PHENOBARBITONE TOXICITY: A RARE ADVERSE DRUG REACTION CASE REPORT EMPHASIZING PATIENT CARE AND CLINICAL MANAGEMENT

Vasantha Priya*[1], Saheena.C[1], Adivesha.SA[1] and Dr. Syed Mohammed Hussaini[2]

[1]VI Pharm D Interns, TVM College of Pharmacy, Karnataka , Ballari – 583104

[2]Pharm D Graduate, KSPC Registered Pharmacist, Karnataka , Ballari – 583104

ABSTRACT

Phenobarbitone is a long-acting barbiturate commonly used in the management of seizure disorders, particularly in resource-limited settings due to its affordability and efficacy. However, its narrow therapeutic index and prolonged half-life predispose patients to potential toxicity, even during chronic therapeutic use. We report a case of a 28-year-old female with a known seizure disorder on long-term phenobarbitone therapy who presented with altered sensorium and reduced responsiveness. Clinical assessment revealed moderate central nervous system depression (E2V4M4) with stable vital parameters. Laboratory evaluation demonstrated severe microcytic hypochromic anemia, and serum phenobarbitone levels were elevated at 59 µg/mL, exceeding the toxic range (>40 µg/mL). The patient was managed with prompt supportive care, monitoring and modification of antiepileptic therapy, leading to gradual clinical improvement without major cardiopulmonary complications. This case emphasizes the importance of therapeutic drug monitoring, periodic laboratory surveillance, and early recognition of toxicity in patients receiving long-term phenobarbitone therapy to ensure safe and effective seizure management.

KEY WORDS : Barbiturate toxicity, Central Nervous System depression, Chronic therapeutic use, Phenobarbitone, Seizure disorder.

INTRODUCTION

Phenobarbital is classified as a short-acting barbiturate, and is used as a sedative hypnotic agent. Pentobarbital is another barbiturate derivative, used as a sedative and anticonvulsant. Both drugs are classified as barbiturates with pharmacological mechanisms involving the same target : the neuronal gamma aminobutyric acid (GABA) receptor. As a result, both suppress neuronal activity.[1] Despite their therapeutic versatility, the clinical use of barbiturates has significantly declined due to the emergence of benzodiazepines and other CNS depressants that provide similar efficacy with improved safety margins. Several barbiturates have been either withdrawn from the market or relegated to niche indications due to their high potential for dependence, narrow therapeutic window and profound CNS and respiratory

depression.[2] Despite a lower rate of barbiturate utilization overall, barbiturate toxicity is still a prevalent cause of significant morbidity and mortality that requires prompt and effective care to mitigate.

Epidemiology –

Barbiturate toxicity increases with greater access to and use of these drugs. In the United States, barbiturate sales increased from approximately 100 tons in 1939 to nearly 2,000 tons in the 1960s, which was associated with increased hospitalizations and deaths. During this period, individuals at higher risk included women over 45 years of age who developed dependence on prescribed barbiturates and young men who abused multiple substances. From the 1970s onward, the introduction of safer alternatives such as benzodiazepines, along with stricter regulatory measures, led to a significant reduction in barbiturate use and toxicity. By 2002, barbiturate toxicity had become rare in the United States, with only 375 cases and 21 deaths reported. Currently, only a limited number of barbiturates are used therapeutically, and accidental toxicity is uncommon; however, most contemporary cases result from intentional overdose. Approximately two-thirds of hospital admissions for barbiturate toxicity are related to suicide attempts, with younger individuals more likely to have underlying mental health conditions and substance use disorders, while older individuals commonly have chronic illnesses, bereavement and palliative care needs. Increased online availability and occupational exposure among veterinary, laboratory, and medical professionals continue to contribute to this risk.[3]

