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Research Article

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Antagonistic Effect of Flumazenil on Isoflurane in the Emersion of General Anesthesia

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Abstract

Introduction and Objectives: *Isoflurane, an inhalational general anesthetic widely used in medical practice, belonging to the group of volatile liquids together with desflurane and sevoflurane. Volatile inhalational anesthetics (halogenated) as mechanism of action, has the property of increasing inhibitory synaptic transmission at postsynaptic level by potentiating ion channels regulated by ligand activated by alpha-aminobutyric acid (GABA). Flumazenil is a benzodiazepine. It is currently known that there is no specific drug capable of antagonizing the effects of halogenates that allow the rapid and complete recovery of general anesthesia, for this reason this work focuses its efforts on demonstrating whether flumazenil has the ability to reverse the actions of the patient. isoflurane and allow an early restoration of the level of consciousness.*

Materials and Methods: *The study to be performed is a clinical type of longitudinal, prospective, unicentric and double blind. The sample will be formed by patients who are going to be subjected to a balanced general anesthesia. The sample will be divided into 2 large groups: group C (control) and group F (Flumazenil). At the end of the surgery, the mixture will be administered according to the selected group in a random manner (Flumazenil 0.25mg or 0.9% solution in a 20cc syringe) and the time of extubation, recovery time of the level of consciousness, time of discharge UCPA and hemodynamic state (FC, TAM and SO_2).*

Results: *The flumazenil group showed a significantly shorter time from injection to extubation than the placebo group (p= 0.007). Differences in terms of shorter times needed to achieve Aldrete of 9 points in the flumazenil group (P = 0.04) were observed as were shorter anesthetic arousal times represented by a Ramsey 2. Heart rate, mean arterial pressure and saturation they had similar values between the 2 groups.*

Conclusion: *The study showed that a single dose of 0.25 mg of flumazenil administered at the end of the surgical act, just after completing all surgical stimulation was beneficial (P= 0.007) in the context of extubation times and shorter anesthetic arousal times.*

Keywords: Flumazenil, Isoflurane, Antagonism, Extubation, Receptors, Gaba, Anesthesia.

Introduction

Isoflurane is a general inhalational anesthetic widely used in medical practice, belonging to the group of volatile liquids together with desflurane and sevoflurane, with various properties among which are sedation, hypnosis and anesthesia of patients undergoing surgery [1].

Volatile inhalational anesthetics (halogenated) as mechanism of action, has the property of increasing inhibitory synaptic transmission at the postsynaptic level by potentiating the ion channels regulated by ligand activated by alpha-aminobutyric acid (GABA) and glycine, at an extrasynaptic level, potentiating GABA receptors and leakage currents, and presynaptic level increasing the basal release of GABA. Classically, inhalational anesthetics suppress excitatory synaptic transmission at the presynaptic level by reducing the release of glutamate, and postsynaptically by inhibiting the excitatory ionotropic receptors activated by glutamate [1,2].

Flumazenil is a benzodiazepine antagonist belonging to the group of imidazobenzodiazepine. It is a partial agonist with minimal intrinsic activity and very high antagonistic activity, so that at very high doses some anticonvulsant action is revealed, while in other studies it shows a small action of inverse agonist type [3,4].

The drug binds very avidly to specific sites of the GABA a receptor, in which it shows competitive antagonism with the binding and allosteric effects of the benzodiazepines and other ligands. The electrophysiological and behavioral effects of the agonist or of the agonist benzodiazepines are antagonized. In animal studies, the intrinsic pharmacological actions of flumazenil have been

mild, so their actions concentrate on antagonizing the effects of benzodiazepines [3,5,6].

Its main therapeutic utility lies in anesthetic practice, to reverse sedation, hypnosis and anesthesia caused by benzodiazepines. It can also be useful for the differential diagnosis of benzodiazepine poisoning and for its treatment [7,8].

