Changes in Neurotransmitter Values with Inhalational Agents

A Tiwari, L Mishra, R Agrawal, Priyanka, A Singh

Citation

A Tiwari, L Mishra, R Agrawal, Priyanka, A Singh. *Changes in Neurotransmitter Values with Inhalational Agents*. The Internet Journal of Anesthesiology. 2006 Volume 11 Number 2.

Abstract

Background: We did a study with the aim to compare the changes in neurotransmitter values after halothane and isoflurane anesthesia in craniotomies.

Method: 40 patients, of either sex, ASA group I and II, 20-60 years age group were included with exclusion of patients with systemic diseases like uncontrolled DM, HT ^{n} , anaemia and respiratory, cardiac, renal or hepatic insufficiency and allocated to two groups of 20 each. Group I received halothane and group II isoflurance for maintenance. Before induction a CSF sample of 3-5ml was taken through lumbar puncture L_3-$_4$, L_4-$_5$, subarachnoid space. After induction 2 nd CSF sample taken from ventricular puncture 1 hour later and 3 rd sample taken after 3 hours or before skull closure. In all 3 samples, levels of neurotransmitters-glutamate, aspartate serotonin and GABA was measured.

Result: Glutamate and aspartate showed a decrease at 1 and 3 hour and GABA a neuroinhibitory transmitter showed an increase. However, serotonin a neuroexcitatory transmitter showed progressive increase.

Conclusion: Decrease in Glutamate at 1 hr was more with isoflurance but the value returned near normal (base line) after 3 hrs. The increase in GABA 1st and 3rd hr was more in halothane group. Regarding Aspartate and serotonin there was no significant difference between both the groups.

INTRODUCTION

Effect of volatile anaesthetic agents on neurotransmitters is a subject of recent focus. Various inhalational anaesthetics either increase or decrease neurotransmitter values in certain areas of brain.

Our plan was to systematically study the relationship, if any, between inhalational anaesthetic agents namely halothane and isoflurane, with neurotransmitter levels in the cerebro-spinal fluid (CSF) like serotonin, gamma amino-butyric acid (GABA), glutamate and aspartate in patients undergoing craniotomy.

Available literature does not reveal any substantive work having been done on human subjects and in particular with halothane and isoflurane anaesthesia in relation to neurotransmitter levels in the CSF.

Our aim was to understand the neurohormonal changes during inhalational anaesthesia. Such information is important for selecting optimal anaesthetic regimens for neurosurgical procedures in the already compromised brain.

MATERIAL AND METHODS

The present study was under taken to see changes in neurotransmitter values after halothane and isoflurane anaesthesia for craniotomy.

SELECTION OF PATIENTS

40 patients, ASA group I and II, of either sex, in the age group of 20 to 60 years presenting for craniotomy were included in the study. The patients with systemic diseases like uncontrolled diabetes mellitus, hypertension, anaemia and respiratory, cardiac, renal or hepatic insufficiency were excluded from the study.

The selected patients were randomly allocated into any one of the two treatment groups of 20 patients each.

- Group I: Patients maintained on halothane anaesthesia
- Group II: Patient maintained on isoflurane anaesthesia

STUDY PROCEDURE

All the patients taken into the study were premedicated with tab. Alprazoam 0.5 mg the evening before surgery and at 7 AM on the day of surgery. Just before induction of general anaesthesia, all patients in both the groups received the following drugs intravenously

- 0.5 mg/kg body weight of pentazocine repeated after 2 hours during the course of anaesthesia.
- 100 #181;g/kg body weight of ondansetron
- 0.05 mg/kg body weight of midazolam

In the operating room, before induction of general anaesthesia, a CSF sample of 3-5 ml was taken through lumbar puncture form L.3-L.4 or L.4-L.5 subarachnoid space. After removal of the CSF sample. The general anaesthesia was induced. Patients of group I were maintained on halothane and all from group II were maintained on isoflurane anaesthesia in nitrous oxide (N_2O) and oxygen (O_2).

One hour after induction of general anaesthesia, the 2 nd CSF sample was taken from a ventricular puncture and the 3 rd sample was taken after 3 hours or just before the skull closure which ever was earlier. In all three samples levels of neurotransmitters were measured.

STATISTICAL ANALYSIS

Test significance was calculated by using student 't' test as applicable to comparison between two groups. Critical value of 'p' indicating the probability of the significant difference was taken as 0.05 or less for all the comparisons.

RESULTS

The two study groups consisting of 20 patients each, were as follows:

- Group I Anaesthesia maintained on halothane and, N2O in O2
- Group II Anaesthesia maintained on isoflurane and N2O in O2

As shown in Table 1, the mean age of both the groups was identical (37.05 Vs 37.7 yrs). The duration of surgery in both the groups was also identical (2.45 Vs 2.50 hrs).

Figure 1

Table 1: Mean µ SE of Demographic characters and duration of surgery for two treatment groups.

