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Delirium in Acute Poisoning with 1,4-Butandiol and Its Correction

Andrey G. Sinenchenko[1]*, Chamit B. Batotsyrenov[2], Alexey N. Lodyagin[1],
Georgy I. Sinenchenko[3], Alexey L. Kovalenko[4]

[1] I. I. Dzhanelidze Saint-Petersburg Research Institute of Emergency Medicine,
3 Budapeshtskaya Str., 192242 Saint-Petersburg, Russia
[2] Academician Pavlov First Saint-Petersburg State Medical University, Ministry of Health of Russia,
6–8 Lev Tolstoy Str., 197022 Str. Petersburg, Russia
[3] Kirov Military Medical Academy,
6 Academician Lebedev Str., 194044 St. Petersburg, Russia
[4] Institute of Toxicology, Federal Medico-Biological Agency of Russia,
1 Bechtereva Str., 192242 Saint-Petersburg, Russia

Делирий при острых отравлениях 1,4-бутандиолом и его коррекция

А. Г. Синенченко[1]*, Ч. Б. Батоцыренов[2], А. Н. Лодягин[1],
Г. И. Синенченко[3], А. Л. Коваленко[4]

[1] НИИ скорой помощи им. И. И. Джанелидзе,
Россия, 192242, г. Санкт-Петербург, ул. Будапештская, д. 3
[2] Первый Санкт-Петербургский государственный медицинский университет им. акад. И. П. Павлова Минздрава России,
Россия, 197022, г. Санкт-Петербург, ул. Льва Толстого, д. 6–8
[3] Военно-медицинская академия им. С. М. Кирова,
Россия, 194044, г. Санкт-Петербург, ул. Академика Лебедева, д. 6
[4] Институт токсикологии Федерального медико-биологического агентства России,
Россия, 192019, г. Санкт-Петербург, ул. Бехтерева, д. 1.

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Summary

Delirium complicating regular use of psychoactive substances remains one of the major issues of critical care, toxicology, and psychiatry. However, the pathogenetic mechanisms of delirium development in patients with 1,4-butanediol poisoning have been poorly studied until now.

The aim of the study was to reveal specific patterns of delirium in patients with 1,4-butanediol poisoning as well as to study the changes in systemic hemodynamic parameters, respiratory function, and body fluid compartments during the treatment.

Material and methods. The study was prospective and treatment-randomized. Forty-eight male patients aged 20 to 45 years with delirium and acute 1,4-butanediol poisoning were enrolled. Of them, 24 patients were administered with succinate-containing drug 40 ml daily, 24 patients received standard treatment without antihypoxic agents. We studied the evolution of delirium, changes in anaerobic metabolism parameters, systemic hemodynamics, respiratory function, and the volume of fluid compartments. Impedance measurement method adjusted for interference was used in the study.

Results. At the «peak» of delirium (days 1–3), the hyperdynamic circulation, increased systemic arterial tone, stroke output, respiratory function parameters, and metabolic lactate acidosis were recorded. A decrease in total fluid volume and extracellular fluid volume was clearly observed during day 1 of intoxication delirium along with increased permeability of cell membranes. On day 3 of delirium, a decrease in intracellular fluid volume and increase in extracellular fluid volume were noted. After the cytoflavin administration, shorter delirium duration (7.5 [6; 8] days), more rapid correction of lactate acidosis, stabilization of respiratory parameters and stabilization of cell membrane permeability by day 5 were found. In the control group, delirium persisted for up to 14 [11; 15] days (z=-5.9; P=0.00011) with more frequent development of complications such as nosocomial pneumonia (χ^2=8.4, P<0.001).

Conclusion. The severity of delirium in acute poisoning with 1,4-butanediol was associated with metabolic lactate acidosis, changes in systemic hemodynamics and pulmonary function. A positive effect of adjunctive antihypoxic therapy with succinate-containing agent on cardio-respiratory parameters, cell membrane permeability, water balance due to elimination of tissue hypoxia and prompt switching to tissue aerobic metabolism has been found.