It is known that anesthesia is not a completely risk-free technique and that the extubation and early recovery of the same, as well as an early discharge of the Post-Anesthesia Recovery Unit reduces the incidence of complications and morbidity in patients. It is currently known that there is no specific drug capable of antagonizing the effects of halogenates that allow the rapid and complete recovery of general anesthesia, for this reason this work focuses its efforts on demonstrating through hemodynamic and clinical parameters if flumazenil has the ability to reverse the actions of isoflurane and allow an early restoration of the level of consciousness, an early extubation, a lower rate of portoperative complications and an early discharge from the Post Anesthesia Care Unit [2,7].

Multiple clinical trials attempt to highlight the ability of flumazenil to reverse sedation, hypnosis and anesthesia caused by inhaled anesthetics; specifically isoflurane, directing its hypotheses to the actions that the halogenation exerts on specific sites of the GABA A receptor, acting as an inhibitor of GABA inhibition, an effect that can theoretically be antagonized by flumazenil. This receptor, described a while ago in the physiology of the brain, is the binding site of several anesthetics, such as benzodiazepines and barbiturates [4].

It has been shown that inhalational anesthetic drugs are very closely related to a slow and quite unpleasant anesthetic awakening for the patient characterized mainly by lethargy, psychomotor agitation and disorientation; as well as a higher index of respiratory depression that can coincide with the presence of bronchoaspiration and in the worst cases reintubation or death. For the above described the present work justifies its studies in avoiding the appearance of such complications by demonstrating the ability of flumazenil to reverse the effects of isoflurane [3,7].

At present it has been seen with great concern how the number of patients who come every year to the hospital centers looking for help has increased. Hospital centers that are occupied in more than 80% and even then thousands of visits per month of patients that warrant hospitalization for various reasons. One of them is the need to solve a surgical medical pathology. Pathology that I will rouse of preoperative and postoperative care that generate large expenses to the hospital center and ultimately to the state. The use of flumazenil is intended to demonstrate its usefulness in the emersion of general anesthesia with isoflurane that leads to a faster recovery, the early discharge of UCPA which will result in a decrease in the length of stay and lower hospital costs.

Materials and Methods

Type of study

The study to be performed is a longitudinal, prospective, unicentric and double-blind clinical trial in which the efficacy of flumazenil was compared to reverse the effects hypnotics of the halogenated, in this case, the agent selected is isoflurane in patients undergoing balanced general anesthesia in the Central Hospital of Maracay Autonomous Service from April - October 2017.

Population and Sample

The population will be made up of patients who go to the surgical area of the Autonomous Service Central Hospital of Maracay to be operated on surgically, the sample will be formed by patients who are going to be subjected to balanced general anesthesia in the period between April - October 2017 at the Central Hospital of Maracay Autonomous Service and who meet the inclusion criteria and exclusion mentioned a with Follow-up:

Inclusion Criteria

- Adult patients of both sexes.
- Ages between 18 and 65.
- Good health or mild illness completely controlled by the regular use of medications (ASA I or II, according to the classification scheme of the American Society of Anesthesiologists) Exclusion Criteria
- History or presence of neurological diseases, seizures or panic disorder.
- History of malignant hyperthermia.
- Hearing disorders.
- Chronic use or premedication with benzodiazepines.
- Chronic use of narcotic drugs.
- Patient with acute or chronic liver or kidney pathology.
- Patients with acute or chronic pulmonary pathologies.
- Patients in shock or hemodynamically unstable.

Clinical Procedure

The authors will go to the surgical area of the Central Hospital of Maracay Autonomous Service where patients who are in the pre-anesthetic station will be selected. To balanced general anesthesia, we will proceed to select from these patients, only those who meet the inclusion criteria and who do not have exclusion criteria, will explain to the patient what the study consists of and proceed to sign the informed consent. After this, the sample will be divided into 2 large groups: group C (control) and group F (Flumazenil). This division will be carried out in a randomized standardized manner, using a closed envelope technique: in a group C consisting of the patients who will receive the placebo and group F those who will be administered the flumazenil bolus once the maintenance administration is suspended inhalation with Isoflurane.

