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Metabolic Disorders in Delirious Syndrome in Patients with Acute Poisoning with Gamma-Hydroxybutyric Acid and its Precursor

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ABSTRACT In 21 male patients aged 20 to 40 years, metabolic disorders in post-toxic delirious syndrome caused by gamma-hydroxybutyric acid poisoning and its precursors were studied. In the examined group of patients, hyperammonemia was detected in 71.4% of cases, metabolic lactic acidosis was revealed in 76.2%. The direct correlation between the severity of metabolic disorders and delirious syndrome according to DRS-R-98 scale was established. The statistically significant increase in capillary blood levels of lactate on day 3 of psychotic period was 4.9 mlmol/L and ammonia on day 5 was 187.0 mmol/L. The greatest severity of metabolic disorders was found in patients over the age of 27 years who systematically use the studied substances with narcotic effects for 7 months or more and combine their intake with other psychoactive substances.

Keywords: metabolic disorders, acute poisoning, gamma-hydroxybutyric acid, gamma-butyrolactone, hyperammonemia, metabolic lactic acidosis

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GBL – gamma-butyrolactone
GHB – gamma-hydroxybutyric acid
PAS – psychoactive substances
RICU – Resuscitation and Intensive Care Unit
THC – tetrahydrocannabinol

It is known that over the past decade in a number of European countries, Australia and the USA, in the Netherlands and since 2015 in a number of regions of the Russian Federation, an increase in the number of poisonings and mental disorders has been observed due to the systematic use of gamma-hydroxybutyric acid (GHB) and its precursor (gamma-butyrolactone (GBL) [1, 2]. Gamma hydroxybutyric acid and its precursors are popular drugs among young people for their euphoric, relaxing and sexual arousal effects. Also of great importance are their free availability and the possibility of their preparation at home and the absence of a withdrawal syndrome after single episodes of use [3]. In turn, the systematic use of these psychoactive substances (PAS) leads to severe withdrawal symptoms up to death [4]. According to foreign and domestic authors, delirious syndrome among those hospitalized in toxicological and narcological departments with GHB and GBL poisoning is diagnosed in 2.8–20% of cases, is characterized by a protracted course (up to 9 days) and severe somato-neurological and mental disorders that do not respond to correction with high doses of benzodiazepines [5, 6]. It is known that one of the main pathological processes that determine the severity of the condition of patients with delirious disturbance of consciousness with the systematic use of psychoactive substances is hypoxia, which leads to metabolic disorders. However, in the available literary sources there is no information about metabolic disorders in acute poisoning with GHB and GBL complicated by delirious syndrome. The question of the role of ammonia in the pathogenesis of delirious syndrome remains unexplored. The aim of the study was to study the severity of metabolic disorders in acute poisoning with GHB and its precursor (GBL), complicated by delirious syndrome.

MATERIAL AND METHODS

We examined 21 male patients aged 20 to 40 years (29.2 ± 4.47) with poisoning with GHB and its percursor, who were treated in the resuscitation and intensive care unit (RICU) of the acute poisoning center of a multidisciplinary hospital. The inclusion criteria for the study were: the presence of post-intoxication delirious syndrome with the severity of symptoms on the DRS-R-98 scale (Trzepacz et al., 1988) 18 points or more, the presence of GHB in biological media according to gas chromatography with mass spectrometric detection GCMS-QP2010 SE (Shimadzu, Japan) and the severity of the condition on the Acute Physiology And Chronic Health Evaluation II (APACHE II) scale (Knaus WA, 1985) not higher than 7 points. The diagnosis of delirious

syndrome was established in accordance with the criteria of the 10th revision of the International Classification of Diseases. The exclusion criteria were poisoning with other psychoactive substances, depression of consciousness and the severity of the condition on the APACHE II scale more than 7 points.

Control examinations of patients were carried out from the 1st day of treatment, then on the 3rd, 5th, 7th, 9th and 11th days.

