

Zyloprim* (allopurinol)

Indications: ZYLOPRIM is intended for the treatment of gout as well as primary and secondary hyperuricaemia. ZYLOPRIM is indicated in the treatment of primary or secondary uric acid nephropathy. ZYLOPRIM is especially useful in patients with gouty nephropathy, in those who form renal urate stones, and those with unusually severe disease. ZYLOPRIM is effective in preventing the occurrence and recurrence of uric acid stones and gravel. ZYLOPRIM is useful in the therapy and prophylaxis of tissue urate deposition, renal calculi and for acute urate nephropathy in patients with neoplastic disease who are particularly susceptible to hyperuricaemia and uric acid stone formation, especially after radiation therapy or the use of antineoplastic drugs.

Contraindications: Zyloprim should not be given to patients who are hypersensitive or who have had a severe reaction to this drug.

Precautions and Warnings: Acute gouty attacks may be precipitated at the start of treatment with Zyloprim in new patients, and these may continue even after serum uric acid levels begin to fall. Prophylactic administration of colchicine and a low dosage of Zyloprim are advisable, particularly in new patients and in those where the previous attack rate has been high. Zyloprim is not recommended for use during pregnancy or in women of child-bearing potential unless in the judgement of the physician, the potential benefits outweigh the possible risks to the fetus. Zyloprim should not be given to children except those with hyperuricaemia secondary to malignancy or with Lesch-Nyhan syndrome. Patients with impaired renal or hepatic functions should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in hepatic or renal functions appear.

Uricosuria and Zyloprim: Combined therapy of Zyloprim and uricosurics will result often in a reduction in dosage of both agents.

Purineol or Imuran with Zyloprim: In patients receiving PURINETHOL* (mercaptapurine) or IMURAN* (azathioprine), the concomitant administration of 300-600 mg of ZYLOPRIM per day will require a reduction in dose to approximately 1/2 to 1/4 of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of PURINETHOL or IMURAN should be based on therapeutic response and any toxic effects.

Chlorpropamide with Zyloprim: In the presence of allopurinol, there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor, the recognised risk of prolonged hypoglycaemic activity of chlorpropamide may be increased if ZYLOPRIM is given concomitantly.

Coumarin anticoagulants with Zyloprim: It has been reported that under experimental conditions allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical significance of this has not been established, but this interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Adverse reactions: Skin reactions associated with exfoliation, fever, chills, nausea and vomiting, lymphadenopathy, arthralgia and/or eosinophilia are the most common and may occur at any time during treatment. Gastrointestinal disorders were reported but may diminish if Zyloprim is taken after meals.

Symptoms and treatment of overdose: Overdosage of allopurinol is usually manifested by nausea and vomiting. No treatment is normally required, provided the drug is withdrawn and adequate hydration is maintained to facilitate excretion of the drug. If, however, other forms of acute distress are observed, gastric lavage should be considered, otherwise the treatment is symptomatic.

Pharmacology: When taken orally, allopurinol is rapidly metabolized. The main metabolite is oxypurinol, which is itself a xanthine oxidase inhibitor. Allopurinol and its metabolites are excreted by the kidney, but the renal handling is such that allopurinol has a plasma half-life of about one hour, whereas that of oxypurinol exceeds 18 hours. Thus, the therapeutic effect can be achieved by a once-a-day dosage of ZYLOPRIM in patients taking 300 mg or less per day.

Dosage and administration: ZYLOPRIM, administered orally should be divided into 1 to 3 daily doses. Daily doses up to and including 300 mg may be taken once daily after a meal. Divided doses should not exceed 300 mg. The minimum effective dose is 100 to 200 mg. The average is 200 to 300 mg/day for patients with mild gout, 400 to 600 mg/day for moderately severe tophaceous gout, and 700 to 800 mg/day in severe conditions. The maximal recommended dose is 800 mg per day in patients with normal renal function.

Treatment with 600 to 800 mg daily for two or three days prior to chemotherapy or x-irradiation is advisable to prevent uric acid nephropathy. Treatment should be continued at a dosage adjusted to the serum uric acid level until there is no longer a threat of hyperuricaemia and hyperuricosuria. It is essential that a daily urinary output of two litres or more be maintained during ZYLOPRIM therapy, and neutral or alkaline urine is desirable.

