

SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium)

double-strength capsules—for oral administration

Contraindicated: In patients who have previously exhibited intolerance to it; patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding.

Precautions: General—Ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

Renal failure, sometimes acutely associated with nephrotic syndrome has been reported. Closely monitor patients with impaired renal function; they may require lower doses.

TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.

In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

TOLECTIN should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.

As with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among nonsteroidal anti-inflammatory drugs, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds, particularly zomepirac sodium. Patients who have had anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamines, and/or steroids.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), discontinue TOLECTIN (tolmetin sodium).

Usage in Pregnancy—Because TOLECTIN has not been studied in pregnant women, use during pregnancy is not recommended.

Nursing Mothers—Because TOLECTIN may be secreted in human milk, nursing should not be undertaken while a patient is on this drug.

Drug Interactions: There have been rare reports that prothrombin time may increase and bleeding may occur.

Adverse Reactions: Incidence Greater Than 1%. The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia,* gastrointestinal distress,* abdominal pain,* diarrhea,* flatulence,* vomiting,* constipation, gastritis, and peptic ulcer.

Body as a Whole: Headache,* asthenia,* chest pain

Cardiovascular: Elevated blood pressure,* edema*

Central Nervous System: Dizziness,* drowsiness, depression

Metabolic/Nutritional: Weight gain,* weight loss*

Dermatologic: Skin irritation

Special Senses: Tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.

Urogenital: Elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with TOLECTIN (tolmetin sodium). Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)

Gastrointestinal: Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: Congestive heart failure in patients with marginal cardiac function

Dermatologic: Urticaria, purpura, erythema multiforme, toxic epidermal necrolysis

Urogenital: Hematuria, proteinuria, dysuria, renal failure

Special Senses: Optic neuropathy, retinal and macular changes

Incidence Less Than 1% (Causal Relationship Unknown)

Body as a Whole: Epistaxis

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdose, see full prescribing information.

2/20/85

LETTERS TO THE EDITOR

The Journal welcomes Letters to the Editor; if found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with journal style.

PERIODIC HEALTH EXAMINATIONS

To the Editor:

I hasten to comment on the editorial in the August 1984 issue by Dr. A.O. Berg¹ and the article by Dr. F. Romm, "Patients' Expectations of Periodic Health Examinations,"² since I am concerned that the conclusions drawn by both of the authors may be based on data that is itself "awry."

I refer specifically to the data collection instrument given to the patients in Dr. Romm's study as they checked in for care. The instrument was not shown in the article, but apparently the patients were given a "shopping list" from which to select items of history, examination, laboratory tests, and procedures that they desired from their physician, and the frequency with which they should be performed. In my view, such an instrument has great potential for biasing subjects to select items that they had not thought about, did not really desire, or even may not have heard about before!

A number of questions regarding the implementation of the study come to mind. For instance, (1) did all the patients understand the terminology used or the implications and costs of the items they were selecting? Maybe this could explain why young women selected mammograms as frequently as older women, a finding that sur-

prised Dr. Romm. (2) Was the reliability of the data tested by repetition? (3) What would have been the result had the subjects been asked to propose and indicate the items they desired without being given a list from which to choose? (4) Were the people attending the Family Practice Center biased in their responses by their reason for visiting the office (ie, chronic disease, acute illness, routine check-up)? (5) What could have been responses of patients of the Family Practice Center who were currently not attending for care?

Although I agree with the author's suggestions that the standards of preventive care, at least based on the audit of medical records, require improvement. I do not think that the gap between the patients' desires for preventive care and its provision by physicians has been demonstrated because the data reported are suspect. Although the medical charts were audited to see whether there was a fit between patient item selection and physician performance, another equally reasonable approach would have been to ask the subjects whether they had received specific care items in previous examinations and whether this was satisfactory.

Finally, I have some difficulties with the semantics of the words *expectations* and *desires*, which seem to be used interchangeably in the paper. Expectations are what patients believe will take place or

anticipate will occur at the periodic examination. These are not necessarily what they wish to be done. This semantic difference does have an impact on the way a data-collection instrument would be developed depending on what the researcher was trying to ascertain. A definition of these items would have helped to clarify the specific purpose of Dr. Romm's study and reduce the confusion I believe has led to unjustified conclusions.

Peter Curtis, MD

Department of Family Medicine
University of North Carolina
at Chapel Hill
Chapel Hill, North Carolina

References

1. Berg AO: The periodic health examination: Expectations gone awry. *J Fam Pract* 1984; 19:165-166
2. Romm FJ: Patients' expectations of periodic health examinations. *J Fam Pract* 1984; 19:191-195

The preceding letter was referred to Dr. Romm, who responds as follows:

Dr. Curtis' comments mainly concern the validity and reliability of the data collection instrument. Indeed, the instrument was in the form that Dr. Curtis suggests, and could be called a "shopping list." I am not sure, however, that the open-ended questionnaire that he suggests would have been better. To apply the shopping list metaphor, if one went to a store only once a year (the annual examination) and had only a brief time to prepare (the 10 or 15 minutes available to the patients to fill out the questionnaire), which would produce a more accurate group of needed items, a preprinted check list or a blank sheet of paper?

