Hippocrates, Still, and Osler: A shared philosophy

Hippocratic philosophy and principles underlie basic osteopathic medical philosophy. George W. Northup, DO, wrote in *Osteopathic medicine: An American reformation*, "While the Hippocratic school emphasized the study of the health of man as an individual, integrated unit, the rival school at Cnidus, a nearby peninsula, steered its attention away from man toward disease, the afflictor of man.... Basically, osteopathic medicine and its physiological principles are supporters of the Hippocratic approach. Although it borrows from both Hippocratic and the Cnidian, the emphasis is clearly on Man rather than the individual diseases that afflict man."¹

See related article on page 1243.

Like Thomas Sydenham and Hermann Boerhaave before him and Sir William Osler after him, Andrew Taylor Still incorporated the Hippocratic thought and philosophy into his own. While there are remarkable similarities between Still and Hippocrates' philosophy, Still apparently did not specifically acknowledge the latter's influence in any of his writings.

In "The rebirth of Hippocratic thought," beginning on page 1243 in this issue, Robert E. Suter, examines the similarities between Still and Hippocrates. He argues that Still was influenced more directly by Hippocrates' teaching than previously recognized. With that in mind, the reference to Hippocrates' special attention to the musculoskeletal system and his description of manipulative approaches to musculoskeletal disorders proves particularly interesting.

Suter draws striking parallels between Still and Osler. These contemporary giants, who apparently never met, developed philosophies similarly influenced by Hippocratic principles. Concludes Suter, "In that teachings of both William Osler and Andrew Taylor Still are to a large extent consistent with those of Hippocrates, the view that American medicine today reflects the influence of these two men can also be seen as a belated return to and rebirth of Hippocratic thought and medicine."

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1. Northup, GW: *Osteopathic medicine: An American reformation*. Ed 2, p 4. American Osteopathic Association, Chicago, 1979.

MEDICAL DIRECTOR'S PAGE

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Home IV Antibiotic Therapy: An Introduction

Lowering health care costs while maintaining high quality care is a goal that all physicians strive for. An important step toward this goal is the development of home health care that is both therapeutically and economically effective. One particular aspect of home health care that is gaining acceptance is home intravenous antibiotic therapy.

Evolution of an Industry

Experts anticipate that over the next several years home IV antibiotic therapy will be one of the fastest growing segments of the home health care market. Today, physicians have access to an industry that provides necessary technology, personal services and pharmaceutical supplies — an industry devoted to home health care. With the growth of this industry, most physicians will be able to successfully manage many patients with a minimum of acute hospital care.

The Home IV Therapy Decision

Almost any patient who requires IV antibiotic therapy, and is hospitalized to receive that therapy, could be considered for treatment at home. However, four criteria are often applied before implementing home IV therapy:¹

1. No suitable oral therapy is available.
2. The patient's condition is stable enough for discharge, and the patient can monitor his/her own therapy.
3. The patient agrees to outpatient therapy after a full disclosure of responsibilities and potential problems.
4. The patient has a suitable home environment, including a phone for emergency communications and a refrigerator for antibiotic storage.

Any infection that responds to IV therapy can potentially be treated at home, including osteomyelitis, endocarditis, wound infections, urinary tract infections, septic arthritis and others.²

Many classes of antibiotics appear suitable for home IV infusion; however, antibiotics used in outpatient care should have low toxicity, a broad spectrum of

activity and a long half-life, allowing for less frequent dosing. Antibiotics with long half-lives enhance the convenience and cost effectiveness of home therapy and facilitate patient compliance.

Advantages

Home IV antibiotic therapy removes the risk of nosocomial infection. Receiving therapy at home in warm and familiar surroundings also provides psychological benefits. Another benefit is that patients in the home care environment become more active in their recovery. These intangibles appear to contribute to more rapid and predictable recovery.

There are also considerable financial advantages to home IV antibiotic therapy. For those patients who are able to work while receiving therapy, the benefits are obvious. Of course, savings are also accrued because patients are not hospitalized for long periods of time. In one study, the calculated savings ranged from \$2,791 to \$4,651 per patient.³

In addition, reimbursement for home services has greatly improved during the past five years. Many insurers now pay for outpatient therapy that can replace treatment given in the hospital. Congress has also provided for such reimbursement in the Medicare population under the catastrophic health insurance law that was recently enacted.

The success of home IV antibiotic therapy depends on a team effort employing sound case management by the physician and quality service from the home health care industry. Teamwork by these two groups will help ease the medical profession into a new era of health care.

