
Phenobarbitone Toxicity: Management of Acute and Chronic Overdose

ABSTRACT

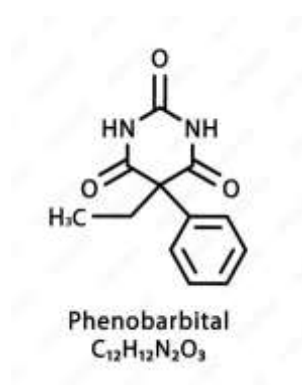
This is the case study of two patients with phenobarbitone poisoning, one of them is acute phenobarbitone poisoning and the other one was chronic phenobarbitone poisoning. These two cases were managed differently one with Forced alkaline diuresis and the other one with the Haemodialysis. Phenobarbitone is a long-acting barbiturate which can cause CNS depression, respiratory failure and hemodynamic instability when consumed in overdose.

Keywords: Phenobarbitone poisoning; CNS inhibition; antiepileptics; anaesthetic agent.

1. BACKGROUND

Phenobarbitone is barbiturate with the chemical formula 5-ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione. Barbiturate act by potentiating the neuroinhibitory effect of GABA (Gamma aminobutyric acid). Barbiturate act by two mechanism one of them is, it can bind to Beta subunit of GABA-A receptor and increase the duration of chloride ion channel hence potentiating the neuroinhibitory effect of GABA and the other mechanism is barbiturate directly stimulate GABA-A receptor outside GABA itself [1] in large doses. Barbiturate causes CNS inhibition and hence are used clinically anxiolytic, sedation, antiepileptic or as anaesthetic agents. Phenobarbitone belongs to class of long-acting barbiturates with half life of around 5 days.

Phenobarbitone has narrow therapeutic index and has a variable rate of metabolism in different individuals. Narrow therapeutic index 10-30 mg/litre. In this narrow range of drug patient is prescribed for anxiety and for sedation effects and this is very close to those associated with toxicity. Phenobarbitone toxicity can cause CNS depression, respiratory failure along with hemodynamic instability. Since the half life $t_{1/2}$ of drug is around 5 days, the patient can remain comatose for several days [2]. Barbiturate poisoning is usually treated by supportive management; lavage by activated charcoal; and forced alkaline diuresis along with hemodialysis, But the benefits of one approach over another cannot be said as there is less recent data to support one approach over another.



With the availability of Benzodiazepines, and newer antiepileptics Barbiturate use is rapidly declined in the west. Barbiturate poisoning occurs more easily cause Barbiturate act by binding to GABA -A and also can directly open chloride channel as compared to Benzodiazepines, BZDs can effectively be antagonised by flumazenil, which competitively binds to GABA-A receptor and inhibit the effect of BZD and hence flumazenil treatment can counteract the BZD toxicity but not Barbiturates.

Fig. 1. Chemical structure of Phenobarbital

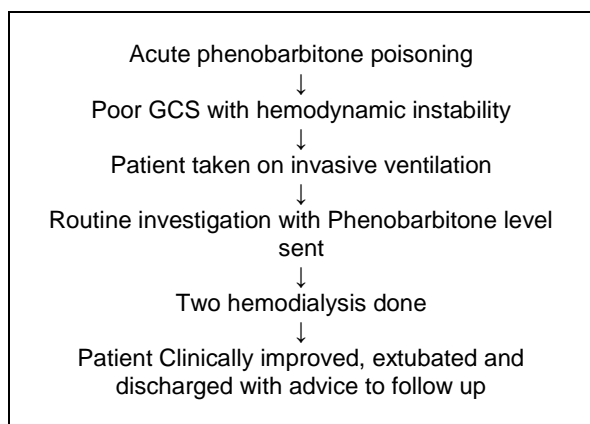
Continued usage of Barbiturate elsewhere in world; hence Barbiturate poisoning can easily occur as it is widely available and widely prescribed drugs. And hence it will be very interesting to see what will be the effective treatment of phenobarbitone poisoning.

Case 1: Acute Poisoning

A patient 25 year old male resident of Mirzapur UP with alleged history of consumption of unknown amount of Phenobarbitone taken at unknown point of time within 24 hours. Patient was brought by his relatives to the emergency medicine unit (EMU) with GCS E1V1M1 at presentation. Patient was hemodynamically unstable and in shock Blood pressure 80/50 mm/Hg. Gastric lavage was done and after that patient was immediately intubated and shifted to medicine intensive care unit (MICU). Routine investigations were sent along with phenobarbitone level. Patient was aggressively managed with fluid resuscitation.

Routine investigations were Normal but phenobarbitone level were 103mg/dl (therapeutic range 10-30 mg/dl) and hence early call for haemodialysis were taken. Two slots for haemodialysis (2.5 hours duration, dialyser flow rate 500ml/min with pump speed 200 ml/min) taken.

