

Intravenous Streptokinase for Treatment of Acute Myocardial Infarction in Small Hospitals

Richard Henry, MD, and Frank deGruy, MD, MSFM
Mobile, Alabama

Streptokinase has been available for the treatment of thrombolysis in acute myocardial infarction for over 25 years.^{1,2} The efficacy of streptokinase has been documented most convincingly when it has been infused by the intracoronary route,³⁻⁸ but intravenous infusion has also been shown to be effective.⁹⁻¹⁷ Although the drug is effective by either route if given within six hours after onset of the coronary event, the sooner the drug is administered after the onset of symptoms, the better the outcome.¹⁴

For patients in rural areas, transfer to a tertiary institution with cardiac catheterization facilities is necessary for intracoronary infusion, which may not be possible before the six-hour therapeutic "window" has passed.

In contrast, intravenous administration of streptokinase only requires access to a peripheral vein, the ability to monitor the patient for bleeding or overanticoagulation, a thorough knowledge of the actions and contraindications of streptokinase, and a protocol for its use. Simple protocols are available¹⁰; moreover, the safety and efficacy of streptokinase in the rural setting has been established in at least one study.¹⁷ Candidates for intravenous streptokinase generally include those with onset of symptoms within six hours and acute ST-segment elevation characteristic of myocardial infarction. The drug is contraindicated in patients currently on oral anticoagulants or with recent surgery or trauma (including cardiopulmonary resuscitation), recent bleeding or stroke, severe hypertension, known bleeding disorder, or a known adverse reaction to streptokinase. Heparin is generally infused for 48 or more hours after the dose of streptokinase, and the partial thromboplastin time must be monitored during the administration of both drugs. Thus, most patients presenting to the hospital with acute myocardial infarction would qualify as candidates for thrombolysis with streptokinase. One might expect, therefore, that the use of intravenous

streptokinase would have rapidly become the standard of care in the small community hospital. The study reported here was designed to assess the extent to which streptokinase has become a therapy for acute myocardial infarction in this setting.

METHODS

A questionnaire was mailed to all 76 primary care physicians (family physicians, general practitioners, and general internists) practicing in nine counties in southern Alabama. These physicians use 16 hospitals ranging in size from 30 to 99 beds (mean, 58 beds); all hospitals are equipped to manage patients with acute myocardial infarction.

The questionnaire inquired about the physicians' management of acute myocardial infarction, with particular reference to their use of intravenous streptokinase.

RESULTS

Of the 76 questionnaires mailed, 52 were returned, for a 68 percent return rate. In Table 1 are shown the sample and response rates by specialty, and in Table 2, the responses to the questions on the questionnaire. Nearly all responding physicians perform initial evaluation and management of patients with acute myocardial infarction, and most (90 percent) manage at least some of these patients throughout their hospitalization. Of those 47 who continue management, about one half do so with uncomplicated cases only. Thirty-six respondents answered the question concerning their consultants' use of intravenous streptokinase, and of these, 30 (83 percent) responded positively. This finding contrasts with the finding that of the 47 physicians who themselves continue management of acute myocardial infarction, only 21 (45 percent) have ever used streptokinase. The differences between specialties are not significant (Table 3). Two thirds of these physicians are affiliated with hospitals having a protocol for

Submitted, revised, December 1, 1987.

From the Department of Family Practice, University of South Alabama College of Medicine, Mobile, Alabama. Requests for reprints should be addressed to Dr. Frank deGruy, Department of Family Practice, University of South Alabama, 1620 N University Dr, Mobile, AL 36688.

TABLE 1. DESCRIPTION OF PHYSICIAN SAMPLE BY SPECIALTY

Specialty	Questionnaires Mailed	Questionnaires Returned	Response Rate
Family physicians	33	28	85
General practitioners	34	19	56
General internists	9	5	56
Total	76	52	68

TABLE 2. USE OF INTRAVENOUS STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION (n = 52)

Protocol	Yes	No	Total No. (%)
	No. (%)	No. (%)	
Do you provide initial management for patients with acute myocardial infarction?	51 (100)	0 (0)	51 (100)
Do you continue management of these patients throughout their hospitalization?	47 (90)	5 (10)	52 (100)
Do you manage complicated and uncomplicated myocardial infarctions?	25 (52)	23 (48)	48 (100)
If you use a consultant, does he or she use intravenous streptokinase?	30 (83)	6 (17)	36 (100)
Have you ever used intravenous streptokinase for myocardial infarction?	21 (45)	26 (55)	47 (100)
Does your hospital have a protocol for intravenous streptokinase?	33 (66)	17 (34)	50 (100)

intravenous streptokinase, whereas one third practice in hospitals where such a protocol is not established.

