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Pharmacokinetic analysis of a phenobarbital overdose treated with urinary alkalinization alone

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ABSTRACT

Phenobarbital is a long-acting barbiturate used to treat alcohol withdrawal and epilepsy. Acute overdoses present with varying levels of central nervous system depression and large overdoses can be life threatening. Phenobarbital is an attractive candidate for enhanced elimination using urinary alkalinization given it is a weak acid with a long half-life and extensive urinary elimination. Limited human data exist regarding use of urine alkalinization for the treatment of phenobarbital overdose. We present a fourteen-year-old female who was treated with urinary alkalinization alone following an intentional ingestion of 3800 mg (84.4 mg/kg) of phenobarbital tablets. Urine drugs of abuse screening was preliminary positive for barbiturates and confirmed to be phenobarbital only. The initial serum phenobarbital concentration, drawn nine hours post-ingestion, was 97.4 mcg/ml (normal range 15–40 mcg/ml). Urinary alkalinization with sodium bicarbonate was started approximately 12 h post-ingestion and stopped at 72 h post-ingestion; clinical toxicity resolved by hospital day 5. The infusion was titrated to a urinary pH of greater than 7.5. Serial serum and urine phenobarbital measurements were obtained to determine elimination half-life and urinary excretion. The elimination half-life while undergoing urinary alkalinization was 81.3 h. Prior to initiation of urinary alkalinization, the urine phenobarbital concentration was 37 mcg/ml. Approximately 8.75 h after initiation, it was greater than 200 mcg/ml at a urine pH of 8.5. Urinary alkalinization appeared to augment urinary phenobarbital excretion, though with no discernible effect on elimination half-life and unclear clinical benefit. Further research is needed to better characterize the clinical effects of urinary alkalinization for phenobarbital overdose.

1. Introduction

Phenobarbital is a long-acting barbiturate commonly prescribed as a first line treatment for canine epilepsy and human alcohol withdrawal, and as a less commonly used medication for human epilepsy [1,2]. In general, barbiturate overdoses are rare; 1274 exposures were reported in the United States to domestic poison centers in 2022 [3].

The effects of acute phenobarbital overdoses are well reported, presenting with varying levels of central nervous system depression depending on the amount ingested and individual tolerance developed from chronic use [4–6]. Overdoses have been associated with potentially life threatening cardiac, pulmonary, and central nervous system depression that can mimic brain death, especially in phenobarbital-naïve patients [7].

Phenobarbital has a long elimination half-life of 75–126 h in therapeutic use, though its elimination half-life in overdose is not well characterized. It undergoes primarily hepatic metabolism, though a significant portion (25–50 %) is excreted in the urine unchanged [2]. Phenobarbital is a weak acid (pKa 7.24) which makes it an attractive candidate for enhanced elimination using urinary alkalinization [6]. Urinary alkalinization is thought to augment urinary excretion of weak acids like phenobarbital by increasing urinary pH which maintains more of the target xenobiotic in ionized form and reduces renal tubular reabsorption [8]. Unfortunately, limited human data exist regarding the effectiveness of urine alkalinization alone for the treatment of phenobarbital overdose [9].

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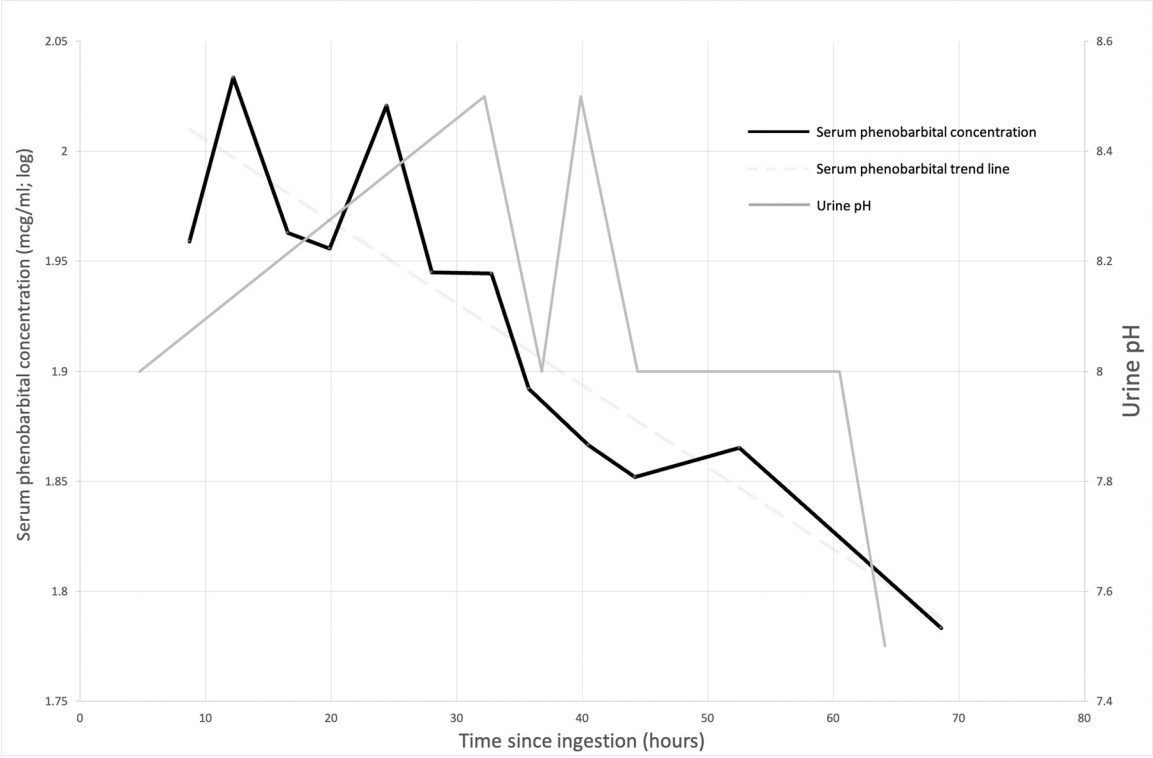

