



WCP2023

2 - 7 JULY 2023

GLASGOW | SCOTLAND

19TH WORLD CONGRESS OF BASIC AND CLINICAL PHARMACOLOGY

Register now

You could save nearly 40%*

*Early bird deadline: 17 March 2023



wcp2023.org



CASE REPORT

Non convulsive refractory status epilepticus induced by thiocolchicoside (TCC) intrathecal injection: A case report

Giacomo Evangelista¹  | Fedele Dono¹ | Stefano Consoli¹ | Valeria Pozzilli¹ | Dario Calisi¹ | Mirella Russo¹ | Claudia D'Orazio¹ | Anna D'Andreagiovanni² | Giovanna Montesano² | Sabina Rapini² | Massimo Caulo¹ | Marco Onofri¹ | Francesca Anzellotti³

¹Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

²Department of Neurology, "S Spirito" Hospital, Pescara, Italy

³Department of Neurology, Epilepsy Center, "SS Annunziata" Hospital, Chieti, Italy

Correspondence

Fedele Dono, MD; Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Via dei Vestini 1, 6610, Chieti, Italy. Email: fedele.dono@unich.it

[Correction added on 19 May 2022, after first online publication: CRUI funding statement has been added.]

TCC is a semisynthetic molecule widely used in clinical settings as a pain killer and myorelaxant. Several neurological side effects have been reported in association with TCC treatment including somnolence, confusion and seizure, the latter in a lower percentage of patients. Some previous reports described seizure onset after TCC intake in adulthood. However, major epileptological complication, namely status epilepticus, has never been previously reported in association with TCC treatment. In our report, we describe a case of acute refractory non-convulsive status epilepticus (NCSE) in the context of a TCC-induced acute toxic encephalopathy (ATE) in a woman without any previous neurological or physical comorbidities.

KEYWORDS

acute toxic encephalopathy, amnesia, case report, non-convulsive status epilepticus, thiocolchicoside

1 | INTRODUCTION

Thiocolchicoside (TCC) is a semisynthetic molecule frequently used in humans for its muscle-relaxant as well as anti-inflammatory and analgesic effects. TCC is frequently used in the management of low back pain in association with non-steroidal anti-inflammatory drugs (NSAIDs). According to the literature, treatment with intra-muscular TCC is effective and well-tolerated and its clinical efficacy and safety have been demonstrated in randomized double-blind clinical trials.¹ TCC is an analogue of colchicine since they share the same benzo (alpha)heptalenic moiety.²

Even though the mechanism of action of TCC is not yet well understood, previous studies have suggested the interaction of this compound with a cortical subtype of the gamma-aminobutyric acid type A (GABA-A) receptor, inhibiting GABAergic transmission.³ This peculiar mechanism could explain its pro-epileptogenic properties. In

fact, TCC was described to reduce seizure threshold and cause convulsions in rat models.⁴

In the present report, we describe a case of acute non-convulsive status epilepticus (NCSE) in a healthy adult patient with no previous history of epilepsy, brain injury or blood-brain barrier disruption after erroneous TCC intrathecal injection for the treatment of muscle contracture and low back pain.

2 | CASE REPORT

A 43-year-old woman was admitted to the emergency room complaining of the abrupt onset of cognitive motor-slowness, blurred vision, sensory deficits in her lower limbs followed by loss of consciousness. The patient's recent as well as past medical history was unremarkable. No prior history of epilepsy, psychiatric comorbidities

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

as well as a documented previous cognitive impairment was reported. The patient was not taking any home drug therapy.

Thirty minutes before admission, the patient was treated with an erroneous intrathecal injection of TCC, performed by her chiropractor, for lumbar muscle contracture and low back pain. At the physical examination, the injection site was extremely close to the patient's L2 spinous process.

