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Amantadine and Anticholinergics

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INTRODUCTION

Amantadine and anticholinergics have been used for several decades as therapy for Parkinson's disease (PD). In spite of reduced interest in these compounds with the advent of more specific dopaminergic therapies, there remain clinical situations where amantadine and anticholinergics retain clinical usefulness and a role in the contemporary treatment of PD.

AMANTADINE

History

Amantadine (Symmetrel®) was initially marketed in the 1960s as an antiviral agent. Its use as an antiparkinsonian agent was first described in 1969 when a woman with advanced PD serendipitously noted transient relief

of tremor, rigidity, and bradykinesia during a 6-week course of flu prophylaxis with amantadine (1). Since that time, further studies confirmed a mild antiparkinsonian effect for amantadine (2). For years, amantadine was generally used either in early PD or as a mild adjunctive agent in later stage PD. The use of amantadine has remained limited in PD. This has been likely due to (1) the development of dopamine agonists, (2) better tolerance of levodopa with the advent of carbidopa, and (3) the misconception of transient benefit, known as tachyphylaxis. Investigators have sought to confirm or document the potential clinical uses of amantadine. Modulating effects of amantadine on motor complications in later stage PD have been documented in several studies (3–5).

Many different mechanisms of action have been proposed for the antiparkinsonian effects of amantadine, but clear attribution has remained obscure. Traditional mechanisms for amantadine were usually ascribed to dopaminergic or anticholinergic mechanisms such as the proposed mechanism of promoting endogenous dopamine release (6). However, further studies have demonstrated a variety of biological effects beyond these systems. For instance, recent studies have suggested that amantadine possesses glutamate blocking activity (7), a mechanism of substantial current interest in neurology for its role in a variety of different conditions.

Pharmacokinetics and Dosing

Amantadine is an aliphatic primary amine formulated as a hydrochloride salt for clinical use as an oral preparation. It is a relatively inexpensive drug available as a 100 mg tablet or 50 mg/mL liquid. Other than some anticholinergics and apomorphine, it is also one of the few PD medications available in a parenteral formulation (amantadine-sulfate). This intravenous preparation, however, is not available for use in the United States (8).

The bioavailability of amantadine is nearly 100% in oral form. It is excreted virtually unmetabolized via the kidneys and has a large volume of distribution. In fasting, healthy patients, peak plasma concentration was found 1–4 hours after a single oral dose of 2.5–5 mg/kg. Plasma half-life in healthy elderly men has been reported between 18 to 45 hours, suggesting that steady state may take up to 9 days (9). Serum amantadine levels are not routinely drawn and are probably of limited clinical utility. Pharmacological studies have reported serum levels between 0.2 and 0.9 μg/mL at dosages of 200 mg/day (10). Fahn et al. reported a case of one patient with psychosis following acute intoxication with amantadine who was found to have a level of 2.37 μg/mL (11).

Few drug interactions have been reported with amantadine. Other than a case report suggesting amantadine toxicity from an interaction with

hydrochlorothiazide-triamterene (12), little else has been reported in the literature.

Routine dosing starts at 100 mg twice daily. Because of the relatively long half-life, increases are generally not recommended any sooner than once per week. Doses up to 500 mg have been reported for the use of diminishing motor complications in PD patients (13). The maximum tolerable doses are suggested at 400–500 mg each day in patients with normal renal function (14). Doses over 400 mg produce no added benefit and an increased incidence of side effects.

Clinical Uses

Early Parkinson's Disease

Amantadine is generally considered a mild antiparkinsonian agent with effects on rigidity and bradykinesia and a very well tolerated side effect profile. In this context, major uses have been in early treatment of PD or as a mild adjunctive agent in moderate PD. Its use in early PD may be helpful when considering levodopa-sparing strategies or when symptoms are mild and do not warrant more aggressive therapy. Amantadine has been studied in early PD as monotherapy and in combination with anticholinergics in limited series and small controlled studies with relatively short follow-up (15–17).

