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NEW MEDICATIONS—1981

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The *Annual Review of Pharmacology and Toxicology* begins a new feature —a brief review of some important new therapeutic agents approved for use in the United States.

The data contained in this chapter were obtained from the United States Food and Drug Administration and the editors are most thankful for their cooperation. Of necessity, the information was condensed greatly but primarily to be of some use to teachers of pharmacology and toxicology.

The editors hope this information is valuable to our readers and welcome their comments and criticisms.

METYROSINE

Metyrosine (Demser ®, 250 mg capsules) is indicated in patients with pheochromocytoma for (*a*) preoperative preparation of patients for surgery, (*b*) management of patients when surgery is contraindicated, and (*c*) chronic treatment of patients with malignant pheochromocytoma.

The recommended initial dosage of metyrosine for adults and children 12 years of age and older is 250 mg orally four times daily. This may be increased by 250 mg to 500 mg every day to a maximum of 4.0 g/day in divided doses. When used for preoperative preparation, the optimally effective dosage of metyrosine should be given for at least five to seven days.

Optimally effective dosages of metyrosine usually are between 2.0 and 3.0 g/day, and the dose should be titrated by monitoring clinical symptoms and catecholamine excretion. In patients who are hypertensive, dosage should be titrated to achieve normalization of blood pressure and control of clinical symptoms. In patients who are usually normotensive, dosage should be titrated to the amount that will reduce urinary metanephrines and/or vanillylmandelic acid by 50% or more.

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If patients are not adequately controlled by the use of metyrosine, an α-adrenergic blocking agent (phenoxybenzamine) should be added.

Metyrosine is chemically α-methyl-L-tyrosine (AMT). It is a specific competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines from tyrosine. Studies in mice, rats, dogs, and monkeys have demonstrated that, as expected, the administration of metyrosine caused depletion of norepinephrine and dopamine in body tissues. In rats and mice, the depletion was greater in brain tissue than in heart tissue, but no such difference was seen in dogs and monkeys. Metyrosine has no demonstrable effect on brain serotonin. The many pharmacological activities of the drug in animals are essentially the direct or indirect result of depletion of tissue catecholamines. The most important effect is hypotension which, in some cases, is preceded by transient hypertension, brachycardia, and sedation. The drug also blocks ovulation, increases plasma prolactin, and increases ACTH secretion and adrenocorticoid activity in rats.

Absorption and excretion were studied in dogs and man. Most of the drug was found in the urine unchanged; trace amounts of metabolites such as α-methyl-dopa, α-methyl-dopamine, α-methylnorepinephrine, and α-methyltyramine were identified in urine also.

Bioavailability was measured using tritiated AMT given to patients on maintenance AMT therapy, both normals and patients with pheochromocytoma. In these studies the cold and tracer drugs were given together in capsules. Both AMT and its principal (but still minor) metabolites, α-methyldopa and α-methyldopamine, were measured chromatographically. Results indicate absorption of 53–88%.

More than 99% of absorbed radioactivity was excreted as intact AMF.

Plasma level curves for the 2–8 hr periods give $T_{½}$ values of 3.5 hr. The peak plasma values are 12–14 μg/ml.

Sedation was seen in 44 out of 66 patients given 1000 mg or more AMT and some became sedated at 300–600 mg. Anxiety, insomnia, diarrhea, galactorrhea, and neuromuscular adverse effects were seen in five patients, ranging from fine to gross tremor and including "tightness of the mouth" in two patients, suggesting an "extrapyramidal syndrome" that might be explained by the inhibition of dopamine biosynthesis caused by AMT.

All adverse effects were reversible within a few days of stopping the drug.

DAUNORUBICIN

Daunorubicin hydrochloride (Cerubidine ®, 20 mg vials) is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) in adults. Once complete remission has been achieved, an appropriate maintenance program should be instituted.

