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Anticholinergic withdrawal and benzhexol treatment in Parkinson's disease

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SUMMARY The effects of slow withdrawal of anticholinergic medication and addition of benzhexol (8 mg/day) have been studied in patients with Parkinson's disease on stable levodopa therapy. Withdrawal of anticholinergic drugs led to measurable and often severe deterioration in about two-thirds of patients. Addition of benzhexol produced a slight but definite additional improvement in those patients in whom anticholinergics were withdrawn before the trial. Anticholinergic drugs thus still have a part to play in the treatment of Parkinson's disease, for they produce benefit in addition to that provided by levodopa.

Levodopa is established as the best treatment for Parkinson's disease, so what is the place now of anticholinergic drugs which had been the mainstay of treatment for 100 years? A number of authors have commented that patients stabilized on levodopa do not tolerate withdrawal of their anticholinergic medication (for example, Yahr, 1971) and Hughes *et al.* (1971) have shown that withdrawal of anticholinergic drugs in patients receiving a stable dose of levodopa leads to measurable deterioration in function, whether the withdrawal is abrupt or gradual. However, this is one of the only studies of anticholinergic drugs in which their effect has been established by using disability measurement techniques similar to those used to assess the benefits of levodopa. The results of anticholinergic drug trials before the advent of levodopa suggested that they are moderately effective, comparatively cheap, drugs which are simple to administer, although side-effects are frequent. Their value in combination with levodopa is less certain, so we have studied the effects of withdrawal and addition of anticholinergics in a group of patients with Parkinson's disease receiving stable doses of levodopa.

METHODS

ANTICHOLINERGIC WITHDRAWAL Twenty-five patients with idiopathic Parkinson's disease (13 male, 12 female; age range 41–77 years, median 63 years) entered the trial. All had been treated with levodopa in stable dosage (mean 2·5 g/day) for three months or more before entry and this was continued unaltered throughout the trial. All were taking anticholinergic drugs in addition to levodopa; 17 were taking benzhexol, four benztropine methanesulphonate, three orphenadrine hydrochloride, three biperiden, one procyclidine hydrochloride, one methixene hydrochloride, and one hyoscine (20 patients were taking one anticholinergic drug and five were taking two). In view of the wide variety of anticholinergics taken by these patients, it was not possible to arrange placebo substitution during withdrawal. Each patient was told there was doubt as to whether they really needed these drugs in addition to the levodopa they were taking, and that an attempt was to be made to gradually withdraw anticholinergic therapy. They were instructed to reduce the dosage of anticholinergic drugs by one tablet a week, and to aim to discontinue treatment at the end of four weeks. Each patient was assessed before the start of withdrawal of medication and was seen at weekly intervals thereafter before a final assessment if withdrawal was completed. The severity of disability was determined by the use of a score proforma of 41 items, as described previously by Marsden *et al.* (1973), a high score indicating a severe disability (maximum score 123). Individual scores for total disability, functional disability, tremor, rigidity, akinesia, posture, and autonomic function were analysed separately. The

patients were questioned as to the occurrence of side-effects according to a standard protocol, enquiring for the existence of and severity (graded mild, moderate, or severe) of a dry mouth, nausea and vomiting, constipation, blurred vision, hallucinations and mental confusion, and involuntary movements.

BENZHEXOL ADDITION Twenty-three patients with idiopathic Parkinson's disease entered this trial (nine male, 14 female; age range 41–77 years, median 67 years). In 14 of these patients anticholinergic drugs had been successfully withdrawn in the previous trial. The remaining nine patients were not currently taking anticholinergic drugs, although seven had taken them before levodopa treatment but had then discontinued their use. All patients were on levodopa in stable dosage (mean 2·4 g/day) for three months or more before entry to the study. This, together with amantadine in 16 patients (200–300 mg/day) was continued unaltered throughout the trial.