Laboratory diagnostics included the assessment of metabolic disorders and lactate accumulation in the blood as an indicator of the severity of tissue hypoxia and ammonia as a marker of endotoxemia. The material for the study was capillary blood. The measurement of the level of ammonia in the blood was carried out using a portable PocketChem BA PA-4140 device (Arkray, Japan). The device is based on microdiffusion. The method for measuring the change in color of the test strip is photometric. The analyzer was automatically calibrated. The lactate content was determined by reflection photometry using test strips (BM-lactat) and a portable biochemical analyzer Accutrend Plus (Roche Diagnostics, Germany). The DRS-R-98 psychometric scale was used to assess the severity of delirious syndrome. Withdrawal symptoms were assessed with CIWA-Ar scale (Sullivan J.T., 1989). The assessment of the severity of liver failure was carried out in accordance with the classification of L.B. Kantsilev (1984). The results were statistically processed using the Statistic for Windows software (version 10). Calculated statistics (M ± SD, min-max, Me [Q25; Q75]). To study the dynamics of changes in the parameters within the groups (comparison of the median values of the parameters at different points in time within the same group), a nonparametric method was used - the Wilcoxon test; for intergroup comparisons of the median values of the parameters, a nonparametric test - the Mann – Whitney U test was used. Differences between the studied characteristics were considered significant if p was 95% or more ($p < 0.05$).

RESULTS AND DISCUSSION

The analysis of sociodemographic characteristics of patients showed the predominance in the group of patients with delirium (n = 21) of persons aged 27 to 31 years, who accounted for 76.1% (n = 16) of the total number of patients (Table 1).

Table 1

Sociodemographic characteristics of patients with delirium on the background of the systematic use of GHB and its precursor

No.	Parameters	Indicators (*n*=21)
1	Age (Year) *Me* (*Q*25; *Q*75)	29.0 (27 ; 31)
2	Duration of GHB consumption (months) *Me* (*Q*25; *Q*75)	7.0 (4; 8)
3	Daily dose of GHB (ml) *Me* (*Q*25; *Q*75)	60.0 (40; 80)
4	Concomitant disorders associated with the use of PAS, abs. (%):	
	Occasional drinking	3 (18.8%)
	Occasional amphetamine use	9 (56.2%)
	Occasional use of THC	4 (25.0%)
	Combined dependence on several PADs	7 (43.7%)
	Total	16 (76.1 %)
5	Abstinence with delirium in history, abs. (%)	2 (9.5 %)
6	Treatment in drug treatment centers and toxicology due to GHB poisoning, abs. (%)	7 (33.3%)

Notes: GHB — gamma-hydroxybutyric acid; PAS — psychoactive substances; THC — tetrahydrocannabinol

During the collection of the anamnesis, it was found that patients used GBL more often in order to achieve a euphoric effect and sexual arousal in a daily dosage of 40 to 80 ml, an average of 61.4 ± 16.1 ml. The duration of use in 75% of cases was 7 months, on average 6.47 ± 2.1 months. Most of the patients (16, or 76.1%) had concomitant dependence on the use of other substabces: ethanol - in 3 (18.8%); amphetamines - in 9 (56.2%); tetrahydrocannabinol - in 4 (25.0%). Dependence on several surfactants was diagnosed in 7 cases (43.7%). Most of the patients have not previously received treatment in specialized institutions. In 2 cases (9.5%), a delirious episode was observed in the anamnesis.

All patients were taken by the ambulance team to the toxicology RICU. Most of the patients were transported from the street - 12 (57.1%); the others - from the place of residence - 9 (42.9%). At the time of admission to the hospital in most of the patients, acute intoxication was manifested by psychomotor retardation with stunning consciousness - 14 (66.4%). Seven patients (33.3%) were hospitalized with signs of psychomotor agitation against the background of confusion.

