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Case Report

# Death Due to Gabapentin-Nortriptyline Overdose

**Kattamreddy Ananth Rupesh*** **Esanakula Varshini Reddy****
**C. Lakshmi Kalavathi***** **Pravin Pandit Rao Kalyankar******
*Forensic Medicine and Toxicology, ACSR Govt. Medical College, Nellore, Andhra Pradesh, 524004
**Medical Officer, 104 Services, Tirupati Rural, Govt. of Andhra Pradesh, ***Pathology, ACSRGMC, Nellore, A.P.
****Fortis Hospital, Faridabad, Delhi, India.

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***Corresponding author :*** Kattamreddy Ananth Rupesh, Forensic Medicine and Toxicology, ACSR Govt. Medical College, Nellore, Andhra Pradesh, 524004.
Email: ananth.kattam@gmail.com

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***Abstract :***

In this article, we present a case report of a gabapentin-nortriptyline overdose causing the death of an elderly Indian woman. This combination medication is increasingly being prescribed for chronic peripheral neuropathy in our part of the world and has a high potential for misuse/abuse. The safety profile of tricyclic antidepressants should always be gauged while prescribing them to the elderly population. With the increasing use of gabapentinoids in practice, Indian emergency care physicians should start considering them as one of the differential diagnoses in all cases of elderly patients presenting to ER with altered consciousness.

***Keywords :*** Gabapentin; Nortriptyline; Forensic Toxicology; Drug Abuse; Pharmaceutical Toxicology.

## Introduction:

The fixed-dose combination medication of gabapentinoids and tricyclic antidepressants are being increasingly prescribed for neuropathic pain and chronic peripheral neuropathy among the Indian geriatric population. The abuse potential of these drugs in the Indian context needs to be studied in view of occasional case reports of intentional self-harm. It is also interesting to note that gabapentinoid abuse has peaked at epidemic proportions in the western world and several instances of gabapentinoid withdrawal have been reported in the literature. On the other hand, tricyclic antidepressants are known to have very low safety profiles and are always a source of concern for inadvertent overdose in the elderly population.

## Case Report :

Mrs. N, a 58 years old patient with chronic back pain was prescribed *Gabagesic NT 400*HS by her attending physician. She was referred to our tertiary care hospital's department of Emergency Medicine after overdosing withan unknown quantity of *Gabagesic NT 400* (Gabapentin 400 mg+ Nortriptyline Hydrochloride 10 mg I.P.). She underwent treatment at a primary health care centre, a sub-district hospital and a private hospital for a total duration of 24 hours before admission at our institute. As per information received from her family members, no gastric lavage was done in the immediate aftermath of overdosing. There were no medical records available to know about the treatment the patient received before our institute

admission. At the time of admission, the patient was unconscious, her BP was not recordable and her pulse was recordable (40bpm, irregular). She succumbed to the poisoning within a few hours after admission despite all efforts for resuscitation. Investigations including complete blood picture, liver function, and renal function tests revealed no abnormality. ECG at the time of admission showed very broad QRS complexes (160ms), extreme axis deviation and AV dissociation.

The autopsy revealed the following significant findings. Pleurae were adherent to the chest wall. The lower lobes of both lungs showed patchy areas of consolidation and emanated purulent material on the cut section. The heart showed presbycardian changes with increased tortuosity of vessels. Further, greyish-white patches were present on the anterior wall of the left ventricle and the ventricular wall is thinned out in the corresponding region. Large blood vessels showed atherosclerotic changes. The stomach contained about 200 ccs of a yellowish viscous material with two partly dissolved white-coloured pills. The stomach mucosa was haemorrhagic and contents emanated the smell of medicines. The liver appeared yellowish and hard on the cut section. The spleen was enlarged and rubbery on the cut section. The surface of both kidneys showed multiple cysts of varying sizes 7.5 mm to 45 mm.

