pansion will continue until the two compartments are isosmotic. In this case report the patient ingested, in addition to the salt, a large amount of jam, which resulted in another osmotically active solute in the extracellular space. Using the formula summarized by Loeb, we calculated that the serum osmolarity reached 414 mOsm per liter as opposed to the normal 285 to 295 mOsm per liter with the salt contributing approximately 84 percent of the elevation, the sugar 16 percent.[9] Therefore, a greater shift of water from the intracellular space to the extracellular space could be expected due to the salt plus the glucose than from just the salt alone. The role of the glucose ingestion in this particular patient was probably more significant since carbohydrate metabolism is known to be altered in the Prader-Willi syndrome. The rapid shift of water from the cells to the extracellular space produces "shrunken" cells and an expanded vascular space. In the brain, this leads to distended cerebral vessels and subarachnoid, subdural and intravascular hemorrhage. Evidence of passive congestion may also be seen in the lungs and kidneys.[10] Acidosis has been described in hypertonic states and is ascribed to the shift of free hydrogen ions to the extracellular space.[11]

Acute salt poisoning has occurred under various circumstances including eating salt directly.[2] This report is unique in that a woman, because of her condition (Prader-Willi syndrome) and not age, ate a large amount of table salt with jam. The insatiable appetite and mental retardation commonly present in the Prader-Willi syndrome were the major contributory factors responsible for the ingestion.[12,13]

It is worth noting that there is no record of this patient's having vomited after the ingestion of the table salt. This supports the efforts of other authors to condemn the use of salt water as an emetic to treat acute poisoning.[2,4,5,7] To emphasize this point, it should be noted that within the year, five additional deaths consequent to the use of saline as an emetic have been reported; in one patient the serum sodium level was recorded at 227 mEq per liter.[14-16] Recommendations for the use of saline emetics must be expunged from first aid manuals.

Summary

A 45-year-old woman with Prader-Willi syndrome ate an excessive amount of jam and table salt. She became comatose and died within six to seven hours of the ingestion. Laboratory data confirmed hypernatremia, hyperchloremia, hyperglycemia, hyperosmolarity and acidosis. Once again this ubiquitous substance is documented as having lethal potentials. Its possible use as an emetic agent is decried.

REFERENCES

1. Finberg L, Kiley J, Luttrell N: Mass accidental salt poisoning in infancy. JAMA 184:184-190, Apr 20, 1963

2. Calvin ME, Knepper R, Robertson WO: Hazards to health: Salt poisoning. N Engl J Med 270:625-626, Mar 19, 1964

3. Carter RF, Fatheringham BJ: Fatal salt poisoning due to gastric lavage with hypertonic saline. Med J Aust 1:539-541, Mar 6, 1971

4. De Genaro F, Nyhan WL: Salt—A dangerous "antidote." J Pediatr 78:1048-1049, Sep 1971

5. Robertson WO: A further warning on the use of salt as an emetic agent. J Pediatr 79:877, Nov 1971

6. Barer J, Hill L, Hill R, et al: Fatal poisoning from salt used as emetic. Am J Dis Child 125:889-890, Jun 1973

7. Chin L: Induced emesis—A questionable procedure for the treatment of acute poisoning. Am J Hosp Pharm 29:877-879, Oct 1972

8. Moseley PK, Segar WE: Fluid and electrolyte disturbances as a complication of enemas in Hirschsprung's disease. Am J Dis Child 115:714-718, Jun 1968

9. Loeb JN: The hyperosmolar state (Current Concepts). N Engl J Med 290:1184-1187, May 1974

10. Elton NW, Elton WJ, Nazareno JP: Pathology of acute salt poisoning in infants. Am J Clin Pathol 39:252-264, Mar 1963

11. Sotos JF, Dodge PR, Talbot NB: Studies in experimental hypertonicity—II. Hypertonicity of body fluids as a cause of acidosis. Pediatrics 30:180-193, Aug 1962

12. Zellweger H, Schneider HJ: Syndrome of hypotonia, hypomentia, hypogonadism obesity (HHHO) or Prader-Willi syndrome. Am J Dis Child 115:588-598, May 1968

