

Blink reflex studies in patients with Parkinsonism before and during therapy

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SUMMARY Electrophysiological analysis of the blink reflex makes it possible to quantitate the reflex changes observed in pathology. The authors therefore propose a 'habituation index' to be determined by recording the electromyographic reflex response during stimulation at controlled frequencies. Several populations of subjects were tested. It was confirmed that marked differences in blink reflex habituation exist between normals and patients with Parkinson's disease. It was also found that when patients with Parkinsonism were treated with the classical anticholinergic drugs their habituation index remained virtually unchanged. However, treatment with either L-dopa or amantadine caused a rise in the index in almost all patients tested. On the basis of these findings it is suggested that these two new drugs have a highly similar mechanism of action.

In neurology it is often difficult to measure clinical signs and hence to acquire an objective view of clinical change during therapy. The objective of the present study was to quantitate changes in the blink reflex by means of an electrophysiological test.

An abnormally brisk blink reflex was described in extrapyramidal syndromes as early as 1924 by Guillain, Alajouanine, and Marquézy, who wrote that 'even a light tap to the glabella evokes polykinetic reflex closing of the eyelids'. Clinical tradition has since modified this view, at least in French-speaking countries; clinicians now accord special importance to the modifications in the blink reflex after repeated tapping of the glabella. In normal subjects the glabellar reflex disappears after a few stimuli (habituation). In patients with Parkinsonism, however, blinking persists and shows virtually no change in response to regular repeated glabellar tapping. This lack of reflex habituation is considered by Garland (1952) to be 'certainly the most characteristic sign . . . of the Parkinsonian state'. A study of the clinical utility of the blink reflex by Pearce, Aziz, and Gallagher (1968) confirmed that a positive glabella sign is found in almost 100% of patients with Parkinson's disease but is very rarely seen in normals.

As compared with clinical examination of the reflex, an electrophysiological analysis of the blink reflex offers two refinements: a controlled frequency of stimulation and a quantitative measure of the reflex response.

The blink reflex was studied electromyographically first by Kugelberg (1952) and then by Rushworth (1962, 1968). The reflex can be evoked by electrical stimulation of the fronto-orbital region. The ensuing response consists of two components which prove to be highly distinct on electromyographic analysis. The first component (R1) occurs after a brief latent period, appears to be relatively stable, and is generally diphasic. The second component (R2) has a longer latency (25 to 30 msec) and is polyphasic. The nature of R1 is still under discussion (Kugelberg, 1952; Shahani and Young, 1968; Penders and Delwaide, 1969). R2, however, is unanimously recognized as an exteroceptive response corresponding to an avoidance reflex. Electromyography demonstrates clearly that when repeated stimuli are delivered the amplitude of R2 declines at frequencies as low as 0.2/sec in normal subjects but that no change in R2 occurs in patients with Parkinson's disease (Rushworth, 1962, 1968).

In this study we attempted to determine how the blink reflex would be modified in Parkinsonism in general and in those patients being treated with L-dopa and amantadine.

METHODS

The blink reflex was evoked by delivering an electrical stimulus through silver electrodes applied to the skin of the supraorbital region. This technique has been described in detail elsewhere (Penders and Delwaide, 1969).

Painless single shocks of 3 to 8 mA intensity and 0.7 msec duration were used. The intensity of the stimulus was determined for each subject on the basis of the recruitment curve of the first reflex component R1 (60 to 80% of maximum R1). Silver recording electrodes were firmly attached to the skin at the midpoint of the lower eyelid and at the root of the nose. The subjects were seated comfortably in an armchair with a headrest. No special instructions were given.

By modifying the frequency of stimulation we were able to determine the 'habituation index'. This index was defined as the fastest stimulation frequency at which the fifth stimulus of a series still evoked a response R2 with an amplitude at least 20% of that of the control value. Measurement of the blink responses was achieved in some cases with planimetry. However, in order to increase precision of measurement and reproducibility of the results the amplitude of the polyphasic response R2 was most often measured by an integration procedure (Fig. 1) and the results read with a digital oscilloscope. An interval of 2 min was allowed to elapse between stimulation series so as to avoid interference.

Thirty-five normal subjects were used as controls (group A). A series of 24 patients with Parkinson's disease treated with anticholinergic drugs was also studied (group B), some of them both before and during treatment. In addition, 21 patients with Parkinsonism (group C) were examined before and during therapy with new drugs or a placebo. Group C was divided into three subgroups. Six patients received 200 mg amantadine per day for an average of 78 days. Seven patients received increasing doses of L-dopa up to a mean maximum dose of 4 g per day; treatment lasted several months. Finally, eight patients received a placebo (lactose) by mouth for two or three months.

