J Appl Biomed
DOI: 10.32725/jab.2022.007
journal homepage: http://jab.zsf.jcu.cz

Journal of Applied Biomedicine

Case report

Rare case of alimentary butylbiphenyl intoxication

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Abstract
Background: Unexpected accidental intoxication by uncommon industrial substances is a rare, but challenging and perilous event. To our best knowledge, this is the first reported case of 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol intoxication.
Case report: A 20-year-old man was referred to the Department of Emergency Medicine after seven days of nausea and vomiting triggered by drinking mead. Very high doses of 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol were detected in mead, blood, and urine samples. To prove the intoxication, gas chromatography – ion trap was performed. Symptoms of intoxication persisted for two weeks without significant organ damage. The case report illustrates the need for a multistep approach, focused mainly on the analysis of possible sources of intoxication.

Keywords: Alimentary intoxication; Butylbiphenyl intoxication; Toxicology

Highlights:
- This is the first report on intoxication by 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol.
- The toxin may cause long-lasting, intense dyspepsia without significant organ damage.
- Diagnosis of intoxication by unusual substance requires a multistep approach.
- Recognizing the source of intoxication is of paramount importance.

Case report

A 20-year-old man with a history of bronchial asthma and persistent allergic rhinitis visited the Department of Emergency Medicine of a tertiary hospital after experiencing seven days of nausea and vomiting, which had resulted in substantial restriction of oral intake and weight loss of 2 kg. Nausea was not accompanied by diarrhoea, abdominal pain, fever, or any other subjective complaints.

In the initial assessment, a total amount of about 0.06 l of mead was determined as a possible trigger of nausea. The mead was produced by an established distillery, and before drinking it was originally sealed. No other person drank from the same bottle of mead.

Blood pressure was 125/80 mmHg, but sinus tachycardia 120 beats per minute was present. The patient was tired, but conscious. Overall physical findings were normal. The abdomen was soft, non-tender, with no signs of peritoneal irritation or other relevant finding.

ECG revealed incomplete right bundle branch block. Abdominal ultrasonography was entirely normal. Initial blood count, coagulation testing, and biochemical analysis revealed no significant findings (Table 1). As the diagnosis remained unclear, we processed the patient's serum, urine, and captured bottles of mead of firstly unknown origin, which our patient drank as part of the emergency toxicological analysis.

Table 1. Partitional primary results of toxicology GC/MS testing

	Area of the key mass (339.2 m/z)	Signal to noise (s/n)	Area ratios to references	s/n ratios to references
Serum sample of the patient	34685924	86918	106	332
Urine sample of the patient	62011938	178286		
Mead sample	47354356	138146		
Mean values of serum references	326269	262		

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http://doi.org/10.32725/jab.2022.007
Submitted: 2021-10-28 • Accepted: 2022-05-31 • Prepublished online: 2022-06-10
J Appl Biomed 20/2: 80–82 • EISSN 1214-0287 • ISSN 1214-021X

Toxicological analysis

Although we carried out these analyses on the platform of the hyphenated ultra-high performance liquid chromatography (UHPLC)/Orbitrap system (Q Exactive Focus, Thermo Fisher Scientific), which we set for the high-tech detection of wide clinical spectrum of analytes, especially drugs, addictive substances or some plant toxins, the analysis was not successful in detecting a possible toxin. It was evident that the aforementioned device cannot be used as an absolute, universal analytical tool for identification of any chemical individuals, especially in the field of environmental pollutants. For this reason, we used the gas chromatograph (GC)-ion trap (ITQ, Thermo Scientific) system for biphenyl capture in submitted samples of serum, urine, and incriminated mead liqueur (Suppl. 1–3). Therefore, we revealed the presence of the described biphenyl-diol as a very probable cause of the patient's complaints. This is, of course, a qualitative analysis, so in addition to these primary results, we performed a sequence of about 50 analyses of randomly selected serum samples from routine blood collections for basic biochemistry tests, which are stored in plastic tubes (Suppl. 4), and we compared individual areas of the mass peaks. Since this biphenyl is used, inter alia, as an additive in plastics to prevent premature embrittlement, we assumed that it enters the samples by gradual release from the packaging material. We thus obtained so-called normal value (mean peak area) of the plastic tube background.

Materials and methods

Sample screening acquisition

Chemicals and reagents used in analysis are summarized in Suppl. 5. Methanolic HCl was used as an elution reagent in SPE performance after 1 ml precondition of SPE disc by the same solvent. We adjusted 100 µl of the raw sample (serum, urine, and mead) on the bed of SPE disc, and eluted for 1 ml of methanolic HCl. The serum samples were ten times diluted by distilled water for a blockage of protein precipitate prevention. The urine sample was centrifugated before extraction. The obtained eluents were evaporated to dryness under nitrogen, reconstituted in hexane (70 µl), transferred to 200 µl tubular inserts, and then placed in 1.5-ml autosampler vials. One microliter of each analytical sample was injected onto a Focus GC, coupled with ITQ ion trap MS from Thermo Scientific (splitless mode, injector at 220 °C, column TG-5MS, 30 m × 0.25 mm × 0.25 µm). We operated the mass spectrometer under the following conditions: Ion source set up 245 °C, start of scan at 3.00 min, multiplier offset 25, full scan with mass range from 35 to 650 amu, positive electron ionization, 5 microscans, 35 ms (max ion time), mass defect (mmu/100 amu : 1).

