Hydergine®

in the treatment of diffuse cerebral insufficiency

PRESCRIBING INFORMATION

DOSAGE

for 4 weeks

for 6 weeks

Afterward the daily dose can, if warranted, be reduced to 2 tablets.

Patients should be convinced of the necessity and importance of taking their medication regularly every day, preferably with their meals and at bedtime. The difference between success and failure is often directly related to the way the patient follows the dosage schedule.

Composition — Tablets: Each 1 mg tablet contains the methanesulfonates of dihydroergocornine, dihydroergocristine and dihydroergokryptine in equal proportions. Ampoules: Each 1 ml ampoule contains 0.3 mg Hydergine consisting of the methanesulfonates of dihydroergocornine, dihydroergocristine and dihydroergokryptine in equal proportions.

Side Effects — Hydergine is usually well tolerated even in larger doses. Side effects are few and very slight. In addition to nasal stuffiness, there may be nausea, gastric pressure, anorexia, and headache, especially in patients with autonomic lability. In such cases, it is advisable to reduce the dose or administer it during or after meals.

Contraindications — Severe bradycardia and severe hypotension.

Supply: Bottles of 100 and 500 tablets; Boxes of 6 and 100 ampoules.

Full prescribing information is available upon request.

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Efficacy of Allopurinol in Single Daily Dose

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SUMMARY

Allopurinol 300 mg once daily was compared with allopurinol, 100 mg tid in 17 patients with gouty arthritis and/or gouty nephrolithiasis. Weekly serum uric acid levels showed small but statistically significant differences between dosage regimens in four patients. Two acute attacks of gouty arthritis occurred in two different patients during once daily dosing of the allopurinol. There were no side effects attributable to the once daily dosage regimen.

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ALLOPURINOL, an inhibitor of xanthine oxidase, is commonly used in various hyperuricemic states (see Table 1). Multiple daily doses were recommended until the recent availability of a 300 mg tablet. Since there appears to be an inverse relationship between compliance with medication regimens and the number of doses taken per day,[1] simplified dosage schemes should improve compliance. However, they should have an equal therapeutic effect and should not increase the incidence of side effects. This study compared the efficacy of allopurinol 100 mg three times daily to allopurinol 300 mg once daily, in a direct crossover trial.

Method

Seventeen male patients, age range 33-90 years, gave verbal informed consent to participate in the study. All patients had a history of gouty arthritis or uric acid nephrolithiasis and were already taking allopurinol 100 mg three times daily or 300 mg once daily for periods ranging from four weeks to six years. The study consisted of four consecutive weeks on allopurinol (Zyloprim) 300 mg once daily and three consecutive weeks on allopurinol (Zyloprim) 100 mg three times daily in a crossover trial. Thirteen of the 17 patients were treated as outpatients. Serum uric acid (phosphotungstate method) was measured on the same day each week. Patients were questioned weekly from a standard data collection form about the appearance of any acute attacks of gout or renal colic, possible side effects and the use of concomitant medications. They were asked not to take salicylates during the study, and were questioned about this weekly. Any salicylate intake was recorded. Drugs such as thiazide diuretics or probenecid were allowed if the dose remained constant throughout the study. Compliance was approximated by weekly pill counts. There were no dietary restrictions. Mean serum urate levels of each treatment period were

compared statistically by student's t test.[2]

Results

All but one patient had serum uric acid levels in the normal range (3.2-8.4 mg/dl) at the beginning of the study. Patient J. M. had a serum uric acid level of 10.3 mg/dl but was asymptomatic. Serum creatinine levels remained stable in all patients throughout the study. Table 1 records the weekly serum uric acid levels during the study. There were small but statistically significant differences in the mean serum uric acid levels between dosage regimens in four of the patients; in three of the four patients the statistically significant lower serum uric acid level occurred during once daily dosing. Two acute gouty attacks occurred during the study, both during the single daily dose, one in patient J. M., the other in J. G. Subsequently both patients have remained free of attacks for over 12 months on once daily administration. No patients complained of any side effect that might be attributed to the 300 mg od dosing regimen. All the ambulatory patients, on questioning, expressed a preference for the once daily regimen.