Histopathology of the kidney revealed normal histology. Histopathology of the liver showed extensive hydrophic degeneration (fatty change and steatosis). Histopathology of the spleen showed dilated sinusoids. The chemical analysis of viscera established gabapentin overdose. However, there was no comment on nortriptyline in the report. The exact quantitative levels of the pharmaceutical toxicants were not carried out at the regional forensic science laboratory for want of infrastructure.

**Discussion:**

The gabapentin-Nortriptyline combination drug is generally prescribed to manage chronic neuropathic pain in patients suffering from peripheral neuropathy.

Gabapentin and pregabalin are anti-seizure drugs that consist of GABA molecules covalently bound to a cyclohexane ring or isobutane, respectively. Although these drugs were purported to be GABA agonists, their exact molecular mechanism of action remains unknown. Both these compounds bind with high affinity to a protein in cortical membranes with an amino acid sequence identical to that of the Ca2+ channel subunit α2δ1. In a nutshell, gabapentinoids are γ-aminobutyric acid analogues that exert their therapeutic effects by inhibiting voltage-gated calcium channels and decreasing neurotransmitter release.

Gabapentin and pregabalin are orally absorbed and are not metabolised in humans, not plasma protein bound and excreted unchanged in the urine. The half-life is approximately 6 hours and there is no data suggesting interaction with other anti-epileptic drugs. Gabapentin usually is effective in doses of 900-1800 mg daily in 3 doses, although 3600 mg may be required in some patients. Therapy usually is begun with a low dose (300 mg/day), which is increased by 300 mg /day until an effective dose is reached. Gabapentin is well tolerated. Common adverse effects include mild to moderate somnolence, dizziness, ataxia, and fatigue that resolve within 2 weeks of onset during continued treatment. Gabapentin and pregabalin are listed in pregnancy category C.[1]

Gabapentin was originally intended to be used as a muscle relaxant and anti-spasmodic medication before its anti-convulsant potential was unleashed. Currently, gabapentin has FDA approval for:

- Postherpetic neuralgia.
- Adjunctive therapy in the treatment of partial seizures with or without secondary generalization in patients over the age of 12 years old with epilepsy, and the paediatric population, 3- to 12-year-olds with a partial seizure.
- Moderate to severe restless leg syndrome (RLS).

The off-label use of this drug for managing alcohol withdrawal is interesting from an addiction psychiatry perspective apart from several other uses.[2]

In a study where gabapentin was determined

to be a cause of death, the blood concentrations of the drug ranged from 1.1 to 134.0 mg/L.There is an increase in recreational abuse of gabapentin in the western world and there are several case reports explaining the same.[3]

Epidemiological and case report evidence suggests gabapentin is being misused internationally, with substance abuse populations at special risk for misuse / abuse.[4] In a case of suicide by overdosing on the drug, the post-mortem peripheral blood gabapentin concentration as determined by high-performance liquid chromatography/tandem mass spectroscopy was 88 μg/mL.[5] In another reported case of a 59-year-old female, she consumed 90g of gabapentin during a self-harm attempt. Her serum gabapentin level was 72.8 mcg/mL approximately 3 hours after ingestion. Her renal function panel, complete blood count, and liver function panel were normal. Her urine drug screen, aspirin, ethanol, and acetaminophen level were negative. Her electrocardiogram was normal, including a normal QTc interval. Her only symptoms were nausea and mild sedation. The authors opined that gabapentin has a wide therapeutic margin and may be safe in overdose.[6]

Rhabdomyolysis and acute tubular injury were reported as important features in the autopsy of cases with gabapentin poisoning.[7] Although adverse events of gabapentinoid-only ingestion are relatively benign, a growing body of evidence indicates that gabapentinoids significantly increase opioid-related morbidity and mortality when used concomitantly. [8,9]