Mechanism of action –

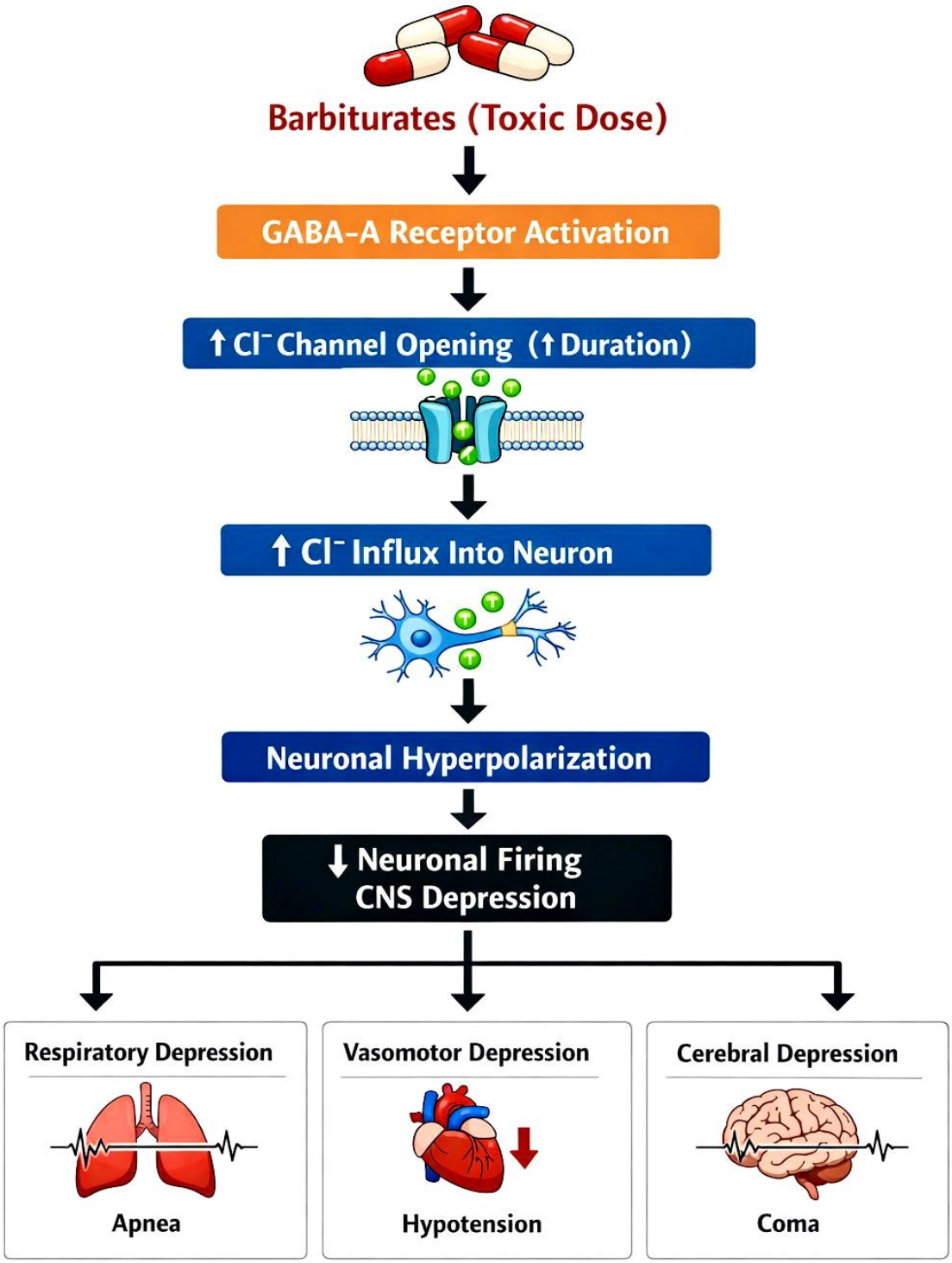


Fig 01 – Schematic Representation of Barbiturate Toxicity Mechanism[2]

Barbiturate Toxicity : Systemic effects –

Affected System	Mechanism / Pathophysiology	Clinical Manifestations
Central Nervous System (CNS)	Potentiation of GABA-A receptor–mediated inhibitory neurotransmission causing dose-dependent CNS depression.	Drowsiness, confusion, slurred speech; ataxia; nystagmus; deep coma with loss of brainstem reflexes in severe toxicity.
Respiratory System	Depression of medullary respiratory centers leading to hypoventilation.	Reduced respiratory rate and depth; carbon dioxide retention with respiratory acidosis; apnea requiring mechanical ventilation.
Cardiovascular System	Myocardial depression and peripheral vasodilation.	Hypotension due to reduced cardiac output; bradycardia; circulatory collapse in massive overdoses.
Renal System	Secondary renal injury due to hypotension or muscle breakdown; reduced elimination.	Acute tubular necrosis secondary to hypotension or rhabdomyolysis; decreased drug clearance in renal impairment, particularly with long-acting barbiturates.
Hepatic System	Hepatic enzyme induction and direct hepatocellular toxicity at high doses.	Enzyme induction with chronic exposure; hepatocellular injury at toxic concentrations.
Muscular and Skeletal System	Prolonged immobilization and severe CNS depression.	Generalized muscle flaccidity; rhabdomyolysis associated with prolonged coma or immobility.
Skin and Ocular Manifestations	Pressure-related ischemia during prolonged unconsciousness.	Bullous skin lesions (“barbiturate blisters”); conjunctival congestion or corneal injury in comatose patients.