Fig. 1. Trends of serum and urine pH following initiation of sodium bicarbonate.

We present pharmacokinetic data following a large adolescent oral phenobarbital overdose treated with urinary alkalinization alone.

2. Case description

A healthy fourteen-year-old 45 kg female on no medications presented initially to an outside hospital emergency department following an intentional ingestion of 3800 mg (84.4 mg/kg) of phenobarbital tablets originally prescribed to the family dog for epilepsy. Vital signs, obtained in the emergency department approximately one hour after ingestion, were heart rate 90 beats per minute, blood pressure 95/56 mmHg, respiratory rate 19 breaths per minute, oxygen saturation 96 % on room air, and core temperature 36.5 °C. The patient was transferred to our intensive care unit approximately eight hours after ingestion. She was noted at that time to be unresponsive to noxious stimuli and areflexic but maintaining her airway with adequate spontaneous respirations.

Initial laboratory testing and electrocardiogram performed at the outside hospital were all within normal limits. Serum ethanol was undetectable. The initial serum phenobarbital concentration, drawn approximately nine hours post-ingestion, was 97.4 mcg/ml (normal range 15–40 mcg/ml). The initial urine phenobarbital concentration, obtained approximately 10 h post-ingestion and performed using gas chromatography/mass spectrometry was 37 mcg/ml (detection limit: 5 mcg/ml). Urine drugs of abuse screening performed approximately 10 h post ingestion using an enzyme-linked immunosorbent assay-based platform was preliminary positive for barbiturates and negative for opiates, fentanyl, methadone, oxycodone, benzodiazepines, and cannabinoids. Confirmatory testing using liquid chromatography/tandem mass spectrometry was positive for phenobarbital and negative for amobarbital, butabarbital, butalbital, pentobarbital, and secobarbital at a detection limit of 100 ng/ml.

The medical toxicology service was consulted and recommended treatment with urinary alkalinization. A 2 mEq/kg (180 ml) bolus of 4.2 % sodium bicarbonate was administered approximately 12 h post-ingestion, which was immediately followed by initiation of an infusion of 150 mEq sodium bicarbonate in one liter of 5 % dextrose solution at an initial rate of 9.6 mEq/hour (64 ml/hour). The sodium bicarbonate infusion was titrated to a urinary pH goal of greater than 7.5. The initial urine pH, measured at approximately 12 h post ingestion, was 6.5 and, on the next urine pH check approximately 17 h post ingestion, the pH was noted to be 8.0. She did not receive any other treatments.

By approximately 24 h post-ingestion (12 h post initiation of treatment), the patient began withdrawing to noxious stimuli. She was able to follow commands and speak at 72 h post-ingestion, at which point urinary alkalinization was discontinued. By hospital day five, the patient had fully recovered and was transferred to a psychiatric facility.

3. Pharmacokinetic analysis

The patient underwent serial blood and urine phenobarbital measurements to determine the elimination half-life and extent of urinary excretion. The first serum phenobarbital concentration obtained during urinary alkalinization, approximately 5.5 h after initiation, was 91.0 mcg/ml. The final serum phenobarbital concentration obtained during urinary alkalinization, drawn approximately 59 h after the first, was 60.7 mcg/ml. The elimination half-life while undergoing urinary alkalinization was then derived. From these results, we calculated an elimination constant (k) of 0.008521/hour. Using the formula $0.693/k$, we determined the elimination half-life during urinary alkalinization to be 81.3 h. The calculated volume of distribution was 0.93 L/kg. Insufficient measurements were obtained prior to initiation of urine alkalinization to determine the pre-intervention elimination half-life. Fig. 1 demonstrates the trend of blood phenobarbital concentrations over time.

