

5. Allan SG, Knox J, Kerr F: Interaction between diuretics and indomethacin. *Br Med J* 283:1611, 1981
6. Kramer HJ, Dusing R, Stinnesbeck B, et al: Interaction of conventional and antidiuretic diuretics with the renal prostaglandin system. *Clin Sci Mol Med* 59:67, 1980
7. Smith DE, Brater DC, Lin ET, et al: Attenuation of furosemide's diuretic effect by indomethacin: Pharmacokinetic evaluation. *J Pharmacokinetic Biopharm* 7:265, 1979
8. Chennavasin P, Seiwel R, Brater DC: Pharmacokinetic-dynamic analysis of the indomethacin-furosemide interaction in man. *J Pharmacol Exp Ther* 215:77, 1980
9. Brater DC: Analysis of the effect of indomethacin on the response to furosemide in man: Effect of dose of furosemide. *J Pharmacol Exp Ther* 210:386, 1979
10. Tobert JA, Ostaszewski T, Reger B, et al: Diflunisal-furosemide interaction. *Clin Pharmacol Ther* 27:289, 1980

Toxic Shock Syndrome Associated with Diaphragm Use

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Hymowitz¹ has suggested that if toxic shock syndrome^{2,3} is associated with the obstruction of menstrual flow by tampons, the use of a diaphragm during menstruation should be associated with the syndrome. Too few cases of this important possibility have been reported²⁻⁴ to establish it in clinical consciousness or to decide whether such a connection will require a change in instructions for use of diaphragms. The following case is reported and discussed.

Case Report

Mrs. D. is an 18-year-old white woman, gravida 1, para 1, in good health prior to the episode reported. She had a low transverse cesarean section for fetal distress three months prior to admission

and had not yet resumed menstruation. Forty-eight hours prior to admission, after unprotected intercourse, she developed a vaginal discharge requiring use of a pad. Twelve hours later she used a diaphragm, left it in place overnight, and failed to remove it the next morning. During the day pelvic and lumbar pain developed, followed by vomiting and a fever as high as 103°F. That evening, 12 hours before admission, the diaphragm was removed with drainage of copious purulent discharge. The edges of the diaphragm and the discharge were blood streaked. She also developed a diffuse macular blanching rash, sparing only the circumoral region.

At the time of admission the following morning her blood pressure was 60/0 mmHg; pulse, 180 beats/min; and temperature, 102°F. Significant physical findings included the rash, conjunctivitis, a pharyngeal infection, and a lack of adenopathy. Pelvic examination showed a vaginal discharge, a very tender, slightly enlarged warm uterus, and normal adnexa.

Cultures of the vaginal discharge were positive for *Staphylococcus aureus*, resistant to penicillin and ampicillin, and sensitive to methicillin, cepha-

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lothin, erythromycin, colistin, chloramphenicol, tetracycline, sulfisoxazole, and aminoglycoside antibiotics. Cultures of the blood and urine and anaerobic and gonococcal cervical cultures were all negative. Wet mount and Gram stain showed polymorphonuclear leucocytes and gram-positive cocci. The white blood count rose from 11,000/mm³ on admission to a high of 13,000/mm³ with a left shift the next day. Urinalysis showed a sterile pyuria. Significant chemical findings included an initial elevation of the fibrinogen to 330 mg/100 mL (control, 220 mg/100 mL), prothrombin time to 15 seconds (control, 11 seconds), and Ivy bleeding time to 11 minutes. The sodium level was 141 mEq/L (normal, 135 to 148 mEq/L); potassium, 3.5 mEq/L (normal, 3.5 to 5.0 mEq/L); chloride, 104 mEq/L (normal, 95 to 108 mEq/L); carbon dioxide, 18 mEq/L (normal, 24 to 32 mEq/L); blood urea nitrogen, 33 mg/100 mL (normal, 7 to 23 mg/100 mL); creatinine, 2.9 mg/100 mL (normal, 0.7 to 1.4 mg/100 mL); glucose, 138 mg/100 mL (normal, 65 to 110 mg/100 mL); SGOT, 81 U/L (normal, 7 to 50 U/L); and bilirubin, 2 mg/100 mL (normal, 0.2 to 1.2 mg/100 mL).