Table 01 - Systemic Clinical Manifestations of Barbiturate Toxicity[4]

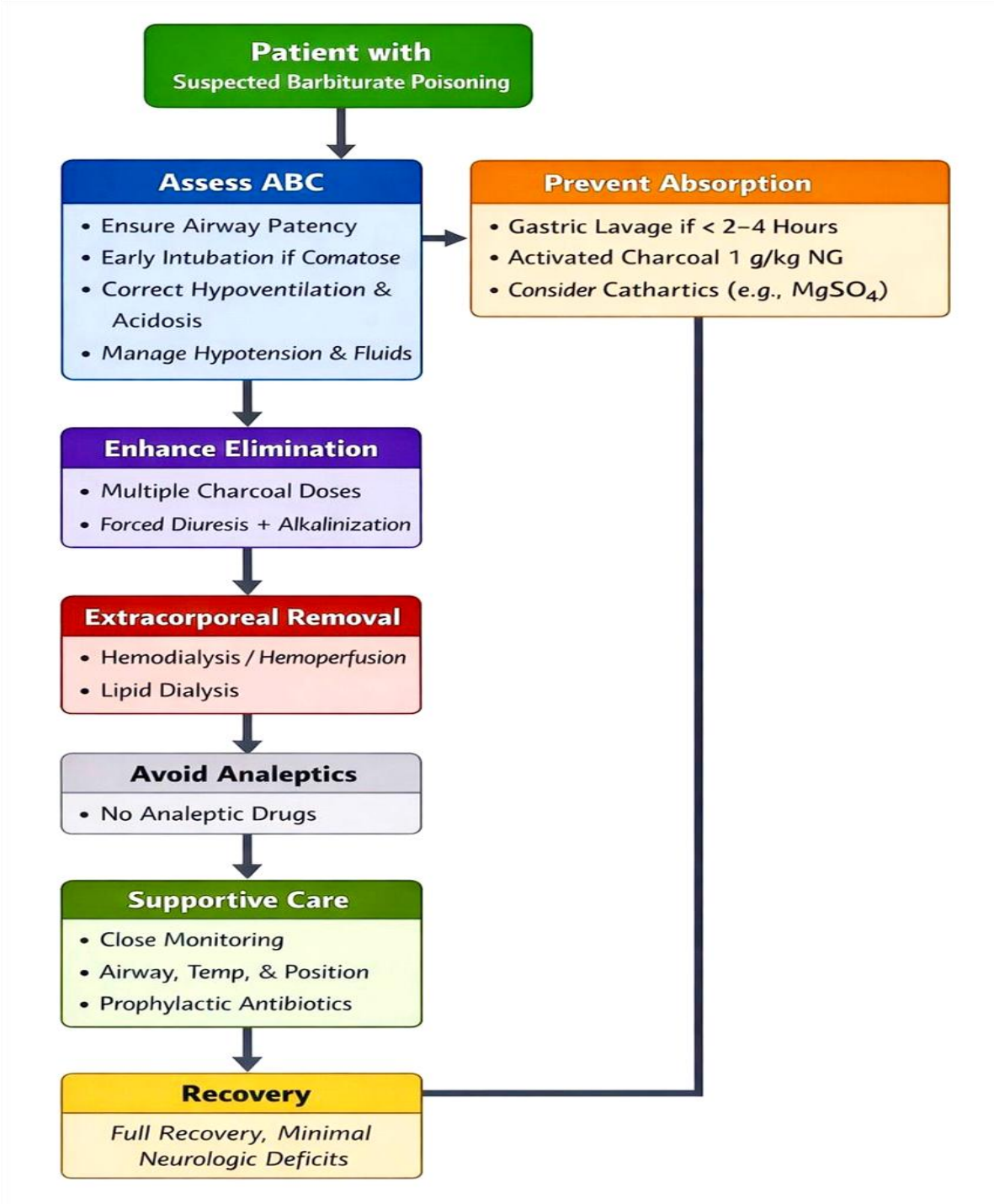


Fig 02 - Algorithmic Approach to the Treatment of Barbiturate Poisoning[5]

Recommended Dosing Strategies for Barbiturates -

FUNDAMENTAL GUIDELINES :

1. Start low : Begin with the lowest effective dose to minimize side effects.
2. Titrate cautiously : Adjust doses slowly to achieve the desired effect.
3. Monitor for toxicity : Watch for sedation, cognitive impairment or respiratory depression.

