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Intravenous Total Anesthesia in Neuroanesthesia: Influence of Gender and Gender/Age over Fentanyl Consumption

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SUMMARY

Background: The search for differences of perception of pain and the opioid action over it between both sexes have drawn to multiple and often puzzling results. A great number of papers and efforts are dedicated to bring light over the possible role of sexual steroids on the pain mechanism and on the opioids receptors. In animal investigation a majority of evidence is pointing toward a greater efficacy in males than in females. In human research the results are incongruous. **Objective:** To investigate if fentanyl anesthetic consumption is different related to sex and if it is age dependent on the neurosurgical patient under total intravenous anesthesia. **Method:** In 500 neurosurgical patients, divided by age in 3 groups: from 40 or less, 41 through 60 and more than 60 years old, measuring fentanyl consumption and comparing means in the same age group using the Student t test. **Results:** Fentanyl consumption was always higher in women patients in the 3 groups, although the difference was only statistically significant in the younger group. This sex related difference trends to disappear in elderly patients. **Conclusions:** Women patients consume more fentanyl than male patients during neurosurgical procedures under total intravenous anesthesia.

Key words: Fentanyl, opioids, pain, sex, age, anesthesia, intravenous.

RESUMEN

Antecedentes: *Las investigaciones orientadas a dilucidar las posibles diferencias relacionadas con el sexo, son recientes y sus resultados antagónicos. La línea de investigación más importante está orientada a la participación de los esteroides sexuales en el mecanismo del dolor y su interrelación con los opioides. La mayoría de los estudios en animales indican que los opioides son más efectivos en los animales machos que en las hembras. En humanos los resultados son mixtos y paradójicos.* ***Objetivo:*** *Investigar si existe diferencia en el consumo de fentanyl transanestésico por sexo y si la edad influye en la misma en el paciente neuroquirúrgico bajo anestesia total endovenosa.* ***Método:*** *En 500 pacientes neuroquirúrgicos, divididos en tres grupos etarios de 40 o menos, 41 a 60 y más de 60 años, se cuantificó el consumo de fentanyl, contrastando los promedios en cada grupo con la prueba t de Student.* ***Resultados:*** *Las mujeres consumieron siempre más fentanyl, aunque resultó estadísticamente significativo sólo en el grupo de 40 años y menores. Con la edad esta diferencia tiende a desaparecer.* ***Conclusiones:*** *Las mujeres en este contexto consumen más fentanyl que los hombres.*

Palabras clave: *Fentanyl, opiáceos, dolor, sexo, edad, anestesia, intravenosa.*

The development of the knowledge about the action of inter-individual factors in general medicine and particularly in anesthesia has been slow. Variables such as age, ethnical origin and, overall, sex were frequently and largely ignored because they were considered irrelevant. Just recently, it has been promoted a trend to include members of both sexes equitably as subjects of study in projects of medical research. Under this scope, the difference in response to opiate analgesics according to sex has drawn an increasing attention during the last years.

The studies on the action of opiates performed on laboratory animals show a remarkable difference in results between both sexes. In rats and mice, most of the studies report that the power and efficacy of morphine analgesics administrated in a systemic way are higher for males than for females individuals[1]. The increase of this sensitivity to analgesics through morphine compounds has been documented through several methods of provoking pain, among which it can be found those thermal, somatic, chemical, visceral and electric types of methods. The results from the aforementioned studies allow us to establish some theories that imply that the differences in opiate analgesia regarding sex may be generated, at least in part, by the sensitivity of the Central Nervous System to opiates. Another proposed possibility expresses that it might be a higher morphine brain concentration in the case of systemic opiate administration. This may be because of differences in sex with regard to drug disposition. However, there are many studies against this theory devoted to discover this last fact, and they have found that the serum levels of opiates are the same in both sexes at the moment of the tests[2].

Furthermore, it was proposed the possibility that it might be a different amount of opiate receptors (OR) in both sexes. It has been found that there is no difference in mu and delta receptors density between the brains of male and female rats[3]. From a different perspective, it has been studied the action of sex hormones over the morphine analgesic expression. With regard to this last fact, it has been demonstrated that, in ovariectomized rats, there are two different phenomena: morphine analgesia increases regarding control female subjects and there is an increase of the affinity of ORs to morphine in these female rats. The cause why this phenomenon occurs is still unknown[4,5]. Nevertheless, it is well known that in female rats both the treatment with ovarian steroids and ovariectomy alter brain OR sites. This aforementioned fact may be caused by the coexistence of both opiate receptors and sex hormones in the mesencephalic central grey area (GCt), as well as in tonsil (amygdalae) and supraoptic area. It may be possible that this causes pain modulation by part of sex hormones. This theory is gaining many adepts lately[6].