The patient received 1.2 million units of intravenous penicillin every four hours, 80 mg of gentamicin every eight hours, and 300 mg of clindamycin every six hours, as well as fluid replacement and 2 g of methylprednisolone followed by 1 g every six hours. The gentamicin dosage was adjusted after the initial dose through the use of peak and trough levels. The initial antibiotics and steroids were stopped after 24 hours, and treatment continued with 1 g of methicillin every six hours.

The shock, fever, and rash resolved in the following 48 hours. Two days after admission there was circumoral exfoliation. The discharge and electrolyte and renal abnormalities cleared in three days. Laboratory abnormalities corrected in 24 to 48 hours, except for liver function tests. The SGOT peaked at 321 U/L in three days, then returned to normal by discharge after eight days. Other liver function tests followed a parallel course.

After eight days in the hospital, the patient was discharged on 500 mg of cloxacillin every six hours. Repeat cervical and vaginal cultures at the time of discharge were negative, and she had been afebrile for five days. The cloxacillin was stopped two days later upon development of a diffuse maculopapular pruritic rash.

One month later she again developed malaise, a low-grade fever, and a vaginal discharge and was admitted to another hospital. On this occasion, although the sterile pyuria persisted, neither shock nor rash occurred, and all cultures were negative. A monilial vaginitis responded to nystatin vaginal suppositories, and she recovered in three days. The patient has remained well since. Menstruation resumed three months later.

Discussion

This case satisfies the criteria of the Centers for Disease Control for diagnosis of toxic shock syndrome with fever, orthostatic dizziness or hypotension, rash and desquamation, involvement of multiple organ systems, and absence of evidence of other causes, and it was reported to the Tennessee State Health Department. This particular case is unusual because it began with development of a vaginal discharge without vaginal obstruction, developed during a 24-hour period when a diaphragm was in place, and was not associated with menstruation. Whether the discharge represented staphylococcal infection is unknown, but the diaphragm certainly seems to have contributed to the course of events.

Toxic shock syndrome was first described in children⁵ and has now been reported in neonates, men, and postmenopausal women. It has been associated with vaginal and cesarean delivery, therapeutic abortion, infected surgical wounds, hydradenitis, lymphadenitis, deep abscesses, and infected skin lesions including burns, abrasions, lacerations, furuncles, and insect bites.^{2,3} Even though 85 percent of cases are still associated with menstruation, this percentage has declined in the last two years primarily because of a decline in the number of menstrual cases reported and hypothetically because of changes in tampon availability and use.

Increasing recognition of non-tampon-related cases has argued against simple obstruction as the cause. Search is in progress for alternative explanations, such as the special absorbancy of some forms of tampons and suture material.⁶ Staphylococcal septicemia with a scarlatiniform rash has

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Brief Summary

Enduronyl® Methylothiazide and Deserpidine

Oral thiazide-rauwolfia therapy for hypertension.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indications: ENDURONYL (methylothiazide and deserpidine) is indicated in the treatment of mild to moderately severe hypertension (see boxed warning). In many cases ENDURONYL alone produces an adequate reduction of blood pressure. In resistant or unusually severe cases ENDURONYL also may be supplemented by more potent antihypertensive agents. When administered with ENDURONYL, more potent agents can be given at reduced dosage to minimize undesirable side effects.

Contraindications: Methylothiazide is contraindicated in patients with renal decompensation and in those who are hypersensitive to this or other sulfonamide derived drugs.

Deserpidine is contraindicated in patients with known hypersensitivity, mental depression especially with suicidal tendencies, active peptic ulcer, and ulcerative colitis. It is also contraindicated in patients receiving electroconvulsive therapy.

Warnings: METHYLOTHIAZIDE — Methylothiazide shares with other thiazides the propensity to deplete potassium reserves to an unpredictable degree.

