
Communications

Interaction of Indomethacin with Furosemide

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Indomethacin and other nonsteroidal anti-inflammatory drugs (NSAID) are widely used for the treatment of arthritis, gout, and pain. Although it has been recognized that NSAIDs may cause fluid retention, several investigators have also demonstrated evidence of an interaction between furosemide and indomethacin.^{1,2} Many of these studies, however, have involved normal volunteers in controlled situations. The following report demonstrates such an interaction in a patient with congestive heart failure.

Case Report

A 75-year-old woman with a 10-year history of congestive heart failure, sick sinus syndrome, mild

aortic stenosis, gouty arthritis, anemia of chronic disease, and status post left mastectomy for carcinoma was admitted to the hospital with a one-week history of worsening congestive heart failure that was not responding to outpatient management.

The patient had experienced an attack of gouty arthritis two weeks prior to admission and had begun taking 25 mg of indomethacin three times daily, which she had at home and had previously used for gouty arthritis. One week later the patient consulted her physician because of increased dyspnea on exertion and two-pillow orthopnea. Examination at that time revealed a grade 2/6 murmur suggestive of aortic stenosis and a grade 1/6 murmur suggestive of aortic regurgitation, clear lung fields, and pretibial ankle edema (1+). The liver was palpable 4 cm below the right costal margin. No jugular venous distention was noted. The patient's dose of furosemide was doubled from 80 mg each morning to 80 mg twice daily. Over the next week the patient only lost 1 lb

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Continued on page 614

ALDOMET® (Methyldopa | MSD)

Tablets, containing 125, 250, or 500 mg methyldopa; Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1%.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstated. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstated in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetoid movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetoid movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatulence, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Dermatologic:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyperprolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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Continued from page 610

and her symptoms of dyspnea on exertion had worsened. She continued to have severe orthopnea and was admitted for hospital treatment of congestive heart failure.

The admission examination showed a white woman in mild to moderate distress with a respiratory rate of 24 per minute and blood pressure of 140/66 mmHg. Pulmonary examination revealed wet rales bilaterally. Cardiovascular examination revealed a pulse rate of 60 beats/min. There was a grade 2/6 to 3/6 murmur suggestive of aortic stenosis, a grade 2/6 murmur suggestive of aortic regurgitation, and jugular venous distention to the jaw at 45 degrees. The hepatojugular reflex was present, and the liver edge was 6 cm below the right costal margin. There was pitting sacral edema (1+) and pretibial and ankle edema (trace to 1+). Findings of acute gouty arthritis had resolved.

Admission laboratory evaluation showed the following: serum sodium, 141 mEq/L; potassium, 3.7 mEq/L; chloride, 96 mEq/L; BUN, 24 mg/100 mL; creatinine, 1.6 mg/100 mL; and glucose, 111 mg/100 mL. A complete blood count disclosed a mild anemia with a hemoglobin of 10.5 g/100 mL and a white blood count of 6,100 mm³. The serum digoxin level was within the therapeutic range at 1.6 ng/mL. Compared with x-ray films taken three months earlier, an admission chest roentgenogram revealed increased cardiomegaly and bilateral interstitial edema. A 12-lead electrocardiogram was essentially unchanged from a tracing done one month prior to admission.

The patient was placed on a low-salt diet and bed rest and her medications (digoxin, quinidine, propranolol, colchicine, probenecid, imipramine, ferrous sulfate, and diethylstilbestrol) were continued unchanged, except that the indomethacin was discontinued. The patient's hospital course was characterized by rapid improvement over the next 48 hours. The patient underwent a brisk diuresis with a net output of greater than one liter each day and a documented weight loss from 169 lb to 162.5 lb. The patient's murmur of aortic insufficiency became barely perceptible. An echocardiogram showed findings consistent with moderate calcific aortic stenosis and only mild aortic regurgitation. A carotid tracing was also

consistent with predominantly aortic stenosis and minimal aortic regurgitation. During the next two days the patient's weight decreased to 157 lb, the pulmonary rales cleared, the peripheral and sacral edema resolved, and the liver edge was 4 cm below right costal margin. At this point the patient no longer complained of orthopnea or dyspnea. After discussion of the risks involved, it was decided not to rechallenge the patient with indomethacin. She was discharged on the fifth hospital day.

Since the time of discharge the patient's weight has remained stable between 154 lb and 158 lb, and her congestive heart failure has remained well controlled without other changes in her medications. The maintenance dose of furosemide was 80 mg twice daily.

Comment

It is difficult to prove a drug interaction without rechallenge; however, the temporal relationship between the initiation of indomethacin and the patient's weight gain and worsening congestive heart failure provide strong evidence of a drug interaction. Withdrawal of the indomethacin, while on the same dose of furosemide, was followed by a brisk diuresis and weight loss.

Prostaglandins have been shown to have potent natriuretic effects in humans.³ Indomethacin and the other nonsteroidal anti-inflammatory agents suppress the synthesis of prostaglandins.¹ This action may be responsible for the sodium retention seen when the nonsteroidal anti-inflammatory agents are used. Indomethacin and other agents have been reported to interact with the natriuretic effect of furosemide.^{1,4,5} This might be anticipated, since the ability of furosemide to increase renal sodium excretion is speculated to be through increased prostaglandin activity.^{1,6}

The interaction between furosemide and indomethacin has been investigated in normal volunteers and patients with hypertension.^{1,7-9} The bulk of the evidence points toward prostaglandin inhibition as the mechanism of interaction, rather than pharmacokinetic interaction.^{7,8} Although there is some evidence that the effect of indomethacin on

the response to furosemide differed with the dose of furosemide,⁹ case reports indicate little improvement with increased doses of furosemide in patients taking the combination.^{4,5} This patient failed to respond to an increased dose of furosemide, but she had an excellent therapeutic response to furosemide when the indomethacin was discontinued.

It is interesting to note that the interaction of nonsteroidal anti-inflammatory agents and furosemide may not occur with all anti-inflammatory agents. Diflunisal apparently causes no deleterious effect on the action of furosemide.¹⁰ Ibuprofen and naproxen, however, have been reported to interact.⁵ Anti-inflammatory agents may also antagonize the natriuretic effects of hydrochlorothiazide and abolish the potassium-sparing effect of spironolactone.⁶

The practice of using a combination of nonsteroidal anti-inflammatory agents and diuretics appears to be more common than the reported interactions. As with other drug interactions, this interaction may not occur or be clinically significant in all patients. Nevertheless, clinicians should be aware of the potential problems, especially in patients with congestive heart failure. Perhaps ill effects of this interaction could be appropriately anticipated and in most cases prevented.

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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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