As for the other comments, it is not clear that patients understood all the terms. Patients may have selected items because they were on the list, perhaps believing that if the clinic provided them, they must be worthwhile. But this potential bias does not seem an adequate explanation for all the results: there was substantial variation in selection among the history, examination, and laboratory groups as well as within these categories; patients also had the opportunity to check an "other" or "don't know" column if they did not understand an item sufficiently.

The reliability of the data was not tested. There was a mix of problems presented by the patients who participated, and only a relatively small number came for general examinations. The demographic and disease characteristics of the study participants were not different from the overall center patient population.

As to the semantic problem with regard to the use of the words *expectations* and *desires*, the questionnaire was worded, "How often should the item be part of your check-up" (page 192). My dictionary's definition of "should" includes "used . . . to express what is probable or expected." This justifies the use of expectations in the title and body of the paper. Desires, as Dr. Curtis points out, are things that are wished for. In the context of an examination that is seen as potentially beneficial to an individual, I would think that an item that is expected would also be wanted and, thus, I have no problems with the use of desires as an alternative to expectations in the paper.

I believe that Dr. Curtis has pointed out some possible limita-

tions that are in addition to those expressed in the discussion. Certainly this is not the last word on this subject. More detailed study is needed to clarify what patients know about preventable diseases and screening tests and what they expect and desire from their physicians. Despite the limitations, I think the conclusions, expressed in the typical academic terminology of "suggest" and "apparent," with "notes of caution," are justified from the data.

Fredric J. Romm, MD, MPH

Department of Family
and Community Medicine
Bowman Gray School of Medicine
Winston-Salem, North Carolina

SCREENING FOR GESTATIONAL DIABETES

To the Editor:

With regard to the article by Dr. Barbara Reed, "Screening for Gestational Diabetes—Analysis by Screening Criteria" (*J Fam Pract* 1984; 19:751-755), I have several comments. Dr. Reed gives a thoughtful and complete evaluation of several possible approaches to screening for gestational diabetes. However, I must disagree with her choice of 150 mg/dL as a cutoff for proceeding to a three-hour glucose tolerance test (GTT) following the 1-hour glucose screening test (GST).

Based on data presented by Carpenter and Coustan,¹ which Dr. Reed mentions but discounts in her article, lowering the cutoff to 135 mg/dL would increase the sensitivity of the glucose screening test to near 100 percent while maintaining a specificity of 80 percent. Even

Continued on page 128

Antihypertensive therapy that does not increase cholesterol

Brief Summary

Before prescribing, consult the complete package circular.

Indications and Usage: Treatment of hypertension, alone or in combination with a thiazide diuretic.

Contraindication: Known sensitivity to the drug.

Precautions: 1. Sedation. Causes sedation or drowsiness in a large fraction of patients. When used with centrally acting depressants, e.g., phenothiazines, barbiturates and benzodiazepines, consider potential for additive sedative effects. 2. Patients with vascular insufficiency: Like other antihypertensives use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure. 3. Rebound: Sudden cessation of therapy with central alpha agonists like Wyntensin may rarely result in "overshoot" hypertension and more commonly produces increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS. Advise patients on Wyntensin to exercise caution when operating dangerous machinery or motor vehicles until it is determined they do not become drowsy or dizzy. Warn patients that tolerance for alcohol and other CNS depressants may be diminished. Advise patients not to discontinue therapy abruptly.

LAB TESTS: In clinical trials, no clinically significant lab test abnormalities were identified during acute or chronic therapy. Tests included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term use there was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction. In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease.

DRUG INTERACTIONS: Wyntensin was not demonstrated to cause drug interactions when given with other drugs, e.g., digitalis glycosides, amphetamines, anesthetic and antiinflammatory or antineoplastic agents, in clinical trials. However, potential for increased sedation when given concomitantly with CNS depressants should be noted.

DRUG/LAB TEST INTERACTIONS: No lab test abnormalities were identified with Wyntensin use.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: No evidence of carcinogenic potential emerged in rats during a two-year oral study with Wyntensin at up to 9.5 mg/kg/day, i.e., about 10 times maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, Wyntensin at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Saccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, Wyntensin produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9.6 mg/kg), suggesting impairment of fertility. Fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy.