At first, the patient underwent a computed tomography (CT) of the brain which ruled out subdural haematoma, stroke or subarachnoid haemorrhage. A complete blood examination assessment (which

included electrolytes, azotaemia, ammonia, glycaemia, and blood gas analysis) was performed, with all results within normal ranges. In the context of the emergency setting, according to the hospital local guideline, an electroencephalogram (EEG) with reduced montage (i.e., eight electrodes, four per hemisphere) was performed. EEG showed rhythmic high amplitude 2–3 Hz delta activity with superimposed diphasic sharp waves and spikes in the bilateral temporal derivations (Figure 1A). Thus, the patient was treated with an intravenous (i.v.) bolus of midazolam (MDZ) 10 mg with a sudden electroclinical improvement. According to Salzburg Criteria,⁵ continuous

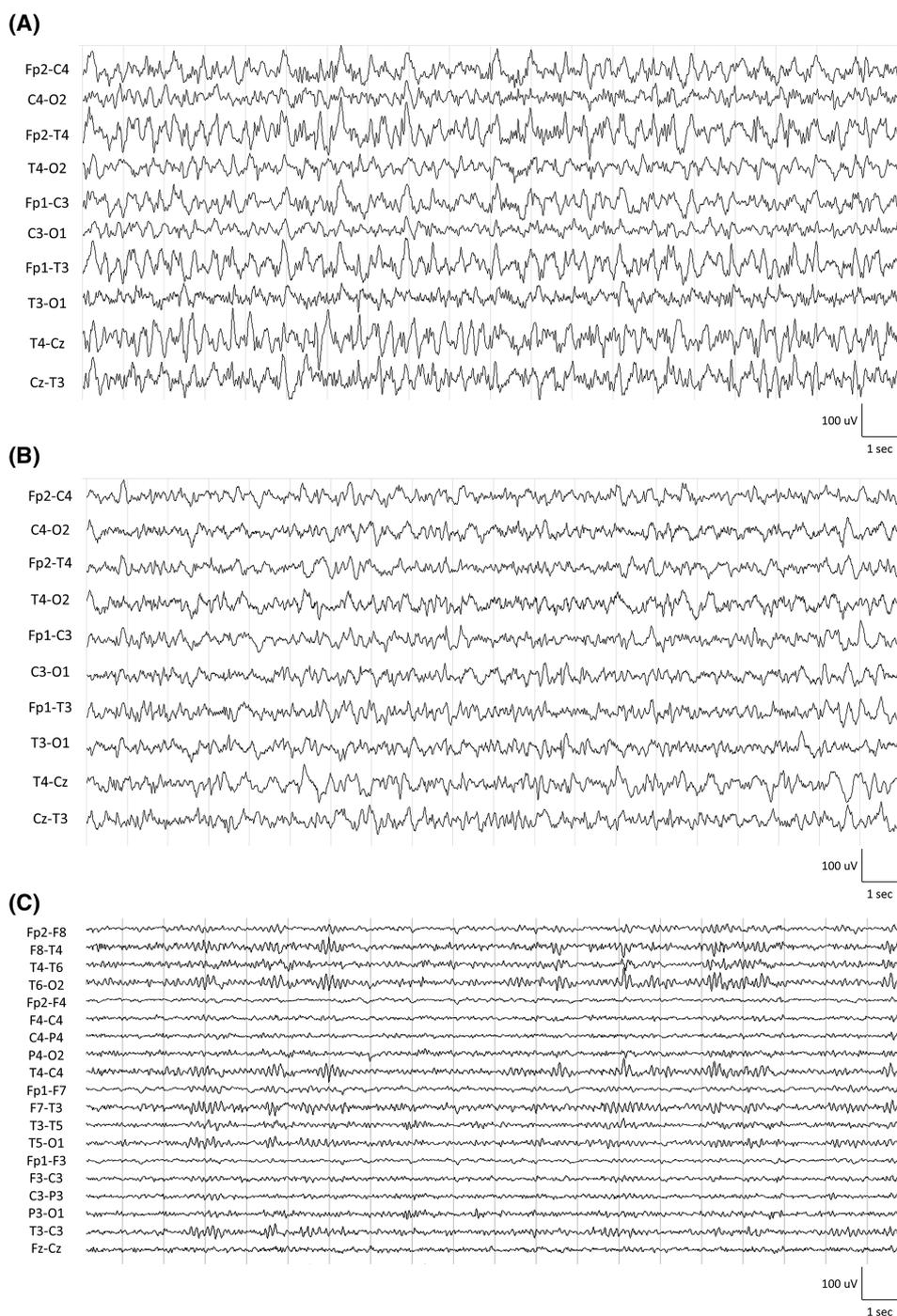


FIGURE 1 Electroencephalogram (EEG). (A) High amplitude (150–200 uV), 2–3 Hz delta activity with superimposed diphasic sharp waves and spike in the bilateral temporal derivations. (B) EEG performed by i.v. bolus of levetiracetam and lacosamide. (C) EEG performed after 2 weeks showed normal background alpha activity with sporadic 6–7 Hz slow abnormalities in the bilateral temporal derivations (Figure 1C)

(quasi-)rhythmic delta-theta activity with frequency >0.5 cycles per second, when associated with a clear clinical response, enables diagnosis of non-convulsive status epilepticus (NCSE).

The Naranjo Scale⁶ was used to assess the adverse reaction after intrathecal injection of TCC. A score of 6/13 was obtained, indicative of probable adverse drug injection reaction.

After 20 minutes, a subsequent worsening of the EEG was observed. In addition, constant pulse oximetry monitoring was performed, showing reduced partial pressure of oxygen (paO_2) that, however, never went below 87%. Due to the risk of a worsening in respiratory function, additional benzodiazepines were not administered. Hence, an i.v. bolus of levetiracetam (LEV) 2000 mg and lacosamide (LCS) 200 mg was administered with a poor electroclinical response (Figure 1B).

