Medical Toxicology 2: 383-387 (1987)
0112-5966/87/0009-0383/$02.50/0

Primidone Crystalluria Following Overdose
A Report of a Case and an Analysis of the Literature

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Summary

Seven cases of crystalluria following primidone overdose have been reported since the 1950s. An eighth case of primidone crystalluria following overdose is presented. Because of low aqueous solubility (600 mg/L at 37°C) which is directly proportional to temperature, any factor increasing renal excretion of unchanged primidone predisposes to crystal formation. Renal clearance is dependent on dosage because of negligible protein binding, zero-order conversion to phenobarbitone (phenobarbital) and first-order conversion to phenylethylmalonamide. Therapy with other anticonvulsants known to induce the metabolism to phenobarbitone does not appear to be protective against crystalluria in overdose situations. The critical serum primidone concentration for crystalluria presence seems to be 80 mg/L. There is evidence for nephrotoxicity of the crystals themselves if formed in vivo *(actual crystal presence during voiding). The chemical phenomenon of supersaturation of a solution is protective against* in vivo *crystal formation with subsequent nephrotoxicity. Vigorous hydration to augment elimination and to lessen the propensity for renal toxicity is recommended.*

Crystalluria following overdose with primidone has been reported 7 times since the drug was first marketed in the early 1950s (Bailey & Jatlow 1972; Brillman et al. 1974; Cate & Tenser 1975; Lagenstein et al. 1977; Morley & Wynne 1957; Turner 1980; van Heijst et al. 1983). In addition to reporting an eighth case of massive crystalluria after an overdose of primidone, this account discusses some factors which affect the renal clearance of unchanged primidone and thus have the potential for altering the predisposition to crystalluria. In addition, the physicochemical characteristics of primidone are considered, specifically with regard to potential for nephrotoxicity from the crystals themselves.

Case Report

A 34-year-old comatose white female was brought to the Truman Medical Center Department of Emergency Services by ambulance. The patient had reportedly been very depressed recently, but was on no medication. She had been drinking alcoholic beverages steadily for 12 to 16 hours prior to presentation. Approximately 1 hour prior to arrival in the emergency room she had consumed 40 to 60 250mg primidone tablets (total dose = 10 to 15g). Physical examination upon presentation revealed a comatose female responsive only to painful stimuli. Vital signs were: blood pressure 100mm Hg palpable; respiration 28, shal-

low; pulse 88 beats/min, regular; temperature normal. No abnormal posturing was present. Deep tendon reflexes were present and symmetric. Pupils were equal, constricted and unreactive to light. The gag reflex was intact. Rapid intravenous administration of 0.9% NaCl solution brought the blood pressure up to 110/70. She was intubated and placed on a mechanical ventilator. A nasogastric tube was inserted and gastric lavage was begun with activated charcoal (Matzke et al. 1981) every 4 hours and magnesium sulphate 15g as a single dose. Routine laboratory data, including renal and hepatic function tests, were normal. She was transferred to the intensive care unit where hourly intakes and outputs were recorded. Urine remained clear until 8 hours after ingestion, when it suddenly contained a chalky white precipitate.

Microscopic examination of the urine revealed the presence of large numbers of hexagonal crystals, singly and in conglomerates. Intravenous fluids were increased to maintain a high urine output. The crystalluria continued for 12 to 18 hours. Gas chromatographic analysis later revealed the crystals to be unchanged primidone. Serum drug concentration determinations correlated with crystalluria presence are shown in table I. No urine drug concentration determinations were obtained. The patient was extubated within 12 hours of admission, was fully alert and oriented by 18 hours, and recovered without neurological sequelae 4 days after admission.

Table I. Serum drug concentrations and crystalluria

Hours after ingestion	Primidone (mg/L)	Phenobarbitone (mg/L)
1-2	80	0
8	130[a]	0
24	75	0
48	48	5.4
68	27	7.8
75	23	9.5
96	6	9.0

a Crystalluria present.