All patients took placebo tablets for the first four weeks of the study. Thereafter 11 patients switched to benzhexol, 2 mg four times daily, for a further four weeks, while the remaining 12 patients continued with placebo for two weeks and later switched to benzhexol for a further two week period. The placebo and benzhexol tablets looked and tasted identical and neither the patients nor the observers were aware of the time at which the switch to active medication occurred. Thus, 11 patients were scored according to the proforma for the two periods of placebo and two periods of benzhexol, and 12 patients were scored for three periods of placebo and one on benzhexol. Each patient was assessed clinically by using the methods described before entry into the trial and at fortnightly intervals thereafter. The average of the placebo and benzhexol scores for each patient are presented.

ANALYSIS OF RESULTS The mean total disability scores for all patients were analysed; the results of anticholinergic withdrawal and benzhexol addition were compared with pre-trial or placebo scores by appropriate non-parametric tests, which are detailed in the text and Tables. In order to obtain a measure of objective change to compare with the patients' subjective report of the effects of withdrawal and addition of drugs, the change in total disability score on placebo medication was studied. Two consecutive total disability scores were available on 38 occasions in 26 patients taking placebo medication; the mean change was only 0·08 ($\pm 4{\cdot}5 = 1$ SD). Accordingly, a change of plus or minus 4·5 has been used to indicate an objective change for better or for worse in any individual patient.

RESULTS

ANTICHOLINERGIC WITHDRAWAL Six of the 25 patients who entered the withdrawal trial were unable to tolerate it because of a considerable increase in disability so that their previous medication had to be reinstated. All described a great increase in immobility, and tremor became more severe. Deterioration commenced within 48 hours of reducing anticholinergic drugs. The initial total disability score of these six patients was not significantly different from that of the 19 patients in whom anticholinergics were successfully withdrawn. Of the 19 patients in whom withdrawal of anticholinergic drugs was completed, 12 considered themselves worse after withdrawal, five said there had been no change, two reported improvement (Table 1). Thus, approximately two-thirds of patients were subjectively worse after withdrawal of anticholinergic therapy, while one-third reported no change or improvement.

TABLE 1

SUBJECTIVE RESPONSE TO WITHDRAWAL OF ANTICHOLINERGIC DRUGS AND BENZHEXOL TREATMENT

	Better	*Same*	*Worse*
Anticholinergic withdrawal (n = 25)	2	5	18
Benzhexol addition (n = 23)	7	7	9
Benzhexol in patients previously taking anticholinergics (n = 14)	7	3	4
Benzhexol in patients who were not taking anticholinergics (n = 9)	0	4	5

In the 19 patients who completed withdrawal there was an objective and significant deterioration in mean total disability score of 14% (Table 2) and mean scores for functional disability, tremor, rigidity, and akinesia all deteriorated. Table 3 shows the correlation between the patient's subjective report after withdrawal of anticholinergic drugs compared with the objective measurement of change of total disability score. Fifteen of the 19 patients who completed withdrawal showed a strict correlation between their subjective report and objective measurement. Furthermore, the change in total disability score in the 12 patients who reported deteriora-

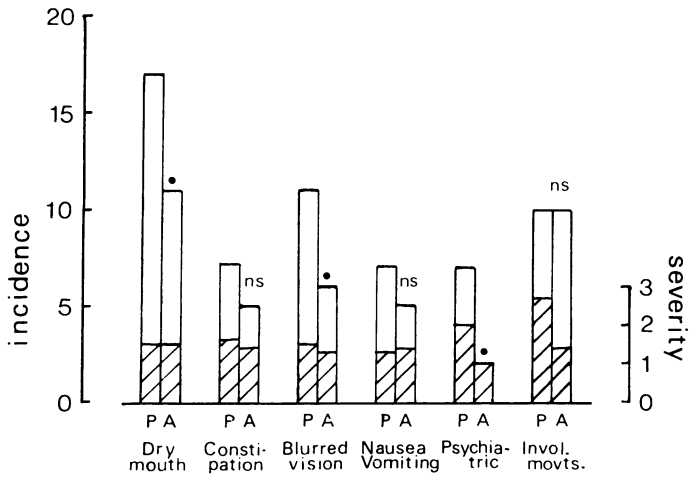

FIG. 1. *Incidence and severity of side-effects prior to (P) and after (A) withdrawal of anticholinergic drugs. Incidence in the 19 patients is shown by the open bars. Mean severity in those patients with side effects is shown by the hatched bars (on a 0–3 scale). Changes were analysed by sign tests and solid circles indicate differences significant at the 5% level (ns = no significant difference).*