The first stage of delirious syndrome was diagnosed within 6–8 hours after the reduction of the toxicogenic stage of poisoning in 18 cases (85.7%), on average after 7.1 ± 1.1 hours. The main symptoms were somato-neurological disorders and affective instability. The total duration of this period averaged 3.5 ± 1.1 hours.

The second and third stages of delirious disturbance of consciousness were distinguished by an atypical clinical picture due to the prevalence of scene-like visual illusions of perception in the structure of delirium, verbal hallucinosis against the background of a constant affect of fear, disorientation in space and time, and significant somatoneurological disorders in the absence of delusion. The total duration of the main symptoms of delirious syndrome in 75% of cases was 9 days, on average 7.57 ± 0.48 days. The most significant signs of delirious syndrome according to the DRS-R-98 scale were diagnosed on the 3rd and 5th days of the examination, from the 7th to the 11th days there was a gradual reduction in psychopathological symptoms (figure).

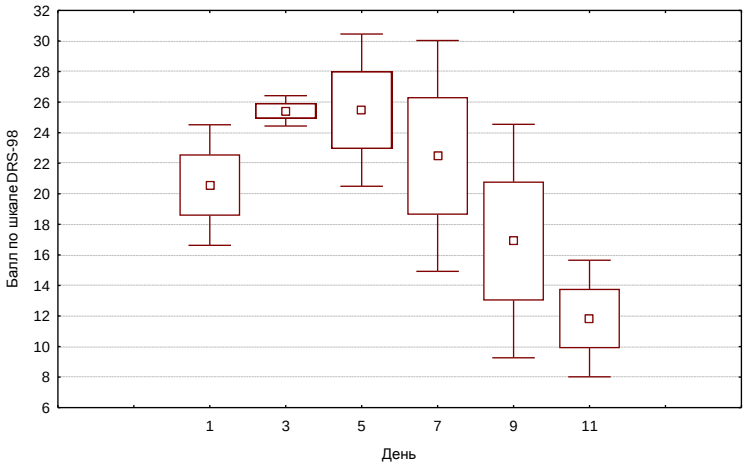

Fig. The dynamics of the delirious syndrome severity in patients with GBH and its precursors poisonings (Me ± SD)

In the examined group of patients, hyperammonemia was detected in 15 cases (71.4%), starting from the first day of the examination (Table 2). As can be seen from the Table 2, on the first day after GBL poisoning in capillary blood in patients in a greater percentage of cases, the concentration of ammonia was 115.0 mcmol / L, which was 2.3 times higher than the reference values. The peak concentration of ammonia was observed in the active phase of the psychotic period - by the 3rd day the indicator increased to 175.0 mcmol / L, and by the 5th - to 187.0 mcmol / L (3.5 and 3.7 times higher than normal). In this time period, the maximum severity of delirium symptoms was observed on the DRS-98-R scale: on the 3rd day - 25.7 ± 0.57, and on the 5th - 26.0 ± 4.02 points. Subsequently, on the 7th and 9th days of observation, a gradual decrease in the concentration of ammonia was diagnosed - from 141.0 to 44.0 mcmol / L and to 15.0 mcmol / L by the 11th day.

Table 2

The dynamics of ammonia concentration in the capillary blood of patients with delirium syndrome in acute poisoning with GBH and its precursor