Discussion

Pharmacokinetic Factors Affecting Predisposition to Primidone Crystalluria

Peak primidone concentrations occur about 3 hours after a normal dose, but have a wide intersubject variability (Gallagher & Baumel 1972a). The drug exhibits negligible protein binding (Gallagher & Baumel 1972a), which facilitates filtration at the glomerulus and increases the ultimate urinary concentration. Primidone is metabolised to both phenylethylmalonamide (PEMA) and phenobarbitone (phenobarbital), and is excreted in the urine unchanged. The percentages of dose administered that are metabolised to phenobarbitone and excreted as unchanged primidone vary depending on dose, duration of therapy, and treatment with concurrent hepatic enzyme inducers (Gallagher & Baumel 1972b).

The ring cleavage reaction yielding PEMA is a first-order, non-saturable process with doses of 250mg to 1g of primidone (Gallagher & Baumel 1972b). In contrast, the oxidation of primidone to phenobarbitone shows zero-order kinetics, with saturation being evident at doses below 1g (Gallagher & Baumel 1972b). If the ring cleavage reaction remains first-order in doses exceeding normal (500 to 1500 mg/day) the percentage of primidone metabolised to PEMA would remain fixed, while the percentage metabolised to phenobarbitone would decrease. This would cause a greater percentage to remain as unchanged and unbound primidone, thus increasing the renal clearance and predisposing to crystalluria. Furthermore, any factor which would cause induction of the oxidative pathway would decrease the percentage of unmetabolised primidone, so that higher doses of primidone would be required to cause crystalluria. Concurrent anticonvulsant therapy (especially phenytoin and carbamazepine) causes induction of the mixed function oxidases responsible for primidone conversion to phenobarbitone (Cloyd et al. 1981). Zavadil and Gallagher (1976) have demonstrated a decrease in renal clearance of unchanged primidone in patients receiving phenytoin concomitantly. The suggestion has been made that

primidone itself can induce its own metabolism (Huisman 1969), but data on clearance of primidone contrasting short and long term dosing have been equivocal (Gallagher et al. 1972).

Patients who are on combination anticonvulsant therapy and who overdose on primidone would be expected to require a higher dose to produce crystalluria. Of the 7 cases previously reported, 2 received phenytoin concurrently (Cate & Tenser 1975; Turner 1980) and 6 received long term primidone administration (Bailey & Jatlow 1972; Brillman et al. 1974; Cate & Tenser 1975; Lagenstein et al. 1977; Morley & Wynne 1957; Turner 1980). The status of the medication history for the other case is unknown (van Heijst et al. 1983). In the case presented here the patient was not concurrently receiving anticonvulsants. The possibility exists, however, that ethanol abuse existed with resultant hepatic enzyme induction (Sellers 1979). However, it has never been demonstrated that ethanol ingestion increases the rate at which phenobarbitone is produced from primidone.

Serum primidone concentrations have been followed in 6 of the 7 cases thus far reported (Bailey & Jatlow 1972; Brillman et al. 1974; Cate & Tenser 1975; Lagenstein et al. 1977; Turner 1980; van Heijst et al. 1983). There seems to be a correlation between serum concentrations of approximately 80 mg/L or greater and onset of crystalluria (Lagenstein et al. 1977). This is in accordance with the findings presented here (table I). In the case of this patient, crystalluria was not detected until 8 hours post ingestion at a time when her serum concentration was 130 mg/L. Upon admission (1 to 2 hours after ingestion) she had a serum concentration of 80 mg/L with no signs of crystalluria. Likewise, 24 hours after ingestion, her serum primidone concentration was 75 mg/L and the crystalluria had cleared.