DISCUSSION

These results indicate that treatment with intravenous streptokinase has found its way into the smaller hospital setting, but not to the extent that its advantages and indications would suggest is appropriate. While nearly all the primary physicians' consultants are experienced in the use of intravenous streptokinase, less than one half of the primary physicians themselves are experienced with its use, and one third of them practice in hospitals where protocol for the use of this drug is unavailable. Why is this apparently efficacious drug neglected by such a sizable percentage of rural physicians?

TABLE 3. USE OF INTRAVENOUS STREPTOKINASE BY SPECIALTY

Respondent	Number of Respondents Who Manage Patients with Acute Myocardial Infarction	Number of Respondents Who Use Intravenous Streptokinase No. (%)
Family physicians	26	12 (46)
General practitioners	16	6 (38)
General internists	5	3 (60)

One reason is lack of knowledge about and experience with the drug. Most of the literature on the efficacy of streptokinase is recent and was not available when most of the physicians in the field today were in medical school or residency training. The use of this drug, therefore, should be the focus of continuing medical education efforts made available to rural physicians.

There may be a more fundamental reason. While this drug seems to be efficacious in the hands of research-oriented subspecialists based in tertiary care referral centers, its efficacy is less certain in the rural setting. The generalizability of the studies done so far is limited. Until more studies on intravenous streptokinase for the treatment of acute myocardial infarction are done in the rural setting by primary care physicians, the present findings should be interpreted with caution. If and when such results become available, the use of this modality may become more universal.

References

1. Fletcher AP, Sherry S, Alkjaersig N, et al: The maintenance of a sustained thrombolytic state in man: II. Clinical observations on patients with myocardial infarction and other thromboembolic disorders. *J Clin Invest* 1959; 38:1111-1119
2. Simon TL, Ware JH, Stengle JM: Clinical trials of thrombolytic agents in myocardial infarction. *Ann Intern Med* 1973; 79:712-719
3. Cowley MJ, Hastillo A, Vetrovec GW, Hess ML: Effects of intracoronary streptokinase in acute myocardial infarction. *Am Heart J* 1981; 102:1149-1158
4. Weinstein J: Treatment of myocardial infarction with intracoronary streptokinase: Efficacy and safety data from 209 United States cases in the Hoechst-Roussel registry. *Am Heart J* 1982; 104: 894-898
5. Smalling RW, Fuentes F, Freund GC, et al: Beneficial effects of intracoronary thrombolysis up to eighteen hours after onset of pain in evolving myocardial infarction. *Am Heart J* 1982; 104: 912-920
6. Anderson JL, McIlvaine PM, Marshall HM, et al: Long-term follow-up after intracoronary streptokinase for myocardial infarction: A randomized, controlled study. *Am Heart J* 1984; 108:1402-1408
7. Kennedy JW, Gensini GG, Timmis GC, Maynard MA: Acute myo-

continued on page 442

MICROX[®]

(metolazone) 1/2 mg Tablets

Brief Summary of prescribing information

DO NOT INTERCHANGE. MICROX[®] TABLETS ARE A RAPIDLY AVAILABLE FORMULATION OF METOLAZONE FOR ORAL ADMINISTRATION. MICROX TABLETS ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN[®] TABLETS. FORMULATIONS BIOEQUIVALENT TO MICROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.

INDICATIONS AND USAGE Microx Tablets are indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class.

MICROX TABLETS HAVE NOT BEEN EVALUATED FOR THE TREATMENT OF CONGESTIVE HEART FAILURE OR EDEMA DUE TO RENAL OR HEPATIC DISEASE. MICROX TABLETS SHOULD NOT BE USED WHEN DIURESIS IS DESIRED.