Ammonia content, mmol/L	*N*	*Me*	*Q* 25; *Q* 75	*Min*	*Max*	*M* ± *SD*	*p*
Day 1	21	87.0	65.0 ; 115.0	12.0	154.0	84.3 ± 42.3	-
Day 3	21	126.0	72.0 ; 175.0	11.0	210.0	119.1 ± 64.0	0.044
Day 5	21	175.0	81.0 ; 187.0	5,0	220.0	134.5 ± 77.4	0.012
Day 7	18	99.0	71.0 ; 141.0	5,0	189.0	99.3 ± 54.6	0.309
Day 9	16	41.5	39.5 ; 44.0	11.0	45.0	38.5 ± 9.1	0.016
Day 11	14	11.5	10.0 ; 15.0	9.0	24.0	13.8 ± 4.3	0.000
Ammonia content, mmol / L	*N*	*Me*	*Q* 25; *Q* 75	*Min*	*Max*	*M* ± *SD*	*p*
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Day 5	21	175.0	81.0; 187.0	5.0	220.0	134.5 ± 77.4	0.012
Day 7	18	99.0	71.0; 141.0	5.0	189.0	99.3 ± 54.6	0. 309
Day 9	16	41.5	39.5; 44.0	11.0	45.0	38.5 ± 9.1	0.016
Day 1 1	14	11.5	10.0; 15.0	9.0	24.0	13.8 ± 4.3	0. 000

Note: *p* - values reflect intragroup differences with indices of the 1st day of study

The intensity of ammonia toxicity correlated with the severity of delirious syndrome (Table 3).

Table 3

The dependence of the delirious severity on the concentration of lactate and ammonia in the capillary blood of patients with poisonings with GBH and its precursor

Indicators		The severity of delirium, *DRS*-98-*R* scale					
		Day					
		1	3	5	7	9	11
Lactate	*R*	0.41	0.40	0.7	0.42	0.53	0.46
	p	0.61	0.05	0.00	0.05	0.04	0.05
Ammonia	*R*	0.32	0.47	0.61	0.62	0.54	0.48
	p	0.145	0.025	0.00	0.00	0.02	0.05

Note: *R* is the absolute value of the correlation coefficient; *p* is the level of statistical significance; gray color indicates the statistically significant correlation ($p \leq 0.05$)

As follows from the Table 3, in the period from 3 to 11 days, there was a statistically significant relation between these disorders and the severity of psychotic symptoms. Thus, it can be seen that hyperammonemia serves as a marker of the progressive course of delirious syndrome. In our opinion, this is due to a decrease in the activity of enzyme systems involved in the formation of urea in the citrulline-arginine-ornithine cycle and the direct effect of ammonia on the functions of the central nervous system, which is consistent with the data of other authors [9]. In patients with hyperammonemia, no significant signs of liver failure and statistically significant changes in the activity of cytolytic enzymes were observed. Hepatic failure was only mild, mainly due to an increase in the level of lactate in capillary blood, indicating metabolic acidosis due to tissue hypoxia. In turn, metabolic lactic acidosis was diagnosed in 16 cases (76.2%) (Table 4).

Table 4

The dynamics of lactate concentration in the capillary blood of patients with delirium syndrome in acute poisoning with GBH and its precursors

The content of lactate, mmol/L	*N*	*Me*	*Q* 25; *Q* 75	*Min*	*Max*	*M* ± *SD*	*p*
Day 1	21	3.5	2.4; 3.9	0.4	4.5	3.04 ± 1.27	-
Day 3	21	4.2	3.7; 4.9	1.1	5.7	4.28 ± 1.0	0.000
Day 5	21	3.4	3.2; 3.7	2.7	4.2	3.44 ± 0.4	0.078
Day 7	18	2.1	1.1; 2.4	0.9	3.1	1.90 ± 0.71	0.000
Day 9	16	1.4	1.05; 1.6	0.7	1.9	1.34 ± 0.33	0.000
Day 11	14	1.1	0.9; 1.2	0.4	1.2	0.95 ± 0.30	0.000

Note: *p* - values reflect intragroup differences with indices of the 1 st day of study

As you can be see from the Table 4, the maximum concentration of lactate in capillary blood was observed on the 1st-3rd day of the delirious syndrome (3.9 mmol / L and 4.9 mmol / L, respectively) against the background of its progressive course (r1 = 0.41, r3 = 0.40). A gradual decrease in the blood level of the studied indicator occurred in direct connection with a decrease in the severity of delirium starting from the 5th day - from 3.7 to 2.4 mmol / l on the 7th day, to 1.6 mmol / l on the 9th day. day and with a minimum value on the 11th day of the study (1.2 mmol / l).