Part of the rationale for considering amantadine monotherapy are suggestions that amantadine itself may have neuroprotective properties to slow the progression of PD. Uitti and colleagues (18) found that amantadine use was an independent predictor of improved survival in a retrospective analysis of all parkinsonism patients (92% PD) treated with amantadine compared to those not using this medication. The results are suggestive of either an ongoing symptomatic improvement or the presence of an inherent neuroprotective property. There has been no confirmatory evidence to suggest neuroprotection from studies in PD patients, although basic science work on potential neuroprotective mechanisms with amantadine remains intriguing (see below).

In the 2002 American Academy of Neurology (AAN) guidelines on initiation of PD treatment, amantadine is not mentioned. The bulk of discussion has now focused on current literature involving selegiline, levodopa, and dopamine agonists (19).

Moderate Parkinson's Disease

In moderate PD, where symptoms necessitate treatment with levodopa or dopamine agonists, amantadine may be of benefit as an adjunctive medication.

Many patients report that they may be initial non-responders to amantadine, but that they may respond at a later point in time as their PD progresses (20). Patients with moderate PD who require additional mild benefit to their existing dopaminergic therapy are good candidates for amantadine.

Late Parkinson's Disease

Use of amantadine in managing late-stage PD motor complications was first described in 1987 by Shannon et al. (3) in a small open-label study. They reported improved motor fluctuations using a qualitative scale weighing changes in relative "on" and "off" function in 20 PD patients. This notion has gained further support from Metman et al. (21), who reported the results of double-blind, placebo-controlled, crossover studies of amantadine in 14 PD patients. They described a 60% reduction in both peak dose "on" choreiform dyskinesias and severity of "off" periods along with a decreased duration of "off" time (21). One year later, these patients had maintained significant benefit (5).

The above studies by Metman et al. did not distinguish between types of dyskinesia. The recognition of different motor dyskinesia phenomenology may be potentially important in the response to amantadine. For instance, dystonic dyskinesias have shown varied interindividual effects (some improving, some worsening) with amantadine in a few studies (3,4). Specific efficacy for sudden "on-offs" or biphasic dyskinesias has not been formally investigated.

Evidence suggests that amantadine produces antidyskinetic effects via a glutamate *N*-methyl-D-aspartate (NMDA) antagonism (22). This independence from dopaminergic mechanisms was proposed as an explanation for the ability of amantadine to ameliorate levodopa-induced dyskinesias without worsening parkinsonism (21).

Miscellaneous Considerations

One frequent assumption about amantadine is that it offers only transient efficacy, typically lasting less than a year. However, this apparent loss of efficacy for ameliorating parkinsonian symptoms has been reviewed and was attributed largely to the progression of the disease itself. It has also been reported that early-stage PD patients may be treated effectively for years with amantadine and still find that their symptoms noticeably worsen following drug withdrawal (13).

Side Effects

Amantadine is generally well tolerated with a favorable side effect profile. The most common idiosyncratic side effects include livedo reticularis and pedal

edema. Livedo reticularis is a mottled bluish-red reticular skin discoloration, which blanches to pressure. It is more common in women (23) and is usually predominant in the lower extremies. The appearance is nonspecific and skin biopsies of the area are normal (24). Livedo reticularis usually appears after weeks of treatment and is of unclear etiology. The cosmetic appearance is usually far more apparent than any physical adverse effects.

Pedal edema can also appear idiosyncratically and is independent of either renal or cardiac failure. Its presence has generally been attributed to a redistribution of fluid and does not appear to represent a fluid excess. Quinn reported a few cases of congestive heart failure occurring in association with the use of amantadine, but this appears to be an exception to routine clinical use (25).