Considering the lack of clinical response to the antiseizure treatment, the patient was transferred to the intensive care unit (ICU), where she was intubated and treated with propofol 2 mg/kg/h. A regimen of intravenous daily administration of levetiracetam (LEV) 3000 mg/day and lacosamide (LCS) 200 mg/day was set. To evaluate the electroclinical response, serial 60-minute EEG monitoring was performed every 24 hours. On Day 1, the EEG showed middle amplitude, 4–5 Hz slow abnormalities in the bilateral temporal derivations.

On Day 2, the patient underwent magnetic resonance imaging (MRI) of the brain which showed a non-specific bilateral periventricular hyperintensity (Figure 2A–2F). On Day 3, due to the EEG improvement, propofol therapy was discontinued, and the patient was transferred to sub-intensive care and discharged on Day 10, transferred to a rehabilitation clinic.

After the hospitalization, cognitive impairment was noted, with prominent attention deficits and retrograde amnesia (i.e., the patient

declared not to remember the last 2 years). Folate and vitamin B₁₂ deficiency, as well as hypothyroidism, were excluded. Afterwards, a comprehensive neuropsychological evaluation documented the presence of a single-domain amnesic mild cognitive impairment (MCI), with verbal and visual explicit memory deficits, along with working memory impairment (Table 1). The other cognitive domains (i.e., executive, visuo-praxis, language) were unaffected.

Two weeks later, a control EEG showed slow 6–7 Hz abnormalities in the bilateral temporal derivations (Figure 1C). A repeated brain MRI, performed after the hospitalization, confirmed the non-specific periventricular white matter abnormalities without signs of brain atrophy. A 3-month follow-up visit documented the persistence of cognitive dysfunction with a single-domain amnesic MCI, associated with verbal and visual explicit memory deficits.