Thiazides should be used with caution in patients with renal disease or significant impairment of renal function, since azotemia may be precipitated and cumulative drug effects may occur.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

DESERPIDINE — Extreme caution should be exercised in treating patients with a history of mental depression. Discontinue the drug at the first sign of despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide.

Usage in Pregnancy and Lactation: METHYLOTHIAZIDE — Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Thiazides appear in breast milk. If use of the drug is deemed essential, the patient should stop nursing.

DESERPIDINE — The safety of deserpidine for use during pregnancy or lactation has not been established, therefore, it should be used in pregnant women or in women of childbearing potential only when in the judgment of the physician its use is deemed essential to the welfare of the patient. Increased respiratory secretions, nasal congestion, cyanosis, and anorexia may occur in infants born to rauwolfia alkaloid-treated mothers, since these preparations are known to cross the placental barrier to enter the fetal circulation and appear in cord blood. They also are secreted by nursing mothers into breast milk.

Reproductive and teratology studies in rats reduced the mating index and neonatal survival indices; the no-effect dosage has not been established.

Precautions: Periodic determinations of serum electrolytes should be performed at appropriate intervals for the purpose of detecting possible electrolyte imbalances such as hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when a patient is vomiting excessively or receiving parenteral fluids. All patients should be observed for other clinical signs of electrolyte imbalances such as dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any other potent diuretic, especially when brisk diuresis occurs, severe cirrhosis is present, or when corticosteroids have been given concomitantly. Interference with the adequate oral intake of electrolyte determinations will also contribute to the possible development of hypokalemia. Potassium depletion, even of a mild degree, resulting from thiazide use, may sensitize a patient to the effects of cardiac glycosides such as digitalis.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening.

In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Thiazides have been reported, on rare occasions, to have elevated serum calcium to hypercalcemic levels. The serum calcium levels have returned to normal when the medication has been stopped. This phenomenon may be related to the ability of the thiazide diuretics to lower the amount of calcium excreted in the urine.

Because rauwolfia preparations increase gastrointestinal motility and secretion, this drug should be used cautiously in patients with a history of peptic ulcer, ulcerative colitis, or gallstones, where biliary colic may be precipitated.

Caution should be exercised when treating hypertensive patients with renal insufficiency since they adjust poorly to lowered blood pressure levels.

Use deserpidine cautiously with digitalis and quinidine since cardiac arrhythmias have occurred with rauwolfia preparations.

Preoperative withdrawal of deserpidine does not assure that circulatory instability will not occur. It is important that the anesthesiologist be aware of the patient's drug intake and consider this in the overall management, since hypotension has occurred in patients receiving rauwolfia preparations. Anticholinergic and/or adrenergic drugs (metaraminol, norepinephrine) have been employed to treat adverse vagocirculatory effects.

Adverse Reactions: METHYLOTHIAZIDE — **GASTROINTESTINAL SYSTEM REACTIONS:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

CENTRAL NERVOUS SYSTEM REACTIONS: Dizziness, vertigo, paresthesias, headache, xanthopsia.

HEMATOLOGIC REACTIONS: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

DERMATOLOGIC — **HYPERSENSITIVITY REACTIONS:** Purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis).

CARDIOVASCULAR REACTION: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates, or narcotics.

OTHER: Hyperglycemia, glycosuria, hypercalcemia, hyperuricemia, muscle spasm, weakness, restlessness.

There have been isolated reports that certain nonedematous individuals developed severe fluid and electrolyte derangements after only brief exposure to normal doses of thiazide and non-thiazide diuretics. The condition is usually manifested as severe dilutional hyponatremia, hypokalemia, and hypochloremia. It has been reported to be due to inappropriately increased ADH secretion and appears to be idiosyncratic. Potassium replacement is apparently the most important therapy in the treatment of this syndrome along with removal of the offending drug.

Whenever adverse reactions are severe, treatment should be discontinued.

DESERPIDINE — The following adverse reactions have been reported with rauwolfia preparations. These reactions are usually reversible and disappear when the drug is discontinued.