Testing was conducted under double-blind conditions; the electrophysiologist who administered the test was

unaware of the treatment being received by the patients in the study. None of the subjects in the three groups had undergone stereotactic surgery.

RESULTS

Habituation as defined above is expressed as the inverse of stimulation frequency. In normals the mean habituation index is 5.3 sec, with extremes of 3.2 and 8.0 sec (Fig. 3A). These values are relatively stable over successive examinations, provided that the psychophysiological testing conditions remain essentially unchanged. More apprehensive subjects tend to have slightly lower values.

In patients with Parkinsonism the habituation index (mean value 1.6 sec) is markedly lower than in normals (Fig. 3B). All our patients were found to have low values; none had an index higher than 4 sec. The stability of the values over successive trials, in the presence of a stable clinical picture, was remarkably clear-cut (Fig. 2). As Fig. 3 indicates, there was practically no overlap between the normal (Fig. 3A) and Parkinsonian (Fig. 3B, C) histograms. The difference between group A and groups B and C was highly significant ($P < 0.01$). Generally speaking, a correlation was noted between the clinical severity of the disease and the lowering of the index. The most severe case in the present series had a value of 0.25 sec. (An equally low value had previously been found in two patients with neuroleptic-induced Parkinsonism.) In contrast, subjects with only mild Parkinsonian syndromes had indices of 3 and even 4 sec. Lowering of the habituation index appeared

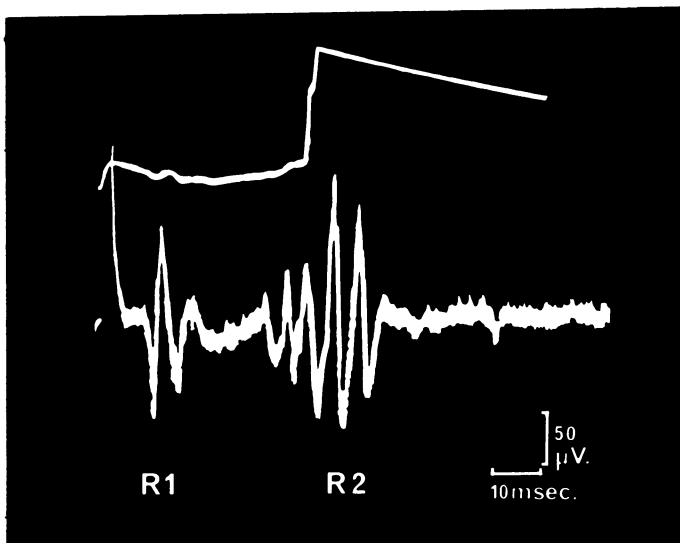


FIG. 1. Blink reflex evoked by supra-orbital electrical stimulation in a normal subject. The electromyographic response comprises two components, R1 and R2. Integration of the response 25 to 65 msec after stimulation permits quantitation of R2.

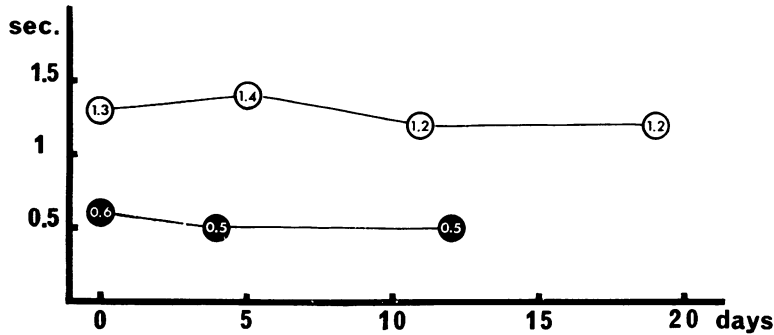


FIG. 2. Stability of the habituation index in two patients with Parkinson's disease being treated with anticholinergic drugs. Several tests were made a few days apart. The index values measured over the successive trials were found to be comparable.

to correlate with the severity of akinesia rather than with rigidity or tremor.

In so far as the effects of treatment on the index are concerned, no noteworthy differences were observed between several patients who had not yet received

any treatment and those patients who were being treated with classical anticholinergic drugs (Fig. 3B).

Treatment with L-dopa or amantadine, however, gave rise simultaneously to clinical improvement and amelioration of the habituation index (Fig. 3C). The index rose from a mean of 1.6 sec to a mean of 2.3 sec. Despite the spectacular clinical improvement in most of these patients, the index never exceeded 3.5 sec. Table 1 shows the values obtained before and during treatment in group C. No change was observed in the placebo-treated patients. This finding confirms the stability of the habituation index in Parkinsonism cases where the clinical condition remains stationary. In contrast, a clear-cut rise in the index was seen in the patients receiving new drugs. The change was especially marked in the L-dopa-treated group, where the initial values happened to have been lower.