3 | DISCUSSION

TCC is a semisynthetic molecule widely used in clinical settings as a pain killer and myorelaxant. Several neurological side effects have been reported in association with TCC treatment including somnolence, confusion and seizure, the latter in a low percentage of patients.³ However, a major epileptological complication, such as status epilepticus, has never been previously reported in association with TCC treatment. In the present report, we described a case of acute refractory NCSE in the context of a TCC-induced acute toxic encephalopathy (ATE) in a woman without any previous neurological or physical comorbidities. Diagnosis of acute toxic NCSE was made according to Salzburg Criteria,⁵ considering the EEG features combined with the clinical improvement after i.v. benzodiazepine

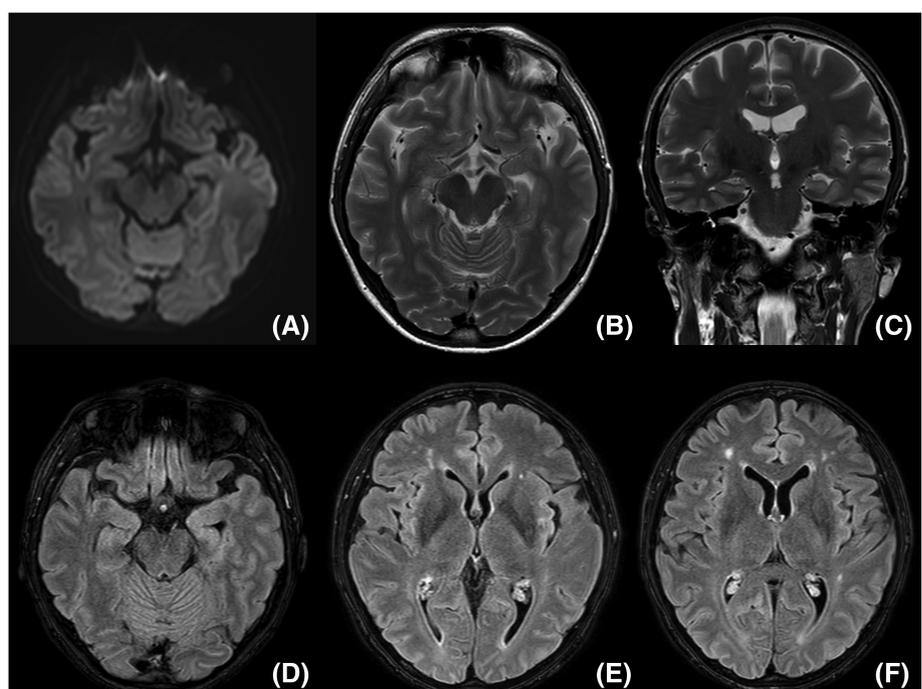


FIGURE 2 Magnetic resonance imaging (MRI) performed during the acute phase of TCC toxic encephalitis. (A) Axial diffusion weighted imaging (DWI), (B) axial T2 weighted scan, and (C) coronal T2 weighted scan of the brain did not show any abnormalities. (D), (E) and, (F) Fluid attenuated inversion recovery (FLAIR) scan of the brain showed non-specific bilateral periventricular hyperintensity

TABLE 1 Neuropsychological assessment

Neuropsychological assessment	Score (equivalent score)
Mini-mental state examination (MMSE)	28
Digit span	
• Forward	7 (4)
• Backward	2 (0)
Corsi block-tapping test	
• Forward	6 (4)
• Backward	5 (3)
Babcock story recall	
• Immediate recall	4.7 (2)
• Delayed recall	6.4 (3)
Free and cued selective reminding test	
• IFR	24 (1)
• ITR	36/36
• DFR	8 (1)
• DTR	12/12
Trail making test (TMT)	
• Part A	24.72" (4)
• Part B	84" (3)
Fluency	
• Phonemic	45 (4)
• Semantic	49 (4)
Rey-Osterrieth figure	
• Copy	35 (4)
• Delayed	11 (0)

Test scores were calculated with correction for age and education. Mini-mental state examination (MMSE): a score of 24 or over is considered normal. For each score, equivalent score is reported in brackets. Equivalent score key: (4) over average; (2) and (3) normal score; (1) below average; (0) severe deficit.

injection. We acknowledge that also ATE itself can be associated with a similar EEG pattern. However, in ATE the administration of antiseizure medications should not determine any clinical improvement.