- **Dosing by Agent:**

  - Phenobarbital : Start 30–60 mg/day; maintenance 1–3 mg/kg/day.
  - Pentobarbital : Start 50–100 mg/day; maximum 200 mg/day.

- **Appropriate Candidates:**

  - Treatment-resistant seizures : When standard antiepileptics fail.
  - Severe short-term insomnia : Typically <2 weeks.
  - Pre-surgical sedation : To calm patients before procedures.

- **Contraindications / Not Recommended:**

  - Pregnant or breastfeeding individuals.
  - History of substance abuse.
  - Severe liver or lung disease due to depressant effects.[4]

CASE PRESENTATION –

A 28-year-old female patient was admitted to vijayanagara institute of medical science (VIMS), Ballari (Karnataka) with chief complaints of altered sensorium since evening in the form of reduced responsivness, patient responses only to the pain.

Past history – k/c/o Seizures disorder since 7 years on medication - T.Levetiracetam 500mg BD and T.Phenobarbitone 60mg BD

Family history – Nothing significant.

On examination –

- BP - 110/70 mmHg.
- PR – 102 bpm.
- SPO_2 - 98% decreased at RA.
- GRBS - 132mg/dl.
- CNS- B/L PERL, E2V4M4 and pupil-BERL.

- B/L NVBS (Normal vesicular breathing sounds) heard
- S1 S2 heard.
- P/A was soft and non-tender.

Laboratory investigations –

PARAMETERS	RESULT (06-01-26)	RESULT (08-01-25)	RESULT (11-01-26)	RESULT (13-01-26)	RESULT (14-01-26)	REFERENCE RANGE
Haemoglobin	5.9	6.2	6.1	7.7	9.8	12.5-16gm
WBC	9010	8490	7950	8600	10870	4000-11000cells/cumm
RBC	3.81	3.68	3.30	4.21	4.62	4.5-5.5millions/cumm
Neutrophils	65	75	90	88	74	40-70%
Lymphocytes	30	21	05	08	22	20-40%
PCV	21.5	20.6	20.0	30.6	31.0	35-46%
MCV	56.4	55.9	60.6	72.7	67	60-100fl
MCH	16.6	16.9	18.6	18.2	21.3	27-34pg
MCHC	29.5	30.2	30.7	25.1	31.7	31-36%
RDW-CV	21.5	21.9	25.2	20.9	33.4	11.5-14.5%
PDW-CV	44.3	18.1	44.5	8.6	49.1	10-18%
Blood urea	14			16	17	15-45mg/dl
Sr. creatinine	0.8			0.6	0.6	0.7-1.4mg/dl
Reticulocyte count		0.4%				
Phenobarbitone Gardinal			59			Toxic range- >40

Table 02 - Laboratory parameters adviced in hospital

Other investigations –

1. **Pheripheral smear** :- Microcytic hypochromic anemia

Treatment –

SL. NO	NAME OF MEDICATIONS	DOSE	ROUTE	FREQUENCY
01.	INJ.LEVETIRACETAM	1gm	IV	BD FOR 10 DAYS
02.	INJ.PANTOPRAZOLE	40mg	IV	OD FOR 10 DAYS
03.	INJ.ONDANSETRON	4mg	IV	BD FOR 10 DAYS
04.	SYP.SUCRALFYL	5ml	PO	BD FOR 10 DAYS
05.	INJ.CEFRIAXONE	1gm	IV	BD FOR 10 DAYS
06.	INJ. METRONIDAZOLE	100ml	IV	TID FOR 10 DAYS
07.	DNS+MULTIVITAMIN	At 75ml/hr	IV	BD FROM DAY 2 TO DAY 10
08.	NEB.IPRAVENT+BUDECORT			6^{TH} HOURLY FROM DAY 8 TO DAY 10

Table 03 - Treatment given in the hospital

Discharge medication -

SL.NO	NAME OF MEDICATIONS	DOSE	ROUTE	FREQUENCY
01.	TAB.LEVETIRACETAM	500gm	po	BD FOR 15 DAYS
02.	TAB.IRON FOLIC ACID	333mg	PO	BD FOR 15 DAYS
03.	TAB.B COMPLEX	1TAB	PO	OD FOR 15 DAYS
04.	TAB.FOLIC ACID	5mg	PO	BD FOR 15 DAYS

Table 04 - Treatment adviced during discharge

Advice on discharge - Review after 15 days with CBC reports.

