Iodine Absorption After Topical Administration

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Absorption from povidone-iodine preparations after topical administration has been reported to be negligible, but an elderly woman had increased serum iodine levels with possible metabolic complications after povidone-iodine solution was applied to decubitus ulcers.

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Iodine is a topical germicidal agent effective against a wide spectrum of organisms including bacteria, viruses, fungi and protozoa.[1] Iodine is available as solutions and alcoholic tinctures and as iodine compounds such as iodophors. Iodophors were developed following early reports of skin irritation, severe hypersensitivity reactions and systemic absorption of iodine from iodine tinctures.[2,3] Iodophors are compounds of iodine linked to surfactants that act as carriers or solubilizing agents for iodine. A small amount of free iodine is released in solution, thereby minimizing toxicity while preserving moderate germicidal activity of the element.[1]

One of the most extensively used iodophors is the complex of polyvinylpyrrolidone (povidone) and iodine. Initial studies of this agent in animals indicated negligible systemic absorption of iodine following topical administration.[4] Since then there have been a number of reports of possible iodine toxicity occurring after topical administration of the product in humans.

Most cases have involved the application of povidone-iodine to burn wounds involving extensive areas of the body surface. In this report we describe a case of increased serum iodine levels associated with metabolic abnormalities after topical povidone-iodine treatment in a patient with decubitus ulcers involving a relatively small body surface area. We also present a review of topical iodine absorption and systemic complications associated with topical administration.

Report of a Case

The patient, an 83-year-old woman, had a history of hypertension, congestive heart failure, type II diabetes mellitus and asthma. Early in February 1985 she sustained a left parietal lobe infarct resulting in right hemiparesis. After stabilization, the patient was transferred to a rehabilitation institute. Five weeks after the stroke, however, she was readmitted to her local hospital for treatment of decubitus ulcers located on the anterior surface below each knee. The patient was subsequently transferred to Cook County Hospital (Chicago) a week later.

Upon transfer the patient was noted to be afebrile and somewhat lethargic. Remarkable findings on physical examination included an expressive aphasia along with right-sided motor weakness and bilateral ankle clonus. Two decubitus ulcers were observed approximately 5 cm below each patella. The right ulcer was 10 by 10 cm and the left was 6 by 6 cm. The ulcers were granulating well without any foul odor or discharge. They were estimated to comprise 2% to 3% of her total body surface area.

The patient had been receiving gauze soaked with 10% povidone-iodine solution (1% free iodine, Pharmadine, Sherwood) packed into her wounds every four hours over the preceding three to five weeks. Other medications the patient had been receiving were digoxin, methyldopa, a sustained-release theophylline preparation, nitroglycerin patches (Nitro-Dur, Key) and subcutaneous injections of heparin. No iodine dye study had been done over the previous month.

During the succeeding week, a number of complications developed, including persistent diarrhea, an upper gastrointestinal tract hemorrhage due to erosive gastritis and bronchospasm due to congestive heart failure. During this time the patient also had increasing renal insufficiency, primarily manifested by a rise in the serum creatinine level from 1.8 to 3.5 mg per dl, along with a metabolic acidosis: pH 7.34, serum bicarbonate decreasing from 19.8 to 10.8 mEq per liter and a corresponding anion gap of 18. A lactate level was 46.9 mg per dl. Her serum chloride concentration peaked at 127 mEq per liter and serum sodium at 156 mEq per liter. The calculated serum osmolarity increased to 340 mosm per liter.

Because of these findings, a serum iodine level was measured and found to be 2,700 μg per dl (normal 4 to 9). Povi-

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done-iodine dressings were discontinued, and over the next ten days the patient's serum creatinine level declined and stabilized at 2.9 mg per dl. Her acidosis and anion gap resolved. The serum chloride level decreased to 89 mEq per liter, the serum sodium to 126 mEq per liter and serum osmolarity to 286 mosm per liter. A repeat serum iodine concentration 15 days later showed that the serum iodine level had declined to 21 μg per dl. Thyroid function test results remained within normal limits.

The patient died six weeks following transfer due to multiple complications including sepsis, congestive heart failure and respiratory failure. Necropsy was not done.

Comments

Iodine Absorption

Povidone-iodine is available in a number of different formulations including solutions, ointments, foams, surgical scrubs and vaginal preparations. The available iodine content in the preparations varies from 0.2% in the ointment to 1% in the solution and vaginal preparations.[5]

The reports of iodine absorption from topical povidone-iodine solution suggest that absorption is enhanced when the compound is applied to denuded skin, mucosal surfaces with high absorptive capacity or extensive areas of intact skin. The evidence for iodine absorption includes documented serum iodine concentrations and thyroid function abnormalities.