The presence of either livedo reticularis or pedal edema does not always necessitate discontinuation of amantadine. There is no specific treatment for the cosmetic discoloration associated with livedo reticularis. Diuretics may be used if the pedal edema is uncomfortable, though specific benefit tends to be uncertain. Symptoms are generally expected to resolve with discontinuation of the drug, but may take up to several weeks. Rarely, these conditions may be severe and associated with leg ulceration and peripheral neuropathy (26). A prudent combination of discontinuing the drug and of providing appropriate referrals to exclude important secondary causes (such as a superimposed renal failure, cardiac failure, autoimmune or vasculitic livedo, and ruling out deep vein thrombosis) must be an important part of continued clinical follow-up for patients on amantadine.

Nonspecific symptoms such as lightheadedness, insomnia, jitteriness, depression, and concentration difficulties are potential side effects of amantadine (9). Amantadine itself also possesses mild anticholinergic properties, which contribute to further reported side effects such as dry mouth, orthostatic hypotension, constipation, dyspepsia, and urinary retention. Therefore, reasonable care should be taken when administering amantadine in conjunction with anticholinergics (27). Cardiac arrhythmias have been reported with amantadine in one report (8). Amantadine is not recommended during pregnancy as it has more teratogenic potential than other PD medications (28).

Acute toxicity presenting as delirium (15) and psychosis (11) has been reported. Abrupt withdrawal has also been reported to produce delirium (29) as well as neuroleptic malignant syndrome (30). In many of these cases patients had either baseline cognitive deficits, psychiatric background, or excessive amantadine use. In general, the cognitive side effects such as confusion and concentration difficulties are more common in those with underlying, preexisting cognitive dysfunction. In advanced PD, amantadine may even carry comparable propensity for cognitive side effects to levodopa

(31). As such, conservative use in the elderly and avoidance of use even in the mildly cognitively impaired patient is necessary.

Because of the renal predominant excretion of amantadine, patients with impaired kidney function carry a higher risk of toxicity. Dosing schedules have been developed for patients with poor renal function according to creatinine clearance (32). However, as a practical matter, with the availability of many other antiparkinsonian agents, it is best to avoid the use of amantadine in patients with poor renal clearance. In the event of suspected toxicity, dialysis is not helpful in decreasing toxic levels, probably due to extensive tissue binding (33).

Mechanisms of Action

Many studies have suggested putative mechanisms of action for amantadine that may explain antiparkinsonian effects, but the clinical significance of any given individual mechanism remains uncertain. It seems likely that amantadine has a combination of multiple effects on both dopaminergic and nondopaminergic systems.

Dopaminergic mechanisms described for amantadine include findings of increased dopamine release (34), increased dopamine synthesis (35), inhibition of dopamine reuptake (36) and modulation of dopamine D2 receptors producing a high affinity state (37). This latter effect may speculatively play a role in modulating levodopa-induced dyskinesias. The relevance of these dopaminergic mechanisms is uncertain given that studies have demonstrated that the antiparkinsonian effects can occur without changes in brain concentrations of dopamine or its metabolites (38) and without evidence for dopamine synthesis or release (39).

Other neurotransmitter effects reported with amantadine include serotonergic, noradrenergic, anticholinergic, and antiglutaminergic properties (40). The anticholinergic properties suggest a well-described antiparkinsonian interaction (41,42). Renewed interest has arisen in the antiglutamate properties of amantadine. These can be attributed to two important clinical implications. First, it may provide a putative neuroprotective mechanism and be added to the list of drugs that may be examined for such clinical effects. Second, converging lines of evidence provide support to the idea that the antiglutamate properties of amantadine may be important for modulating motor complications in late-stage PD.

Amantadine possesses mild anti-NMDA properties that have led to the suggestion that the drug may contribute to a possible neuroprotective effect in PD (43,44). Glutamate excitotoxicity, mediated via persistent or sustained activation of NMDA receptors, produces an excess calcium influx activating a cascade of molecular events leading to the common final

pathway of neuronal death. Blockade of NMDA glutamate receptors has been shown to experimentally diminish the excitotoxic effects of this cascade of reactions (45,46). In cell cultures, preexposure of substantia nigra dopaminergic neurons to glutamate antagonists provided protection when subsequently exposed to MPP^+ (1-methyl-4-phenyl-pyridium ion, the active metabolite of MPTP), a common specific nigral toxin used to produce animal models of PD (47). Extension of these preclinical findings to clinical applicability in PD patients remains speculative, but probably best serves a role to stimulate future studies.