Correspondence to:

*Andrey G. Sinenchenko
E-mail: andreysin2013@yandex.ru

Адрес для корреспонденции:

*Андрей Георгиевич Синенченко
E-mail: andreysin2013@yandex.ru

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Introduction

Intoxication delirium is a severe complication of regular use of psychoactive substances and one of the main factors of mortality, which makes our research especially relevant [1–6].

The studies have shown that intoxication delirium is primarily caused by neurotransmitter dysfunction, as indicated by the correlation between high blood dopamine levels and delirium severity [7–9]. In turn, researchers associate an excessive neurotransmitter release with tissue hypoxia, which determines the severity of the medical condition [10, 11]. Despite the popularity of the neurotransmitter theory among most authors, there is no complete understanding of the mechanisms of delirium development [12].

Currently, special emphasis in the study of intoxication delirium is placed on patients with chronic alcoholism, as evidenced by the literature data [13–16].

The current reality, witnessing the appearance of new substances with narcotic effects and their precursors on the «illegal market», naturally indicates an increase in acute poisonings with these substances [17–19]. At present, poisonings with precursors of gamma-hydroxybutyric acid (GHBA) (1,4-butanediol (1,4-BD), gamma-butyrolactone), available for purchase via Internet, prevail in metropolitan areas [20, 21].

1,4-BD is an industrial alcohol [22]. Systematic use of 1,4-BD leads to a wide range of psychiatric and medical disorders resistant to standard therapy and psychotropic drugs [23–25].

In our opinion, to develop the effective treatment methods for patients with 1,4-BD poisoning complicated by delirium, changes in systemic hemodynamics, respiratory function, and fluid compartments should be considered. Bioimpedance measurement test based on the assessment of electrical conductivity of various body tissues and blood flow impedance remains the most accessible and proven method of their diagnosis [26, 27]. However, there are no data on the use of this diagnostic method in patients with 1,4-BD poisoning complicated by delirium receiving standard therapy, which highlights the novelty of our study.

The aim of the study was to reveal the specific clinical patterns of delirium in patients with 1,4-butanediol poisoning as well as to assess the changes in systemic hemodynamic parameters, respiratory function, body fluid compartments during the therapy.

Material and Methods

A prospective (treatment-randomized) study was performed. The study included male intensive care unit (ICU) patients aged 20 to 45 years (main group) (n=48) with acute 1,4-BD poisoning complicated by delirium.

Patients of the main group were further divided into two groups based on a treatment strategy. Group 1 (n=24) included patients whose intensive therapy included cytoflavin (OOO NTFF POLYSAN, St. Petersburg) 20 ml twice a day in 10% glucose solution, intravenously administered with 10-hours interval between injections. Group 2 (n=24) included patients whose standard treatment regimen did not contain cytoflavin or other antihypoxic agents. The median ages of the group 1 and group 2 patients were similar (29.5 [26; 35] years and 31.5 [26; 37] years, respectively).

The patients were studied days 1, 3, 5, and 7 after delirium diagnosis, all investigations were made in the morning time. The instrumental methods included GHBA measurement in biological fluids using gas chromatography on GCMS-QP2010 SE mass spectrometric detector (Shimadzu, Japan); systemic hemodynamic parameters assessment using stroke and cardiac indices (SI and CI), reserve ratio (RR) based on stroke volume of blood, systemic arterial tone (SAT) index, respiratory effort index (REI), severity index based on cell membrane permeability (SICMP) measured by integral thoracic rheography method by Tishchenko (1973) and Sramek (1994); electrical equivalents of the total (TFV), extracellular (EFV) and intracellular (IFV) fluid volumes by integral dual frequency impedance measurement method using the computerized hardware and software complex «Diamant-v.11.06.2018» (Diamant CJSC, St. Petersburg, Russia). The severity index was calculated based on reference impedance values at the applied frequencies as a percentage ratio of impedance at 28 KHz/115 KHz (with its values of 83.3% and less considered as high, and that of 88.3% and higher taken as low). The following types of circulation were identified based on RR: normodynamic (90 to 110%), hyperdynamic (>110%) and hypodynamic (<90%).