The drug-induced rise in the habituation index occurred after different latency periods in the L-dopa and amantadine groups. A period of two to three weeks elapsed before the index rose in the patients treated with L-dopa (at this point the dose was 1.5 to 2 g/day). The index then increased until the patients were receiving doses of 3 g/day. This pattern is illustrated for patients L.E. and C.O. in Fig. 4.

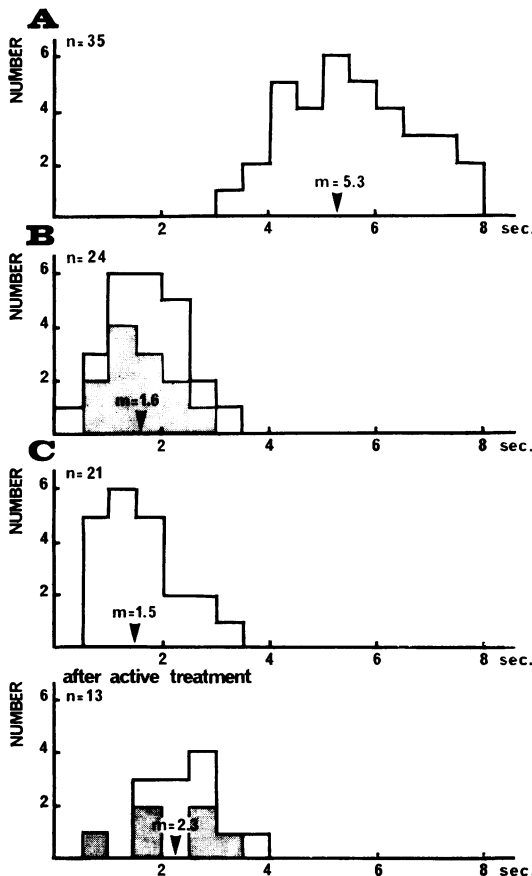


FIG. 3. Histograms of the habituation index in three groups. Group A: normal subjects. Group B: patients with Parkinsonism receiving anticholinergic drugs. Shaded area indicates the values of patients examined before the commencement of treatment. Group C: patients with Parkinsonism (receiving anticholinergic drugs or no medication at all) before treatment with L-dopa, amantadine, or a placebo. Group C after active treatment: shaded area indicates patients treated with amantadine; unshaded area indicates patients treated with L-dopa. It will be noted that Parkinsonism lowers the habituation index (B, C) with respect to normal values (A). These low values are unaffected by treatment with anticholinergic drugs but are raised by L-dopa and amantadine.

TABLE 1
HABITUATION INDEX VALUES IN PATIENTS OF GROUP C
BEFORE AND DURING TREATMENT WITH L-DOPA, AMANTADINE, OR PLACEBO

Before		During		Before		During		Before		During	
L-dopa		Amantadine		L-dopa		Amantadine		Placebo		Placebo	
0.5	2.2	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
1.0	2.8	1.2	1.6	0.6	0.6	0.6	0.5	0.6	0.5	0.5	0.5
1.2	2.2	1.6	2.5	0.8	0.8	0.8	0.7	0.8	0.7	0.7	0.7
1.3	2.5	1.8	1.7	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
1.4	2.0	2.2	2.7	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1.6	1.8	2.6	3.1	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
1.8	3.6			2.7	2.8	2.7	2.8	2.7	2.8	2.7	2.8
				3.3	3.4						
m = 1.25	2.44	1.65	2.02	1.60	1.60						

It will be noted that no patient had a net decrease in his habituation index compared with his pretreatment value.

Improvement was much more rapid in the amantadine-treated group. In all patients a rise in the habituation index was visible by the first week of treatment. The index often remained high for several months—for example, in patient V.D.S. (Fig. 4)—but in some cases where clinical improvement reversed itself the rise in the index also proved to be temporary—for example, in patient L.A. (Fig. 4). In two patients the values obtained after three

months of treatment were comparable with their pretreatment indices.

Despite the small number of patients in this series, a statistical analysis comparing the results of untreated patients and of the 13 patients treated with either L-dopa or amantadine confirmed that the change in the habituation index was significant ($P = 0.05$ according to the unilateral test of Wilcoxon).