Physicochemical Characteristics of Primidone

The basic question to be considered is whether any renal toxicity can result from the crystals. Primidone has an aqueous solubility of 600 mg/L at 37°C (Gallagher & Baumel 1972c). Primidone solubility is dependent on temperature, and cooling of urine containing primidone to room temperature causes further precipitation of crystals (Bailey & Jatlow 1972; Morley & Wynne 1957). Based upon the 600 mg/L solubility at body temperature, crystal precipitation *in vivo* would occur if the urine concentration of primidone exceeded that value. Evidence of renal toxicity has been reported in 2 cases (Turner 1980; van Heijst et al. 1983). Van Heijst et al. reported a patient who developed hypotension and transient acute renal failure following an overdose of primidone. She did not develop crystalluria upon voiding and it is unclear whether the acute renal failure related to primidone nephrotoxicity or to hypotension. Turner reported a case of a patient who had crystalluria upon voiding and had proteinuria and haematuria which cleared following resolution of the crystalluria. This patient had no other reason for having abnormal renal function. Unfortunately, in neither case were urine primidone concentrations determined.

Three cases have reported urine primidone concentrations. Bailey and Jatlow (1972) have shown that as little as 200 mg/L can cause crystal precipitation at room temperature. The concomitant serum primidone concentration was 175 mg/L. Their patient, as expected, showed no signs of renal toxicity. The 2 other cases reported urine primidone concentrations exceeding 600 mg/L [1570 mg/L (Cate & Tenser 1975) and 2150 mg/L (Morley & Wynne 1957)]. Cate and Tenser reported a concomitant serum concentration of 95 mg/L. Morley and Wynne did not report any serum concentrations. However, no evidence of renal damage was found and crystalluria was not evident upon voiding. Our patient showed no signs of renal toxicity and no voiding crystalluria, but urine concentrations of primidone were not measured.

The 2 case reports of urine primidone concentrations exceeding the known solubility for primidone in an aqueous solution are examples of the phenomenon of supersaturation of a solution. In each case, as in the case presented here, crystalluria appeared massively and rapidly. Morley and Wynne (1957) described the 'shimmering white crystals

rapidly forming until a very heavy crystalline precipitate had been collected.' This occurred in a small sample of 10ml of urine which had previously been totally clear. Supersaturation of a solution is defined as an unstable system in which the solute remains dissolved in the solvent, but at a higher concentration than its accepted solubility (point of saturation) [Brady & Holum 1981]. The excess solute will remain in solution until a seed of the solute or any foreign particulate matter is added to the solution. Other factors which will cause precipitation are agitation of the solution or scratching the side of the container which holds the solution (Brady & Holum 1981). Thus, the phenomenon of supersaturation of primidone in an aqueous solvent seems to be a protective factor in preventing crystal precipitation and subsequent nephrotoxicity.

Therapeutic Implications

The presence of crystalluria following large ingestions of primidone can be a unique and alarming finding to the clinician. Analysis of these crystals is of singular diagnostic importance in ingestions in which the substance taken is not known. Based on the information gained from the small number of case reports available at this time, crystalluria may be correlated with serum concentrations exceeding 80 mg/L. Factors decreasing primidone renal clearance, such as the presence of enzyme inducers, have yet to be shown to have an effect on diminishing the predisposition to crystalluria in an overdose situation. As the dose of primidone increases, a greater percentage of circulating drug exists in unchanged form, and since primidone is unbound to plasma protein, increasing the glomerular filtration rate should facilitate a greater clearance. Forced alkaline diuresis has been used successfully (Lagenstein et al. 1977). Therefore, vigorous hydration, with or without forced alkaline diuresis, is recommended both from the standpoint of lessening the potential for renal toxicity and of improving elimination. Haemoperfusion has been successful and is recommended in life-threatening intoxications unresponsive to conventional supportive measures (van Heijst et al. 1983). Crystal formation *in vivo* with concomitant crystalluria upon voiding appears to be associated with renal damage. However, in all cases of overdose it would be prudent to follow renal function parameters, both from the standpoint of potential toxicity and ability to excrete unchanged primidone. Urine primidone concentrations should also be determined to select those patients at highest risk of developing *in vivo* crystalluria.

Acknowledgement

I thank Herbert Swick, M.D. and Roger Eskridge, Pharm. D. for their valuable advice in the preparation of the manuscript.

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