Children: For the treatment of secondary hyperuricaemia associated with malignancies and in the Lesch-Nyhan syndrome, ZYLOPRIM should be given in doses of 10 mg/kg/day. The response should be evaluated after approximately 48 hours by monitoring serum uric acid and/or urinary uric acid levels and adjusting the dose if necessary.

Presentation: ZYLOPRIM 100 mg scored white tablets. Bottles of 100 and 500 tablets; Code: Wellcome U4A. ZYLOPRIM 300 mg scored peach coloured tablets. Bottles of 100 tablets. Code: Wellcome C9B.

Product Monograph available on request.

*Trade Mark



W-8006



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- WESTBURY RC: *The Content of a Calgary Family Practice, 1967-1971*, MD thesis, Cambridge U, Cambridge, England (submitted)
- TARRANT M: What price admitting privileges? A study of hospital admis-

sions by two family physicians. *Can Fam Physician* 23: 837, July 1977

- International Classification of Health Problems in Primary Care*, American Hospital Association, Chicago, 1975
- HEBB AMO: Reports on Nova Scotia Fetal Risk Project, 1971-76, national health grant 602-7-147

Adverse drug reactions: uncommon or unrecognized?

Clinically important drug interactions that are predictably beneficial to the patient are the mainstay of optimal drug therapy for such disorders as malignant disease, hypertension, arrhythmias and infections. Harmful drug interactions have been unduly emphasized with respect to overall importance, and their mechanisms are considerably misunderstood.¹

The reported frequency of interactions is dependent on the definitions and criteria applied. For example, when drug interactions were "diagnosed" by comparing patients' prescriptions with a computer bank of 24 000 drug interactions reported in the literature, it was found that every day 9% of patients had an adverse interaction.² When strict criteria for what is a potentially serious interaction were applied, the maximum predicted frequency was 1.2%. In contrast, in the Boston collaborative drug surveillance program only 0.28% of patients had a clinically recognized adverse interaction.²

For almost all specific adverse drug interactions the true frequency is not known since the frequency of coadministration of two drugs without interaction is not known; conversely, the frequency with which undetected interactions occur is also unknown. Even if the frequency of interaction is known, the concurrent prescription of two drugs with a potential for serious adverse interactions does not have any predictive value as to the likelihood of such an interaction in a particular patient. In the absence of more specific information, combinations of frequently implicated drugs should be avoided; for example, coumarin anticoagulants (e.g., warfarin), orally administered hypoglycemics (e.g., tolbutamide), antiseizure medications (e.g., pheny-

toin) and anti-inflammatory agents (e.g., phenylbutazone). However, drugs that are proven to frequently induce clinically important adverse drug interactions can safely be given, when it is essential, with dose adjustment or extra observation of the patient or both.

In this issue of the *Journal* (beginning on page 1261), Cass, Kadar and Stein focus attention on a large number of potential and often predictable interactions among drugs that affect the autonomic nervous system. Interactions among β -blockers, sympathomimetic agonists (e.g., ephedrine, phenylephrine and salbutamol), tricyclic antidepressants, phenothiazines and antihypertensive agents must occur commonly, and occasionally will be important. When drugs with such pharmacologic potential are given together, the patient should be watched carefully when administration of the second drug is started or stopped. For example, if phenylephrine is given to a patient taking reserpine or guanethidine, both α -adrenergic receptor sensitivity and blood pressure will increase.³ The fatal outcome in the case reported by Cass and colleagues was due to the presence of an aneurysm, which made any increase in blood pressure dangerous for the patient. The administration of eye drops containing 10% phenylephrine can alone raise the blood pressure a little in some patients.⁴ The magnitude of the increase and the probability that it will be clinically important are determined by the dose of phenylephrine, the technique used to instil the eye drops, whether there is conjunctival inflammation, whether the drops reach the nasal mucosa and whether the responsiveness of the cardiovascular system is altered. In the patient

described by Cass and colleagues 5 to 10 times the recommended intravenous dose of phenylephrine could have been absorbed.

Propranolol is effective and, in most instances, safe to use in the management of hypertension, angina pectoris and arrhythmias. However, its nonselective reversible blockade of β_1 - and β_2 -receptors can result in a variety of potential interactions with sympathomimetic drugs. The bradycardia produced by propranolol abolishes the reflex lowering of the heart rate if the blood pressure increases; with blockade of the β_2 -receptor-mediated vasodilation in muscles one mechanism of decreasing peripheral vascular resistance is impaired. Since it is not known when Cass and colleagues' patient last took propranolol, the possibility of β -receptor hypersensitivity, which occurs 24 to 48 hours after propranolol is discontinued, might be considered.