DISCUSSION –

Although the clinical use of barbiturates has declined substantially with the advent of benzodiazepines and newer antiepileptic drugs, phenobarbitone continues to be widely utilized for seizure control in resource-constrained settings due to its cost-effectiveness and established efficacy. Contemporary literature indicates that most current cases of barbiturate toxicity are associated with intentional overdose; however, therapeutic misadventures and chronic drug accumulation remain recognized but underreported causes. The present case is analytically significant because toxicity occurred in a patient receiving long-term prescribed therapy rather than following an acute overdose. This reinforces the concept that chronic exposure, combined with the drug's long half-life (2–5 days) and narrow therapeutic index, can predispose patients to accumulation even at standard therapeutic doses.

The patient's presentation with altered sensorium (E2V4M4) aligns with established pharmacodynamic principles described in toxicology literature, wherein phenobarbitone potentiates GABA-A receptor–mediated inhibitory neurotransmission, leading to dose-dependent central nervous system depression. Published data demonstrate that serum levels above 40 µg/mL are associated with toxicity and levels exceeding 50–60 µg/mL often correlate with significant neurological impairment. The measured concentration of 59 µg/mL in this case demonstrates a strong concentration–clinical effect relationship, supporting previously documented pharmacokinetic–pharmacodynamic correlations.

Unlike severe cases reported in the literature that progress to respiratory failure, hypotension and the need for mechanical ventilation, this patient maintained stable hemodynamic and respiratory parameters. This comparatively milder systemic involvement suggests early detection and prompt supportive intervention, highlighting the prognostic importance of timely hospital presentation. Evidence-based management guidelines consistently emphasize supportive care, airway monitoring and prevention of complications as the cornerstone of treatment, given the absence of a specific antidote. The favorable outcome observed in this case aligns with these recommendations.

When compared with the case reported by Dr. Shashi Kiran et al, several similarities and distinctions are evident. In the published case of acute suicidal phenobarbitone ingestion, the patient presented with Grade III coma, areflexia, respiratory compromise, metabolic acidosis and required mechanical ventilation followed by haemodialysis. In contrast, our patient exhibited moderate CNS depression without severe respiratory failure or hemodynamic instability, and oxygen saturation remained relatively preserved. This difference may be attributed to chronic therapeutic exposure with possible cumulative toxicity rather than massive acute overdose.

An additional analytical dimension is the presence of severe microcytic hypochromic anemia. While barbiturates are more commonly associated with megaloblastic changes secondary to folate deficiency,

chronic enzyme induction and nutritional interference may contribute to hematological derangements. Although direct causation cannot be definitively established, the coexistence of long-term phenobarbiturone therapy and hematological abnormalities warrants consideration of systemic monitoring, as suggested in pharmacovigilance literature.

Furthermore, this case underscores the importance of therapeutic drug monitoring in chronic antiepileptic therapy. Studies emphasize that interindividual variability in hepatic metabolism, drug interactions and adherence patterns can significantly alter serum concentrations. Periodic serum level estimation is therefore recommended, particularly in patients receiving long-term therapy.

CONCLUSION -

Phenobarbitone toxicity, though uncommon in modern practice, can occur during long-term therapeutic use due to its long half-life and narrow therapeutic index. This case demonstrates that chronic administration may lead to drug accumulation and central nervous system depression even at standard doses. Early recognition, therapeutic drug monitoring, and prompt supportive management were crucial in achieving a favorable outcome without severe cardiopulmonary complications. The presence of associated hematological abnormalities further underscores the need for comprehensive laboratory surveillance in patients receiving prolonged therapy. Regular dose reassessment, individualized treatment, and vigilant pharmacovigilance are essential to ensure patient safety in long-term antiepileptic management.

REFERENCES –

1. Takei S, Kinoshita H, Jamal M, Kumihashi M, Yamashita T, Tanaka E, et al. Case report: Fatal poisoning caused by additive effects of two barbiturates. *Front Pharmacol*. 2023;14:1196565. doi:10.3389/fphar.2023.1196565.
2. Buckley NA, Dawson AH, Whyte IM, O'Connell DL. Relative toxicity of benzodiazepines in overdose. *BMJ*. 1995;310(6974):219–21. doi:10.1136/bmj.310.6974.219.
3. Coupey SM. Barbiturates. *Pediatr Rev*. 1997 Aug;18(8):260-264. doi:10.1542/pir.18-8-260.
4. Brent J. Barbiturate poisoning. In: Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW, editors. *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 2nd ed. Philadelphia: Elsevier Mosby; 2017.
5. Kiran S, Chhabra B, Nandini. Management of barbiturate poisoning – A case report. *Indian J Anaesth*. 2002;46(6):480-482.