Serial random urine phenobarbital concentrations were also sent to evaluate urinary phenobarbital excretion following initiation of urinary alkalinization. The initial urine phenobarbital concentration was obtained approximately 1.5 h prior to initiation of urine alkalinization (10.5 h after ingestion) and was measured at 37 mcg/ml; urine pH was

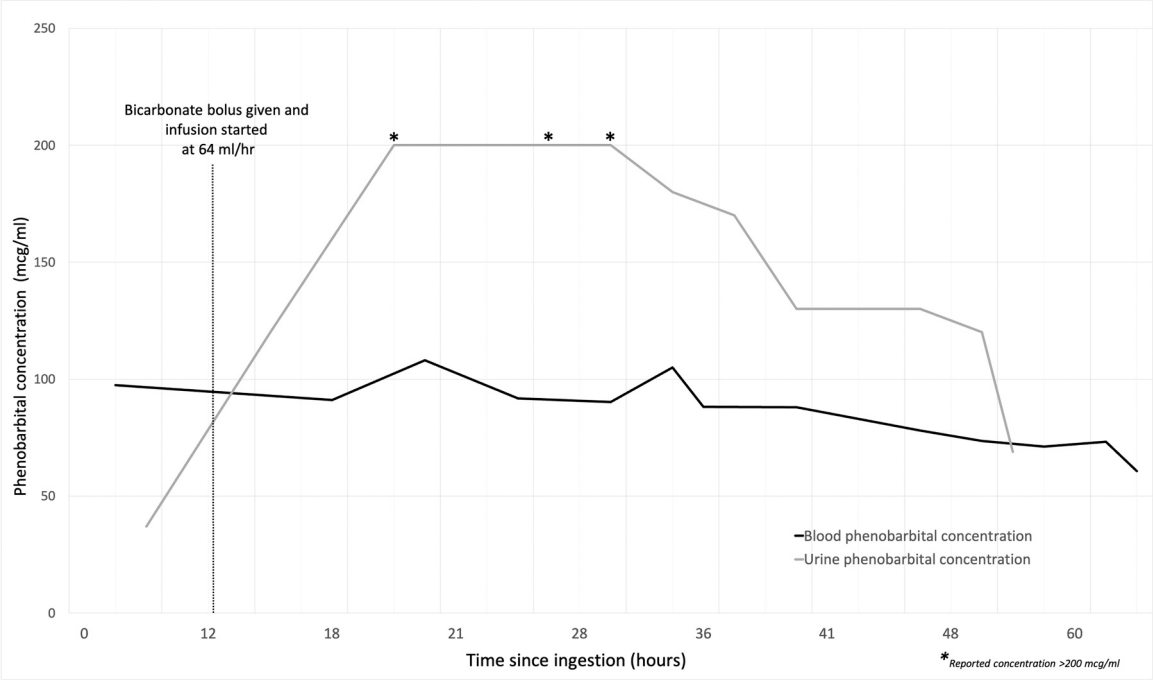

Fig. 2. Trends of serum and urine phenobarbital concentrations following initiation of sodium bicarbonate.