Laboratory tests included arterial blood gas and acid-base evaluation using COBAS B221 analyzer (Roche, Germany), lactate concentration in

capillary blood using Accutrend Plus portable biochemical analyzer (Roche Diagnostics, Germany).

The level of consciousness was assessed by the Glasgow Coma Scale (Teasdale G. M., Jennett B. J., 1974), the severity of delirium using the DRS-R-98 psychometric scale (Trzepacz et al., 1988). The diagnosis of delirium was made in accordance with the ICD-10 (WHO, 1992).

The study was approved by the local Ethical Committee of the institute (protocol No.1 from 07.02.2020).

Statistical analysis. Statistical analysis of the data was performed using Statistica for Windows (version 10) software. The data were presented as medians (*Me*) and 25–75 percentiles [Q25; Q75]. To study the parameter changes within groups we used the nonparametric Wilcoxon criterion, to make intergroup comparisons we used nonparametric Mann–Whitney *U*-criterion. Differences between the studied parameters were considered significant at $P<0.05$. Nonparametric correlation analysis (ρ-Spearman) was used to compare quantitative parameters. Qualitative variables were compared using Pearson Chi-square test (χ^2) with adjustment for continuity. Odds ratio (OR) with upper and lower 95% confidence intervals (95%CI) were calculated to assess the association between specific outcomes and risk factors.

Results and Discussion

The severity of patients with acute 1,4-BD poisoning on admission was caused by toxic encephalopathy with depressed consciousness down to coma I level (7.7±0.48 points on Glasgow scale).

Delirium was diagnosed 8 [6,3; 9,8] hours after admission.

Tables 1, 2, and 3 show intra- and intergroup comparisons of the main studied laboratory and instrumental parameters.

On day 1, the severity of patients was due to metabolic lactate acidosis, hyperdynamic circulation, increase in CI up to 4.5 in group 1 and to 4.3 l/min×m² in group 2, SI up to 50.6 in group 1 and to 49.8 ml/m² in group 2, SAT up to 82.9 and 82.6 units in groups 1 and 2, respectively, and REI up to 44.2 and 43.5 units in groups 1 and 2, respectively (Table 1). Clinical manifestations of acute delirium included allopsychic disorientation, confusion, restlessness, and intense anxiety with «horror» expression on the face. Hallucinations during the advanced psychotic period were characterized by «frightening images» of a «scene-like, violent nature». Anthropomorphic «teasing» visual true hallucinations predominated, «beckoning» or «closely approaching» the patient. The patients made repeated attempts to «shout out» the imaginary «interlocutors», made defensive actions, trying to shield themselves with their arms, or «to drive them away».

On days 1–3 changes in the fluid compartments were recorded. Extracellular dehydration dominated in both groups on day 1 (decrease of EFV by 3.8 and by 3.7% in groups 1 and 2, respectively), along with the loss of TFV up to 4.9 and 4.6% (Table 2), respectively, plasma low osmolarity, low blood electrolyte level, and relative intracellular hyperhydration. However, clinically, dry skin, especially in axillary and inguinal areas, dry tongue, tachycardia up to 115.6 [105.3; 119.9] per minute,