13. Cohen MM, Gorlin RJ: Prader-Willi syndrome. Am J Dis Child 117:213-218, Feb 1969

14. Roberts CJC, Noakes MJ: Fatal outcome from administration of a salt emetic. Postgrad Med J 50:513-515, Aug 1974

15. Winter M, Taylor DJE: Danger of saline emetics in first aid for poisoning. Br Med J 3:802, Sep 28, 1974

16. Bird A: Danger of saline emetics in first aid for poisoning. Br Med J 4:103, Oct 1974

Refer to: Boyer TD, Sun N, Reynolds TB: Allopurinol-hypersensitivity vasculitis and liver damage. West J Med 126:143-147, Feb 1977

Allopurinol-Hypersensitivity Vasculitis and Liver Damage

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ALLOPURINOL is a xanthine oxidase inhibitor and is used in the treatment of hypercuricemia. The drug is well tolerated, with mild skin rash and gastrointestinal upset being the most common side effects.[1-3] Rare occurrences of alopecia,[4] agranulocytosis,[5] xanthine stones,[6] granulomatous

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hepatitis[7] and toxic epidermal necrolysis[8] have been reported. We describe three patients with severe reactions to allopurinol that included hepatocellular necrosis, hepatic granulomata, renal failure and exfoliative dermatitis secondary to a hypersensitivity vasculitis. A subsequent controlled challenge to allopurinol in one patient elicited a positive response. Since most hepatic reactions that occur during therapeutic drug usage are not accompanied by renal failure, the significance of a history of allopurinol ingestion may not be appreciated in patients like those described below.

Reports of Cases

CASE 1. A 29-year-old black man, a security guard, had been followed at Los Angeles County-University of Southern California Medical Center (LAC-USCMC) since 1973 for exogenous obesity, idiopathic hypoventilation and cardiomyopathy. Medications taken since 1973 were digoxin, furosemide and chloral hydrate. The patient was readmitted to LAC-USCMC in August, 1974 for difficulty in breathing felt to be secondary to a viral pneumonitis. A uric acid level of 14 mg per 100 ml prompted the use of allopurinol, 100 mg three times per day, beginning on August 28. He was then transferred to another hospital for long-term weight reduction and convalescence. Administration of the furosemide, digoxin and allopurinol was continued.

He did well until September 29 when a temperature of 103°F (39.4°C) developed. The fever was followed by deteriorating hepatic and renal tests, as listed in Table 1. Generalized pruritus was first noted on October 3 and the patient was transferred back to LAC-USCMC on October 4.

On readmission the patient was febrile to 102°F (38.8°C) and obtunded. An erythematous scaling rash was present on his face. He was icteric but the liver could not be palpated. Urine output was maintained at 1,000 to 1,200 ml per day. Findings on analysis of urine included 2+ protein, 5 to 8 leukocytes, occasional red blood cells, and numerous hyaline and granular casts. Mild leukocytosis (12,000 cu mm) without eosinophilia was present. The prothrombin time, initially 30 percent, rose to 89 percent following an intramuscular injection of vitamin K.

A liver biopsy was done on October 8. The hepatocytes were swollen and there was moderate hepatocellular necrosis, more pronounced centrally (Figure 1). Kupffer cell hyperplasia was present and the portal areas were widened with a mixed inflammatory cell infiltrate with a few eosinophils.

TABLE 1.—*Laboratory Values in Three Cases of Allopurinol Hypersensitivity*

Date	*Creatinine mg/100ml*	*SGOT†/SGPT‡*	*Serum Bilirubin§ mg/100ml*	*Alkaline Phosphatase¶*	*Albumin/Globulin gm/100ml*
Patient Number 1					
8/21/74	1.3	30/15	1.4/0.2	2.2	2.8/4.3
*8/28					
10/5	2.4	1300/940	14.4/11.9	4.0	2.7/5.0
10/16	5.7	1020/623	52.0/30.0	3.4	3.7/4.2
10/31	1.2	68/87	4.8/2.4	..	....
2/13/75	0.9	20/5	0.6/0.1	..	4.1/4.5
Patient Number 2					
*5/18/73	1.7	28/24	0.4/0.1	2.0	3.5/3.9
6/23	3.5	135/165	1.8/0.9	7.5	3.7/4.4
6/26	7.0	128/93	1.8/0.9	3.5	2.3/3.0
6/30	6.7	....	....	..	....
7/5	7.8	53/31	....	..	....
7/11	9.1	49/35	....	..	....
Patient Number 3					
8/12/74	1.7	35/30	0.4/0.2	2.4	3.3/7.0
*1/4/75					
2/14	11.3	40/35	3.1/1.6	6.3	2.4/3.5
2/21	8.4	....	....	..	....
2/24	5.7	110/150	2.8/1.2	8.5	3.0/4.0
3/16	2.0	35/60	1.0/0.4	3.4	3.2/3.9
5/12	1.5	35/12	0.3/0.1	1.6	3.4/3.9

*Date allopurinol begun.
†Serum glutamic oxaloacetic transaminase (5-40 units).
‡Serum glutamic pyruvic transaminase (5-35 units).
§Total/direct.
¶Bessy Lowry units (1-3).