Once the study group has been selected, it will proceed to the operating room where the surgical intervention will be performed, it is important that it should not be premedicated with any type of benzodiazepines or opioids, the patient will be monitored and the patient will proceed to perform the anesthetic induction: preoxygenate the same with oxygen 100% at a rate of 6 l/min, the induction will be done intravenously with Fentanyl 3 mcg/kg/dose + Lidocaine 1 mg/kg/dose + Propofol 2.5 mg/kg/dose and Rocuronium 0.6 mg/kg/dose; Orotracheal intubation will be performed and it will be connected to a closed system of partial recirculation with canister, it will undergo mechanical ventilation; the anesthetic maintenance will be carried out by inhalation with Isoflurane at a rate of 1.15 Vol% with a flow of 2 liters of oxygen at 100%; and endovenous with Fentanyl 1mcg/kg/dose and Rocuronium 10 mg every 35 min. As adjuvants of anesthesia, each patient will be administered intraoperatively gastric protective (Ranitidine 50mg), antiemetics (Ondasetron 4mg) and analgesics (Dipirona 2gr) while not contraindicated.

At the end of the surgery, all patients will receive an intravenous infusion of two previously prepared solutions, according to the group to which they have been assigned at random. Group C will receive 20 mL of saline and group F will receive 0.25 mg of flumazenil (diluted in 20 mL of saline).

Both solutions will be administered in an intravenous infusion, immediately after the administration of isoflurane has been completed. The anesthesiologist will not have knowledge of the content of the solution to infuse and will proceed to evaluate: 1) the anesthetic plane of the patient at minute (T1) during the first 5 minutes (T5), then at 10 minutes (T10) and at 15 minutes (T15); 2) calculate the time that elapses from the suspension of isoflurane until the patient regains full consciousness, evidencing a scale of ramsay 2 and where he is able to maintain a coherent conversation with the operator;3) calculate the time that elapses from the suspension of isoflurane until the moment of extubation; 4) monitor vital signs during the process of extubation at the 1st minute (T1), at 5 min (T5), at 10 (T10) and at 15 min (15) after the closure of isoflurane; 5) register the presence of any complication or adverse reaction in case of evidence and 6) determine the time of stay in the Post Anesthetic Care Unit.

The study was approved by the Bioethics Committee of the Central Hospital of Maracay. The study was carried out in the operating rooms of the Central Hospital of Maracay in the period April - October 2017. After receiving the invitation to participate in the study and information about it, all the participants signed an informed consent document.

Results

Of the 66 patients who were initially included in the study, 2 were excluded due to a delay in the anesthetic awakening which does not correspond to the usual times of the general anesthetic inhaler used in the study. The other 64 patients remained in the study until the end (discharge from the post anesthetic recovery room) and their data were analyzed.

There were no significant differences between the 2 groups in terms of sex and age (Table 1), but there was a difference in surgical time, with 40.6% being represented by surgeries with a duration of 90min.

Table: Demographic characteristics of the sample

Demographic	Control	Flumazenil	Total
Sexo (M/F)	12/19	18/15	30/34
Edad	39	40	40

Table 2: Comparison of the groups in terms of the parameters studied

Parameters	Control	Flumazenil	P
TAM (mmhg)	84 +- 3	82 +- 5	NS
FC (lpm)	94 +- 1	95 +- 2	NS
Saturation O_2 (%)	96 +- 2	97 +- 1	NS
Time Extubation*	10,96	7,46	0,007
Time Ramsey*	22,18	20,68	NS
TimeAldrete*	34,66	28,61	0.04

* Time defined in minutes. NS Not Significant.