PREGNANCY: Pregnancy Category C. WYNTENSIN[®] MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice indicated possible increase in skeletal abnormalities when Wyntensin is given orally at doses 3 to 6 times maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral Wyntensin given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies in rats have shown slightly decreased live-birth indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. These are statistically significant, well-controlled studies in pregnant women. Wyntensin should be used during pregnancy only if potential benefit justifies potential risk to fetus.

NURSING MOTHERS: Because no information is available on Wyntensin excretion in human milk, it should not be given to nursing mothers.

PEDIATRIC USE: Safety and effectiveness in children less than 12 years of age have not been demonstrated; use in this age group cannot be recommended.

Adverse Reactions: Incidence of adverse effects was ascertained from controlled clinical studies in U.S. and is based on data from 859 patients on Wyntensin for up to 3 years. There is some evidence that side effects are dose-related. Following table shows incidence of adverse effects in at least 5% of patients in study comparing Wyntensin to placebo, at starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%)		Wyntensin (%)	
	n = 102	n = 109	n = 102	n = 109
Dry mouth	7	28		
Drowsiness or sedation	12	39		
Dizziness	7	17		
Weakness	7	10		
Headache	6	5		

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20%. Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less: Cardiovascular—chest pain, edema, arrhythmias, palpitations. Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort. Central nervous system—anxiety, ataxia, depression, sleep disturbances. ENT disorders—nasal congestion. Eye disorders—blurring of vision. Musculoskeletal—aches in extremities, muscle aches. Respiratory—dyspnea. Dermatologic—rash, pruritus. Urogenital—urinary frequency, disturbances of sexual function. Other—gynecomastia, taste disorders.

Drug Abuse and Dependence: No dependence or abuse has been reported.

Overdosage: Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both. Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. Adequate airway should be maintained and, if indicated, assisted respiration instituted. No data are available on Wyntensin dialyzability.

Dosage and Administration: Individualize dosage. A starting dose of 4 mg b.i.d. is recommended, whether used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response. Maximum dose studied has been 32 mg b.i.d., but doses this high are rarely needed.

How Supplied: Wyntensin (guanabenz acetate) Tablets, 4mg, bottles of 100 and 500; 8mg, bottles of 100. 1/5/84

Wyeth Laboratories
Philadelphia Pa 19101

Continued from page 125

conservatively assuming a 96 percent sensitivity, 24 of 25 cases would be detected in the hypothetical population presented in her article. This would be at a total cost of \$14,950 incurred from 1,000 glucose screening tests and 199 oral glucose tolerance tests. While slightly higher than the \$13,688 resulting from the test as recommended by Dr. Reed, the actual cost per case would be only \$623 because of the additional number of cases that would be picked up using this method.

A screening test should be very sensitive, even at the expense of specificity, in detecting serious illness for which there is effective treatment. I feel that the most accurate, yet cost effective, approach is to screen all pregnant women and to perform a GTT in those whose serum glucose is 135 mg/dL or higher during the GST.

John Jurica, MD
University of Illinois College of
Medicine at Rockford
Rockford, Illinois

Reference

1. Carpenter MW, Coustan DR: Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982; 144:768-773

The preceding letter was referred to Dr. Reed, who responds as follows:

I appreciate Dr. Jurica's comments regarding the importance of the choice of glucose level criteria in the glucose screening test for gestational diabetes. The level at which a screening test is considered abnormal clearly affects the sensitivity and specificity, as well as the predictive value, of that test.

Dr. Jurica's argument rests on

the assumption that a near 100 percent sensitivity is obtained by using the lower screening criteria. The data presented in the Carpenter and Coustan article, however, are insufficient to determine the sensitivity of this criterion because three-hour glucose tolerance tests were not performed on those patients with screening glucose values less than 130 mg/dL. Furthermore, they studied only those patients older than 25 years. Therefore, the sensitivity of the lower criteria for younger women is unknown.

Carpenter and Coustan's data do indicate that 16.7 percent (4/24) of their known true positive patients aged over 25 years did fall in the level of glucose screening determinations that would have been missed by O'Sullivan's criteria.

Clearly, a repeat study utilizing both the screening test and the three-hour glucose tolerance test for all patients would clarify the value of a lower screening cutoff. If large patient numbers were obtained, a more precise false-negative rate could also be determined. Until this is done, it is not unreasonable to perform a three-hour glucose tolerance test when the result of the glucose screening test is below 150 mg/dL. Data are inadequate to accurately compute a cost per case detected, but the point is well taken that the added cost of a greater number of glucose tolerance tests may be offset by a higher detection rate and, hence, may hold down the cost per case detected.

Barbara Reed, MD, MSPH
Department of Family
and Community Medicine
University of Utah
Medical Center
Salt Lake City, Utah