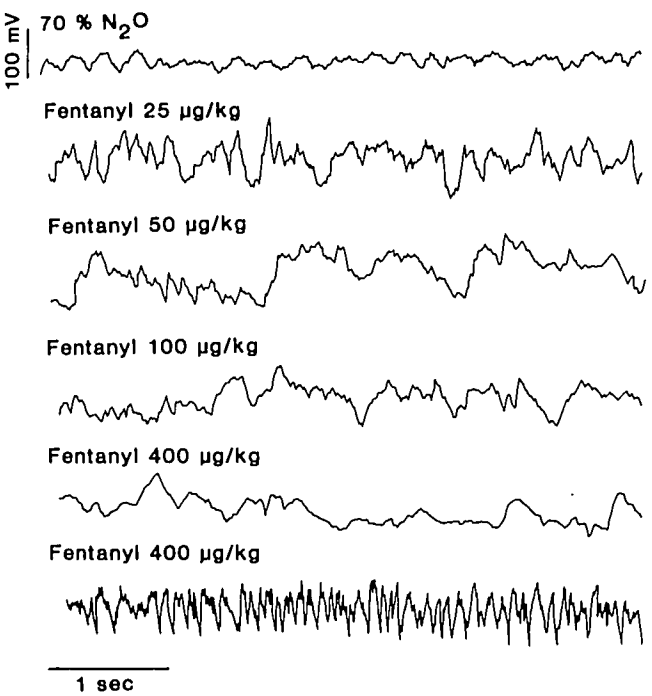

FIG. 3. Representative fronto-occipital EEG tracings from animals ventilated with nitrous oxide–oxygen or given various doses of fentanyl. The last trace is from an animal who developed epileptic EEG activity following 400 μg/kg fentanyl.

currently in use.[12,27] Finally, most investigations of high-dose fentanyl anesthesia have not reported EEG findings, and seizure activity may be missed in paralyzed patients. Seizures in humans have been reported after diacetylmorphine injection.[28] Thus, the lack of seizures noted so far with fentanyl are probably related to inadequate dose or concomitant use of other drugs that alter the seizure threshold.

Our results indicate that even with a background of metabolic depression the presence of seizures increases oxygen consumption. Others have demonstrated that severe seizure activity may lead to brain damage.[29] Recently, Ingvar and Shapiro[30] speculated on the possibility that localized seizure foci may produce regional ischemia and damage. Thus, the occurrence of seizures after narcotics in animals may have clinical relevance in humans.

Doses of fentanyl less than those that cause frank seizures may also be of pathologic significance. For example, doses of lidocaine less than those required for cortical seizures will produce subcortical seizure activity and concomitant increases in cerebral metabolism in the active areas.[30] Since narcotic-induced seizures also most likely originate in subcortical nuclei,[31,32] it is possible that fentanyl may produce seizure activity in subcortical areas which are not detectable with surface electrodes.[33]

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