CONCLUSION

The data obtained during the study indicate metabolic disorders that determine the severity of the delirious syndrome. The direct influence of hyperammonemia, metabolic lactic acidosis on the severity of clinical symptoms of delirium has been proven. Additional factors contributing to the development of delirious syndrome were the systematic use of gamma-butyrolactone for 6.47 ± 2.1 months and the combined use of gamma-butyrolactone and other psychoactive substances.

CONCLUSIONS

1. The effect of hyperammonemia and metabolic lactic acidosis on the clinical severity of intoxication psychosis with delirious disturbance of consciousness was confirmed with the systematic use of gamma-hydroxybutyric acid and its precursor (gamma-butyrolactone).

2. Metabolic lactic acidosis and hyperammonemia are predictors of the progressive course of post-intoxication delirious syndrome in case of poisoning with gamma-hydroxybutyric acid and its precursor (gamma-butyrolactone).

REFERENCES

1. Neu P. Course and complications of GHB detoxification treatment: a 1-year case series. *Nervenarzt*. 2019;90(5):509–515. PMID: 30362026 https://doi.org/10.1007/s00115-018-0636-8.
2. Sabaev AV. Gospitalizirovannaya zabolevaemost' naseleniya goroda Omska v rezul'tate ostrykh otravleniy khimicheskoy etiologii za 2001–2013 gg. *Eurasian Union of Scientists*. 2014;8(6):92–95. (In Russ.)
3. Brunt TM, Koeter MW, Hertoghs N, van Noorden MS, van den Brink W. Sociodemographic and substance use characteristics of γ-hydroxybutyrate (GHB) dependent inpatients and associations with dependence severity. *Drug Alcohol Depend*. 2013;131(3):316–319. PMID: 23332440 https://doi.org/10.1016/j.drugalcdep.2012.12.023.
4. Beurmanjer H, Kamal RM, de Jong CAJ, Dijkstra BAG, Schellekens AFA. Baclofen to Prevent Relapse in Gamma-Hydroxybutyrate (GHB)-Dependent Patients: A Multicentre, Open-Label, Non-Randomized, Controlled Trial. *CNS Drugs*. 2018;32(5):437–442. PMID: 29651711 https://doi.org/ 10.1007/s40263-018-0516-6.
5. Dijkstra BA, Kamal R, van Noorden MS ,de Haan H, Loonen AJ, De Jong CA. Detoxification with titration and tapering in gamma-hydroxybutyrate (GHB) dependent patients: The Dutch GHB monitor project. *Drug Alcohol Depend*. 2017;170:164–173. PMID: 27923198. https://doi.org/10.1016/j.drugalcdep.2016.11.014.
6. Sofronov AG, Lodyagin AN, Prokopovich GA. Potrebiteli GOMK i ego prekursorov: klinicheskaya kartina otravleniy i sindrom otmeny. *Ekstrennaya Meditsina*. 2017;6(3):340–341. (In Russ.)
7. Kamal RM, van Iwaarden S, Dijkstra BA, de Jong CA. Decision rules for GHB (γ-hydroxybutyric acid) detoxification: a vignette study. *Drug Alcohol Depend*. 2014;135:146–151. PMID: 24380737 https://doi.org/10.1016/j.drugalcdep.2013.12.003.
8. McDonough M, Kennedy N, Glasper A, Bearn J.Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. (2004). Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug and Alcohol Depend*. 2004;75(1):3–9. PMID: 29933901 https://doi.org/10.1016/j.drugalcdep.2004.01.012
9. Alekseenko SA, Ageeva EA, Polkovnikova OP. Modern approaches to diagnostics and treatment of hyperammonemia in patients with chronic liver disease at a precirrhotic stage. RMJ. *Medical Review*. 2018;7(I):19–23. (In Russ.)

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