**Table 1: Clinical Toxicology Profile of Gabapentin.[10]**

| | |
|---|---|
| **Signs and Symptoms**<br>• Most prominent symptoms are CNS effects like somnolence, ataxia, dizziness, slurred speech, diplopia, dysarthria, tremors, difficulties in cognition and motor incoordination.<br>• Gastrointestinal effects like diarrhoea.<br>• Cardiovascular and neurological sequelae are rare.<br>• Laboratory parameters are generally normal because of exclusive CNS action. | **Management of Toxicity**<br>• Decontamination with Activated Charcoal in 70% sorbitol within the first hour after ingestion.<br>• Supportive Care.<br>• No Specific Antidote.<br>• 2-15mcg/ml is the therapeutic level of the drug.<br>• Careful attention to the airway is important considering the risk of somnolence and aspiration.<br>• Monitoring parameters include pulse oximetry, blood gasses and chest X-ray.<br>• Haemodialysis if needed |
| **Autopsy Findings**<br>• Always check for Co-Contributory Pathological causes responsible for the death.<br>• Non-specific findings<br>• Bear acute on chronic abuse as one of the reasons in mind in the event of any gross or histopathological findings in the liver or kidney during autopsy. | **Analytical Toxicology Considerations**<br>• HPLC<br>• GCMS<br>• Post-mortem level interpretation requires caution because factors like post-ingestion survival may lead to originally lethal levels subsiding to therapeutic or even lower levels.<br>• Always have a wide panel of Tox-Screen given the high chance of concomitant drug abuse.<br>• Samples should be shipped at once to the lab or kept frozen until processing.<br>• Sodium Fluoride is the preservative for biological fluids unless something else is indicated by the processing laboratory<br>• It is advisable to use EDTA tubes for sending blood from peripheral veins for analysis. |

The EXTRIP workgroup suggests against performing ECTR in addition to standard care rather than standard care alone (weak recommendation, very low quality of evidence) for gabapentinoid poisoning in patients with normal kidney function. If decreased kidney function and coma requiring mechanical ventilation is present, the workgroup suggests performing ECTR in addition to standard care (weak recommendation, very low quality of evidence).[11]

Patients with chronic kidney disease often receive inappropriately high gabapentin dosage for their kidney function, occasioning overt toxicity; advanced age & comorbidity predispose these patients to toxicity.[12,13]

Gabapentinoids alone rarely cause death but clinically relevant doses can prove fatal, possibly due to reducing tolerance to opioids. In 25.3% of gabapentinoid deaths in England, the gabapentinoid had been co-prescribed with an opioid.[13]

Nortriptyline is an antidepressant that falls under the category of Tricyclic Anti-Depressants. The consensus is that nortriptyline inhibits the reuptake of serotonin and norepinephrine by the presynaptic neuronal membrane, thereby increasing the concentration of those neurotransmitters in the synapse. Additionally, nortriptyline inhibits the activity of histamine, 5-hydroxytryptamine and acetylcholine. The pharmacokinetics i.e., ADME data, adverse effect profile and pharmacogenomics considerations of the drug can be accessed from here.[14] However, properties like high affinity for plasma and tissue protein binding are worth mentioning from a toxicology angle.

**Table 2: Clinical Toxicology Profile of Nortriptyline[15]**

| | |
|---|---|
| **Signs and Symptoms**<br>• Cardiovascular system : Sinus tachycardia, vision ST/T wave changes, Prolonged PR/QRS/QT, Cardiogenic shock, Ventricular fibrillation/tachycardia, asystole, Heart block, Vasodilatation, Hypotension<br>• Central nervous system : Drowsiness, Coma, Convulsions, Pyramidal signs, Delirium, Respiratory depression, Ophthalmoplegia.<br>• Anticholinergic effects : Dry mouth, Blurred vision, Dilated pupils, Urinary retention, Rigidity, Absent bowel sounds Pyrexia, Myoclonic twitching. | **Management of Toxicity**<br>Management plan for treatment of tricyclic overdose<br>1. Assess and treat ABCs as appropriate.<br>2. Examine for clinical features. Check urea and electrolytes—look for low potassium. Check arterial blood gases—look for acidosis Perform electrocardiograph—look for QRS>0.16 seconds<br>3. Consider gastric lavage only if within one hour of a potentially fatal overdose.<br>4. Give 50 grams of charcoal within one hour of ingestion.<br>5. Give sodium bicarbonate (50 ml of 8.4%) if a pH of 0.16. Check for arrhythmias and hypotension<br>6. Arrhythmias: Avoid antiarrhythmics. Correct hypoxia, hypotension, acidosis, and hypokalaemia. Give sodium bicarbonate.<br>7. Hypotension: Give intravenous fluids Consider inotropes<br>8. Cardiac arrest : Prolonged resuscitation may be successful<br>9. Monitoring: Patients who display signs of toxicity should be monitored for a minimum of 12 hours |
| **Autopsy Findings**<br>• Always check for Co-Contributory Pathological causes responsible for the death.<br>• Non-specific findings<br>• Anato-morphological findings are rare considering the mechanism of action being exerted at a physiological and biochemical level. | **Analytical Toxicology Considerations**<br>• HPLC<br>• GCMS<br>• Same as stated for Gabapentin. |