Table 1. Effect of treatment on systemic hemodynamics and respiratory function in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
SI, ml/m²	I	50.6 [43.1; 51.6]	53.7 [45.5; 57.5] P=0.02*	44.8 [33.7; 47.1] P=0.001*; P=0.02#	40.7 [38.1; 49.2] P=0.001*; P=0.03#
	II	49.8 [43.3; 54.1]	56.9 [46.2; 51.3] P=0.001*	50.3 [42.6; 51.1] p=0.03*	44.4 [40.8; 50.1] P=0.001*
CI, l/min×m²	I	4.5 [2.9; 6.1]	4.8 [2.5; 6.5]	3.9 [2.4; 4.3] P=0.02*; P=0.03#	3.4 [3.2; 3.9] P=0.02*
	II	4.3 [3.2; 5.6]	4.5 [3.2; 5.4]	4.2 [2.3; 5.1]	3.6 [3.7; 4.1] P=0.03*
RR, %	I	119.1 [101.1; 123.1]	124.1 [117.5; 134.1] P=0.04*	105.6 [97.9; 106.3] P=0.03*; P=0.001#	109.2 [98.2; 104.4] P=0.03*
	II	116.7 [111.1; 121.1]	129.4 [108.1; 136.7] P=0.04*	112.3 [95.4; 116.6]	110.7 [104.5; 117.7] P=0.04*
SAT, units	I	82.9 [76.2; 83.3]	80.7 [80.2; 80.8] P=0.04*; P=0.03#	75.6 [74.1; 78.4] P=0.01*; P=0.001#	77.7 [76.1; 75.3] P=0.02*; P=0.04#
	II	82.6 [74.2; 83.2]	83.4 [82.1.4; 84.6] P=0.04*	81.8 [76.1; 82.7]	79.5 [76.6; 80.4] P=0.02*
REI, units	I	44.2 [27.5; 54.8]	54.5 [29.7; 51.1] P=0.001*; P=0.04#	28.8 [21.4; 29.6] P=1.4×10⁻⁴*; P=0.04#	24.3* [24.1; 25.9] P=1.2×10⁻⁴*; P=0.03#
	II	43.5 [24.6; 53.9]	56.7 [34.6; 64.6] P=0.002*	30.8 [24.6; 31.9] P=1.4×10⁻⁴*	30.6 [24.1; 31.5] P=1.4×10⁻⁴*

Note. SI — stroke index; CI — cardiac index; RR — reserve ratio; SAT — systemic arterial tone; REI — respiratory effort index; P* — significant intragroup differences; P# — significant differences between groups 1 and 2.

Table 2. Effect of treatment on water and electrolyte balance in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
IFV, %	I	+2.1 [+1.1; +2.7]	–3.3 [–2.3; –3.9]	+1.1 [–0.7; +1.9]	+0.8 [+0.1; +2.2]
	II	+2.7 [+1.7; +2.9]	–3.5 [–2.2; –4.1]	–3.9 [–2.3; –4.5]	+ 0.2 [–0.8; +2.6]
EFV, %	I	–3.8 [–0.8; –4.9]	+3.9 [+4.8; +3.2]	+1.5 [+1.5; +1.8]	+1.3 [+0.8; +1.7]
	II	–3.7 [–1.1; –4.5]	+4.1 [+4.5; +3.8]	+0.2 [–5.1; +3.4]	+1.1 [+1.3; +1.7]
TFV, %	I	– 4.9 [–2.2; –5.1]	–2.7 [–2.1; –3.9]	+1.2 [+1.1; +2.1]	+2.6 [+1.3; +3.1]
	II	–4.6 [–1.5; –4.8]	–3.1 [–2.7; –4.4]	–0.7 [–4.3; +1.1]	+0.5 [+0.3; +3.1]
Blood osmolarity, mOsm/l	I	278.5 [272.5; 281.2]	279.5 [273.5; 284.7]	279.4 [272.5; 282.3]	286.7 [279.5; 289.2] *P*=0.02*
	II	275.5 [272.5; 281.2]	276.3 [269.1; 283.2]	275.2 [274.5; 284.5]	281.2* [270.1; 281.3] *P*=0.002*
Cl, mmol/l	I	98.1 [95.1; 100.5]	94.3 [94.7; 97.7] *P*=0.04*	98.9 [95.1; 99.1]	98.4 [95.7; 99.1]
	II	96.6 [94.1; 99.4]	95.3 [94.9; 96.6] P=0.04*	97.2 [95.6; 97.4] *P*=0.03*	98.1 [96.4; 99.7] *P*=0.03*
K, mmol/l	I	3.5 [3.2; 3.9]	3.5 [3.1; 4.0]	4.7 [3.6; 4.9] *P*=0.001*	4.6 [4.2; 4.7] *P*=0.001*
	II	3.7 [3.1; 3.5]	3.9 [3.5; 4.4] *P*=0.04*	4.3 [3.9; 4.4] *P*=0.03*	4.4* [3.5; 4.5] *P*=0.02*
Na, mmol/l	I	139.2 [137.1; 141.6]	139.2 [139.1; 142.3]	138.1 [136.1; 140.2]	140.4* [136.8; 142.1] *P*=0.03*
	II	138.4 [135.9; 140.2]	136.8 [134.4; 141.5]	135.8 [135.2; 137.8]	141.2* [130.1; 143.9] *P*=0.03*