TABLE 2

MEAN TOTAL DISABILITY SCORES ON WITHDRAWAL OF ANTICHOLINERGIC DRUGS AND BENZHEXOL TREATMENT

	Number	*Pre-trial*	*After withdrawal*	*On placebo*	*Benzhexol*
Anticholinergic withdrawal					
Patients who were unable to tolerate withdrawal of anticholinergics	6	36·1	—	—	—
Patients in whom anticholinergics were withdrawn	19	33·6	38·4*	—	—
Benzhexol addition					
Patients previously taking anticholinergics	14	33·7	36·1*	37·0	31·0†
Patients who were not taking anticholinergics	9	—	—	30·2	31·2
All patients who entered benzhexol trial	23	—	—	34·2	31·1

* Deterioration significant at 5% level (Wilcoxon matched-pairs signed-rank test).
† Improvement significant at 5% level (Wilcoxon matched-pairs signed-rank test).
None of the differences between the groups of patients before the trial or on placebo was significant.

tion after withdrawal was considerably greater than that reported by the seven patients who noted no change or improvement after withdrawal. There was no significant difference in initial total disability between those who became worse after withdrawal and those who reported no change or improvement.

The incidence and severity of side-effects before and after withdrawal are shown in Fig. 1. There was a significant reduction of dry mouth, blurred vision, and confusion and hallucinations after withdrawal of anticholinergics. The incidence of constipation, nausea and vomiting, and abnormal movements produced by levodopa was unchanged. However, the severity of abnormal movements decreased in nine of the 10 patients who showed this side-effect of levodopa before withdrawal of anticholinergic drugs.

BENZHEXOL ADDITION Of the 25 patients who completed the double-blind placebo *v.* benzhexol trial, seven stated that they were subjectively better on benzhexol, seven said they were unchanged, and nine said they were worse. Five

TABLE 3

COMPARISON OF SUBJECTIVE RESPONSE AND OBJECTIVE CHANGE*

	Objective change					
	Anticholinergic withdrawal (n = 19)			*Benzhexol addition (n = 23)*		
	Better	*Same*	*Worse*	*Better*	*Same*	*Worse*
Subjective response						
Better	1	1	—	5	2	—
Same	—	5	—	1	6	—
Worse	1	2	9	3	4	2

* A change of ±4·5 in total disability score is taken to indicate an improvement or a deterioration.

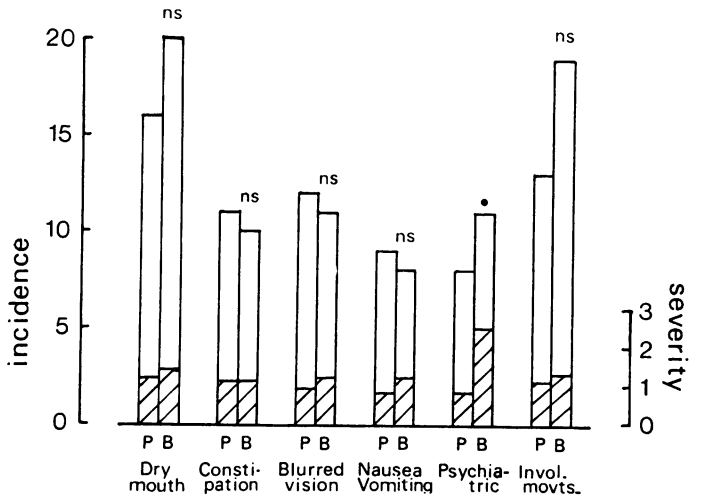

FIG. 2. *Incidence and severity of side-effects during placebo (P) and benzhexol (B) (23 patients). Symbols as for Fig. 1.*

