Today’s Drugs

Treatment for Parkinsonism, Other than Levodopa

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The treatment of Parkinsonism with levodopa has recently been reviewed in this series of articles. It was emphasized that, while levodopa was beneficial in some 60-70% of cases, there remained a group of patients for whom this drug was unhelpful. The present article reviews the various forms of treatment which are available other than levodopa.

Anticholinergic Drugs

For the last century Parkinsonism has been treated with drugs which block certain actions (the muscarinic effects) of acetylcholine. Charcot first advocated atropine and subsequently other belladonna alkaloids such as hyoscine were employed. After the second world war synthetic agents with actions resembling atropine were introduced. These were considered to possess similar therapeutic properties with fewer unwanted effects. There is now a wide choice of these drugs, such as benzetropine, benztropine, orphenadrine, orphenadrine, ethopropazine, methixene, procyclidine, cymetrine, chlorphenoxyamine, and biperiden.

PHARMACOLOGY

The therapeutic action of these agents is thought to arise by blockade of the muscarinic actions of acetylcholine in the central nervous system. There is evidence that acetylcholine is a synaptic neurotransmitter in the corpus striatum. In the normal brain there is a balance between excitatory effects of acetylcholine (which are muscarinic) and the inhibitory influences of another striatal transmitter, dopamine. In Parkinsonism the dopaminergic system appears to be impaired, so that the normal balance between acetylcholine and dopamine is disturbed in the direction of cholinergic dominance. Drugs which block the muscarinic action of acetylcholine tend to restore the balance and so bring about a therapeutic effect.

THERAPEUTIC USE

The beneficial actions of anticholinergic drugs are limited. The main clinical features to respond are rigidity and tremor. The most disabling motor deficit in Parkinsonism is hypokinesia, which disrupts everyday activities such as washing, dressing, walking, and eating. Unfortunately this motor disorder is seldom helped by anticholinergic agents. In reviewing the overall value of these drugs Esplin considered that a 30% improvement in 80% of patients was an optimistic estimate.

Benzetropine is one of the most widely employed anticholinergic drugs. A dose of 2 mg three times a day may be increased by 2 mg per day every week until unwanted effects are encountered, when the intake should be reduced by some 2-5 mg. Benefit may be achieved from doses as low as 1 mg daily. Some patients find one anticholinergic agent suits them better than another and the choice of drugs is sufficiently large to allow many alternatives to be tried if necessary. In general, orphenadrine (50 mg three times a day) is less toxic than benzetropine, and benztrpine (2 mg at night) has a more prolonged action. There is no convincing evidence that any one drug is specially useful for any particular clinical feature. Sometimes a favourable result is achieved by a combination of two drugs. Further details of dose regimens with the numerous anticholinergic drugs have appeared in several reviews.

ADVERSE EFFECTS

The common dose-limiting side effects of anticholinergic drugs are those of parasympathetic blockade consequent on impaired muscarinic function. They include defective ocular accommodation, dryness of the mouth, constipation, and retention of urine. Adverse reactions involving the central nervous system may also occur; confusion and hallucinations have been reported in some 30% of patients receiving benzetropine.

Caution is desirable when stopping anticholinergic therapy, as sudden complete withdrawal of drugs may precipitate a syndrome of severe rigidity and tremor.

INDICATIONS

Anticholinergic drugs are particularly useful in patients with Parkinsonism induced by administration of phenothiazines such as chlorpromazine or butyrophenones such as haloperidol. Phenothiazines and butyrophenones block dopaminergic receptors and this effect is probably responsible for their production of Parkinsonism. In these circumstances little benefit can be achieved by increasing the levels of striatal dopamine with levodopa. On theoretical grounds treatment should be directed at restoring the balance between acetylcholine and dopamine by reducing cholinergic function. Practical experience has shown that anticholinergic agents are very useful in this context. Indeed, many psychiatrists prescribe anticholinergic drugs as routine prophylaxis against Parkinsonism when treating psychotic patients with pheno-thiazines or butyrophenones.