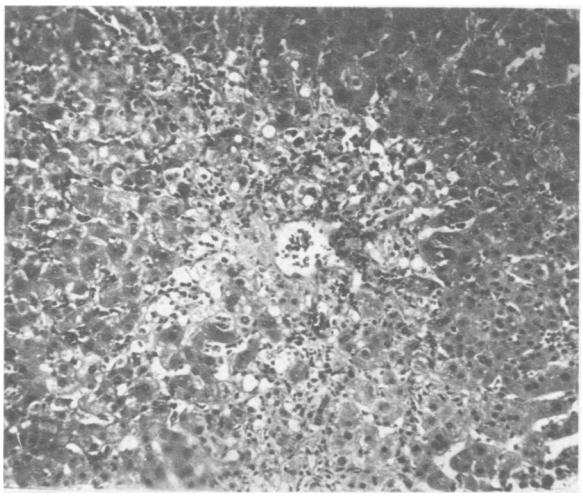

Figure 1.—Needle liver biopsy specimen in case 1 showing centrilobular necrosis with numerous acidophilic bodies. Paraffin section with hematoxylin and eosin stain; reduced from original magnification ×140.

Despite discontinuation of all medications the skin, hepatic and renal lesions progressed and therefore administration of prednisone, 60 mg per day, was begun on October 16. Concomitant with the use of prednisone, findings on the hepatic and renal tests showed improvement and the skin rash resolved. Administration of prednisone was discontinued after one month without a relapse of the clinical illness.

The patient was readmitted to hospital in February 1975 for a controlled challenge with allopurinol. He was taking no medications and results of repeat hepatic and renal tests were within normal limits. After obtaining informed consent, 100 mg of allopurinol was given orally. Three hours later generalized pruritus and a temperature of 102°F (38.8°C) developed. The fever subsided within 24 hours, but a mild exfoliating dermatitis developed four days later. The rash cleared in one week without treatment. Results of serial hepatic and renal function tests were within normal limits, with the only laboratory abnormality being a leukocytosis without eosinophilia.

CASE 2. A 59-year-old man was first admitted to LAC-USCMC in May 1973 because of syncope. He was known to be diabetic and taking insulin and also took hydrochlorothiazide for mild hypertension. The syncopal episode was thought to be secondary to an idiopathic seizure disorder and administration of diphenylhydantoin, 300 mg per day, was begun. Mild heart failure was treated with digoxin, and because of an elevated serum uric acid (10.8 mg per 100 ml), administration of allopurinol, 100 mg twice a day, was started on May 18. The patient was discharged on May 30 taking insulin, digoxin, diphenylhydantoin and allopurinol.

He returned to LAC-USCMC on June 23 with a seven-day history of fever and a two-day history of generalized pruritus. Ampicillin had been prescribed three to four days before admission to hospital. He was febrile to 102°F (38.8°C) and a generalized macropapular skin eruption was present. Findings on physical examination were otherwise unremarkable. No further ampicillin was given but there was continued administration of allopurinol, diphenylhydantoin and digoxin.

Results of the initial and subsequent laboratory tests are listed in Table 1. The leukocyte count was 5,800 to 7,500 per cu mm with 2 to 8 percent eosinophils. Urine output initially was greater than 1,000 ml per 24 hours; however, toward the end of his hospital course it fell to less than 500 ml a day. Analysis of urine consistently showed 1+ to 2+ proteinuria with occasional red blood cells but no casts.

Fever persisted and the skin rash worsened, with exfoliation. Administration of allopurinol was discontinued on July 2 and the diphenylhydantoin was stopped on July 9. A peritoneal dialysis was done on July 8 and hydrocortisone therapy begun on July 10. The patient died suddenly on July 12 with no preceding change in clinical status.