In human beings, opiate analgesia related to sex has been scarcely explored and it keeps on being poorly understood. The results are not only diverse but also opposed: while in women presenting dental post-surgery pain, it was reported a higher pain relief than in men –as the product of the administration of opiate agonists, such as pentazocine, nalbuphine and butorphanol–, once morphine administration was introduced, there was no difference between sexes. This fact may indicate a greater sensitivity or a higher number of receptors in women[7]. Sarton *et al*, in a study on volunteers who were administrated morphine in order to relieve pain by electric shock. These researchers measured plasma concentration of both morphine and its 3 (M3G) and 6 (M6G)-glucoronide metabolites, which did not show any difference between men and women. The authors reported a higher morphine power over women[8].

In an open opposition with the results of previous works, Cepeda *et* al established, within a universe of over 700 post-surgery patients, that women presented more pain and required 30% more morphine than men to reach a similar analgesia level[9]. Similarly, Aubrun *et al*, on a population of 4,317 patients, found that women required 11% more morphine than men in order to relieve their pain. Such a difference disappeared in patients being elder than 75 years old[10].

Regarding the power of opiates with relation to sex in the context of trans-anesthesia, Drover and Lemmens compared plasma concentration of remifentanyl necessary for a proper analgesia and they found a higher concentration in women[11].

In the face of the contradictory quoted results, we proposed ourselves to investigate whether in our sphere there are differences in the consumption of trans-anesthetic fentanyl among male and female patients subjected to any kind of neurosurgical procedure and if age, in any case, this influences in that difference.

MATERIAL AND METHODS

We studied 500 cases of patients, 247 men and 253 women, subjected to any kind of neurosurgical procedure (Table I).

In the universe of the study, we included patients presenting ASA I and II classification, without clinical evidence –from laboratory or cabinet– of hepatic, renal, cardiac or pulmonary pathology. The patients' age ranged from 17 to 89 years old. No patients received pre-anesthetic medication. The patients were assigned to one of the three groups, according to their ages: Group 1, 40 years old or younger; Group 2, from 41 to 60 years old; and Group 3, 61 years old or elder. When the patients entered the operating room, they were monitored in the following way: continuous electrocardiography (derivations II and

Table I. Surgery types.

Surgery	Frequency	Percentage (%)
Lumbar disc herniation	132	26.4
Cranyotomy for hematoma or tumor	97	19.4
Lumbar instrumentation	72	14.4
Cervical instrumentation	72	14.4
Lumbar laminectomy	66	13.2
Ventriculoperitoneal shunt	17	3.4
Cranyotomy for aneurysm	17	3.4
Route transsphenoidal hypophysectomy	10	2.0
Carotid endarterectomy	10	2.0
Ventriculostomy	7	1.4
Total	500	100

V5), pulse oximetry, automatic non-invasive blood pressure, and neuromuscular transmission through the placing of equipment for the practice of the train-of-four test. The induction was carried out by means of midazolam 0.05 to 0.07 mg/kg^{-1}, fentanyl bolus from 1 to 2 μg•kg^{-1}, 2% lidocaine at 1 mg•kg^{-1}, propofol at 1.2 to 2.8 mg•kg^{-1}, according to the dose needed to get loss of consciousness. Once the anesthetic induction was completed, the continuous administration of both propofol (10 mg•kg^{-1}•h^{-1}) and fentanyl (1.0 μg•kg^{-1}•h^{-1}) was started through an infusion pump (Anne infusion pump, Abbott Laboratories. North Chicago Ill). Muscle relaxation was obtained by means of a bolus with a dose of 100 μg•kg^{-1} of vecuronium. The orotracheal intubation was performed by a proper-diameter catheter, whose accurate position was checked by capnography and auscultation of both hemithoraces. Then it was performed a mechanical ventilation with 100% oxygen at a respiratory frequency of 10 ventilations per minute and at a flowing volume adjusted to obtain a pressure at the end of the CO_2 expiration between 28 and 32 Torr in the capnograph.