Note. For tables 1–3: Group 1 — studied group administered with cytoflavin; Group 2 — patients not on cytoflavin; IFV — electrical equivalent of intracellular fluid volume (% of reference); EFV — electrical equivalent of extracellular fluid volume (% of reference); TFV — electrical equivalent of total fluid volume (% of reference); Cl — chloride; K — potassium; Na — sodium; * — *P* = significant intragroup differences.

Table 3. Effect of treatment on laboratory parameters, delirium severity and cellular membrane permeability in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
Lactate, mmol/l	I	3.9 [3.4; 4.1]	2.8 [3.4; 3.9] *P*=0.04*; *P*=0.002#	2.1 [1.9; 2.3] *P*=0.001*; *P*=1.1×10^{-4}#	0.74 [1.1; 0.9] *P*=1.3*×10^{-4}*; *P*=1.1×10^{-4}#
	II	3.8 [3.1; 4.2]	4.3 [3.7; 4.9] *P*=0.02*	4.23[7; 4.6] *P*=0.02*	2.7 [1.8; 2.9] *P*=0.001*
pH, units	I	7.27 [7.2; 7.3]	7.37 [7.2; 7.4] *P*=0.04*	7.41 [7.3; 7.4] *P*=0.03*	7.41 [7.4; 7.4] *P*=0.03*
	II	7.29 [7.2; 7.3]	7.29 [7.2; 7.3] *P*=0.02#	7.37 [7.2; 7.4] *P*=0.001*	7.4 [7.3; 7.4] *P*=0.001*
DRS-R-98, points	I	22.5 [22.1; 24.1]	23.3 [22.1–24.2] *P*=0.04*; *P*=0.02#	17.3 [14.1–19.4] *P*=0.001*; *P*=0.01#	12.1 [10.5–13.3] *P*=1.1×10^{-4}*; *P*=0.001#
	II	23.7 [18.6–23.9]	24.9 [19.1–24.1] *P*=0.04*	20.1 [19.1–21.1] *P*=0.02*	18.8 [16.4–19.7] *P*=0.001*
Severity index, %	I	81.7 [79.8; 82.5]	82.3 [78.1; 82.6]	88.9 [86.3; 89.9] *P*=0.001*	89.6 [86.8; 89.6] *P*=0.001*
	II	81.4 [78.9; 82.6]	79.8 [77.7; 80.1] *P*=0.001*; *P*=0.04#	82.2 [81.7; 83.9] *P*=0.001#	87.7 [86.9; 91.3] *P*=0.001*; *P*=0.04#

Note. DRS-R-98 — delirium severity score; * — *P* significant intragroup differences; # — *P* significant intergroup differences.

tachypnoea 23 [21; 24] breaths per minute, depressed peristalsis were noted. Intestinal paresis and, consequently, delayed passage of intestinal contents due to increased sympathetic tone were associated with imbalance of water compartments and body dehydration [28].

At the peak of severity of metabolic lactate acidosis and psychotic manifestations (day 3 of follow-up) with low plasma osmotic pressure, relatively stable levels of blood electrolytes, there was an increase in EFV by 3.9 and 4.1% in groups 1 and 2, respectively, and a decrease of TFV by 2.7 and 3.1% in groups 1 and 2, respectively. Clinically, psychomotor agitation and severe vegetative disorders such as pyrexia up to 37.2 [37.1; 37.4] °C, tachypnea up to 25 [23; 26] breaths per minute, hyperhidrosis, which caused both the general dehydration and redistribution of cellular fluid into the extracellular compartment, as confirmed by data from Goncharov VN et al. (2019) [29] were observed.