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2. Rising JB: Home IV antibiotic therapy: Roles you can play. *U.S. Pharmacist*, Oct 1987:H9-H14.
3. Graves G, Jackson JP, Maxwell A, Woods T: Home intravenous antibiotic therapy in Arkansas. *J Arkansas Med Soc* 1987;84:55-57.

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It's a sad fact, but a fact nonetheless. Substance abuse is so widespread these days that buying cocaine is almost as easy as buying a hot dog or a new pair of shoes.

As a physician, you're in the unique position to detect drug abuse in your patients, using your training, thorough work-ups, and advanced diagnostic techniques.

Through increased detection, you can help curb this growing problem, and help make our towns (both small and large) a home for people, not pushers.

Looking for drug abuse—make it a habit.

Partnership for a Drug-Free America

Who's taking MEVACOR®?

(LOVASTATIN / MSD)

Patient L.J.K.

- Female, age 56
- Elevated total cholesterol of 268 mg/dL after adequate trial of a weight-loss and cholesterol-lowering diet
- Obese—more than 30% above ideal weight
- Has cut down to one pack of cigarettes a day
- After first 6 weeks on MEVACOR, total cholesterol is down to 220 mg/dL (dosage: 20 mg once daily with the evening meal)
- Dosage increased to 20 mg b.i.d.; after 6 additional weeks, total cholesterol is down to 196 mg/dL

Results with MEVACOR

Not everyone will respond as did the patient in this hypothetical case history; however, the mean reduction in total cholesterol in clinical trials was 17% at 20 mg once a day and 27% at 20 mg b.i.d.

MEVACOR is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when response to nonpharmacologic measures has been inadequate.

MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

The effect of lovastatin-induced changes in serum lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

For more details on warnings, precautions, and adverse reactions, including cautionary information regarding liver dysfunction, myopathy, and slit-lamp monitoring, please see Prescribing Information.

For a Brief Summary of Prescribing Information, please see the following page.

MSD
MERCK
SHARP &
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TABLETS, 20 mg

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.
Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In clinical trials and since the drug was marketed, there have been rare reports of severe rhabdomyolysis that precipitated acute renal failure, especially in cardiac transplant patients on immunosuppressive therapy including cyclosporine. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Most of the patients who have developed myopathy while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of niacin (nicotinic acid). In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively. It is not known whether the same phenomenon occurs with fibrates other than gemfibrozil. Therefore, the benefits and risks of using lovastatin concomitantly with immunosuppressive drugs, fibrates, or lipid-lowering doses of niacin (nicotinic acid) should be carefully considered.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

Consideration should be given to temporarily withholding or discontinuing drug therapy in any patient with a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, and uncontrolled seizures.

PRECAUTIONS

General

Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted

at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia

MEVACOR® (Lovastatin, MSD) is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid): See WARNINGS, Skeletal Muscle.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Drug/Laboratory Test Interactions

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p < 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (adjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosome aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy

Pregnancy Category X.

See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose—about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers

Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS

MEVACOR® (Lovastatin, MSD) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR; about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences

Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

	MEVACOR (N = 613)	Placebo (N = 82)	Cholestyramine (N = 88)	Pro (N = 10)
Gastrointestinal				
Constipation	4.9	—	34.1	—
Diarrhea	5.5	4.9	8.0	—
Dyspepsia	3.9	—	13.6	—
Fatigue	6.4	2.4	21.6	—
Abdominal pain/cramps	5.7	2.4	5.7	—
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	—
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	—
Headache	9.3	4.9	4.5	—
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	—
Dysgeusia	0.8	—	1.1	—

Laboratory Tests

Marked persistent increases of serum transaminases have been reported (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions; corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have rarely been reported (see WARNINGS, Skeletal Muscle).

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to concomitant treatment were observed. The adverse reactions observed were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, Skeletal Muscle).

Uncontrolled Clinical Studies

The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function was observed at a higher incidence than in the controlled studies (see WARNINGS, Liver Dysfunction). Myopathy (myalgia with marked elevations) was reported in approximately 0.5% of patients (see WARNINGS, Skeletal Muscle).

Causal Relationship Unclear

Nervous System: A single case of peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline during therapy with lovastatin, 34 had opacities reported at the examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

OVERDOSAGE

The oral LD₅₀ of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A case of accidental overdose has been reported; no patients had specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 52 20-mg tablets (1.04 g).

Until further experience is obtained, no specific treatment of overdose with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with evening meal. The recommended dosing range is 20 to 80 mg/day as single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response. Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for response results.

For those patients with severely elevated serum cholesterol levels (>300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, Skeletal Muscle), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol level falls below the targeted range.

HOW SUPPLIED

Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded M 731 on one side and MEVACOR on the other. They are supplied in unit-of-use bottles of 60 and in unit-dose packages of 100.