The initial infusion of both fentanyl and propofol was kept constant before the incision, when 1 to 2 μg•kg^{-1} of fentanyl were administered. The profopol infusion was reduced to 8 mg•kg^{-1}•h^{-1} at 15 minutes after the incision and, after that, it was kept between 6 and 8 mg•kg^{-1}•h^{-1} until the last stages of the surgery. Taking into account, as the elementary fact, the increase or decrease of artery blood pressure and cardiac frequency of more than the 15% when comparing the basal values that had been obtained during the pre-anesthetic visit, the rate of fentanyl infusion was modified in increments or decreases of 0.25 μg•kg^{-1}•h^{-1}. Moreover, in each case, the administration of bolus of 50 μg was kept up to the moment of achieving the proper analgesic condition. The total consumption of fentanyl, as well as the profopol one, was calculated dividing the drug total amount by the infusion time (in hours and fractions), divided by the patient's weight.

The statistical test used to compare the values of age, body mass index (BMI), anesthesia time and fentanyl consumption was Student's-t-test. The data was obtained by the SPSS 12.0 program for Windows. (SPSS Inc. 233 S Wacker Drive, 11th floor. Chicago, Illinois 60606).

RESULTS

There was no significant difference within each group with regard to age mean, body mass index (BMI) and length of anesthesia time (Table II).

In Group 1, there was significant statistical difference fentanyl consumption between men and women. It was found that the latter consumed a 22% more fentanyl than the men. In the other groups, there was no significant difference between sexes. The women always consumed more than the men did. We also observed that fentanyl consumption was almost the same in the group of eldest people, going from a difference in means of 0.231 μg•kg^{-1}•h^{-1} (11%) in Group 2 to 0.12 μg•kg^{-1}•h^{-1} (8%) in Group 3.

With regard to propofol, there as no difference in consumption in any of the groups (Table III).

DISCUSSION

The difference in the effects of the drugs according to sex is getting increasingly important. In the case of anesthesiologists, it is elementary to know the aforementioned facts in order to determine if, in the clinical practice, it is justified to take into account the differences based on sex[12].

Our results show that in young patients there is a significant difference in trans-anesthetic fentanyl consumption in favor of women over men of about a 22%. This is very interesting because the effect decreases in other age groups

Table II. Demographic data and duration of surgery of studied sample.

	Sex	Number	Age (years)	Duration of surgery (min)	Body mass index (kg/m^2)
Group 1	Male	63	32.05 ± 6.6	215.79 ± 78.33	25.82 ± 2.36
	Female	50	31.30 ± 6.36	224 ± 107.34	23.23 ± 2.17
Group 2	Male	74	48.38 ± 5.44	233.85 ± 93.88	26.55 ± 2.55
	Female	103	49.09 ± 5.66	216.84 ± 73.52	23.75 ± 2.48
Group 3	Male	110	69.11 ± 6.75	227.77 ± 78.61	25.39 ± 2.96
	Female	100	70.17 ± 6.81	242.50 ± 108.07	25.95 ± 2.79

Table III. Propofol and fentanyl consumption in each group.

	Sex	Number	Fentanyl consumption ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	Propofol consumption ($mg \cdot kg^{-1} \cdot h^{-1}$)
Group 1	Male	63	1.989 ± 0.7821	7.761 ± 1.2424
	Female	50	2.440 ± 0.9125*	7.591 ± 1.4801
Group 2	Male	74	2.080 ± 1.2642	7.763 ± 1.3124
	Female	103	2.311 ± 0.8621	7.591± 1.4244
Group 3	Male	110	1.416 ± 0.5540	6.693 ± 1.3505
	Female	100	1.537 ± 0.6055	6.532 ± 1.4104

$p < 0.05$ compared with the same group

to become an 11% in middle-aged patients and an 8% for the eldest group, always in favor of women.