TABLE 1

Indications for Allopurinol

Definite

1. Chronic tophaceous gout
2. Uric acid nephrolithiasis
3. Persistent hyperuricemia with acute intermittent gout
4. Cytolytic therapy of malignancy

Controversial

1. Asymptomatic hyperuricemia (> 9 mg/dl)

Discussion

Since this study was initiated, results of other studies have been published showing the efficacy of once daily dosing of allopurinol.[3-6] While the studies are of short duration compared to the possible lifetime treatment with allopurinol, they do show that once daily dosing with allopurinol controls serum uric acid levels. Our two patients who suffered acute attacks of gout on the single daily dose regimen have continued to take the drug in this manner without further attacks. We were especially concerned about the gastrointestinal tolerance of a large single dose of the drug. It appeared to be well tolerated whether taken with meals or on an empty stomach and there were no other side effects attributed to the change in the dosing regimen.

Although allopurinol itself is cleared relatively rapidly from plasma, oxipurinol (its main active metabolite) has a biological half-life of 17-44 hours.[7, 8] However, the absorption of oxipurinol appears to be erratic and less complete than that of allopurinol,[9] and the latter remains the only available xanthine oxidase inhibitor. Rodnan's study[3] showed that there is no close correlation between

TABLE 2

Serum Uric Acid Levels (mg/dl) at The End of Each Treatment Week

Group 1	Allopurinol 100 mg tid				Allopurinol 300 mg od					
Patients	1 wk.	2 wk.	3 wk.	Mean ± SEM	4 wk.	5 wk.	6 wk.	7 wk.	Mean ± SEM	t Test
J.B.	6.2	6.1	6.4	6.2 ± 0.1	5.6	5.8	5.6	5.6	5.6 ± 0.1	P<0.0005
S.G.	5.8	4.9	4.7	5.1 ± 0.5	5.2	4.9	5.3	6.5	5.4 ± 0.7	NS
J.M.[P]	4.4	4.8	6.2	5.1 ± 0.9	+4.7	4.7	4.6	5.3	4.8 ± 0.5	NS
J.P.	6.0	5.1	6.6	5.9 ± 0.7	6.2	5.9	7.0	6.4	6.3 ± 0.8	NS
C.S.	5.0	5.3	5.4	5.2 ± 0.1	4.9	5.0	4.8	4.9	4.9 ± 0.07	P<0.025
*J.E.	5.4	5.1	5.2	5.2 ± 0.1	5.2	5.0	5.0	5.9	5.2 ± 0.4	NS
*J.McD.	4.4	4.6	4.9	4.6 ± 0.2	4.3	5.0	5.0	4.8	4.7 ± 0.3	NS
H.P.	4.8	4.3	3.8	4.3 ± 0.4	4.6	3.5	4.1	4.6	4.2 ± 0.5	NS

Group 2	Allopurinol 300 mg od					Allopurinol 100 mg tid				
Patients	1 wk.	2 wk.	3 wk.	4 wk.	Mean ± SEM	5 wk.	6 wk.	7 wk.	Mean ± SEM	t Test
H.Y.[HCT]	5.6	5.2	5.5	5.4	5.4 ± 0.1	4.8	4.9	4.7	4.8 ± 0.1	NS
J.G.	6.7	+4.0	5.6	5.0	5.3 ± 1.1	5.4	5.3	5.9	5.5 ± 0.3	NS
W.P.	5.8	5.2	4.6	4.9	5.1 ± 0.5	4.6	5.2	5.2	5.0 ± 0.3	NS
J.S.	7.0	6.1	7.2	6.4	6.6 ± 0.5	6.4	5.4	5.4	5.7 ± 0.5	P<0.05
C.B.	5.2	5.0	4.8	5.4	5.1 ± 0.2	5.6	5.4	5.3	5.4 ± 0.1	P<0.05
*E.P.	5.0	5.0	4.6	5.2	4.9 ± 0.2	4.8	5.4	6.2	5.4 ± 0.7	NS
R.H.[HCT]	6.5	6.2	6.6	7.3	6.6 ± 0.4	6.0	5.8	7.2	6.3 ± 0.9	NS
*W.H.	4.2	4.1	4.1	4.3	4.1 ± 0.1	4.2	4.0	4.3	4.1 ± 0.1	NS
C.H.[HCT]	5.3	6.0	5.0	3.4	4.9 ± 1.4	5.1	5.2	4.8	5.0 ± 0.2	NS

