

Combined Therapy Slows Endometriosis in Teens

BY SHERRY BOSCHERT
San Francisco Bureau

NEWPORT BEACH, CALIF. — Disease stage stabilized or improved in 81 of 90 adolescents who were treated for endometriosis with combined surgical and medical therapy, according to results of a retrospective study.

The goals of treating endometriosis in adolescents generally are to control pain, prevent disease progression, and preserve

fertility. This study is the first to show that a combined surgical/medical approach to treating endometriosis in adolescents retards disease progression, Dr. Joseph O. Doyle said at the annual meeting of the North American Society for Pediatric and Adolescent Gynecology.

These findings are important because they support a strategy of early intervention and treatment to control pain and prevent progression. Some treatments may impair the fertility of these patients, said Dr. Doyle

of Brigham and Women's Hospital, Boston.

The subjects had a mean age of 17 years (range, 12-24 years) and had undergone two laparoscopies separated by a median of 29 months (range, 6-112 months), allowing the researchers to assess disease progression over time.

They underwent the initial laparoscopy for pelvic pain that did not improve adequately after at least 3 months of medical treatment with cyclical hormonal therapy and nonsteroidal anti-inflammatory drugs.

Endometriosis was confirmed on laparoscopy, during which the surgeon destroyed any endometrial lesions that were observed and lysed any adhesions.

Patients were then treated medically with continuous combined oral contraceptives (82 patients), continuous progesterone-only therapy (11 patients), or continuous GnRH agonists (70 patients). Some patients tried more than one medical therapy to control pain.

They underwent the second laparoscopy because of persistent pain. "Our ... study did not include anyone who had one laparoscopy, received their medical portion of treatment, and had adequate treatment response," Dr. Doyle said. "We potentially excluded a large proportion of the treatment effect and biased our population toward those with more progressive disease," yet little disease progression was seen with combined therapy.

The median stage of endometriosis at both the first and second laparoscopy was stage I, using the revised grading system of the American Society for Reproductive Medicine. Most patients had minimal (stage I) or mild (stage II) disease, and no patient had worse than stage III (moderate) disease.

One patient (1%) showed a two-stage improvement in endometriosis at the second laparoscopy, 17 (19%) improved by one stage, 63 patients (70%) had no change in stage; in 9 patients (10%), endometriosis worsened by one stage.

Statistical analysis showed a significant association between stages at first and second laparoscopies after adjusting for the effects of age at first laparoscopy, the interval between laparoscopies, and the type of hormonal therapy used, which "reflects our finding that 70% of patients had stable disease," he said.

Regardless of the disease stage at the first laparoscopy, there were no statistical trends toward disease progression, but a significant likelihood (especially in patients with stage II or III disease) of improvement in endometriosis by the second surgery.

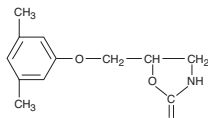
Patients with other or additional pelvic or abdominal pathologies besides endometriosis, those with a history of prior surgeries or pregnancies, and those with significant medical histories, were excluded. ■

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 C₁₁H₁₃NO₂, 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: alginate 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_{max}) 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 _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₄ (ng·h/mL)	t _{1/2} (h)	CL/F (L/h)
400 ^a	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800 ^b	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

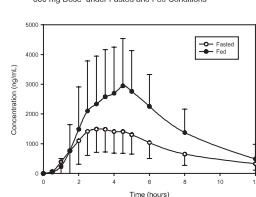
^aSubjects received 1x400 mg tablet under fasted conditions (N=42)
^bSubjects received 2x400 mg tablets under fasted conditions (N=59)

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_{max} by 177.5% and increased AUC (AUC₀₋₄, AUC_{0-∞}) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T_{max}) 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_{max} by 193.6% and increased AUC (AUC₀₋₄, AUC_{0-∞}) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T_{max}) 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	23	23
C _{max} (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)

T _{max} (h)	Younger Volunteers		Older Volunteers	
	Fasted	Fed	Fasted	Fed
N	59	21	23	23
AUC ₀₋₄ (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	20482 (37)
AUC _{0-∞} (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	20815 (37)

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_{max} (2115 ng/mL versus 1335 ng/mL) and AUC_{0-∞} (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 such 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 LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ 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.

DOSAGE 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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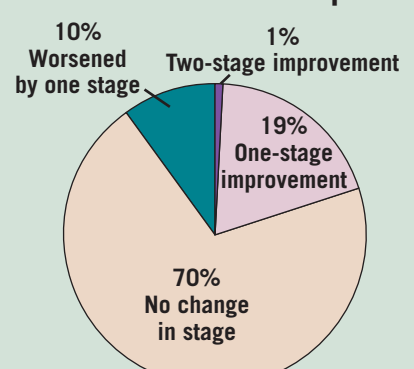
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Most Endometriosis Cases Stabilized or Improved With Combined Therapies



Note: Based on a median 29-month follow-up of 90 adolescents who received combined medical and surgical therapy.
Source: Dr. Doyle