of the nine patients stated they were worse because they developed confusion and hallucinations during benzhexol treatment. Of the 14 patients who had taken anticholinergics previously, seven said they were better and seven said there was no change or that they were worse on benzhexol, while of the nine patients who had not taken anti-cholinergics previously, all said they were unchanged or worse on benzhexol (Table 1).

The total disability score of the 23 patients decreased during benzhexol treatment compared with placebo, but this change did not achieve statistical significance (Table 2). Significant improvement occurred in the 14 patients who had previously been taking anticholinergic drugs, but there was no significant change in the nine patients who were not taking anticholinergics before entry into the trial. Mean scores for functional disability, tremor, rigidity, and akinesia improved in those patients who had been taking anticholinergics.

There was a fair degree of correlation between the patient's subjective report during benzhexol treatment and the objective change in total disability score; 13 of the 23 patients showed an objective change similar to their subjective responses (Table 3).

The incidence of side-effects during placebo and benzhexol treatment in the 23 patients is shown in Fig. 2. The incidence of a dry mouth and abnormal movements increased during benzhexol treatment, but none of the changes reached statistical significance. Four of the eight patients who showed confusion and hallucinations during the placebo period were worse during benzhexol treatment, and seven other patients developed severe mental side-effects for the first time during benzhexol treatment. The incidence of constipation, blurred vision, and nausea and vomiting did not change.

COMPARISON OF WITHDRAWAL AND ADDITION TRIALS Fourteen of the patients entered both the withdrawal and addition of benzhexol trials. Seven of these patients were subjectively worse after withdrawal of anticholinergics, and seven were objectively better after the addition of benzhexol. A comparison of these patients' subjective reports during withdrawal of anticholinergics compared with that during addition

TABLE 4

SUBJECTIVE RESPONSE TO WITHDRAWAL OF ANTICHOLINERGIC DRUGS AND ADDITION OF BENZHEXOL IN 14 PATIENTS WHO COMPLETED BOTH TRIALS

	Benzhexol addition		
	Better	*Same*	*Worse*
Anticholinergic withdrawal			
Better	1	—	1
Same	1	2	2
Worse	5	1	1

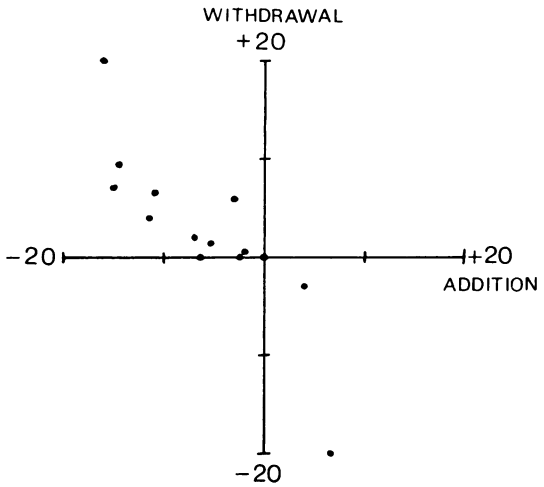

FIG. 3. *Effect of withdrawal of anticholinergics compared with effect of addition of benzhexol. The change in total disability scores due to withdrawal of benzhexol is shown for each patient who completed both trials; a plus score indicates deterioration, a negative score improvement* ($n=14$, $r=0{\cdot}89$, $P<0{\cdot}01$).

of benzhexol is shown in Table 4. Eight of the 14 patients reported appropriate changes during the two periods—that is, they were worse on withdrawal and better on benzhexol (five patients), or vice versa (one patient), or unchanged during both periods (two patients).