Daunorubicin is an anthracycline antibiotic antitumor agent and is intended for intravenous administration to effect remission in acute nonlymphocytic leukemia as a single agent or in combination therapy with cystosine arabinoside. Daunorubicin is strongly myelosuppressive. Structurally it is related to adriamycin, another antitumor antibiotic, and has a similar toxicological spectrum. The most significant toxicologic effect is cardiotoxicity manifested clinically in its most severe form as congestive heart failure.

The drug has liver, renal, and hematosuppressive properties and dosage should not exceed 550 mg/m^2 because of possible cardiotoxicity at cumulative doses over that amount.

DIPIVEFRIN

Dipivefrin HCl (Diopine ® sterile opthalmic solution, 0.1%) is indicated as initial therapy for the control of intraocular pressure (IOP) in chronic open-angle glaucoma. Patients responding inadequately to other antiglaucoma therapy may respond to replacement with or addition of dipivefrin HCl.

The active ingredient, dipivefrin (HCl salt) is the dipivalate ester of epinephrine. This diester was designed to provide a more lipid-soluble drug. Its activity apparently depends upon the release of epinephrine, and qualitatively, it exhibits essentially the same pharmacologic properties as the parent compound. Topically applied dipivefrin proved more potent than epinephrine in reducing IOP in animals (about 11 times more potent in the normal rabbit eye and at least 4 times more potent in the normal or glaucomatous dog eye). With regard to mydriatic effect, dipivefrin applied to the rabbit eye appeared to be 5–12 times more potent than epinephrine.

In controlled studies dipivefrin has been shown to be more effective than placebo both clinically and statistically, and controlled studies comparing it to pilocarpine 2% revealed that it is clinically and statistically comparable to pilocarpine 2% in reducing IOP.

Dipivefrin appears to be a well-tolerated drug with reduced side effects compared to epinephrine. In patients with a history of epinephrine intolerance few (3%) developed a drug intolerance again while using it, while 55% again showed intolerance when using 2% epinephrine.

Dipivefrin does not develop the side effects of miosis and accommodative spasm as seen with pilocarpine therapy.

One study in patients with blind eyes showed that dipivefrin is converted to epinephrine inside the eye. At 30 min after one drop of 0.5% dipivefrin, 80% is converted to epinephrine and at 120 min 100% is present as epinephrine. On a mole-percentage basis, dipivefrin penetrates 17 to 22 times greater than epinephrine.

OXAMNIQUINE

Oxamniquine (Vansil ®, 250 mg capsules) is indicated for all stages of *Schistosoma mansoni* infection, including the acute phase and the chronic phase with hepatosplenic involvement.

Oxamniquine, a synthetic nitro-hydroquinoline compound, is effective against schistosomiasis (*S. mansoni*) in certain laboratory animal models.

The recommended adult human clinical dose of oxamniquine is 12 to 15 mg/kg of body weight given as a single dose. (In children the dose may have to be divided and given over a 12-hr period.) The treatment may have to be repeated as often as every 6 months, should the patient continue residence in an area when *S. mansoni* is endemic.

The liver was the most prominent target organ in preclinical toxicity studies. Susceptibility to hepatic toxicity varied among species.

Oxamniquine, for the treatment of *S. mansoni* in humans, was originally developed as an intramuscular formulation. However, this was later replaced by the oral formulation as a single dose treatment for all stages of *S. mansoni* infection. The drug is used extensively in the endemic areas of Brazil and Africa and is included in the WHO list of essential drugs for developing countries.

A single oral dose of 600 mg of drug was given to volunteers. The serum levels of oxamniquine were found to be very low as compared with those of its nitro-compound metabolites. In the serum the total nitro-compounds peaked between 1 and 4 hr. Urinary excretion of nitro-compounds curing 36 hr was 0.4–1.9% of the administered oxamniquine and 41.4–73.4% of its principal metabolite. No studies are available on the safety and efficacy of the metabolite(s).

In about 50% of the cases the drug caused acute transitory, light to moderate CNS reactions which manifested themselves by dizziness, nausea, headache, or drowsiness, but which did not elicit significant EEG responses.