ATE reflects a global cerebral dysfunction of rapid onset and may be associated with alterations in the level of consciousness. The causative agents include organic solvents or pharmaceutical compounds which can diffusely affect brain function. According to the literature, other cases of ATE associated with status epilepticus secondary to inadvertent intrathecal injections include tranexamic acid⁷ and bupivacaine.⁸ Death after intrathecal administration of daunomycin has also been described.⁹

Three basic principles of neurotoxicology are particularly relevant to the diagnosis of toxic encephalopathy: (1) dose–response relationship between toxic agents and neurological symptoms, (2) non-focal or symmetrical neurological signs and (3) a strong temporal relationship between exposure and symptom onset. In our report, all three criteria were met. In particular, the close temporal relationship

between TCC injection and NCSE onset (as well as the exclusion of any other condition at the basis of the clinical picture), and the peculiar clinical picture (i.e., NCSE) associated with diffuse EEG abnormalities have supported the hypothesis of TCC-induced ATE. Even though the TCC vial contained several excipients such as sodium chloride, hydrochloric acid and water for injectable solutions, none of them were associated with clinical onset of ATE or status epilepticus in experimental or clinical settings.

Management of status epilepticus is based on a stepwise approach. According to the International League Against Epilepsy,¹⁰ the first line of treatment includes benzodiazepines (specifically intramuscular midazolam, intravenous lorazepam or intravenous diazepam), which can be repeated up to two times. After a first attempt with benzodiazepines, second-line therapy consists of the administration of antiseizure drugs (e.g., levetiracetam, fosphenytoin, valproic acid). If the second line of therapy fails to stop the seizures, treatment should include repeating second-line therapy or proceeding to the administration of anaesthetics (e.g., propofol, thiopental, midazolam, pentobarbital). In our patient a first administration of benzodiazepines was performed; the latter was not repeated due to low blood oxygen levels. Therefore, a second line approach was started with subsequent poor response, hence a third line treatment was administered with a complete electroclinical response.

Diagnosis of ATE is generally clinically driven even though neuro-radiological findings may be useful.¹¹ Indeed, in the context of ATE, brain MRI often shows focal or diffuse white matter abnormalities as well as basal ganglia involvement.¹¹ However, MRI findings depend on the specific toxic compound and a normal neuroradiological picture can be found.¹¹ According to our report, no specific brain MRI findings were detected in the acute phase of TCC intoxication.

ATE sequela can include residual cognitive impairment (primarily attention and information-processing impairment resulting in dysfunction in working memory) as well as focal neurological deficits. Previous reports described persisting neurocognitive impairments in the context of ATE caused by intravenous methadone injection,¹² and cognitive decline, parkinsonism, pyramidal signs and polyneuropathy after long-term occupational solvent exposure (toluene, xylene, methyl-ethylketone, resins, carbon disulfide, thinners).¹³ In this report, after TCC exposure, our patient developed a long-lasting amnesic MCI. Hence, TCC exposure may have impaired irreversibly the patient's cognitive performance.

4 | CONCLUSION

The present report describes a case of TCC-induced toxic encephalitis associated with acute NCSE. Care should be taken in the management of low back pain. In accordance with the European Medicines Agency,¹⁴ treatment of lower back pain should initially involve the use of non-steroidal anti-inflammatory drug (NSAID) medications such as ibuprofen. If the patient cannot take NSAIDs, alternative medicines such as codeine may help. Muscle relaxants such as TCC may be prescribed by a general practitioner if the patient has painful muscle

spasms. However, as described in our case report, TCC treatment can be associated with several life-threatening side effects. In line with this evidence, the European Medicines Agency's Committee on Human Medicinal Products (CHMP)¹⁵ has recommended that the authorized uses for thiocolchicoside-containing medicines delivered orally or by intramuscular injection should be restricted across the European Union (EU). Accordingly, intrathecal injection of TCC should be avoided.

ACKNOWLEDGEMENT

Open Access Funding provided by Universita degli Studi Gabriele d'Annunzio Chieti Pescara within the CRUI-CARE Agreement.

