

# Ablation Resolves Dysplasia in Barrett's Esophagus

BY ROBERT FINN  
San Francisco Bureau

SAN DIEGO — Interim results from a randomized, controlled trial suggest that radiofrequency ablation is more effective than frequent surveillance for Barrett's esophagus.

The study compared 84 patients who underwent ablation with 43 who underwent a sham operation. All patients received high-dose acid suppression (40 mg

esomeprazole twice daily). The ablation patients with high-grade dysplasia underwent endoscopic biopsies at 3, 6, 9, and 12 months, whereas those with low-grade dysplasia underwent endoscopic biopsies at 6 and 12 months, Dr. Nicholas Shaheen reported at the annual Digestive Disease Week.

At the end of that time, 80% of the patients in the ablation group with high-grade dysplasia and 90% of those with low-grade dysplasia experienced a com-

plete response, which the investigators defined as having all biopsies free of any histologic evidence of dysplasia, "not a single goblet cell," said Dr. Shaheen of the University of North Carolina, Chapel Hill.

In contrast, 26% of the control patients experienced a complete response. The difference between the ablation and control patients was statistically significant in the intent-to-treat analysis.

Of all the patients who underwent ab-

lation, 77% experienced a complete response for intestinal metaplasia, compared with none of the control patients. Once again, this difference was statistically significant.

There was also a significant difference in the rate of histologic progression from low-grade dysplasia to high-grade dysplasia, and from high-grade dysplasia to cancer. Of the patients who received a sham operation, 19% experienced progression of the disease, compared with just 5% of the ablated patients.

Adverse events in the study were relatively minor. Of the ablated patients, 6% experienced strictures, but all resolved after a mean of two dilations. There were

Significantly more ablation than control patients achieved a complete response of 'not a single goblet cell.'

DR. SHAHEEN

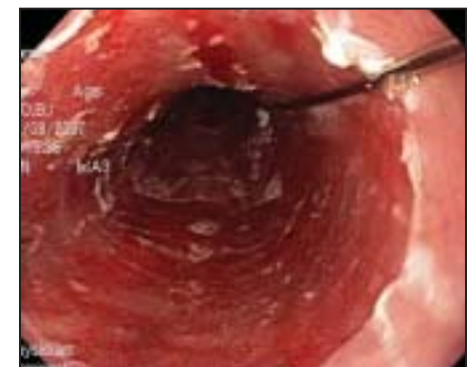


three serious adverse events among the ablated patients and none among the patients who received a sham operation. One patient experienced an upper GI bleed, and two others experienced chest pain and were admitted overnight for observation.

"Patients often do have chest pain after the procedure," Dr. Shaheen said in an interview. "This pain is usually mild to moderate, and was managed successfully in 295 of the 297 procedures performed in the trial with oral pain medications or no medications. Two patients did have to be admitted for chest pain. This is in contrast to our older therapies, such as PDT [photodynamic therapy], after which we hospitalized everyone for pain control."

The study, which is ongoing, is being conducted at 19 medical centers in the United States. It was funded by BARRX Medical Inc., which manufactures the radiofrequency ablation system used in the study.

Dr. Shaheen acknowledged receiving "other financial benefits" from that company, as well as receiving consulting fees, speaking fees, research support, and/or other financial benefits from AstraZeneca Pharmaceuticals LP, TAP Pharmaceutical Products Inc., Procter & Gamble Co., Eisai Co., Merck & Co., and Ethicon Endo-Surgery Inc.



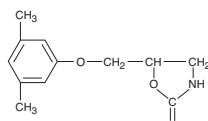
Dysplasia resolved after ablation in 80%-90% of Barrett's esophagus patients.

COURTESY DR. NICHOLAS SHAHEEN

## SKELAXIN® (Metaxalone) Tablets

### DESCRIPTION

SKELAXIN® (metaxalone) is available as an 800 mg oval, scored pink tablet. Chemically, metaxalone is 5-[[3,5-dimethylphenoxy]methyl]-2-oxazolidinone. The empirical formula is C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>, which corresponds to a molecular weight of 221.25. The structural formula is:



Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Each tablet contains 800 mg metaxalone and the following inactive ingredients: alginic acid, ammonium calcium alginate, B-Rose Liquid, corn starch and magnesium stearate.

### CLINICAL PHARMACOLOGY

**Mechanism of Action:** The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

### Pharmacokinetics:

The pharmacokinetics of metaxalone have been evaluated in healthy adult volunteers after single dose administration of SKELAXIN under fasted and fed conditions at doses ranging from 400 mg to 800 mg.

### Absorption

Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions. Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of SKELAXIN from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C<sub>max</sub>) and area under the curve (AUC).

Dose proportionality at doses above 800 mg has not been studied. The absolute bioavailability of metaxalone is not known.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers are shown in Table 1.