At the time of autopsy a generalized, bullous, exfoliative dermatitis was present, involving the skin, external genitalia and oral mucosa. Microscopically skin changes were noted that were consistent with toxic epidermal necrolysis. Disseminated intravascular thrombi with and without vasculitis were seen in numerous organs. A systemic vasculitis, characterized by fibrinoid necrosis, perivascular round cell infiltration, subintimal proliferation, sclerosis and hyalinization of capillaries, arterioles, small arteries and venules, was present in the breast, pancreas, liver, kidneys, prostate, testes, spleen and adrenals (Figure 2). Segmental glomerulonephritis was also present; the liver showed minimal pathology.

CASE 3. 67-year-old black man was followed at LAC-USCMC since 1964 for adult onset diabetes mellitus, mild hypertension, organic heart disease and glaucoma. He had received hydrochlorothiazide, digoxin, potassium chloride and alpha-methyldopa for several years. Administration of allopurinol, 300 mg a day, was begun on January

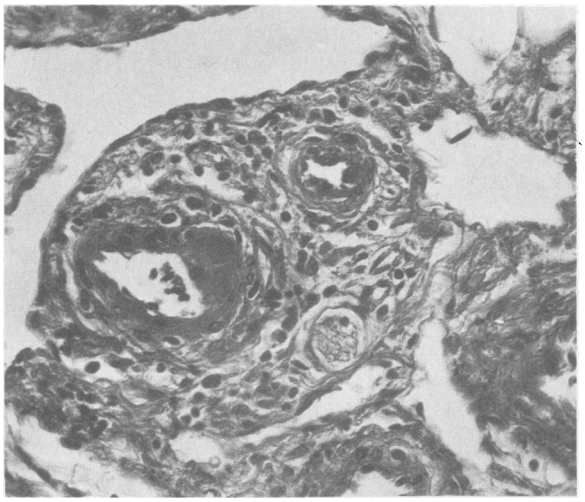

Figure 2.—Section from case 2 with arterioles in the periadrenal fat showing fibrinoid necrosis and perivascular inflammatory cell infiltration. Paraffin section with hematoxylin and eosin stain; reduced from original magnification ×350.

4, 1975 by his private physician. He presented at LAC-USCMC on February 3 with a three-day history of fever and deteriorating mental status. On admission, body temperature was 100°F (37.7°C). He was slightly obtunded; the liver was palpable 2 cm below the right costal margin and there was an erythematous scaling rash on his face. Administration of all medications, including allopurinol, was discontinued on admission. Analysis of urine showed 1+ to 2+ albuminuria, occasional leukocytes, and red blood cells and a few granular casts. Neutropenia developed, with the maximum depression occurring on the 11th hospital day (absolute neutrophil count 513 per cu mm). By the 14th hospital day the neutropenia had spontaneously resolved. Eosinophilia was never present.

A liver biopsy was carried out on the third hospital day. The portal tracts were widened by increase in connective tissue and infiltration by round cells and polymorphonuclear leukocytes. Epithelioid granulomata were present in the periportal areas.

The patient's initial hospital course was marked by fever, decreasing renal function and oliguria. Numerous antibiotics were given during his stay in hospital for possible sepsis; however, several blood and urine cultures revealed no growth. One peritoneal dialysis was done on the 11th hospital day. Administration of prednisone, 60 mg a day, was begun on the 15th hospital day, and coincided with a return of his temperature to normal. Two days after beginning administration of prednisone the urine output began increasing, renal function improved and the skin rash disappeared. In early May 1975 the prednisone was withdrawn without relapse.

Discussion

Nine cases of hypersensitivity reaction to allopurinol similar to the current three cases have been reported.[9-12] All of the salient clinical features are present in our three cases. The onset of illness was about four weeks after institution of therapy with allopurinol and it began with fever and pruritus or dermatitis—or both. Exfoliating dermatitis and renal failure became the dominant clinical features. Liver disease, although always present, was more variable in its severity. Eosinophilia was present in eight of the nine previously described cases but was seen in only one (case 2) of our patients.[9-12] The skin and renal disease progressed despite discontinuation of allopurinol administration and no improvement occurred until steroid therapy was instituted. The dermatitis and renal failure are secondary to a systemic vasculitis and segmental glomerulonephritis.[9,10,12] The hepatic lesion is not consistent and has varied from mild portal inflammation to centrilobular necrosis.[11,12]

