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The Effects of Acute High Dose Fentanyl Administration on Experimental Brain Edema: Analysis of Intracranial Pressure, Systemic Arterial Pressure, Central Venous Pressure and Brain Water Content

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TIZNADO, E , H E JAMES AND S MOORE *The effects of acute high dose fentanyl administration on experimental brain edema Analysis of intracranial pressure, systemic arterial pressure, central venous pressure and brain water content* PHARMACOL BIOCHEM BEHAV 24(4) 785–789, 1986 — In rabbits who had brain edema and intracranial hypertension induced by a combined cold lesion (over the left hemisphere) and a metabolic blocker (6-aminonicotinamide), the authors analyzed the response of multiple parameters following the administration of 6 mcg/kg/dose of fentanyl every 5 minutes for 1 hour (12 doses), combined with nitrous oxide anesthesia All animals were mechanically ventilated and the $PaCO_2$ was maintained at 37–43 torr Gross pathology and extent of Evans Blue extravasation was no different from pretreatment control animals The systolic arterial pressure and the central venous pressure showed no change during the experiment The intracranial pressure remained elevated despite fentanyl, but did not increase or decrease throughout the administration of the agent The brain water content remained unchanged in the right hemisphere, but revealed a significant increase following fentanyl in the cold-lesioned left hemisphere for the gray ($p<0.005$) and white matter ($p<0.05$)

Fentanyl Brain edema Intracranial pressure

FENTANYL is a well established anesthetic agent and the emphasis in its clinical application in cardiac surgery is due to its cardiovascular stability [25,28], and in neurological surgery for its ability to stabilize intracranial dynamics and not increase intracranial pressure (ICP) [17]. It is preferred in other specialties as well because of the rapidity of onset of action, of its short duration, and the fact that it is 80 times more potent as a narcotic than morphine.

Reports of seizures following high dose fentanyl administration in experimental and clinical situations has lead to concerns for its mode and dosage of administration in the clinical setting [20]. Prolonged seizure activity can lead to neuronal damage and death, possibly due to the inability of the blood supply to meet the increased metabolic demand [2,15] Local brain edema may worsen due to a previous insult if there was one, and the inadequate metabolic-blood supply relationship. This, in turn, may create more diffuse or spreading effects which can lead to a disturbance of intracranial dynamics

There is limited information available in reference to the effects of fentanyl on intracranial dynamics, ICP, systemic arterial pressure (SAP), central venous pressure (CVP), blood brain barrier, EEG and brain water content following brain insult. These parameters are of importance in the clinical setting where following brain insults, the patient is at higher risk from complications from anesthetics and narcotics, should these be required.

For this reason we performed the current study in rabbits following the combination of a brain injury created by the administration of a cryogenic left hemisphere (vasogenic) insult [8, 11, 13] and a cytotoxic one, by the administration of a metabolic blocker, 6-aminonicotinamide [10,11].

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TABLE 1
EXPERIMENTAL GROUPS

Experimental Groups		n
Group 1	Sham Operated Animals (without lesion)	12
Group 2	Untreated Controls (cold lesion and 6-ANA*)	10
Group 3	Treated Animals (cold lesion, 6-ANA and fentanyl)	7

*The metabolic blocker, 6-aminonicotinamide

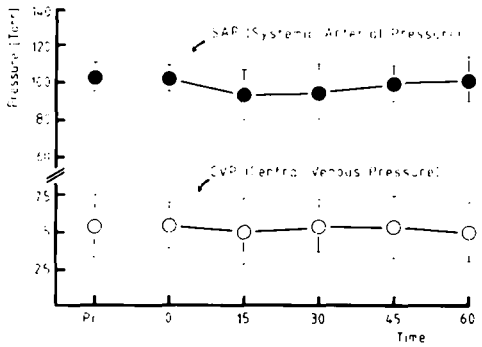

FIG 1 Systolic Arterial Pressure (SAP) and Central Venous Pressure (CVP) following fentanyl administration