* inpatients

HCT hydrochlorothiazide daily (50 mg)

P probenecid, 1500 mg daily

NS not significant

\+ acute attack

steady-state serum oxipurinol levels and serum urate levels; thus we did not measure the serum oxipurinol level in our patients. It would have provided a useful index of compliance, although tablet counts and close weekly supervision showed acceptable compliance in our ambulatory patients. Most patients' serum uric acid levels should be controlled on once daily dosing. The few patients who require 400-800 mg per day may need to split the dose if gastrointestinal intolerance presents. This remains to be determined.

Conclusion

In conclusion, this study has shown that:

1. Allopurinol 300 mg once daily is as effective as allopurinol 100 mg tid in controlling serum uric acid levels.
2. A dose of up to 300 mg of allopurinol given once daily is well tolerated.
3. Patients may be converted directly from the traditional dosing regimen to the once daily dosing regimen. ◉

Acknowledgement

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ELAVIL* 75 mg Tablets
(amitriptyline hydrochloride, MSD Std.)

Indications: In the drug management of depressive illness including that accompanied by anxiety. May also be of value in persistent functional nocturnal enuresis when organic causes have been excluded.
Dosage Summary: *Oral:* Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.
Initial dose for adults: 25 mg three times a day. If necessary, increase doses preferably in the late afternoon and/or bedtime to a total of 150 mg a day.
Hospitalized patients may require 100 mg a day initially; increased gradually to 200 mg a day if necessary. A small number need as much as 300 mg a day.
Adolescent and Elderly Patients: In general, lower dosages recommended: 10 mg three times a day with 20 mg at bedtime or less, may be satisfactory.
Maintenance dose is usually 25 mg two to four times a day. When satisfactory improvement has been reached, reduce to lowest amount that will maintain relief of symptoms.
Intramuscular Dosage: Initially, 20 to 30 mg four times a day. ELAVIL* Tablets should replace the Injection as soon as possible.
Usage in Children: Not recommended for *treatment of depression* in children under 12 years of age.
In Enuresis: Children 5 to 11 years, 10 to 20 mg one hour before bedtime. In older children 25 to 50 mg may be required.
Contraindications: Known hypersensitivity. Should not be given concomitantly with, nor within at least 14 days following the discontinuance of, a monoamine oxidase inhibitor. Then initiate dosage of amitriptyline HCl cautiously with gradual increase in dosage until optimum response is achieved. Not recommended during the acute recovery phase following myocardial infarction, and in the presence of acute congestive heart failure.
Warnings: May block the antihypertensive action of guanethidine or similarly acting compounds. Should be used with caution in patients with a history of seizures or urinary retention, or with narrow-angle glaucoma or increased intraocular pressure. Arrhythmias, sinus tachycardia, and prolongation of the conduction time have been reported, particularly with high doses. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, these drugs should be used with caution in patients with a history of cardiovascular diseases such as myocardial infarction and congestive heart failure. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.
Usage in pregnancy: Safe use during pregnancy and lactation has not been established; in pregnant patients, nursing mothers, or women who may become pregnant, weigh possible benefits against possible hazards to mother and child.
Precautions: Schizophrenic patients and those with paranoid symptomatology may have increased symptoms, manic-depressives may experience a shift to the manic phase. In these circumstances amitriptyline dosage may be reduced or a neuroleptic such as a phenothiazine may be administered concurrently. Close supervision and careful adjustment of dosages are required in patients receiving anticholinergic agents or sympathomimetic drugs including epinephrine combined with local anesthetics, and those who receive large doses of ethchlorvynol concurrently. May enhance the response to alcohol and the effects of barbiturates and other CNS depressants. The possibility of suicide in depressed patients remains during treatment and until significant remission occurs; severely depressed patients should be closely supervised and should not have easy access to large quantities of the drug. Concurrent electroshock therapy may increase the hazards of therapy; such treatment should be limited to patients for whom it is essential. Discontinue the drug several days before elective surgery if possible.