COMPETING INTERESTS

The authors declare no conflicts of interest.

CONTRIBUTORS

G.E. and F.D. contributed to the conception and design of the study. G.E., F.D. and S.C. wrote the manuscript. D.C. and M.R. performed the neuropsychological assessment. C.D. and M.C. interpreted MRI brain images. All authors contributed to manuscript revisions, read and approved the submitted version.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon reasonable request.

ORCID

Giacomo Evangelista  <https://orcid.org/0000-0002-1828-5345>

REFERENCES

- Kumar S, Rani S, Siwach R, Verma P. To compare the efficacy and safety of fixed dose combination of thiocolchicoside and aceclofenac versus chlorzoxazone, aceclofenac and paracetamol in patients with acute lower backache associated with muscle spasm. *Int J Appl Basic Med Res*. 2014;4(2):101-105. doi:10.4103/2229-516X.136789
- De Riu PL, Rosati G, Sotgiu S, Sechi G. Epileptic seizures after treatment with thiocolchicoside. *Epilepsia*. 2001;42(8):1084-1086. doi:10.1046/j.1528-1157.2001.0420081084.x
- Giavina-Bianchi P, Giavina-Bianchi M, Tanno LK, Ensina LF, Motta AA, Kalil J. Epileptic seizure after treatment with thiocolchicoside. *Ther Clin Risk Manag*. 2009;5(3):635-637. doi:10.2147/tcrm.s4823
- Plotka C, Jequier R. Thiocolchicoside, pharmacological study. *Arch Int Pharmacodyn Ther*. 1957;109(3-4):386-399.
- Leitinger M, Beniczky S, Rohrer A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus—approach to clinical application. *Epilepsy Behav*. 2015;49:158-163. doi:10.1016/j.yebeh.2015.05.007
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi:10.1038/clpt.1981.154
- Hatch DM, Atito-Narh E, Herschmiller EJ, Olufolabi AJ, Owen MD. Refractory status epilepticus after inadvertent intrathecal injection of tranexamic acid treated by magnesium sulfate. *Int J Obstet Anesth*. 2016;26:71-75. doi:10.1016/j.ijoa.2015.11.006
- Akil E, Varol S, Guzel A, Gocmez C. Status epilepticus induced by intrathecal bupivacaine use: a case report. *J Clin Exp Investig*. 2014; 5(1):108-111. doi:10.5799/ahinjs.01.2014.01.0371
- Soldozy S, Patel A, Yaeger K, et al. Inadvertent intrathecal administration of daunomycin resulting in fatality: case report and therapeutic considerations. *eNeurologicalSci*. 2020;22:100297. doi:10.1016/j.ensci.2020.100297
- Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*. 2016;16(1):48-61. doi:10.5698/1535-7597-16.1.48
- Valk J, van der Knaap MS. Toxic encephalopathy. *AJNR Am J Neuroradiol*. 1992;13(2):747-760.
- Repple J, Haessner S, Johnen A, et al. Intravenous methadone causes acute toxic and delayed inflammatory encephalopathy with persistent neurocognitive impairments. *BMC Neurol*. 2021;21(1):85. doi:10.1186/s12883-021-02108-9
- Hageman G, van der Hoek J, van Hout M, et al. Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long-term occupational solvent exposure. *J Neurol*. 1999;246(3):198-206. doi:10.1007/s004150050334
- European Medicines Agency. Guideline on the clinical development of medicinal products intended for the treatment of pain. EMA/CHMP/970057/2011.
- European Medicines Agency. European Medicines Agency recommends restricting use of thiocolchicoside by mouth or injection. EMA/40615/2014.

How to cite this article: Evangelista G, Dono F, Consoli S, et al. Non convulsive refractory status epilepticus induced by thiocolchicoside (TCC) intrathecal injection: A case report. *Br J Clin Pharmacol*. 2022;88(7):3495-3499. doi:10.1111/bcp.15240