GASTROINTESTINAL: Including hypersecretion, anorexia, diarrhea, nausea, and vomiting.

CARDIOVASCULAR: Including angina-like symptoms, arrhythmias (particularly when used concurrently with digitalis or quinidine), and bradycardia.

CENTRAL NERVOUS SYSTEM: Including drowsiness, depression, nervousness, paradoxical anxiety, nightmares, extrapyramidal tract symptoms, CNS stimulation manifested by dull sensorium, and deafness.

DERMATOLOGIC — **HYPERSENSITIVITY:** Including purpura, rash, and asthma in asthmatic patients.

OPHTHALMOLOGIC: Including glaucoma, uveitis, optic atrophy, and conjunctival injection.

HEMATOLOGIC: Thrombocytopenic purpura.

MISCELLANEOUS: Nasal congestion, weight gain, impotence or decreased libido, dysuria, dyspnea, muscular aches, dryness of mouth, dizziness, and headache.

Overdosage: Symptoms of thiazide overdosage include electrolyte imbalance and signs of potassium deficiency such as confusion, dizziness, muscular weakness, and gastrointestinal disturbances. General supportive measures including replacement of fluids and electrolytes may be indicated in treatment of overdosage.

An overdosage of deserpidine is characterized by flushing of the skin, conjunctival injection and pupillary constriction. Sedation ranging from drowsiness to coma may occur. Hypotension, hypothermia, central respiratory depression and bradycardia may develop in cases of severe overdosage. Treatment consists of the careful evacuation of stomach contents followed by the usual procedures for the symptomatic management of CNS depressant overdosage. If severe hypotension occurs it should be treated with a direct acting vasopressor such as norepinephrine bitartrate injection.

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TOXIC SHOCK SYNDROME

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been reported sporadically since at least 1927 and probably represents nonmenstrual toxic shock syndrome.

What is new or different remains unknown. New toxin production by staphylococci, new tampon technology, and better disease surveillance are all reasonable hypotheses. However, even as recurrent, mild, and more cases are reported, the sense of something new and different persists.⁷

Vaginal discharges, diaphragms left in for 24 hours or more, and probably even the combination are common. That the combination reported in this case is not seen with any frequency may argue against simple vaginal-cervical obstruction as a sufficient cause of the syndrome.⁸ It is sobering nonetheless. Should patients be warned not to use their diaphragms when they have a discharge? Since instructions for using diaphragms encourage leaving them in place for as long as 6 to 12 hours, and leaving them in place overnight is common, should patients be given a maximum time for use (perhaps 24 or 36 hours)? The disease is rare and the combination common. It seems reasonable to add a sentence to instructions recommending that the diaphragm not be left in place over 12 hours with an untreated vaginal discharge.

Finally, all clinicians must be sensitive to a scarlatiniform rash and postural dizziness in association with any potential staphylococcal infection, since the most likely evolution of this entity may be increasing incidence and decreasing association with menstruation.

References

1. Hymowitz EE: Toxic-shock syndrome and the diaphragm. *N Engl J Med* 305:834, 1981
2. Toxic-shock syndrome—United States, 1970-1982. *MMWR* 31:201, 1982
3. Toxic-shock syndrome—United States, 1970-1980. *MMWR* 30:25, 1981
4. Loomis L, Feder H, Jaffe R: Toxic-shock syndrome associated with diaphragm use. *New Engl J Med* 305:1585, 1981
5. Todd J, Fishant M, Kapral F, et al: Toxic shock syndrome associated with phage-group-I Staphylococci. *Lancet* 2:1116, 1978
6. Goodpasture HC, Voth DW: Toxic shock syndrome—Additional perspectives. *JAMA* 247:1464, 1982
7. Bear K: Complex picture emerges for toxic shock syndrome. *JAMA* 247:2339, 1982
8. Schlech WF, Shands KN, Reingold AL, et al: Risk factors for development of toxic shock syndrome: Association with a tampon brand. *JAMA* 248:835, 1982