Adverse Reactions: *Behavioural:* Activation of latent schizophrenia; high doses may cause temporary confusion or disturbed concentration, or rarely, transient visual hallucinations; hypomanic reactions; drowsiness which usually disappears with continuance of therapy; insomnia, giddiness, restlessness, agitation, fatigue, nightmares, disorientation, delusions, excitement, anxiety and jitteriness.
Neurological: Epileptiform seizures; numbness, tingling, paresthesias of the limbs including peripheral neuropathy; dizziness, fine tremor, headache, ataxia, alteration in EEG patterns, extrapyramidal symptoms, tinnitus and incoordination; severe tremor only observed with high doses.
Autonomic: Evidence of anticholinergic activity, such as urinary retention, reversible dilatation of the urinary tract, constipation, and more rarely paralytic ileus of particular concern in the elderly; dry mouth, blurred vision and disturbance of accommodation.
Cardiovascular: A quinidine like effect and other reversible ECG changes such as flattening or inversion of T waves, and bundle branch block; orthostatic hypotension, hypertension, palpitation, arrhythmias, heart block, and, with toxic doses, ventricular tachycardia and fibrillation; myocardial infarction and stroke. A few instances of unexpected death have been reported in patients with cardiovascular disorders.
Toxic and Allergic Effects: Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura and thrombocytopenia; jaundice rarely. Allergic type reactions manifested by skin rash, urticaria, photosensitization or swelling of the face and tongue and itching occurred rarely.
Gastrointestinal: Nausea, epigastric distress, heartburn, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels.
Metabolic: Increased appetite, weight gain or weight loss in some patients.
Ophthalmologic: Precipitation of latent glaucoma or aggravation of existing glaucoma; blurred vision and mydriasis.
Miscellaneous: Other side effects that may occur include fainting, weakness, urinary frequency, increased perspiration, and alopecia.
Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; these are not indicative of addiction.

Full prescribing information available on request.

How Supplied: Ca 3287 – Tablets ELAVIL* 10 mg, are blue, biconvex, discoid-shaped film coated tablets, 1/4 of an inch in diameter, imprinted MSD 23 on one side and are supplied in bottles of 100 and 1000.
Ca 3288 – Tablets ELAVIL* 25 mg, are yellow, biconvex, discoid-shaped film coated tablets, 1/4 of an inch in diameter, imprinted MSD 45 on one side and are supplied in bottles of 100 and 1000.
Ca 8655 – Tablets ELAVIL* 50 mg, are beige, biconvex, discoid-shaped film coated tablets, 5/16 of an inch in diameter imprinted MSD 102 on one side and are supplied in bottles of 100 and 500.
Ca 3348 – Tablets ELAVIL* 75 mg, are orange, biconvex, discoid-shaped film coated tablets, 13/32" in diameter, imprinted MSD 430 on one side and are supplied in bottles of 100.
Ca 3286 – Injection ELAVIL* 10 mg/ml, is a clear, colorless solution, and is supplied in 10 ml vials.
Ca 3301 – Syrup ELAVIL* (amitriptyline pamoate, MSD Std.) is a light red syrupy suspension containing in each 5 ml amitriptyline pamoate equivalent to 10 mg amitriptyline base, and is supplied in bottles of 225 ml.

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