Parameters	Group I	Group II	't'	'p'
Sample size	20	20		
Age (year)	37.05±1.06	37.7±1.10	0.56	>0.05
Duration of surgery (hours)	2.45±0.29	2.50±0.15	1.42	>0.05
M:F Ratio	16:4	1:9		

EXCITATORY NEURO TRANSMITTER LEVELS

Figure 2

Table 2: Glutamate Values

	Preoperative	1 hr	3 hr	Pre vs 1 hr	Pre vs 3 hr	1 hr vs 3 hr
Group I	2.659 ±0.007	1.798 ±0.007	2.117 ±0.124	341.056 <0.001	25.928 <0.001	22.12 <0.001
Group II	2.698 ±0.009	1.698 ±0.007	2.369 ±0.043	44.7 <0.001	68.928 <0.001	46.417 <0.001
t value	0.557	84.966	3.701			
P value	NS	<0.01	<0.01			

The change in mean concentration of glutamate at different time intervals in both the groups is shown in Table 2. We found that there is a significant decrease in the mean glutamate value after one hour from the baseline. The level showed a tendency to rise during the subsequent period but it still remained lower than the baseline value in the 3rd (last) sample taken at 3rd hour or at the end of surgery before closure of the cranium, if surgery finished earlier than three hours. Similarly the values seen during isoflurane anaesthesia were identical to group I patients but the decrease in glutamate mean concentration was more after isoflurane than after halothane anaesthesia.

Figure 3

Table 3: Serotonin Values

	Preoperative	1 hr	3 hr	Pre vs 1 hr	Pre vs 3 hr	1 hr vs 3 hr
Group I	0.642 ±0.009	0.855 ±0.002	1.075 ±0.0016	387.364 <0.001	18.332 <0.001	66.672 <0.001
Group II	0.640 ±0.004	1.502 ±0.007	0.857 ±0.005	441.289 <0.001	196.289 <0.001	368.03 <0.001
t value	0.12	365.135	59.6			
P value	NS	<0.001	<0.001			

As shown in Table 3 above, there is a marked increase in mean value of serotonin in group I and group II patients after one hour. The serotonin level continued rise with time in group I patients and there was a significant rise in its level in the 3rd sample as compared to the value at 1st hour. The findings in group II samples were little different from in group I. In group II the mean value in the 3rd sample showed a decrease as compared to the 1st hour value.

However the levels remained high when compared to the baseline value.

Figure 4

Table 4: Aspartate Values

	Preoperative	1 hr	3 hr	Pre vs 1 hr	Pre vs 3 hr	1 hr vs 3 hr
Group I	4.496 ±0.003	3.699 ±0.007	5.501 ±0.008	196.177 <0.001	142.452 <0.001	86.12 <0.001
Group II	4.499 ±0.009	3.696 ±0.009	5.470 ±0.111	253.26 <0.001	38.899 <0.001	70.60 <0.01
t value	0.49	0.32	1.204			
P value	NS	NS	NS			

As shown in Table 4 the mean level of aspartate in group I patients, showed a significant decrease after one hour. On the other hand, the values were seen to rise to a highly significant level at three hours which we find difficult to explain.

We also find that, the mean values at one and three hours in Group II patients is identical to Group I patients.

INHIBITORY NEUROTRANSMITTER

Figure 5

Table 5: GABA Values

	Preoperative	1 hr	3 hr	Pre vs 1 hr	Pre vs 3 hr	1 hr vs 3 hr
Group I	2.09 ±0.009	2.793 ±0.013	3.505 ±0.008	211.261 0.001	669.69 0.001	186.018 0.001
Group II	2.013 ±0.070	2.553 ±0.191	3.292 ±0.310	11.876 0.001	17.484 0.001	11.354 0.001
t value	0.189	5.586	3.069			
P value	NS	<0.001	<0.01			

Table 5 shows that in Group I samples there is significant increase in GABA level after one and three hours from the base line value. Similarly in group II, the trend is mostly similar to group I, except that the increase was more during halothane than isoflurane anaesthesia at the 3 rd hour interval.

DISCUSSION

We aimed at studying the changes in neurotransmitter values after halothane and isoflurance anaesthesia separately.

We studied four neurotransmitter out of which three are excitatory (Glutamate, Serotonine and Aspartate) and the fourth is inhibitory (GABA).

GLUTAMATE

Among all the excitatory neurotransmitters, glutamate is very important. We found a decrease in the mean glutamate concentration at 3 or nearly 3 hours from its base line values and the decrease is maximum at one hour from the induction of anaesthesia.

Possible explanation of a decrease in Glutamate level may be that the volatile anaesthetics cause an increase in the Glutamate uptake by astrocytes. (Miyazaki H, Nakamura Y.) $_{1}$ or due to a decrease in the pre synaptic release of glutamate by alteration in intra synaptic calcium ion (Nihg Miao, MJ Frazer) $_{2}$. In our study, we found that the inhibition of glutamate level is more with isoflurane than with halothane after one hour, this could be the reason for its better effect. The neurotransmitter values in 3 rd hour showed a near normal concentration. We do not have any reported evidence in support of this finding.