METHOD

Albino rabbits weighing 2 to 3 kg were anesthetized with intravenous sodium thiopental (20 mg/kg) through the marginal vein of the ear and then placed in a stereotactic device The scalp was incised under local anesthesia (Lidocaine 1%), and the calvarium exposed A 12 5 mm diameter circular trephine hole was then made over the left parieto-occipital cortex A stainless steel probe (area 65 mm^2), previously equilibrated with a liquid nitrogen bath, was applied to the intact dura for 90 seconds following which the skull was closed by suturing the bone remnant into its original position, and the skin sutured Evans Blue (1 mg/kg of 3% solution) was then administered intravenously Following this, a single dose of 6-aminonicotinamide (6-ANA) was administered intraperitoneally (120 mg/kg) as a metabolic blocker [10,11] A group of animals (sham operated) received no freeze lesion or 6-ANA The animals were returned to their cages and were allowed food and water ad lib. Therapeutic trials began 24 hours after the lesion, at the time of maximum white matter edema [8,11]. The animals were reanesthetized with sodium thiopental, tracheostomized and continuously ventilated with a mixture of oxygen (50%) and nitrous oxide (50%) They were then paralyzed with pancuronium (0 5 to 1.0 mg) intravenously, and femoral arterial and venous catheterizations were performed. Systolic arterial and central venous pressure were monitored continuously through appropriate strain gauge transducers and were recorded on a multichannel polygraph (Gilson Model CM-8, West Coast Science Company, Oakland, CA). Arterial blood gases were maintained so that the $PaCO_2$ was in the range of 37 to 43 torr Animals with systolic arterial pressure of less than 80 torr at any time during the experiment were eliminated from the study The animals were again positioned in the stereotactic device and a 20 gauge plastic catheter (Angiocath, Desert Pharmaceutical Company, Sandy, UT) was inserted into the cisterna magna for continuous ICP recording The ICP reference point was the interaural line Bilateral anterior and posterior screws were placed in the calvarium for continuous EEG recording

After stabilization, the animals were divided into three groups The first group was the sham operated population (n=12) which was monitored for 45 minutes after $PaCO_2$ stabilization, and killed by air embolus The second group was the population with freeze lesion and 6-ANA (n=10) (untreated controls) who were monitored like the previous group and then killed 45 minutes after stabilization of the

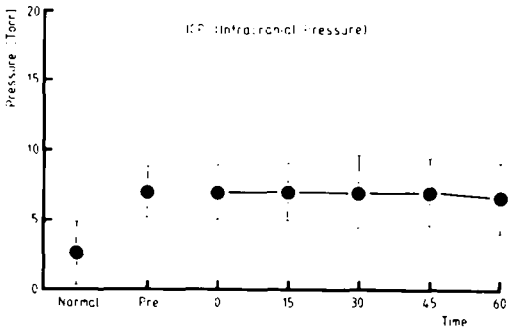

FIG 2 Intracranial Pressure (ICP) in the control group and in the fentanyl group (cold lesion and 6-aminonicotinamide)

$PaCO_2$ by exsanguination The last group was the therapy group (n=7) All of these animals also received a combined cryogenic injury and cytotoxic (6-ANA) insult The surviving animals (n=7) were treated with intravenous fentanyl 24 hours later in the following manner after stabilization of the $PaCO_2$ all animals were given fentanyl in 6 mcg/kg each with rapid bolus IV every 5 minutes, during 60 minutes, for a total of 12 administrations The 3 kg animal thus received a total of 276 mcg The animals were killed by exsanguination

In all groups after the sacrifice the brains were rapidly removed by craniectomy, gray and white matter samples in front and behind the lesion crater, excluding the areas of hemorrhage and necrosis, were taken Homologous samples were then taken from the contralateral hemisphere The water content of the samples was obtained by the microgravimetric technique [14] In the second group (untreated controls), the animals were sacrificed at 24 hours following the combined lesion, and processed as previously described The various experimental groups are listed in Table 1

RESULTS

Behavior

Behavior in the sham operated group was normal In the

TABLE 2
BRAIN WATER CONTENT*

Experimental Group	Hemisphere	Gravimetry	
		Gray	White
Sham Operated (Control, n=12)	L	1 0428 ± 0 0005	1 0414 ± 0 001
	R	1 0428 ± 0 005	1 0414 ± 0 001
Untreated Controls Cold Lesion and 6-ANA (n=10)	L	1 0423 ± 0 0007†	1 0385 ± 0 0008‡
	R	1 0433 ± 0 005†	1 0409 ± 0 0004†
Treated Animals Cold Lesion, 6-ANA and Fentanyl (n=7)	L	1 0411 ± 0 0016§	1 0376 ± 0 0017¶
	R	1 0427 ± 0 0009	1 0410 ± 0 0010

*A reduction of gravimetry indicates an increase in tissue water
†$p<0.05$ from controls
‡$p<0.005$ from controls
§$p<0.005$ from untreated controls
¶$p<0.05$ from untreated controls

untreated control group (freeze lesion and 6-ANA), severe to moderate hypoactivity was noted in 85% of the animals with a 25% mortality after the combined lesion. In the therapy group, morbidity and mortality were equivalent to the animals in the untreated control group.