DISCUSSION

The clinical utility of the glabellar reflex was demonstrated by Pearce and coworkers (1968). The sign, however, is not absolutely specific, as Pearce *et al.* (1968) and Paulson and Gottlieb (1968) have pointed out. There may be some resistance to habituation in cases other than extrapyramidal syndrome—for example, in the presence of severe brain lesions (trauma, tumour with extensive oedema, etc.) and in very old people. Nevertheless, for the ambulatory middle-aged patient the glabella sign is of incontestable value. In the study of Pearce and coworkers (1968), examination of 100 patients by three physicians revealed that the sign was present in 19 of the 20 patients with Parkinson's disease and absent in 23 of the 24 normals. Only one-quarter of the remaining patients in the series, who were suffer-

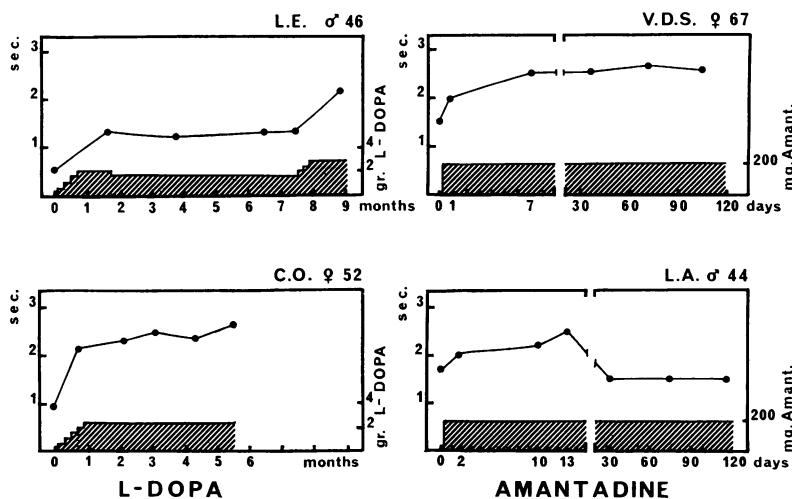


FIG. 4. Four illustrations of changes in the habituation index in the course of treatment by L-dopa and amantadine. Shaded area indicates the dose of the drug (scale at right). With L-dopa improvement occurs as soon as doses of 1.5 g/day are reached (patients L.E., C.O.). The index subsequently continues to rise and then becomes stabilized. With amantadine (200 mg/day) improvement is visible after the first few days of treatment. However, these high values sometimes drop as clinical improvement declines—for example, in the case of patient L.A.

ing from various intracranial diseases, evinced the sign; all these cases were marked by severe and extensive brain lesions.

In so far as the effects of treatment on the sign are concerned, Klawans and Goodwin (1969) in their clinical study of 16 patients with Parkinsonism treated with L-dopa observed that in eight of them the blink reflex recovered its ability to become habituated in response to repeated stimulation.

The utility of the electrophysiological test proposed in this paper is that the glabellar reflex technique gains in precision and reproducibility when the exact frequency of stimulation is known and when the response is measured precisely. This yields a numerical expression of the clinically well-known functional disturbance.

Attention should be drawn to several of our findings. First, the clear-cut difference between the group with Parkinsonism and the normals (Fig. 3) suggests that this test may be helpful in diagnosing clinically mild extrapyramidal syndromes. The fidelity and sensitivity of the test should be recalled in this connection. The correlation found between the test values and the patient's clinical condition, particularly the severity of akinesia, should also be stressed. This finding, which of course requires further verification on a larger series, nevertheless seems pertinent since the clinical methods available for gauging the severity of akinesia are difficult to quantitate. The index measured by our test is probably not a measure of the akinesia itself but most likely reflects the functional disturbance in a reflex arc which undergoes changes parallel to the akinesia. In two patients the test revealed that the exhaustion of the efficacy of amantadine was accompanied by a deterioration in the habituation index. The study also demonstrated that certain drugs are able to ameliorate a functional illness-induced disturbance in a relatively simple reflex arc. The theoretical importance of this fact, which Klawans and Goodwin (1969) recently pointed out in connection with L-dopa, opens up new perspectives for the physiopathological analysis of Parkinsonism in man.

It was interesting to observe that the classical anticholinergic drugs produced no significant change in the habituation index of the blink reflex. L-dopa and amantadine, in contrast, both exerted a specific and comparable effect on index values. L-dopa ap-

peared to be more potent in this respect than amantadine. Although only a limited number of patients were treated with amantadine, the present study is of interest in that it shows that parallel effects are exerted by L-dopa and amantadine. If it is confirmed that only L-dopa and amantadine are capable of modifying the habituation index, this would suggest that the modes of action of the two drugs are very similar and would tend to support the hypothesis that amantadine acts by releasing dopamine (Grelak, Clark, Stump, and Vernier, 1970).

The site of action of amantadine and L-dopa on the blink reflex is difficult to determine. Most likely the two drugs act in the same region. The thalamus cannot be ruled out; it will be recalled that Tokunaga, Oka, Murao, Yokoi, Okumura, Hirata, Miyashita, and Yoshitatsu (1958) have demonstrated in the cat that the thalamus is necessary for the production of the R2 component of the reflex.

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