In the cases being described and in the previously reported cases most patients were taking several drugs, making it difficult to establish a cause and effect relationship with allopurinol. The frequent use of thiazide diuretics in these patients (six out of nine) has led one author to suggest that they may contribute to the development of the allergic reaction.[12] The proven sensitivity to allopurinol in case 1 shows that allopurinol alone can cause two (fever and skin rash) and probably all of the features seen in the above cases. The failure to detect any abnormalities in hepatic and renal tests after challenge with allopurinol probably reflects the brief exposure to the drug, as in one reported case an inadvertent two-day challenge in an acutely ill patient resulted in worsening of his renal function.[11]

The acquired hypersensitivity in these patients could be directed against a metabolic product of allopurinol. Allopurinol has a half-life of only two hours while its major metabolic product, oxipurinol, has a half-life of 18 to 36 hours due to renal tubular reabsorption.[13] The immunologic role of allopurinol in the development of the vasculitis and glomerulitis has received limited

study. Gammaglobulin and complement have been found in glomeruli[10] and no lymphocyte transformation occurred upon exposure to allopurinol in the one patient studied.[12]

Allopurinol should be included with other drugs capable of causing hepatocellular necrosis and renal failure. It is unique in that the liver leison can be similar to that caused by carbon tetrachloride, methoxyfluorane and acetaminophen, but the renal lesion is glomerular instead of the tubular necrosis seen with the other drugs. The variable character of the liver lesion suggests that it is not secondary to the systemic vasculitis and may be a separate immunologic reaction to the allopurinol.

Allopurinol is a safe and useful drug with few side effects. It may, however, cause a severe hypersensitivity vasculitis that can be fatal. In a patient in whom a skin rash or unexplained fever, or both, develops when this drug is being given, hepatic and renal tests should be done. In the patient in whom the vasculitis develops corticosteroid therapy appears to be efficacious.

Summary

Fever, skin rash, renal failure and liver disease developed in three patients three to four weeks after treatment with allopurinol was begun. Two of the patients recovered following therapy with corticosteroids. After recovery from the initial illness, allopurinol was readministered to one patient and fever and skin rash recurred. Allopurinol hypersensitivity should be included in the differential diagnosis of hepatocellular necrosis and renal failure. Early diagnosis is essential because the continued administration of allopurinol may result in a protracted illness and increased mortality.

REFERENCES

1. Scott JT, Hill AP, Grahame R: Allopurinol in treatment of gout. Br Med J 2:321-327, 1966

2. Ogryzlo MA, Uronitz MD, Weber HM, et al: The treatment of gout and disorders of uric acid metabolism with allopurinol. Can Med Assoc J 95:1120-1127, 1966

3. Rundles RW, Metz EN, Silberman HR: Allopurinol in the treatment of gout. Ann Intern Med 64:229-258, 1966

4. Auerbach R, Orentrich N: Alopecia and ichthyosis secondary to allopurinol. Arch Dermatol 98:104, 1968

5. Greenberg MS, Zambrano SS: Aplastic agranulocytosis after allopurinol therapy. Arthritis Rheum 15:413-416, 1972

6. Greene ML, Fujimoto WY, Seegmiller SE: Urinary xanthine stones, a rare complication of allopurinol therapy. N Engl J Med 280:426-427, 1969

7. Simmons F, Feldman B, Geretz D: Granulomatous hepatitis in a patient receiving allopurinol. Gastroenterology 62:101-104, 1972

8. Stratigos JD, Bartsokas K, Capetanakis S: Further experiences of toxic epidermal necrolysis incriminating allopurinol, pyraxolone and derivatives. Br J Dermatol 86:564-567, 1972

9. Jarzobski J, Ferry J, Wombo HD, et al: Vasculitis with allopurinol therapy. Am Heart J 79:116-121, 1970

10. Kantor G: Toxic epidermal necrolysis, azotemia and death after allopurinol therapy. JAMA 212:478-479, 1970

11. Mills R: Severe hypersensitivity reactions associated with allopurinol. JAMA 216:799-802, 1971

12. Young SL, Boswell RB, Nies AS: Severe allopurinol hypersensitivity. Arch Intern Med 134:553-558, 1974

13. Elion G, Yu T, Gutman A, et al: Renal clearance of oxipurinol, the chief metabolite of allopurinol. Am J Med 45:69-77, 1968