Most cases in which increased serum iodine concentrations are reported have involved burn patients.[6-8] In addition, serum iodine concentrations have become elevated following application of povidone-iodine dressings to extensive surgical wounds,[9,10] after vaginal instillation[11] and after application to the umbilical cord and an inch of surrounding skin of neonates.[10] Perinatal exposure to povidone-iodine infusion resulted in elevated iodide levels in both mothers and neonates.[12] Absorption of iodine after povidone-iodine was applied to a decubitus ulcer has been reported in one other case involving a patient with an extensive sacral decubitus ulcer (about 13 by 11 cm).[9] In addition, increased postoperative protein-bound iodine concentrations have resulted from preoperative skin preparation and vaginal douches.[13]

Povidone-iodine applications to surgical wounds of neonates[14] and povidone-iodine baths used to cleanse the entire body surface of young children[15] have resulted in abnormal thyroid function test findings (elevated thyroid-stimulating hormone and normal thyroxine and triiodothyronine levels). Long-term treatment of a perineal fistula with a povidone-iodine scrub and iodoform-impregnated packing has caused clinical signs and symptoms of hypothyroidism.[16]

The absorption and elimination of iodine following topical administration have not been well documented. The extent of absorption appears to be related to the size of the area of application and may possibly be related to the povidone-iodine vehicle.

In their review of burn patients, Hunt and co-workers found that the extent of iodine absorption was directly related to the size of the area of application.[6] Serum iodine concentrations ranged from 595 to 1,440 μg per dl (normal 0 to 3) after application of povidone-iodine ointment to burns of 0% to 15% total body surface area (TBSA); in patients with 15% to 30% TBSA burns, from 910 to 2,390 μg per dl, and in those with burns greater than 30% TBSA, from 1,200 to 4,900 μg per dl. The amount of iodine absorbed may also be directly related to the amount of partial thickness burn.[7,8]

The absorption of iodine has not been associated with a particular formulation of povidone-iodine. The occlusive nature, however, of povidone-iodine ointment would be expected to enhance iodine absorption through intact skin as compared with the solution. Conversely, applying povidone-iodine solution to wounds would be expected to result in greater absorption than applying the ointment because of better diffusion of dissolved iodide to the dermal surface.

At present, the form of iodine absorbed—whether it is povidone-iodine, free iodine or iodide—is unknown.[7] The toxic moiety of iodine is also undetermined. Povidone has been detected in serum by mass spectrometry, evidence that at least partial absorption of povidone occurs.[8] The site of reduction of iodine to iodide is also unknown.[7]

Iodine is excreted primarily by the kidneys, and the renal clearance of iodine is directly related to the glomerular filtration rate.[6,9] Renal function and the duration of povidone-iodine administration would be expected to influence systemic iodine accumulation.

Renal insufficiency results in higher and more prolonged elevations in serum iodine concentrations, although the rate of decline of serum iodine concentrations over time has not been well characterized in patients with either normal or decreased renal function. In our patient, the second serum iodine concentration was still elevated, although greatly decreased from the first measurement, 15 days after the povidone-iodine treatment was discontinued. Urinary iodine excretion in patients with renal failure has been shown to be minimal—that is 150 μg per day—compared with that in patients with normal renal function—912,000 μg per day.[6] Immature kidney function may explain iodine accumulation in neonates.

Even patients with normal renal function show relatively rapid elevations of serum iodine. Hunt and colleagues observed that in patients with normal renal function and greater than 30% TBSA burns, peak serum iodine concentrations ranged from 7,600 to 32,000 μg per dl after five days of topical therapy.[6] Serum iodine concentrations continued to increase until treatment was discontinued and remained high for as long as seven days after the povidone-iodine treatment was discontinued.

There are no data correlating either frequency or duration of povidone-iodine administration with serum iodine concentrations, but longer treatment is expected to potentiate iodine accumulation. In our patient, prolonged application of povidone-iodine dressings to a relatively small surface area may have enhanced iodine accumulation.

Clinical Manifestations of Iodine Absorption

A constellation of metabolic and electrolyte abnormalities has been reported to occur with elevated serum iodine concentrations, including metabolic acidosis,[6-9,17,18] hyperchloremia,[9,17,18] hypernatremia,[6,17,18] hyperosmolarity[17] and renal failure.[7-9,17,18] All of these systemic complications were observed in our patient.