The flumazenil group showed a significantly shorter time from injection to extubation than the placebo group (p = 0.007). Differences in terms of lower times needed to achieve Aldrete were observed in 9 points in the flumazenil group (P = 0.04) as well as shorter anesthetic arousal times represented by a Ramsey 2 (Table 2). The heart rate, mean arterial pressure and saturation had similar values between the 2 groups (Figure 1).

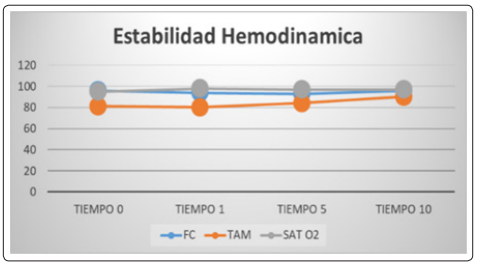

Figure 1: Hemodynamic changes

Throughout the study, no patients showed complications or adverse reactions to flumazenil (convulsions, agitation, anxiety). The variables obtained from the samples were grouped and stored in an Excel 97/2003 spreadsheet as a basis for data. As statistical programs, EpiInfo version 3.5.1 was used to correlate the results through different statistical studies using the frequencies and means of each variable. The JMP 5.1 program was used to correlate the data of the continuous variables.

Discussion

The flumazenil has a great antagonistic power indicated to neutralize the excessive medications with benzodiazepines or in the recovery of the Sedation / hypnosis after a surgery, this through the inhibition of the GABA receptors in the central nervous system. This effect of flumazenil is caused specifically by competitive inhibition of GABA receptors, the targets of benzodiazepines. Receptor that plays an important role on the mechanism of action of inhalation-specific general anesthetics isoflurane and its close relationship with GABA [3,7].

In this study that was carried out in patients not premedicated and who did not receive benzodiazepines demonstrated that the injection of 0.25 mg of flumazenil at the end of the surgical act, just after completing the surgical stimulation significantly reduced (p = 0.007) the time necessary for the extubation and recovery of general anesthesia with isoflurane compared to the control group, as well as shorter times to obtain an Aldrete of 9 points or more (P = 0.04) in the PACU. However, there are multiple studies that question the relationship between benzodiazepines and isoflurane, due to the unclear mechanism of action of inhaled anesthetics [9,10]. Schwieger reported that flumazenil does not affect the MAC of enflurane, isoflurane, or a combination of fentanyl-enflurane; but in this study it was possible to demonstrate the effectiveness of flumazenil to reverse or antagonize the effects of isoflurane and that would correspond to shorter waking times [11].

Domingos Dias Cicarelli in 2016 concluded in his study that a dose of 1 mg of flumazenil at the end of the Surgery was effective in reducing the extubation time of patients undergoing general anesthesia by isoflurane [12]. Yi Jeong Kim himself in 2012 carried out a study in patients who did not receive benzodiazepines and the results showed that the injection of 0.3 mg of flumazenil at the end of the anesthesia significantly reduced the time needed for recovery

from anesthesia and increased the value of BIS compared to the control group [13].

Recently, Karakosta discovered that 0.5 mg of flumazenil can improve the parameters of anesthesia recovery with sevoflurane / remifentanil after administration to non-premedicated patients 30 minutes before the end of the operation [14]. Unlike the previous studies, we were able to demonstrate that a single dose of 0.25 mg of flumazenil is sufficient to antagonize the effects of isoflurane and that higher doses such as 0.5 mg or 1 mg previously described in the literature are not necessary.

Conclusion

The study showed that a single 0.25 mg dose of flumazenil administered at the end of the surgical act, just after completing all surgical stimulation was beneficial (P = 0.007) in the context of time of extubation and shorter anesthetic arousal times compared to those who did not receive it. The patients in this study also benefited from shorter periods of stay in the PACU (P = 0.04) valued by an Aldrete greater than 9 points in those who received flumazenial at the end of the surgery and minimal hemodynamic changes in both groups [15,16].

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