There is an occasional mild and transitory elevation of liver transaminases. In the tested subjects, all of whom had schistosome infection, an unambiguous interpretation of this elevation is not possible; it can be either drug-related or caused by liver tissue reaction due to the parasites.

TRIFLURIDINE

Trifluridine (Viroptic ®, 1% solution) is indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2, and is also effective in the treatment of epithelial keratitis which has not responded clinically to topical administration of idoxuridine or vidarabine or when ocular toxic or hypersensitivity reactions to either idoxuridine or vidarabine have occurred.

Efficacy in healing keratitis is significantly better than standard therapy.

Trifluridine is a true antiviral, and incorporation into DNA is considered a factor in its activity. It has been shown to produce fetal toxicity in rabbits and rats and to exert mutagenic, clastogenic, DNA-damaging, and cell-transforming activity in various test systems. In view of these findings, trifluridine must be regarded as a potential carcinogen.

Trifluridine, 2'-deoxy-5-(trifluoromethyl)uridine, is a synthetic halogenated pyrimidine nucleoside. The antiviral mechanism of action is not fully known, but it appears to be related to inhibition of DNA synthesis.

Viroptic ophthalmic solution 1% was evaluated for ocular and systemic toxicity. No systemic toxicity was observed, and the drug was not detected in the blood, but 15% of patients experienced ocular burning or stinging.

RITODRINE

Ritodrine (Yutopar ®, 50 mg ampules and 10 mg tablets) is indicated for premature labor.

Ritodrine is a β-sympathomimetic drug developed for inhibition of uterine contractions during premature labor and is a potent uterine relaxant effective against both spontaneous and oxytocin-induced uterine activity with only minor cardiovascular and bronchial effects.

Extensive preclinical investigations have shown ritodrine to be a rather specific β-adrenergic receptor stimulant devoid of any significant action on α-receptors. Compared to the β-mimetic isoproterenol, the uterine relaxant activity appears to be greater than the activity on the other systems. Ritodrine is similar in function, but not in degree, to isoproterenol in relaxing the uterus, causing tachycardia, lowering blood pressure, and antidiuretic action as well as CNS depression at higher doses. These actions may be blocked by the β-receptor blocking drugs such as propranolol.

Passage of ritodrine through the placental barrier produces an increase in fetal heart rate.

Patients in premature labor admitted before 33 weeks gestation and treated with ritodrine have pregnancy successfully prolonged (48% vs 27%) over control.

TRANSDERMAL SCOPOLAMINE

Transdermal therapeutic system–scopolamine (Transiderm ®) is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The system is a round flat unit 2.5 cm in area, and is programmed to deliver 0.50 mg of scopolamine over a 3-day period. The system should be applied only to an area of intact postauricular skin. Application should be made several hours before an antiemetic effect is required.

This new transdermal formulation contains, as its sole active agent, the old drug scopolamine, a belladonna alkaloid with well-known pharmacological properties and a long history of oral and parenteral use for central anticholinergic activity, including prophylaxis of motion sickness. This new formulation provides for gradual release of scopolamine from an adhesive matrix of mineral oil and polyisobutylene applied to the postauricular skin.

This system is unique in that it offers a new delivery mode for the use of scopolamine for the prevention of nausea and vomiting in motion sickness. Scopolamine has been recognized as an effective antiemetic agent for several years. It has been available as scopolamine hydrobromide, either orally at a dosage range of 0.6 mg to 1.0 mg, or as an intramuscular injection at 0.2 mg. When scopolamine is administered in a conventional manner it has parasympatholytic effects, especially drowsiness, dry mouth, and blurred vision. However, studies have shown that when scopolamine is administered by this system it is well tolerated by the patient, and these side effects become minimal.

Efficacy studies showed that 17% of the subjects using this system suffered moderate nausea or vomiting and 45% of the subjects using placebo became ill while on a ship on the high seas.

MINOXIDIL

Minoxidil (Loniten ®, 2.5 mg and 10 mg tablets) is indicated in the treatment of severe hypertension that is symptomatic or associated with target organ damage and not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs. At the present time, use in milder degrees of hypertension is not recommended because the benefit-risk relationship in such patients has not been defined.