In laboratory animals, most of the studies report that the power and the efficacy of morphine when administered systemically are greater for males than for females[2,3,13]. The researches that use the central route for opiate administration suggest that the sex differences regarding opiate analgesia are directed, at least partially, by different sensitivities of the Central Nervous System (CNS) to opiates. The effective dose of 50 of morphine or the DAMGO (D-Ala-MePhe-Gly-ol-enkephalin) μ-selective agonist through intra-ventricular via are lower in male individuals[3]. Even when morphine is administered directly in supra-spinal areas of the CNS, which are critically linked to the opiate descendant inhibition of pain, such as the rostral ventromedial medulla, the consequence is a higher analgesia in males than in females[14]. This mentioned difference regarding sex is also seen in other species, such as in the case of rhesus monkeys. In a very interesting study, Neguss and Mello compared the sensitivity of male monkeys and ovariectomized females. The researchers found similarities in thermal sensitivity. Furthermore, they studied the action of morphine, butorphanol and nalbuphine both in ovariectomized females and in females with hormonal replacement by estradiol. These researchers found a greater impact in females with hormonal replacement to whom it was administered butorphanol and nalbuphine, which are opiates of low sensitivity for μ OR (opiate receptors) and high sensitivity for κ OR. These authors concluded that their results suggest that opiate agonists from animals produce higher antinociception in males than in female subjects, and that the amount of these sex differences may be inversely proportional to the efficacy of μ OR because of the selectivity of μ OR *vs.* κ OR, taking into account that in females there are greater presence and action of κ ORs[15]. This last fact opens a series of possibilities in the actions of sex hormones in opiate analgesia.

Since some time ago, It is well known that there is an inter-dependence of receptors both opiates and sex steroids. This fact has been already demonstrated in the periaqueductal grey substance, what would suppose the possibility of sex hormone modulation over opiate analgesia[16]. There are also signs that sex hormones interact as transmitters related to the mechanism of opiate analgesia; for example, serotonin and leu and met-enkephalin peptides, whose concentrations differ in males and females. In fact, estradiol has

demonstrated to have control over opiate peptide synthesis in the hypothalamus, whose quantity differs not only between males and females, but also through the menstrual cycle of females[17]. Ovariectomy (oophorectomy), by its part, alters the levels of opiate leu and met-enkephalin and A and B dynorphins[18]. From the aforementioned facts, it can be deduced that in female animals, both basal nociception and sensitivity to opiate analgesia may be dependent on sexual steroids. With regard to morphine power, it has been demonstrated that it is lower in female animals than in males, and that the mentioned power fluctuates according to the moment of the menstrual cycle. It has been shown that the power is weaker during the estrus; during the diestrus it may be sometimes compared to the power in male animals[19].

In human beings, the results are not so clear. It seems that women have a lower pain threshold than men. At the same time, women present lower tolerance in the experimental field, during the production of pain through both electric and thermal pulses[20]. Frot *et al*, using topic capsicine, demonstrated that pain qualification in women is more intense and disagreeable than in men[21].

It is important to take into account that most of the studies in human beings have been performed on conscious individuals, who are necessarily influenced by a complex perception of pain.

In the biological context, it is very complicated or even impossible to separate the diverse pain components: sensorial, affective and cognitive. Most of the attempts in this sense are oriented towards the affective dimension of pain, which is structured as the memory of sensations, of both displeasure and rejection and negative emotions associated to the future. The spine vias related to the limbic system structures and the medial thalamic nucleus provide a direct feeding for the brain areas that manage the affective condition. This fact integrates a nociceptive knowledge with information and memory that gives the quality of rejecting pain, its negative emotional valence and the immediate and elementary responses to it. This philosophical base is modified with relation to behavior, because of pain within a powerful psychosocial context. There are certain socio-cultural differences between sexes, which undoubtedly influence behaviors and characteristics. Because of this, we have stereotyped behaviors. Men are expected to present certain resistance attitude in front of pain, what has been demonstrated since the early childhood[22].

In the case of patients under anesthesia, these conscious affective factors are probably suppressed. Therefore, the autonomic response to pain is more related to the occupation and action levels of ORs independently from the affective context.

In sum, our results showing that there is higher fentanyl consumption in women in the trans-anesthetic surgery period, lead us to accept the possibility of a greater need of trans-anesthetic fentanyl in women when compared to men. This difference decreases when going from young patients to elderly patients, what someway might indicate that the presence or absence of sexual steroids plays an important in the interaction between opiates and ORs.

The research about the possible difference in the requirement of opiates regarding sex is just beginning. There is no doubt that it is necessary to carry out several studies in order to establish quantity and quality of opiates needed to a proper analgesia in the pre-, trans-, and post-anesthetic periods in patients from both sexes and different ages. These mentioned studies will surely give us greater safeness and efficiency in the use of opiates.

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