Results

We found an absolute dominant peak identified as 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol, with the area on the order a hundred times higher than the average obtained from the measurement of 50 sera stored cold (5 °C) for 3–5 days in plastic tubes for reference. The data provided evidence of biphenyl derivate releases from the packaging materials used for mead storing. Our primary raw data are sufficiently transparent to determine the degree of intoxication (Table 1).

Treatment

As there is no established treatment of 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol intoxication, a supportive treatment containing antiemetic drugs and parenteral rehydration was initiated. With this treatment, vomiting was mitigated. However, nausea persisted for the next seven days. Later, all complaints completely faded out. The follow-up blood count, coagulation, and biochemistry remained completely normal (Table 2). However, the follow-up toxicological examination revealed 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol in a substantial level compared to the randomly selected sera intended originally for routine biochemical analyses.

Table 2. Results of laboratory testing

	Normal range	Initial value	Follow-up value
White blood cell ['9/l]	4–10	4.6	6.07
Red blood cell [^12/l]	4.0–5.8	5.39	5.43
Hemoglobin [g/l]	135–175	162	165
Hematocrit	0.4–0.5	0.466	0.474
Mean corpuscular volume [fl]	82–98	86.5	87.3
Mean cell hemoglobin [pg]	28–34	30.1	30.4
Platelets ['9/l]	158–400	285	297
Glucose [mmol/l]	3.9–5.6	4.9	not available
Natrium [mmol/l]	136–145	138	139
Kalium [mmol/l]	3.5–5.1	3.8	4.2
Chloride [mmol/l]	98–107	99	100
Urea [mmol/l]	2.8–8.1	3.3	3.8
Creatinine [umol/l]	59–104	91.0	90.0
Bilirubin [umol/l]	0–24	24.0	17.0
Alanine transaminase [ukat/l]	0.17–0.83	0.29	0.34
Aspartate transaminase [ukat/l]	0.17–0.85	0.30	0.39
Gamma-glutamyltransferase [ukat/l]	0–1	0.25	0.19
Alkaline phosphatase [ukat/l]	0.67–2.17	0.97	not available
Amylase [ukat/l]	0.47–1.67	1.07	1.04
C-reactive protein [mg/l]	0–5	0.2	not available
Cholinesterase [ukat/l]	89–215	134	156
Prothrombin ratio	0.8–1.2	1.0	0.94
Activated partial thromboplastin time ratio	0.8–1.2	0.96	1.02

Discussion

To our best knowledge, this is the first report of clinically significant intoxication by 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol, thus no exact toxicity threshold level is available. The small volume of ingested spirit resulting in intoxication is an alarming finding. The high toxicological risk of this category of compounds was also confirmed in a recent study (Budde

et al., 2020). This substance is mainly used as a plasticizer added to polymers, while use in agriculture is scarce. The agent is ethanol soluble and can be washed out of fabric of some plastic containers. The release of the plastic substance increases enormously when such containers are exposed to sunlight (Clarke, 1998). Thus we expect that the mead was contaminated by violation of technological processes or storage, rather than by contaminated honey. We base these conclusions on the results of comparative analyses of the set of randomly selected sera stored in plastic tubes intended originally for routine biochemical analyses (Table 1). This suggests that such intoxication is not related only to mead, but may repeat with various nonpolar solvents, like other spirits or vegetable oils. A similar mechanism of contamination may also involve numerous other rare pollutants. The only prevention of such intoxications is strict adherence to proper technological processes.

The exact mechanism of 3,4',5,6'-tetra-tert-butylbiphenyl-2,3'-diol toxicity is unknown. Nausea and vomiting, without any significant organ damage or specific neurological symptoms, suggest nonspecific irritation of the central nervous system (Singh and Kuo, 2016). This does not rule out long-term toxicity, including carcinogenicity. The long-lasting duration of symptoms correlates well with anticipated long plasmatic halftime. Bioelimination of this agent is unknown, but similar substances undergo liver microsomal oxidation with similarly long halftimes (Kania-Korwel and Lehmler, 2016). This would make therapy of severe intoxication demanding, as usual methods of bioelimination would be ineffective.

This case report demonstrates an increasing risk of incidental poisoning by various rare industrial pollutants. In case the unknown toxic agent is suspected, a detailed analysis of environmental samples before blood testing may greatly increase the chance of identifying the exact substance. At the time of the emergency analysis, a standard of this substance was not available, but in the next step we want to continue monitoring this biphenyl-diol in sera of our patients on the basis of a proper quantitative analysis to obtain valid reference data.

Ethical aspects and conflict of interests

We confirm that there is no known conflict of interests associated with this publication. The manuscript contains no copyrighted material.

Funding

The work was supported by the Ministry of Defence of the Czech Republic "Long Term Development Plan – Clinical Fields" of the Faculty of Military Health Sciences Hradec Králové, University of Defence, Czech Republic.

Author contribution

DS was responsible for clinical management of patient and preparing of the manuscript. VV designed and performed toxicological examination, and contributed to the manuscript preparation. MJ supervised clinical management and finalized the manuscript.

Acknowledgements

The authors are grateful to Eva Drahokoupilová, MSc, for language proofreading of the manuscript.

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