The recommended initial dosage of minoxidil for adults is 5 mg orally given as a single dose. The effective dosage range averages 10 to 40 mg per day. The maximum recommended dosage is 100 mg per day.

Minoxidil must be used in conjunction with a diuretic in patients relying on renal function for maintaining salt and water balance. When therapy with minoxidil is begun, the dosage of the β-adrenergic receptor blocking drug used should be the equivalent of 80 to 160 mg of propranolol per day in divided doses.

Minoxidil produced a dose-related reduction in mean arterial blood pressure following oral administration to rats, dogs, monkeys, and minipigs. Accompanying the minoxidil-induced fall in blood pressure in dogs was a reflex-mediated increase in cardiac output, heart rate, and left ventricular dp/dt (index of myocardial contractile force). The antihypertensive action of the drug is due to a reduction in total peripheral resistance. Sympathetic

nerve tone was increased as evidenced by increased urinary excretion of norepinephrine and augmented blood pressure reduction in response to ganglionic blockade. Like hydralazine and diazoxide, minoxidil reduces resistance to blood flow through a direct relaxant effect on vascular smooth muscle.

Minoxidil was rapidly and well absorbed following oral administration in the human, rat, dog, and monkey as judged by blood levels and urinary excretion of the drug and its metabolites. At least 90% of the administered dose was absorbed by each species, and plasma drug concentration was linearly related to the dose of minoxidil. In each species, peak plasma levels were reached within 1 hr of dosing.

Following oral absorption, minoxidil was rapidly and extensively distributed throughout the body as judged by blood levels of drug and metabolites in man, dog, and monkey, and tissue levels in the rat. Drug-related material was absent in the brain but was present in arterial walls of the rat.

Minoxidil disappeared from the circulation $T_{1/2}$ of 1.9 and 1.2 hr in the monkey and dog, respectively, and 4.2 hr and 1.4 hr in two human studies. The half-life for the glucuronic acid conjugate in man was 3.6 hr. The drug and its metabolites were eliminated primarily via the urine by each species. Within 12 hr, at least 70%, and within 72 hr at least 90%, of an orally administered dose of minoxidil had been excreted in the urine by each of the species. There appeared to be at least a small amount of enterohepatic recirculation of minoxidil metabolites in the rat.

In man, chronic drug administration caused a more rapid disappearance from the circulation but, because of an apparent increase in volume of distribution, without a change in its clearance rate. Chronic once-a-day administration of minoxidil did not result in increased serum levels of the drug or its glucuronide.

Each of the species studied had identical urinary metabolites, but in different relative amounts. Minoxidil glucuronide was the major excretory product in monkey and man, with substantially smaller quantities of unchanged drug.

Minoxidil is a highly effective direct vasodilator antihypertensive agent with most of the advantages
effective in lowering both erect and supine blood pressure and it is free of central depressant effects and the consequences of adrenergic neuron blockade. On the other hand, it causes substantial fluid retention and increased cardiac output, which must be corrected by aggressive use of diuretics and an agent to decrease heart rate and cardiac output, usually a β-blocker.

Because minoxidil may be effective in patients with severe hypertension refractory to full doses of other antihypertensive agents and is effective in patients with severely impaired renal function, it is an agent with clear

life-saving potential. It also has several important known and potential risks:

1. The marked fluid retention can lead to congestive heart failure if diuresis is not sufficiently vigorous.
2. Because of the fluid retention or some unrecognized factor, minoxidil can cause pericardial effusion and tamponade. Some cases have been fatal.
3. Increased cardiac output, if not countered by adequate β-blockade, can lead to worsened angina pectoris and, possibly myocardial infarction. In animals, minoxidil and other direct vasodilators cause a characteristic ischemic lesion of the papillary muscle. Because the lesion is also caused by β-agonist agents like isoproterenol and epinephrine, the vasodilator-induced lesion has been attributed to the marked sympathetic response to this agent.

Abnormal hair growth is very common and very bothersome to patients.