The anti-NMDA properties of amantadine have also been implicated in its role modulating motor complications. Evidence has accumulated that glutamate NMDA receptors may play a significant role in the pathogenesis of motor complications. Loss of striatal dopamine and nonphysiological stimulation by extrinsic levodopa both cause sensitization of NMDA receptors on striatal medium spiny neurons in animal models (22). This sensitization may play a key role in altering normal basal ganglia responses to cortical glutaminergic input and produce the disordered motor output that leads to motor complications. Recent studies have reported that striatal injection or systemic administration of glutamate antagonists in primate and rodent models of PD can decrease levodopa motor complications without decreasing benefits of dopaminergic treatment (7,48–51).

Summary

With improved management options for PD, patients are living longer, and, as a result, more are suffering from long-term complications of disease and therapy. Although the influx of new medications has changed the landscape of pharmacological options for PD patients, a reexamination of older medications such as amantadine can offer evident benefit.

Amantadine retains its primary utility as a mild antiparkinsonian agent to be used mostly as adjunctive therapy and occasionally in early monotherapy as a means to avoid early use of levodopa. It is frequently being utilized as the only available antiparkinsonian agent to diminish dyskinesia and offer improvement of PD symptoms simultaneously (52).

ANTICHOLINERGICS

History

Anticholinergics are among the earliest class of pharmaceuticals used for the management of PD. Naturally occurring anticholinergics, such as the belladonna alkaloids, have been used for centuries to treat a variety of

ailments. Since the mid-1900s and until the development of dopaminergic agents, anticholinergics were a major component of therapy for PD (53). In the 1940s, synthetic anticholinergics were introduced with trihexyphenidyl (Artane®) and similar agents replacing impure herbal preparations of belladonna alkaloids in the treatment of PD. Eventually, a wide variety of different anticholinergics, each with varying receptor specificities, blood-brain barrier penetration, and side effect profiles became available. Historically and by physician preference, certain medications have gained popularity or notoriety for treating PD. This has varied throughout the decades (54).

With recent developments in PD therapy, anticholinergics have been relegated to a less prominent role. In particular, levodopa and dopamine agonists have largely replaced anticholinergics as major antiparkinsonian agents. Contemporary reviews and investigations continue to support anticholinergic use in certain clinical situations such as PD-associated tremor or dystonia. Side effects have always been a prominent concern with anticholinergics, particularly in susceptible individuals such as the elderly. As such, careful risk-benefit assessment in anticholinergic use remains a prudent routine practice in PD patients.

Pharmacokinetics and Dosing

Anticholinergics are a diverse group of medications. The majority of the anticholinergic medications have good oral absorption. In general, most have half-lives requiring at least twice and usually three times a day dosing.

The antiparkinsonian effect of anticholinergics is largely attributed to centrally acting acetylcholine receptors that can cross the blood-brain barrier (55). Most synthetic (tertiary) anticholinergics used in PD are predominantly in this class: biperiden (Akineton®), trihexyphenidyl (Artane®), benztropine (Cogentin®), procyclidine (Kemadrin®). Benztropine has useful central effects that can be used for PD management, is more potent than trihexyphenidyl, but has less sedating effects than antihistamines (56).

Anticholinergic effects are often seen as side effects for many other groups of medications. Exploiting these secondary side effects when choosing medications for other indications is a common practice, especially when their anticholinergic effects assist in managing PD symptoms. These include tricyclic antidepressants like amitriptyline, antihistamines like diphenhydramine, and atypical antipsychotics like olanzapine or quetiapine.