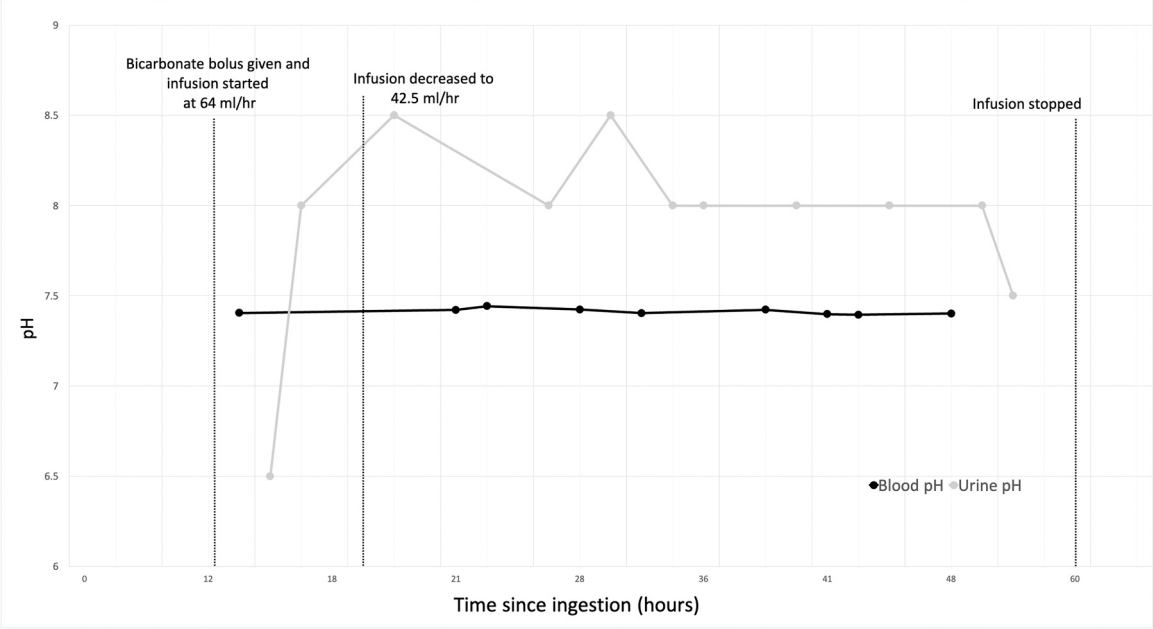

Fig. 3. Blood and urine pH trends following initiation of sodium bicarbonate.

not measured at that time. Subsequent urine phenobarbital concentrations were obtained following initiation of urine alkalinization. At 27 min after initiation, the urine phenobarbital concentration was 120 mcg/ml with a urine pH of 6.5 and a venous blood pH of 7.404. At approximately 8.75 h after initiation, the urine phenobarbital concentration was greater than 200 mcg/ml at a urine pH of 8.5 and venous blood pH of 7.421. The final urine measurement, obtained approximately 39.75 h after ingestion, showed a urine phenobarbital concentration of 69 mcg/ml at a urine pH of 7.5. Fig. 1 demonstrates serum phenobarbital concentrations and urine pH measurements, Fig. 2 demonstrates serum and urine phenobarbital concentrations, and Fig. 3 shows venous blood pH and urine pH over time.

4. Discussion

Urinary alkalinization has been shown to slightly decrease phenobarbital half-life and increase urinary excretion in animal models [8]. Human studies, on the other hand, have mixed results, with some showing improved phenobarbital clearance while others showed no significant change [9,10]. There is no known benefit to addition of forced diuresis to urinary alkalinization and it is not recommended [10,11].

In this case, the elimination half-life of phenobarbital following initiation of urinary alkalinization was calculated to be 81.3 h. This value is nearly identical to the reported elimination half-life of 81.1 ±

14.6 h observed from the study of ten severely phenobarbital poisoned patients treated with urinary alkalinization alone [9]. This is also well within the reported normal range [2].

It is noteworthy that we noted a large increase in urinary phenobarbital concentrations soon after initiation of urinary alkalinization. The patient had been untreated for over 11 h prior to initiation and had a measured urine phenobarbital concentration nearly 70 % lower than the first measured value after initiation of urinary alkalinization approximately 90 min later, even when urine pH was not at goal. This suggests urinary phenobarbital clearance is augmented by urine alkalinization. Unfortunately, several measurements were above the upper limit of detection and urine volumes were not reported by the laboratory, so the true extent of augmented urinary excretion could not be completely determined. However, Fig. 2 clearly visually demonstrates that even at peak urinary phenobarbital excretion in the setting of urinary alkalinization, there was limited if any downward pressure exerted on serum phenobarbital concentrations and thus elimination half-life.

Though this elimination half-life is at the low end of the established normal range for phenobarbital, we did not collect sufficient samples to determine the patient's individual elimination half-life prior to initiation of urinary alkalinization. Consequently, we cannot directly comment on whether and to what extent this treatment shortened the elimination half-life from what would have been the patient's individual baseline without treatment. However, it remains that the measured elimination half-life sits within the established normal range without intervention and therefore the effect of urinary alkalinization on phenobarbital elimination kinetics, if present at all, was likely modest.

5. Conclusion

These data suggest that urinary alkalinization augments urinary phenobarbital excretion. However, our data do not show a clear relationship between increased excretion and decreased serum levels and elimination half-life. Consequently, we could not demonstrate that use of urinary alkalinization alone in this case demonstrated meaningful clinical benefit. Further research is needed to better characterize the potential benefits of urinary alkalinization for the treatment of phenobarbital overdose.

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Conflict of Interest statement

The authors have no relevant conflicts of interest to disclose.

Consent

Consent to publish was obtained from the patient's father

CRediT authorship contribution statement

Justin Seltzer: Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis. **Jeremy Hardin:** Writing – review & editing. **Henrik Galust:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nathan Friedman:** Writing – review & editing. **Bryan Corbett:** Writing – review & editing. **Richard F. Clark:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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