USAGE IN PREGNANCY The routine use of diuretics is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no evidence that they are useful in the treatment of developed toxemia. See PRECAUTIONS.

CONTRAINDICATIONS Anuria, hepatic coma or pre-coma, known allergy or hypersensitivity to metolazone.

WARNINGS Rarely, the rapid onset of severe hyponatremia and/or hypokalemia has been reported following initial doses of thiazide and non-thiazide diuretics. When symptoms consistent with electrolyte imbalance appear rapidly, drug should be discontinued and supportive measures should be initiated immediately. Parenteral electrolytes may be required. Appropriateness of therapy with this class of drug should be carefully re-evaluated. Hypokalemia may occur with consequent weakness, cramps, and cardiac dysrhythmias. Serum potassium should be determined at regular intervals, and dose reduction, potassium supplementation or addition of a potassium-sparing diuretic instituted whenever indicated. Hypokalemia is a particular hazard in patients who are digitalized or who have had a ventricular arrhythmia, dangerous or fatal arrhythmias may be precipitated. Hypokalemia is dose related.

In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Unusually large or prolonged losses of fluids and electrolytes may result when metolazone is administered concomitantly to patients receiving furosemide (see DRUG INTERACTIONS). When Microx Tablets are used with other antihypertensive drugs, particular care must be taken to avoid excessive reduction of blood pressure, especially during initial therapy. Cross-allergy, while not reported to date, theoretically may occur when Microx Tablets are given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

PRECAUTIONS Formulations bioequivalent to Microx and formulations bioequivalent to Zaroxolyn should not be interchanged for one another. All patients receiving therapy with Microx Tablets should have serum electrolyte measurements done at appropriate intervals and be observed for clinical signs of fluid and/or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced, especially with hot weather and a low-salt diet. Serum and electrolyte determinations are particularly important when the patient has protracted vomiting, severe diarrhea, or is receiving parenteral fluids. Warning signs of imbalance are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyponatremia may occur at any time during long term therapy and, on rare occasions, may be life threatening. The risk of hypokalemia is increased when larger doses are used, when diuresis is rapid, when severe liver disease is present, when corticosteroids are given concomitantly, when oral intake is inadequate or when excess potassium is being lost extrarenally, such as with vomiting or diarrhea.

Metolazone may raise blood glucose concentrations possibly causing hyperglycemia and glycosuria in patients with diabetes or latent diabetes. Microx regularly causes an increase in serum uric acid and can occasionally precipitate gouty attacks even in patients without a prior history of them. Azotemia, presumably pre-renal azotemia, may be precipitated during the administration of Microx Tablets. If azotemia and oliguria worsen during treatment of patients with severe renal disease, Microx Tablets should be discontinued. Use caution when administering Microx Tablets to patients with severely impaired renal function. As most of the drug is excreted by the renal route, accumulation may occur. Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs. Hypercalcemia has been noted in a few patients treated with metolazone. Thiazide diuretics have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with Microx Tablets.

DRUG INTERACTIONS Furosemide and probably other loop diuretics given concomitantly with metolazone can cause unusually large or prolonged losses of fluid and electrolytes (see WARNINGS). When Microx Tablets are used with other antihypertensive drugs, care must be taken, especially during initial therapy. Dosage adjustments of other antihypertensives may be necessary. The hypotensive effects of alcohol, barbiturates, and narcotics may be potentiated by the volume contraction that may be associated with metolazone therapy. Diuretic-induced hypokalemia can increase the sensitivity of the myocardium to digitalis; serious arrhythmias can result. Corticosteroids or ACTH may increase the risk of hypokalemia and increase salt and water retention. Serum lithium levels may increase (see WARNINGS). Diuretic-induced hypokalemia may enhance neuromuscular blocking effects of curariform drugs, the most serious effect would be respiratory depression which could proceed to apnea. Accordingly, it may be advisable to discontinue Microx Tablets three days before elective surgery. Salicylates and other non-steroidal anti-inflammatory drugs may decrease the antihypertensive effects of Microx Tablets. Requirements for insulin and other antidiabetic agents may be altered during administration of Microx Tablets. Arterial responsiveness to norepinephrine may be decreased, but not sufficiently to preclude effectiveness of this pressor agent for therapeutic use. Efficacy of methenamine may be decreased due to urinary alkalinizing effect of metolazone.