Recommended doses vary by practitioner, but one rule is to start with a low dose and increase slowly and conservatively (Table 1). Maximum dosing is limited by the side effect profile of these medications. Individual

TABLE 1 Common Anticholinergics Used in Parkinson's Disease

Name	Mechanisms	Preparations	Initial dose	Escalation schedule	Maximum dose per day	Comments
Primary anticholinergics						
Trihexyphenidyl (Artane)	Central antimuscarinic	2, 5 mg tabs; 2 mg/5 ml elixir	1 mg qd-bid	Increase to tid; every 3–4 days increase by 1/2−1 mg each dose	2–3 mg tid	First synthetic anticholinergics
Benztropine (Cogentin)	Central antimuscarinic	0.5,1,2 mg tablets; injection 1 mg/mL	0.5 mg bid	Increase to tid; every 3–4 days increase by 1/2−1 mg each dose	2 mg tid	Also available parenterally
Blperiden (Akineton)	Central antimuscarinic	2 mg tablets & 5 mg/mL ampules	1 mg bid	Increase to tid; every 3–4 days increase by 1/2−1 mg each dose	3 mg tid	Also available parenterally
Ethopropazine (Parsidol, Parsitan)	Central antimuscarinic	50 mg tablets	12.5 mg tid/qid	Increase to tid; every 3–4 days increase by 12.5 mg each dose	50 mg tid-qid	Approved by FDA; not available in U.S.
Secondary anticholinergic effects						
Diphenhydramine (Benadryl)	Antihistamine	12.5, 25 mg tablets; 12.5 mg liquid	25 mg qhs	Increase by 25 mg every 3–4 days	25 mg tid or 25–100 mg qhs	H1 blocker, also available parenterally
Amitriptyline (Elavil)	Tricyclic antidepressant	10, 25, 50, 75, 100, 150 tablets; injection 10 mg/mL	12.5 mg qhs	Increase by 12.5 mg every 2–3 nights	150 mg	
Clozapine (Clozaril)	Atypical antipsychotic	25 mg tablets	6.25–12.5 mg	Increase by 6.25–12.5 mg every 2–3 nights	100 mg	May cause paradoxical increased salivation

practitioners usually have particular anticholinergics they prefer to use due to their clinical impression or experience.

Clinical Uses

Since the advent of specific dopaminergic therapy for PD in the 1960s, the usefulness and popularity of anticholinergics waned dramatically. However, they are still used among many clinicians in certain situations.

Tremor Predominant Parkinson's Disease

The most recognized use of this class of medication is to treat tremor in early- or young-onset PD representing a levodopa-sparing strategy. In general, it appears that anticholinergics help tremor but do not significantly affect other akinetic or rigid features of PD. Original AAN practice parameters in 1993 stated that there was a common use for anticholinergic agents for initial therapy of tremor predominant PD, but concluded on the basis of class II evidence* that anticholinergics are probably no better than levodopa for tremor. Schrag et al. found equivalent reductions in tremor with a single dose of either apomorphine or biperiden, but only the dopamine agonist reduced rigidity and akinesia (58). Although anticholinergics do not appear to have significant effects on akinesia and rigidity as therapy, deterioration of all parkinsonian symptoms has been described following abrupt withdrawal (59).

Anticholinergics are useful in the early treatment of tremor predominant PD in young or mild patients if the primary indication for symptomatic therapy is tremor, and there are relatively minimal associated signs of rigidity or bradykinesia. Anticholinergics can also offer a useful adjunctive option if additional tremor relief beyond the patient's existing antiparkinsonian regimen is needed. Anticholinergics should be avoided in patients with baseline cognitive deficits, significant orthostatic hypotension, or urinary retention as these patients are at higher risk for exacerbation of these symptoms. For similar reasons, anticholinergics are reserved for rare use in elderly PD patients.