Dose (mg)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-4</sub> (ng·h/mL)	t <sub>1/2</sub> (h)	CL/F (L/h)
400 <sup>1</sup>	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800 <sup>2</sup>	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

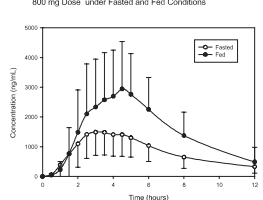
<sup>1</sup>Subjects received 1x400 mg tablet under fasted conditions (N=42)  
<sup>2</sup>Subjects received 2x400 mg tablets under fasted conditions (N=59)

### Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg SKELAXIN tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age = 23.5 ± 5.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C<sub>max</sub> by 177.5% and increased AUC (AUC<sub>0-4</sub>, AUC<sub>∞</sub>) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T<sub>max</sub>) was also delayed (4.3 h versus 3.3 h) and terminal half-life was decreased (2.4 h versus 9.0 h) under fed conditions compared to fasted.

In a second food effect study of similar design, two 400 mg SKELAXIN tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22 females), ranging in age from 18-50 years (mean age = 25.6 ± 8.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C<sub>max</sub> by 193.6% and increased AUC (AUC<sub>0-4</sub>, AUC<sub>∞</sub>) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T<sub>max</sub>) was also delayed (4.9 h versus 3.0 h) and terminal half-life was decreased (4.2 h versus 8.0 h) under fed conditions compared to fasted conditions. Similar food effect results were observed in the above study when one SKELAXIN 800 mg tablet was administered in place of two SKELAXIN 400 mg tablets. The increase in metaxalone exposure coinciding with a reduction in half-life may be attributed to more complete absorption of metaxalone in the presence of a high fat meal (Figure 1).

Figure 1. Mean (SD) Concentrations of Metaxalone following an 800 mg Dose under Fasted and Fed Conditions.



### Distribution, Metabolism, and Excretion

Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution (V/F ~ 800 L) and lipophilicity (log P = 2.42) of metaxalone suggest that the drug is extensively distributed in the tissues. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites.

### Pharmacokinetics in Special Populations

**Age:** The effects of age on the pharmacokinetics of metaxalone were determined following single administration of two 400 mg tablets (800 mg) under fasted and fed conditions. The results were analyzed separately, as well as in combination with the results from three other studies. Using the combined data, the results indicate that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age.

The bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers of varying age is shown in Table 2.

Age (years)	Younger Volunteers		Older Volunteers	
	Fasted	Fed	Fasted	Fed
N	59	21	21	23
C <sub>max</sub> (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)

T <sub>max</sub> (h)	Fasted		Fed	
	(39)	(48)	(40)	(30)
AUC <sub>0-4</sub> (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	23797 (45)
AUC <sub>∞</sub> (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	24194 (44)

**Gender:** The effect of gender on the pharmacokinetics of metaxalone was assessed in an open label study, in which 48 healthy adult volunteers (24 males, 24 females) were administered two SKELAXIN 400 mg tablets (800 mg) under fasted conditions. The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C<sub>max</sub> (2115 ng/mL versus 1335 ng/mL) and AUC<sub>∞</sub> (17884 ng·h/mL versus 10328 ng·h/mL). The mean half-life was 11.1 hours in females and 7.6 hours in males. The apparent volume of distribution of metaxalone was approximately 22% higher in males than in females, but not significantly different when adjusted for body weight. Similar findings were also seen when the previously described combined dataset was used in the analysis.

**Hepatic/Renal Insufficiency:** The impact of hepatic and renal disease on the pharmacokinetics of metaxalone has not been determined. In the absence of this information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment.

### INDICATIONS AND USAGE

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

### CONTRAINDICATIONS

Known hypersensitivity to any components of this product. Known tendency to drug induced, hemolytic, or other anemias. Significantly impaired renal or hepatic function.

### WARNINGS

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

### PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients section).

### Information for Patients

SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

### Drug Interactions

SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of metaxalone has not been determined.

### Pregnancy

Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

### Nursing Mothers

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

### Pediatric Use

Safety and effectiveness in children 12 years of age and below have not been established.

### ADVERSE REACTIONS

The most frequent reactions to metaxalone include: CNS: drowsiness, dizziness, headache, and nervousness or "irritability";

Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions are:

Immune System: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia; hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

### OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

When determining the LD<sub>50</sub> in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD<sub>50</sub> could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

**Treatment** - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

### DOSE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day.

### HOW SUPPLIED

SKELAXIN (metaxalone) is available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 60793-136-01) and in bottles of 500 (NDC 60793-136-05).

Store at Controlled Room Temperature, between 15°C and 30°C (59°F and 86°F).

### Rx Only

Prescribing Information as of April 2007.



King Pharmaceuticals

Distributed by: King Pharmaceuticals, Inc., Bristol, TN 37620  
Manufactured by: Mallinckrodt Inc., Hobart, NY 13788



www.kingpharm.com www.skelaxin.com

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