Acute extrapyramidal syndromes induced by drugs may require parenteral administration of anticholinergic agents such as benzetropine, 2 mg intravenously. Treatment with anticholinergic drugs is also indicated in patients with other forms of Parkinsonism who are not helped by levodopa, and even patients doing well on levodopa may obtain benefit from concomitant administration of anticholinergic agents; apart from any other action their antiemetic effect is useful. Patients with difficulty in micturition (for example, prostatism) should not be given anticholinergic drugs, and there is a risk of raising the ocular tension in patients with glaucoma. Reading difficulties, due to cycloplegia or iridoplegia, may be counteracted by the prescription of appropriate lenses or the regular instillation of 1% eserine eye drops.
Amantadine was developed as an antiviral agent for the treatment of Asian influenza. In 1968 Schwab and his coworkers noticed a remission of neurological symptoms in a Parkinsonian patient who had received amantadine for her influenza. After this chance observation they treated 163 patients with Parkinsonism and found that most experienced worthwhile improvement.

PHARMACOLOGY AND THERAPEUTIC USE

Amantadine is readily absorbed and most is excreted unchanged in the urine. The mechanism of its therapeutic actions in Parkinsonism is not known, but there is some evidence that it acts by releasing dopamine from nerve endings. All three major features of the Parkinsonian syndrome respond; hypokinesia, rigidity, and tremor. Nevertheless, the extent of the clinical improvement induced by amantadine is considerably less than that achieved with levodopa. Comparative studies indicate that amantadine has 12-50% of the therapeutic potency of levodopa. Furthermore, the amelioration of symptoms may not be sustained.

Amantadine is a very easy drug to administer. The problems of prolonged dose titration (necessary when prescribing levodopa) are not encountered. An initial intake of 100 mg a day should be increased after one week to 100 mg twice daily if adverse effects are not encountered. Higher doses are not recommended by the manufacturers, though the optimum dose was found to be 100 mg thrice daily in a recent study.

ADVERSE EFFECTS

Several of the undesirable actions of amantadine resemble those of the belladonna alkaloids, such as atropine. Patients may complain of a dry mouth, defective near vision, and difficulties with micturition. Intermittent confusion, nightmares, hallucinations, restlessness, palpitations, and giddiness have been reported. Myoclonic jerking of the legs and trunk may be experienced. The movements resemble certain forms of dyskinesia which may be produced by levodopa. Nausea and hypotension may also occur, while gross overdosage may result in convulsions.

INDICATIONS

As amantadine is so simple to prescribe its introduction has been followed by its rapid use for treating patients with Parkinsonism. The most disabled patients often respond best and as most people tolerate amantadine without difficulty it is particularly useful when other drugs provoke prominent adverse reactions. Nevertheless, drug-induced Parkinsonism has been found to be refractory to amantadine, presumably for the same reasons that levodopa is ineffective. Some studies have failed to show a therapeutic action of amantadine in patients already receiving levodopa. Caution is necessary when administering amantadine to epileptics or to patients receiving central stimulants such as amphetamine. It is also desirable to exercise care in administering amantadine to patients with peptic ulceration.

Other Drugs

Antihistamines such as promethazine and diphenhydramine have been advocated for Parkinsonism, but they also possess antimuscarinic properties and there is no evidence that their antihistaminic actions are relevant to any therapeutic effects.

Many psychotropic drugs have been claimed to exert beneficial effects in Parkinsonism. These include monoamine oxidase inhibitors, amphetamine, diazepam, imipramine, methylphenidate, and meprobamate. Other drugs which have been used include beta-adrenergic blockers and apomorphine.

There is no evidence that these drugs have any advantage over other forms of therapy, and many have clear disadvantages. They are not employed in the routine management of Parkinsonism.

Other Forms of Therapy

Stereotactic surgery has achieved good results for some patients but a recent analysis of long-term benefits indicates that the early enthusiasm for this procedure may not be entirely justified. Surgery is certainly being performed less frequently now. The advent of levodopa is no doubt related to Cooper's report that 900 operations were performed by his unit in 1967, and only 50 in 1970. Finally, physiotherapy and the encouragement by relatives and medical attendants undoubtedly help patients with chronic neurological disorders such as Parkinsonism. The simplest of practical measures may also be useful, such as replacing fly buttons by zips and shoes with laces by slip-on shoes.

References