Parkinson's Disease–Associated Dystonia

Dystonia can occur in association with PD. Anticholinergics can play an adjunctive role in managing such dystonia. Most PD-associated dystonia occurs in the context of motor complications, but it can occur even in

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Evidence provided by one or more well-designed clinical studies such as case control, cohort studies, and so forth (57). The AAN 1993 practice parameters summary statement has since been revised (19).

levodopa-naïve patients. Most commonly, an "off" dystonia characteristically causes painful foot and toe posturing when dopaminergic medication wears off in the morning. Levodopa-induced "on" dystonias can follow either biphasic or peak-dose patterns. Poewe et al. (60) suggest that anticholinergics can play a role in helping relieve the severity of episodic dystonia in PD. However, limb dystonia as an early symptom in levodopa-naive patients tended not to respond as well compared to dystonia associated with motor fluctuations.

Miscellaneous Considerations

Often anticholinergic agents can be used to treat miscellaneous indications. In this setting, agents are often chosen on the basis of secondary anticholinergic side effects. For example, if antidepressants are needed, a tricyclic antidepressant such as amitriptyline might be chosen for its anticholinergic properties to assist with insomnia or PD-related tremor. Diphenydramine (Benadryl) is an antihistamine commonly prescribed for allergies or insomnia and possesses mild anticholinergic side effects that can be used for PD-associated sialorrhea and may help reduce tremor. Regarding sialorrhea, atropine drops in 1.0% solution administered sublingually twice daily have been reported as beneficial with no significant mental state changes (61).

Another class of medications commonly used in PD is the atypical antipsychotics. Clozapine, in particular, has significant anticholinergic-attributed sedation, but also can reduce tremor (62) and produce paradoxical increased salivation and drooling. Amantadine, discussed earlier in this chapter, shows modest anticholinergic properties, although its antiparkinsonian use is commonly chosen on its own merits (63).

A partial list of commonly used medications with either primary or secondary anticholinergic properties and their use is shown in Table 1.

Side Effects

Side effects of anticholinergic agents are a significant clinical concern, which can limit their usefulness in the treatment of PD symptoms. Most antiparkinsonian effects are assumed to be mediated via central muscarinic acetylcholine receptors. Side effects may occur as either additional unintended central muscarinic effects or as incidental autonomic effects attributed to peripheral binding to muscarinic and nicotinic acetylcholine receptors. In general, most side effects are dose-dependent and respond to dose reductions.

Central Side Effects

Sedation, confusion, memory difficulties, and psychosis are well-described adverse events attributed to central nervous system anticholinergic toxicity. An anticholinergic, scopolamine (Transderm-Scop®), in normal controls was found to have effects on cognitive activities requiring rapid information processing (64). Bedard et al. found a transient induction of executive dysfunction in nondemented PD subjects with an acute subclinical dose of scopolamine (65). These findings underscore the necessity to be aware that even in early PD patients with no clinical intellectual dysfunction, anticholinergics may have adverse effects on cognition. These drug-induced cognitive deficits are reversible. In patients taking anticholinergics who develop psychosis, increased memory difficulties, and confusion, anticholinergic agents should be withdrawn promptly.

Peripheral Side Effects

Peripheral anticholinergic effects can produce a variety of autonomic dysfunction including, but not limited to, dry mouth, orthostatic hypotension, and urinary retention. Rare but potentially serious side effects such as narrow-angle glaucoma have been described.

Similar to central effects, peripheral effects are often exacerbated in PD patients due to an underlying baseline autonomic dysfunction or an increased susceptibility due to advanced age. Concomitant dopaminergic medications may further exacerbate anticholinergic symptoms such as orthostatic hypotension, constipation, or sedation. Orthostatic hypotension is a common problem in PD and can be exacerbated by addition of anticholinergic agents.