Gross Pathology

In the sham operated animals, there was no extravasation of Evans Blue dye and no gross pathological changes were noted In the untreated controls group, there was an area of hemorrhage and necrosis created by the injury, which averaged 15 mm in diameter at the cortical surface, and generally extended 4 to 5 mm into the underlying parenchyma Evans Blue extravasation was noted to extend into a 5 to 8 mm radius in the injured hemisphere, beyond the area of hemorrhage and necrosis. Frequently Evans Blue dye was seen in the white matter of the right hemisphere and a light bluish hue was seen in both lateral ventricles. There were no gross pathological differences on the extent of the Evans Blue extravasation between the fentanyl group and the untreated controls group.

EEG

In the sham operated group, fast activity was present over both hemispheres In the animals with the freeze lesion and 6-ANA (untreated controls), there was pronounced slowing and high voltage waves over both hemispheres, which was more pronounced on the left side In the fentanyl group, there was an increase in the voltage and number of slow waves over both hemispheres, and this was more pronounced during the second half hour of the experimental run

Systolic Arterial Pressure

The SAP in the sham operated group, at a $PaCO_2$ of 37–43 torr, ranged between 150 and 85 torr. In the freeze lesion and 6-ANA untreated group, the mean SAP was 102 9±7 torr. In the fentanyl group, it was 102.1±7 torr (Fig. 1)

Central Venous Pressure

The mean CVP in the sham operated group was 7.2±1.5 torr. The mean CVP in the untreated controls group was 5.3±2.1 torr. In the fentanyl group it was 5.4±1 5 torr. There was no statistical difference between the groups (Fig. 1).

Intracranial Pressure

The mean ICP for the sham operated animals was 2.75±2 3. In the untreated controls group it was 7 1±1 8 torr This is statistically significant. In the fentanyl group it was 7.0±1.9 torr There is no statistical difference between these last two groups (Fig. 2).

Brain Water Content

The gravimetry of the brain in the control animals was 1 0428±0.005 in the gray and 1.0414±0.001 in the white matter. In the untreated controls (freeze lesion and 6-ANA) at 24 hours a significant increase in the water content of the white matter of the left hemisphere was noted ($p<0.005$). This was also noted in the gray matter of the left side. Following fentanyl therapy, there was a decrease in the water content of the left hemisphere, both for the gray and white matter, when compared to the untreated controls (Table 2).

Of interest is the fact that in the right hemisphere (subjected only to the cytotoxic agent), the water content returned to values similar to the sham operated group in the gray matter, following fentanyl (Table 2)

DISCUSSION

Fentanyl has been extensively employed in clinical practice, especially in cardiac surgery and in neuroanesthesia. It has been known not to increase ICP in the clinical setting, and it has also been known to lower it, in the presence of disturbed intracranial dynamics [17]. This stabilization of the intracranial dynamics in pathological situations is felt to be due to a combination of factors. It seems to reduce CBF and, consequently, to reduce cerebral blood volume [16,28]. Likewise, it has been noted to reduce cerebral metabolism of oxygen ($CMRO_2$) [17,28]. This, in itself, can lead to a reduc-

tion of CBF However, it has to be pointed out that these decreases are seen when fentanyl is given with other agents, such as nitrous oxide and/or diazepam [17,27] Also as one may expect, these findings are seen in intubated and ventilated animals and humans, but when fentanyl is given in the non-ventilated otherwise conscious rabbit in progressive doses, it produces hypercarbia from respiratory depression and increased cerebral blood flow [5]