PREGNANCY: Teratogenic Effects—Pregnancy Category B There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Microx Tablets should be used during pregnancy only if clearly needed. Metolazone crosses the placental barrier and appears in cord blood.

NURSING MOTHERS Metolazone appears in breast milk. Because of the potential for serious adverse reactions in nursing infants from metolazone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Not recommended for pediatric use.**

ADVERSE REACTIONS Incidence reported in controlled clinical trials with Microx greater than 2%: dizziness (lightheadedness), headaches, muscle cramps, fatigue (malaise, lethargy, lassitude), joint pain, swelling, chest pain (precordial discomfort). Reported in less than 2% of Microx patients: cold extremities, edema, orthostatic hypotension, palpitations, anxiety, depression, dry mouth, impotence, nervousness, neuropathy, weakness, "weird" feeling, pruritus, rash, skin dryness, cough, epistaxis, eye itching, sinus congestion, sore throat, tinnitus, abdominal discomfort (pain, bloating), bitter taste, constipation, diarrhea, nausea, vomiting, nocturia, back pain. Reported with other marketed metolazone: excessive volume depletion, hemoconcentration, venous thrombosis, syncope, paresthesias, drowsiness, restlessness (sometimes resulting in insomnia), necrotizing anginitis (cutaneous vasculitis) purpura, dermatitis, photosensitivity, urticaria, hepatitis, intrahepatic cholestatic jaundice, pancreatitis, anorexia, aplastic (hypoplastic) anemia, agranulocytosis, leukopenia, hypokalemia, hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, acute gouty attacks, transient blurred vision, chills. Associated, but not reported to date for metolazone: sialadenitis, xanthopsia, respiratory distress (including pneumonitis), thrombocytopenia and anaphylactic reactions.

USUAL INITIAL ONCE-DAILY DOSAGE For initial treatment of mild to moderate hypertension, one Microx Tablet (1/2 mg) once daily. If patients are inadequately controlled with one 1/2 mg tablet, the dose can be increased to two Microx Tablets (1 mg) once a day. An increase in hypokalemia may occur. Doses larger than 1 mg do not give increased effectiveness.

HOW SUPPLIED Microx (metolazone) Tablets, 1/2 mg: White, flat-faced, round tablets embossed, MICROX, on one side and, 1/2, on reverse side.

R-206 10/87

INTRAVENOUS STREPTOKINASE

continued from page 439

- cardial infarction treated with intracoronary streptokinase: A report of the Society for Cardiac Angiography. *Am J Cardiol* 1985; 55: 871-877
8. Kennedy JW, Ritchie JL, Davis KB, et al: The western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: A 12-month follow-up report. *N Engl J Med* 1985; 312: 1073-1078
 9. Valentine RP, Pitts DE, Brooks-Brunn JA, et al: Intravenous versus intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* 1985; 55:309-312
 10. Spann JF, Sherry S, Carabello BA, et al: High dose, brief intravenous streptokinase early in acute myocardial infarction. *Am Heart J* 1982; 104:939-945
 11. Schroder R, Biamino G, Leitner E, et al: Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation* 1983; 67:536-548
 12. The TIMI Study Group, National Heart, Lung and Blood Institute: The thrombolysis in myocardial infarction (TIMI) trial: Phase 1 findings. *N Engl J Med* 1985; 312:932-936
 13. Koren G, Weiss AT, Hasin Y, et al: Prevention of myocardial damage in acute myocardial ischemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985; 313:1384-1389
 14. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico, GISSI: Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; 1:397-401
 15. Satler LF, Kent KM, Fox LM, et al: The assessment of contractile reserve after thrombolytic therapy for acute myocardial infarction. *Am Heart J* 1986; 111:821-825
 16. The ISAM Study Group: A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). *N Engl J Med* 1986; 314:1465-1471
 17. McNamara CA, Burket MW, Brewster PS, et al: Comparisons of thrombolytic therapy for acute myocardial infarction in rural and urban settings. *Am J Med* 1987; 82:1095-1101