Finally, because of the aneurysm and the decreased baroreceptor sensitivity associated with hypertension, the patient's reflexes may not have been called into play quickly enough to offset the rise in blood pressure.

Reports on drug interactions and adverse reactions generally do not critically evaluate the certainty of the suspected link between the drug or drugs and the untoward clinical event.⁵ Several definitions of such events should be kept in mind:⁶

● **Definite:** An event that follows a reasonable temporal sequence from administration of the drug(s), or in which the concentration of the drug(s) has been established in body fluids or tissues; that follows a known pattern of response to the drug(s); and that is confirmed by improvement when administration of the drugs (dechallenge) is stopped and reappearance of the reaction when administration is begun again (rechallenge).

● **Probable:** An event that follows a reasonable temporal sequence from administration of the drug(s); that follows a known pattern of response to the suspected drug(s); that is confirmed by dechallenge; and that could not be reasonably explained by the known features of the patient's

clinical state.

● **Possible:** An event that follows a reasonable temporal sequence from administration of the drug(s); and that follows a known pattern of response to the suspected drug(s); but that could readily have been produced by the patient's clinical state or other modes of therapy.

● **Conditional:** An event that follows a reasonable temporal sequence from administration of the drug(s); that does not follow a known pattern of response to the suspected drug(s); but that could not be reasonably explained by the known features of the patient's clinical state. This category allows for later reclassification of as yet undescribed adverse drug reactions when more information becomes available.

● **Doubtful:** An event that does not meet the above criteria.

On the basis of these definitions, the case reported by Cass and colleagues could be categorized as either a possible or a conditional drug interaction. If one accepts as sufficiently analogous the fact that the administration of epinephrine to volunteer subjects taking β -blockers will increase peripheral vascular resistance⁷ the drug interaction could be considered possible. The reaction could be considered conditional because that particular drug interaction has not previously been reported. Most drug interactions are difficult to categorize unequivocally as to probability and cause because of the lack of uniqueness of the features of the reactions, and because definitive cause-effect tests cannot or have not been performed.

The case reported by Cass and colleagues may illustrate how a combination of drugs, local absorption factors and disease could result in a therapeutic misadventure. In this respect then, case reports are an important means of alerting others to clinically important interactions. However, such case reports, by their very nature, cannot indicate whether the combination of drugs caused the observed clinical problem, what the frequency of that interaction is or when that interaction is clinically important. For answers to these ques-

tions case reports must be followed up by scientific study. Unfortunately, case reports, in vitro studies and laboratory studies of interactions in animals have a tendency to become enshrined as scientific fact, are repeated by well meaning reviewers, lecturers and clinical pharmacists and entered into highly efficient and non-erasable computer retrieval systems.

This case report and evidence in the literature should prompt ophthalmologists to review the routine use of eye drops containing 10% phenylephrine. The smaller amounts of phenylephrine in over-the-counter preparations probably do not constitute a serious hazard for interaction with propranolol and other antihypertensive agents. Nevertheless, this is a conditional statement since a systematic study has not been done. Proper scientific study is needed to determine the clinical importance, absolute frequency and causality of drug interactions with propranolol. Extra care should always be taken when drugs with a potential to interact are administered.

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References

1. SELLERS EM: The clinical importance of interactions based on displacement of protein bound drugs, in *Proceedings of the VIIIth International Congress on Pharmacology* (in press)
2. GOUVEIA WA, MILLER RR: Drug interaction. screening — a screen or sieve? (E). *Am J Hosp Pharmacol* 35: 667, 1978
3. KIM JM, STEVENSON CE, MATHEWSON HS, et al: Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervations. *Am J Ophthalmol* 85: 862, 1978
4. MATTHEWS TG, WILCZEK ZM, SHENNAN AT: Eye-drop induced hypertension (C). *Lancet* 2: 827, 1977
5. KOCH-WESER J, SELLERS EM, ZACEST R: The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 11: 75, 1977
6. KARCH FE, LASAGNA L: Adverse drug reactions: a critical review. *JAMA* 234: 1236, 1975
7. HARRIS WS, SCHOENFELD CD, BROOKS RH, et al: Effect of beta adrenergic blockade on the hemodynamic responses to epinephrine in man. *Am J Cardiol* 17: 484, 1966