There has also been concern about a capability for fentanyl to create EEG changes and seizures [16, 18, 20, 26] DeCastro *et al* [6] found that dogs given intravenous fentanyl at 4 mg/kg/IV developed seizures Because of these results, he labeled the agent an "excitatory" narcotic [6] Dogs require a much larger amount of fentanyl than humans for an effect to be noticeable clinically It is not therefore appropriate to extrapolate the dog data to similar effects in humans Such seizures should not be confused with the phenomenon of "stiffness" and "muscle rigidity" described by various authors [4, 21, 22] which are primarily related to the rapid administration of doses of up to 100–150 mcg/kg This phenomenon has also been reported as a delayed response several hours after the administration of the agent [3]

In human studies, the EEG effect of fentanyl has been seen to produce high voltage slow waves [22] Sharp and spike wave activity following fentanyl administration has also been noted, and because of this other investigators have taken a look at electrical activity and other parameters in animals to better elucidate the nature of the problem Maekawa *et al* [26] looked at local cerebral blood flow following fentanyl induced seizures in rats with C^{14}-iodoantipyrine Fentanyl was infused at a rate of 10 mg/kg/min until the spike, seizure and suppression was seen on the continuous EEG During this spike activity, cerebral blood flow increased in all structures, especially in the superior colliculus, sensorimotor cortex and pineal body This was accompanied by a reduction in the local cerebral vascular resistance the authors concluded that the local blood flow increases seemed to be out of proportion to local metabolic changes [26] Subsequently, Tommasino *et al* [25], in the same laboratory, studied the effects of fentanyl on cerebral metabolism in rats Fentanyl was given in bolus dose over 5 minutes (200 mcg kg^{-1}) and then infused for 50 minutes (8 mcg kg^{-1}) In another group of rats this infusion of fentanyl was doubled Local cerebral metabolism was then studied by the C 14-2-deoxyglucose method (1-CMRG), and epileptoid discharges were monitored with continuous EEG The authors noted that a relationship existed when the different anatomical areas were looked at from a functional point of view In the visual, sensorimotor, white matter and reticular formation, there was a global decrease of 1-CMRG In the limbic system, the 1-CMRG remained at controlled values At the higher fentanyl doses, there was further depression of the former areas, whereas those of the limbic system returned to control values These authors concluded that the observed metabolic redistribution was characteristic of the "limbic seizures" seen in other models, contrary to models of "cortical seizure," where there is increased glucose metabolism throughout the brain The authors then warned of the potential clinical implications, even though there is species differentiation, since the same phenomenon could occur in humans [25]

One of the concerns in the clinical setting is that of the patient with impaired intracranial dynamics, either from mass lesion or from impaired autoregulation Seizures, if unchecked, can increase $CMRO_2$, increase tissue acidosis, increase CBF and intracranial blood volume This in turn can increase ICP What could then follow is a displacement of structures and herniation syndromes, where compression of structures may impair microcapillary circulation, result in local tissue ischemia, which then disturbs local metabolism A vicious cycle could ensue from impaired intracranial dynamics, if it is not recognized and appropriately treated Tissue acidosis and ischemia can add to the disturbed metabolism and favor brain edema, with further deterioration of local perfusion and metabolism [19]

Counteracting this tendency of increased ICP would be the effect of fentanyl's depression of CBF in areas of the brain other than the limbic system [26], which is most likely due to a depression of metabolism in those areas [25] and its effect in stabilizing CSF production [1]

In the current studies the ICP of the untreated controls was no different than the treated controls through the acute stage of fentanyl administration (Fig 2) This speaks favorably for fentanyl not deteriorating already elevated intracranial pressure further in the presence of nitrous oxide anesthesia, as has been demonstrated in previously discussed work Brain water content was not reduced by fentanyl (Table 2) Due to the indications from the work of Tsuyoshi *et al* [26] and Tomasino *et al* [25] employing large doses of fentanyl, 10 mg/kg/min, that global flow and metabolism are reduced following fentanyl administration, and the work by Artru [1] which showed that the CSF production remains unchanged, we believe that the combination of regional blood volume changes (both positive and the negative), stabilizes intracranial volume and hence, ICP The presence of a consistent trend for the EEG to have higher voltage and slow waves in the second half hour of the fentanyl administration follows those electrical changes that have previously been discussed in the rat model [16, 25, 27]

Further investigations in both the experimental and clinical settings are needed before we can apply these findings to the practice of fentanyl therapy in the operating room and intensive care setting

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