There was a significant correlation between the change in total disability score after withdrawal of anticholinergics and that produced by benzhexol treatment (Fig. 3): patients who got worse after withdrawal tended to get better on benzhexol treatment and vice versa.

FACTORS PREDICTING RESPONSE TO ANTICHOLINERGIC THERAPY Since approximately a third of patients who were taking anticholinergic drugs did not appear to need them, for they did not deteriorate when they were withdrawn, and since only approximately one-third of patients improved when given benzhexol, we have looked at factors which might predict which patients would benefit from anticholinergic therapy.

There was no significant relationship between the change in total disability score on withdrawal of anticholinergics or addition of benzhexol, and the patient's initial total disability score. Nor was there any significant relationship between the change in total disability on withdrawal, or addition of benzhexol, and the age of the patient, the duration of their disease, their sex, whether or not they were taking amantadine, their daily dosage of levodopa, or the duration of levodopa treatment.

The only factor that was found to bear any relationship to the response to treatment was whether or not the patient was taking anticholinergic drugs before the trial. As has been noted, those patients who were not taking anticholinergics did not improve subjectively or objectively when given benzhexol, while those who had been taking the drugs up until the time of withdrawal showed significant subjective and objective improvement when benzhexol was reinstituted. Perusal of the case notes and earlier records of treatment of the nine patients who entered the trial not taking anticholinergics showed that seven of these had taken anticholinergics at some time previously and had not found them of any value.

DISCUSSION

Anticholinergic drugs are of value in many patients with Parkinson's disease who are on treatment with stable dosage of levodopa. The improvement from anticholinergic drugs is less than that of levodopa, but it is possible to measure their effect by the same techniques used to establish the value of levodopa. The finding that two-thirds of patients deteriorate both subjectively and objectively when anticholinergic drugs are withdrawn confirms the report of Hughes *et al.* (1971) who found that 23 of 34 patients on stable levodopa therapy could not tolerate anticholinergic withdrawal. Slightly less than half of the patients responded to the addition of benzhexol in the present trial, but this group of patients included several who had previously not responded to these drugs when not on levodopa. Thus, approximately two-thirds of patients will benefit when anticholinergic drugs are given in addition to levodopa. Some patients, however, fail to respond.

The factors which determine anticholinergic drug response are not known. The response to both levodopa and amantadine likewise cannot be predicted, and it is still not known whether

the same patient responds to all three groups of anti-Parkinsonism drugs (levodopa, anticholinergics, and amantadine) or separately to one or two drugs, but not the other. Hughes *et al.* (1971) showed that the response to anticholinergic therapy was related to the dosage of levodopa, but this effect was not observed in our patients. In the absence of factors which will predict response, a clinical trial of anticholinergic drugs is warranted in all disabled patients.

That there is additive therapeutic effect of levodopa and anticholinergic drugs on Parkinson's disease seems to have been established by this and the other studies quoted. This is likely to have an underlying biochemical basis, but its nature is unknown. It has been suggested by Coyle and Snyder (1969) that the mechanism of the therapeutic action of the anticholinergic drugs in Parkinson's disease is related to their ability to inhibit the neuronal re-uptake of dopamine in striatal neurones, thus liberating more dopamine on striatal receptors. This is a possible explanation, but equally plausible is the possibility that anticholinergic drugs restore normal basal ganglia activity by a direct action on the striatal neurones employing acetylcholine as their neurotransmitter, rather than by altering activity in the dopaminergic nigrostriatal tract.

In conclusion, anticholinergic drugs are of additional benefit in many patients with Parkinson's disease already taking levodopa and therefore deserve a trial in any patient who does not respond adequately to levodopa by itself. Furthermore, anticholinergic drugs given alone, or in combination with amantadine, remain our treatment of choice in slightly disabled patients, for they are easy to use and have relatively few mild side-effects in contrast with levodopa. While levodopa therapy is required for moderately or severely disabled patients, it is more difficult to manage by both physician and patients, and carries a higher incidence of unpleasant side-effects.

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