SEROTONIN

Is an important neurotransmitter involved in modulating central nervous system nociception and awareness. Based on the available literature we can say that the serotonin concentration should fall after halothane and isoflurane Anaesthetics (Martine DC, Wafkin CA et al) $_{3}$. According to these studies even though the serotonin uptake is inhibited in synaptosome after volatile anaesthesia, the “overall serotonin level is decreased due to an increase in its metabolism. Thus a decrease in serotonin level (an excitatory substance) may explain the ultimate cerebral effect of inhalational anaesthesia.

Similarly according to Martine DC, Adam RJ, et al $_{4}$ the exposure to clinically relevant concentrations of isoflurane results in a rapid, concentration dependent and reversible inhibition of serotonin. But our findings do not tally with literature findings as we found an increase in mean concentration of serotonin after one hour and also at three hour from its base line value. However this finding is similar to report by “Roizen MF, Kopin IJ, et al $_{5}$ who have found that serotonin concentration can increase in specific brain regions after volatile anesthetics. An other possible explanation for this 5 HT increase can be due to release of certain local neuro chemical modulators like serotonin, histamine and prostaglandin after brain injury and brain edema (Sharma HS, Westman J et al) $_{6}$ and (Sharma HS, Westman J, Nyberg F et al.) $_{7}$ In addition, as we explained above the lumbar CSF sample may not represent the basal cerebral CSF neurotransmitter values.

The brain injury can be hypoxic, ischemic or like in our case, handling and cauterization causing direct injury, leading to release of the foresaid modulators.

ASPARTATE

Like other excitatory neurotransmitters this also showed a decrease in its mean concentration value at one hour from

pre induction or base line value in both the groups and the decrease was almost identical in both the groups. After 3 hours the mean concentration value showed an increase over 1 hour values as well as the base line value. The possible explanation of this significant increase during 3 rd hour can be related to Arai T, Hatano Y et al $_{8}$ findings. The authors reported a significant. Aspartate efflux with high halothane concentration but not with low concentration.

GABA

This is an important inhibitory neurotransmitter of synaptic transmission. In our study, we found a significant increase in the mean concentration of GABA at 1 hr and later 3rd or near 3rd hr from the induction of anaesthesia. The possible explanation of this increase is the dose dependent inhibition of catabolism of GABA by volatile anaesthetic at synaptosomes. As postulated by Cheng and Brunner $_{9}$, the volatile anaesthetics do not affect the uptake or release of GABA at synapse.

As we are aware that the GABA is an inhibitory neurotransmitter, such increase in its mean concentration value may be due to a reduction in synaptic activity. Other factors that might have increased the GABA level may be attributed to midazolam which we used in all the patient as pre medication. Midazolam itself causes an increase in GABA levels by inhibiting the uptake of GABA by the synapses (Cheng SC, Brunner) $_{10}$. We also found that the increase was more with halothane than after isoflurane and it remained high after the 3 hour interval.

References

1. Miyazaki H, Nakamura Y, Arai T, Kataoka K. Increase of glutamate uptake in astrocytes: a possible mechanism of action of volatile anaesthetics. Anesthesiology 1997; 86(6): 1359-66.
2. Miao N, Frazer MJ, Lynch C. Volatile anesthetics depress Ca++ transients glutamate release in isolated cerebral synaptosomes. Anesthesiology 1995; 83(3): 593-603.
3. Martin DC, Watkins CA, Adams RJ, Nason LA. Anesthetic effects on 5-hydroxytryptamine uptake by rat brain synaptosomes. Brain Res 1988; 12: 455 (2): 360-5.
4. Martin DC, Adams RJ, Aronstam RS. Effects of enflurane on 5-hydroxytryptamine transport in synaptosomes from rat brain. Biochem Pharmacol 1990; 15: 40(2): 187-92.
5. Roizen MF, Kopin IJ, Palkovits M et al: The effect of two diverse inhalation anesthetic agents on serotonin in discrete regions of the rat brain. Exp Brain Res 1975; 14:203.
6. Sharma HS, Westman J, Cervos Navarro J, Nyberg F. Role of neurochemicals in brain edema and cell changes following hyperthermic brain injury in the rat. Acta Neuro Chir Suppl (wein) 1997; 70: 269-74.
7. Sharma HS, Esman J, Acta Neuro Chir Suppl (wein) 1997; 70: 269-74.
8. Sharma HS, Esman J, g F, Cervos Navarro J, Dey PK. Role of serotonin and prostaglandins in brain edema induced by heat stress. An experimental study in the study in the young rat. Acta Neurochir supp (Wein) 1994; 60: 65-70.
9. Cheng SC, Bruner EA. Inhibition of GABA metabolism in rat brain slices by halothane. Anesthesiology 1981; 55(1): 26.
10. Cheng SC, Brunner EA. Inhibition of GABA metabolism in rat brain synaptosomes by midazolam (RO-21-3981). Anesthesiology 1981; 55(1): 41-5.

Author Information

A. Tiwari, M.D.
Senior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University

L. D. Mishra, Ph.D.
Reader, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University

R. K. Agrawal, M.D.
Junior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University

Priyanka, M.D.
Junior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University

A. P. Singh, M.D.
Senior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University