After the cytoflavin administration, normalization of cardiac and circulatory function along with reduced blood flow rate were seen, indicating a positive effect of the drug on the vascular tone,

including through sedation-mediated mechanism, as described by Deryugina A.V. and Gracheva E.A. (2020) [30]. We found a direct correlation of CI and SI with changes in delirium severity (*R* for *CI* = 0.32, *P* = 0.03; R for SI = 0.24, *P* = 0.04). Group 2 did not show similar results; a significant decrease in CI and SI was only diagnosed by day 7 of treatment.

The respiratory effort index in group 1 changed linearly with the severity of lactate acidosis (*R* = 0.41, *P* = 0.02). The blood lactate in this group dropped by 28.2%, 46.1%, and 81% on days 3, 5, and 7 of treatment, respectively. In the control group, elevated blood lactate persisted until day 7 (Table 3). Clinically, the patients in the main group showed reduced psychotic symptoms, a statistically significant decrease in the DRS-R-98 score by 23.1% on day 5 and by 46.2% on day 7 vs day 1. In group 2, the severity of delirium was significantly more intense by days 5 and 7.

Notably, as psychotic manifestations and lactate acidosis decreased with cytoflavin use, the balance restoration in fluid compartments with equal replenishment of both IFV and EFV was observed. On day 5 an increase in TFV up to 1.2%, on day 7 — up to 2.6% was recorded. In group 2 no similar changes were noted on day 5. Together with hyperlactatemia, we observed TFV depletion and extracellular dehydration down to 4.3% and 5.1% in 25% of cases, intracellular dehydration down to 4.5% in 75% of cases.

Statistical analysis failed to establish statistically significant intergroup differences among group I and II patients in plasma osmotic pressure and blood electrolyte content on the 5th and 7th days of observation.

The study of severity index, reflecting the permeability of cell membranes, based on reference and measured values of impedance, revealed intergroup differences.

Starting from day 5 of treatment, in group 1 there was an increase in median severity index values by 8.8%, and by 9.6% on day 7, indicating restoration of cellular membrane permeability. There was a high permeability in group 2 patients (χ^2=5.8, *P*=0.008), inverse relationship between severity index and hyperlactatemia (*R*=-0.39, *P*=0.02). In the control group, cellular membrane permeability recovered only on day 7 of therapy. The results obtained are consistent with the research data indicating cell membrane changes and intracellular molecular disturbances under hypoxia [31].

The mean hospital stay of patients with delirium in the main group was 7.5 [6; 8] days, in the control group 14 [11; 15] days (*z*=-5.9; *P*=0.00011).

During the study delirium was complicated by nosocomial pneumonia in group 1 in 7.4% (2), in group 2 in 28.5% (9) cases (χ^2=4.6, *P*=0.03). Thus, in patients with delirium not receiving cytoflavin the risk of complications such as nosocomial pneumonia was 83.6% higher than in those on cytoflavin (OR for group 1=0.07 [95%CI, 0.02–0.29], *P*=0.04; OR for group 2=0.47 [95%CI, 0.26–0.85], *P*=0.04).

Conclusion

The peak of delirium severity in patients with 1,4-BD poisoning occurred on days 1–3 and was characterized by predominantly complex manifestations. Prolonged delirium was associated with metabolic lactate acidosis, systemic hemodynamic and respiratory function disorders. Metabolic disorders in delirium were accompanied by hyperdynamic circulation, increased cardiac output, respiratory effort and cellular membrane permeability, changes in fluid compartments (depending on intensity of psychotic manifestations and hyperlactatemia).

Importantly, the use of an antihypoxic succinate-containing agent (cytoflavin) 40 ml daily reduced the severity of delirium and the risk of complications by preventing tissue hypoxia and stabilizing systemic hemodynamic parameters, respiratory function, and cell membrane permeability.

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