The cause for metabolic acidosis is unclear. It has been postulated to be due to the acidic pH (2.43) of povidone-iodine or to the consumption of bicarbonate by the combination of free iodine with serum sodium bicarbonate, illustrated by the following equation: $6NaHCO_3 + 3I_2 \rightarrow 5NaI + NaIO_3 +$

$6CO_2 + 3H_2O$.[19] The equation is driven to the right by respiratory elimination of carbon dioxide. Determination of a specific cause of metabolic acidosis in previously reported cases has been complicated by concurrent disorders such as sepsis, shock, renal failure, ketoacidosis and lactic acidosis.[8] In one report, these potential causes were not temporally related to the metabolic acidosis.[17] In still other reports, serum lactate levels were normal.[8,9] The metabolic acidosis occurring in our patient may have been partly caused by persistent diarrhea.

Hyperchloremia probably represents spurious elevations in the serum chloride due to interference of the assay by iodine.[9] Serum chloride determinations made by the Technicon STAT/ION autoanalyzers result in false elevations in serum chloride levels in a nonlinear fashion. Thus, serum chloride concentrations may be falsely high even at low iodide levels when this method is used.[20] In the presence of elevated iodine concentrations, the silver halide precipitation assay should be used for an accurate measurement of serum chloride concentration.

Hypernatremia has been reported in burn patients treated with topical povidone-iodine,[6,17,18] but Hunt and associates observed metabolic acidosis and serum sodium concentrations greater than 150 mEq per liter in only three burn patients with renal failure. Serum electrolytes remained within normal limits in all patients with normal renal function, even with increased iodine concentrations. Although the hypernatremia could be attributed to excessive insensible and respiratory water loss, exogenous sodium administration, renal dysfunction and sepsis, it has been reported to occur shortly after starting povidone-iodine treatment and to resolve within 24 hours of discontinuation in two other cases.[17,18]

Elevations in the serum osmolarity may result from the osmotic effects of free iodine in the blood.[6] It may also be caused by hypernatremia or perhaps by povidone, although the latter is unproved.

Nephrotoxicity due to iodine has not been confirmed by pathologic examination in humans.[8] The possibility of drug-induced nephropathy due to drugs such as aminoglycosides or cephalothin or renal dysfunction due to sepsis and volume contraction cannot be excluded in some cases. The nephrotoxic potential of povidone is unknown.[7]

Clinical hypothyroidism[16,21] and hyperthyroidism[22] have been associated with topical povidone-iodine therapy, as have laboratory abnormalities consistent with depressed thyroid function.[12,15,23] There was no evidence of thyroid dysfunction in our patient.

Other symptoms attributed to iodine toxicity in the literature include elevated serum aminotransferase levels,[7] hyperbilirubinemia,[8] changes in sensorium (agitation, confusion, hallucinations),[7,24] neutropenia[24] and hypoxemia.[24] Topical povidone-iodine therapy has also been implicated as a possible cause of severe stomatitis and diarrhea in a burn patient.[24] Again, in each case, the patient course was complicated by other potential causes of symptoms, such as infection, sepsis and cardiopulmonary arrest. Death has not been directly attributed to topical iodine toxicity up to this time.

In summary, high iodine concentrations imply toxicity. Clinical evidence of cell or organ toxicity, however, is as yet undetermined. There are no clinical correlations with serum iodine determinations, and the actual concentration at which toxic symptoms may occur is unknown. Metabolic abnormalities have been reported to occur concurrently with elevated serum iodine concentrations, but increased iodine concentrations have also occurred without any clinical or laboratory manifestations of possible toxicity.[6,7] Thus, there does not appear to be a characteristic syndrome of iodine intoxication following topical administration. It is possible that a certain patient population may be at greater risk, such as patients with renal dysfunction.

We believe that the metabolic acidosis, hypernatremia and renal insufficiency observed in our patient were partly due to iodine based on their temporal relationship with serum iodine concentrations. Our case provides evidence that absorption of iodine after prolonged application of povidone-iodine to a relatively small surface area of denuded skin can result in considerable iodine absorption.

We suggest that an alternate form of therapy be used and that serum iodine determinations be considered in patients receiving topical iodine preparations who display unexplained metabolic abnormalities or organ dysfunction.

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