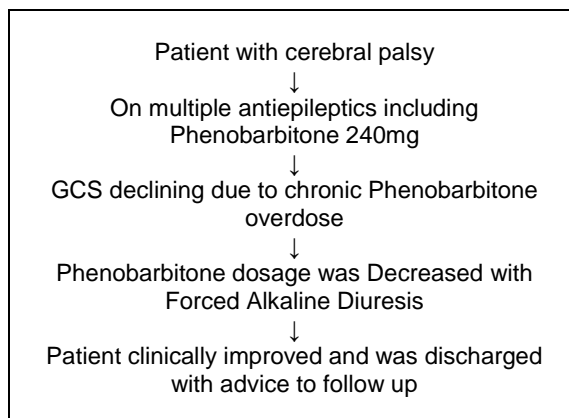
Patient GCS dramatically improved after haemodialysis with spontaneous eye opening after first haemodialysis and full GCS after second slot of haemodialysis. Within next few hours patient became haemodynamically and clinically stable and suitable for extubation and hence extubated within 72 hours of presentation. The patient recovered completely within next few hours. Complete psychiatric workup was done before discharging the patient.



Flow Chart 1. Flow chart showing psychiatric workup
Case 2: Chronic Poisoning

A 23 year old male with known case of cerebral palsy with Epilepsy on multiple antiepileptics presented with fever, cough and respiratory distress for 3-4 days. On Examination patient was febrile, tachypnoeic with Glasgow coma scale E2V2M5, lab investigations were done and suggestive of Sepsis with TLC 14000 cells/mm³ with normal LFT, RFT, ABG and Chest X ray of the patient. Fever subsided with IV antibiotics and supportive care but the patients GCS was not improved. His CT head was also normal. Patients antiepileptics usage was reviewed.

He was taking Phenobarbitone 240mg, valproate 1 gm, zonisamide 200mg, oxcarbamazepine 600mg. His neurological examination didn't show any focal deficits hence the possibility of chronic phenobarbitone overdose was considered. His serum phenobarbitone level was 70mg/l. In view of the patients long-term barbiturate usage patient was given supportive treatment with forced diuresis and a reduction in dosage of phenobarbitone to 90mg. Dose of valproate was increased to 1500mg. The patient GCS improved to E4V3M6 and was discharged with the advice of follow up.



Flow Chart 2. Flow chart showing improvement to E4V3M6

2. DISCUSSION

Lethal dose of Phenobarbital is usually in range of 6-10 gm [3], the concentration of 80 mg/l is fatal [4]. The patient has ingested higher dose than fatal dose in acute poisoning and is currently hemodynamically unstable. Hemodialysis produced rapid reduction of phenobarbitone level which can be seen as an improvement in GCS and hence clinical recovery of patient. Early call for haemodialysis significantly reduces the stay in ICU and hence associated infections and also reduces the cost bearing to the patient. Trinder R et al. [5] showed a similar result in the treatment of

phenobarbitone intoxication in 18 month old male. There is several literature available which show similar success like in Balme et al [6], Quan and winter [7] and Palmer [8].

There are plenty of successfully treated case of Phenobarbitone by hemodialysis are already reported in literature. Patients with chronic poisoning are relatively well tolerated and hence haemodynamically stable and hence managed conservatively with forced alkaline diuresis.

There is a different consensus regarding hemodialysis vs hemoperfusion in treating barbiturate poisoning. Historically hemoperfusion was sought to be superior because barbiturates (Phenobarbitone) has 40-60% protein binding but previously hemoperfusion was compared with low efficacy dialysis with low blood flow rate but with new and more superior HD machine leads us to rethink the traditional treatment modality as hemoperfusion vs hemodialysis through newer haemodialysis machine.

Phenobarbitone poisoning is one of the ideal conditions for Haemodialysis removal of the drug as it has low molecular weight, high water solubility and small volume of distribution. It has been shown that Phenobarbitone clearance through high flux dialysis is 30 times than hepatic clearance and 10 times that with activated charcoal.

Nowadays in tertiary care centre with easy availability of Haemodialysis option it can be an appealing choice for Phenobarbitone poisoning as it is cost-effective and widely available.

3. CONCLUSION

There is two cases of Phenobarbitone overdose:

One is acute overdose of phenobarbitone toxicity resulting in phenobarbital coma, which required immediate intubation after which two slots of haemodialysis were done, patient clinically improved and extubated and successfully discharged.

Second is chronic overdose of phenobarbitone resulting in declining GCS, as patient was on chronic phenobarbitone usage hence it was relatively well tolerated and hence managed conservatively with the forced alkaline diuresis. These are the two cases of phenobarbitone poisoning managed successfully with different approaches of treatment, According to patients clinical status. There is several kinds of literature available to support haemodialysis as a

successful mode of treatment of phenobarbitone poisoning but to make the preferred mode of treatment several investigations are required to know the level above which Haemodialysis should be done and to decide which Haemodialysis regime should be preferred. Hence more and more literatures are required to answer these questions.

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CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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