Dry mouth due to parasympathetic depression of salivary glands is an extremely common and potentially uncomfortable side effect (66). In some patients with drooling, this effect may be advantageous. The severity of dry mouth also improves with a decrease in anticholinergic dose and may improve with prolonged exposure. Anticholinergics can also result in urinary retention due to excess parasympathetic inhibition, so caution must be exercised. Risks are particularly great in elderly men due to bladder outlet obstruction from benign prostate hypertrophy. If there is any history of urinary hesitancy or urgency, a urology evaluation is reasonable prior to initiation of anticholinergic therapy.

Blurred vision is another common side effect with anticholinergics. This symptom is often attributed to relatively reduced accommodation due to parasympathetic blockade and excessive dryness of the cornea. For persistent symptoms, consultation with an ophthalmologist may be appropriate. Rarely, anticholinergic therapy can precipitate narrow angle

glaucoma (closed angle glaucoma), an ophthalmic emergency. The acute increase in intraocular pressure presents with pain and redness in the affected eye. In practice, this condition is extremely rare. Risk of narrow angle glaucoma is minimal if there are normal pupillary responses and intact vision. Ophthalmology consultation should be sought during anticholinergic treatment should vision diminish or pupillary responses become abnormal. In contrast, the more common open angle glaucoma presents minimal risk for treatment with anticholinergics (54).

Careful consideration of risk-benefit analysis is needed when prescribing anticholinergic medications. Patients should be counseled about the potential for side effects and instructed to call with any problems. In younger patients without comorbidity besides mild PD, anticholinergics are generally very well tolerated and represent a viable option for tremor-predominant symptoms. In more susceptible patients with clinically relevant autonomic dysfunction, cognitive dysfunction or advanced age, anticholinergics should be used very sparingly.

Mechanisms of Action

Antiparkinsonian benefit is generally attributed to inhibition of central muscarinic acetylcholine receptors. For instance, Duvoisin and Katz (55) reported an antiparkinsonian benefit to benztropine and scopolamine, both centrally acting anticholinergics, with an exacerbation of parkinsonism after a trial of physostigmine, a centrally acting anticholinesterase. In contrast, peripheral anticholinergics (methyl scopolamine and propantheline) and a peripheral anticholinesterase (edrophonium) did not affect parkinsonian symptoms (55). Details of how centrally acting anticholinergics can modify PD symptoms, usually attributed to dopaminergic deficiency, remain unclear.

Abnormalities in the central acetylcholine neurotransmitter system have been described in PD patients (67,68). An oversimplified but clinically useful conceptualization is that the anticholinergic use corrects an imbalance between dopamine and acetylcholine (69). The depleted nigro-striatal dopaminergic system in PD causes a relative increase in striatal acetylcholine-dopamine ratio, which can be normalized by use of anticholinergics. Other miscellaneous proposed mechanisms include inhibition of dopamine reuptake (70) and mild NMDA glutamate antagonism (71). The clinical significance of these findings remains to be determined.

Summary

Anticholinergics have relatively few clinical uses in PD other than the treatment of tremor in young-onset patients. Anticholinergics can be used in younger patients with problematic PD-associated dystonia unresponsive to or intolerant of dopaminergic manipulation. Secondary anticholinergic effects may occasionally be helpful for insomnia, sialorrhea, or urinary frequency. Appropriate caution remains in judging risks of side effects versus benefits in anticholinergic use, particularly in patients who may be more susceptible to either the central or peripheral anticholinergic effects.

SUMMARY

With the advent of specific dopaminergic agents, the roles of amantadine and anticholinergics have taken a back seat. Traditional uses still dominate with amantadine used as a mild antiparkinsonian agent with a well-tolerated side effect profile and anticholinergics used to treat tremor predominant PD. In addition, evidence that amantadine has efficacy in the modulation of later stage PD motor complications is clinically helpful information. Careful judgment of use of both of these agents related to their respective side effect profiles remains a concern, particularly with anticholinergics in susceptible elderly patients. In summary, amantadine and anticholinergics are helpful agents in the practicing clinician's arsenal when dealing with particular clinical PD scenarios.

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