In a reported case, a 31-year-old male committed suicide by overdosing himself on nortriptyline, an unusually high heart blood concentration of 86.4 mg/L is reported, along with high femoral blood and tissue concentrations.[16] Tako-tsubo cardiomyopathy or myocardial stunning is also seen due to nortriptyline overdose.[17] The problem of delayed cardiotoxicity by way of ventricular arrhythmias should always be borne in mind in cases of massive toxicity.[18]

The therapeutic index of TCAs is narrow, and therefore, the ingestion of 10 to 20 mg/kg is potentially life-threatening. Symptoms usually start in 30 to 40 minutes, and signs of toxicity are usually clinically apparent within 2 hours, but delayed toxicity may occur. A history of co-ingestion or access to other medications, including acetaminophen and aspirin, is essential. Close attention to the patient's vital signs and repeated physical examination for evidence of an anticholinergic toxidrome, cardiac toxicity, and neurologic toxicity should be done and will help guide proper management.[19]

In the present case under discussion, the combined toxic effect of both gabapentin and nortriptyline could be the cause of death in the presence of several co-morbid conditions like senility, fatty liver and presbycardia. The CNS effects of Gabapentin and delayed cardiac complications of nortriptyline can be held responsible for this death due to intentional self-harm.

## Conclusion:

The mainstay of gabapentinoid toxicity is supportive whereas in a case of intentional or unintentional tricyclic anti-depressant poisoning, apart from the traditional toxidrome of TCA toxicity, the patient may also present with metabolic acidosis because of tissue hypoxia consequent to seizures/ cardiovascular abnormality. A QRS interval of more than 100 milliseconds is the basis of treatment with intravenous sodium bicarbonate. Gastric lavage and administration of activated charcoal will serve any purpose only if administered immediately after the overdose.

**Conflicts of interest :** Nil

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**Ethics Committee Approval :** Taken

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**Image 1 : Photo-micrographs showing fatty liver (40X, H & E)**

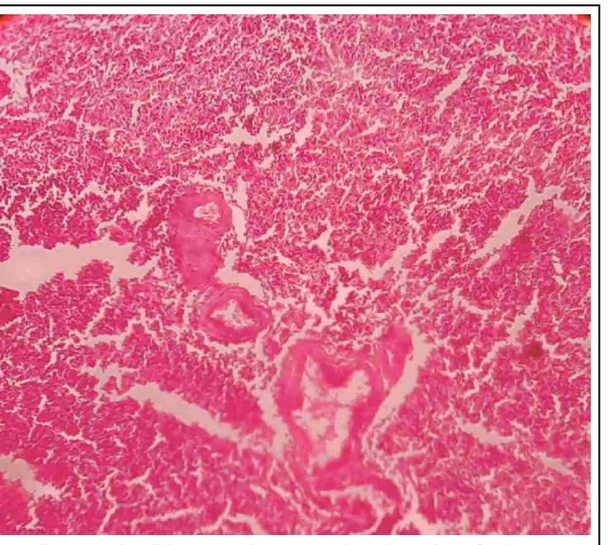

**Image 2 : Photo-micrographs showing Spleen with dilated sinusoids (40X, H & E)**

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