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REAPPRAISAL OF TEMPORARY LEVODOPA WITHDRAWAL ("DRUG HOLIDAY") IN PARKINSON'S DISEASE

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Abstract Transient withdrawal of therapy has been advocated as a method of dealing with the complications of long-term use of levodopa in the treatment of Parkinson's disease. We retrospectively examined the effect of a 10-day period of levodopa withdrawal, or "drug holiday," in 28 patients. We then compared the subsequent clinical course of these patients over one year with that of 30 other randomly selected, similar patients with Parkinson's disease. In both groups the disease progressed; there was no difference in disease severity, capacity for daily living activities, or total amounts of dopamine agonists eventually used. For some patients, it was possible to reduce dopamine agonists used immediately after the drug holiday without causing deterioration, but a pulmonary embolus and other complications occurred. Subsequent complications related to long-term dopamine-agonist therapy during the follow-up period were similar in the two groups. This investigation indicates that a drug holiday carries some risk and does not improve the efficacy of levodopa therapy or prevent the problems that occur with long-term administration. (N Engl J Med 1985; 313:724-8.)

TEMPORARY withdrawal of levodopa, or a "drug holiday," may seem to be a radical way to manage the complications of long-term levodopa therapy in Parkinson's disease. However, investigators report fewer drug-related psychiatric complications and better motor responsiveness when levodopa therapy is resumed, even at a lower dosage.[1-4] Functional improvement in daily activities can also last up to one year.[5]

Nevertheless, the drug holiday is controversial. Some investigators have therefore advocated only weekend or alternate-day withdrawal of levodopa.[6,7] Benefits other than a transient improvement in psychiatric complications are difficult to document, and the drug holiday itself may generate complications.[8]

We have retrospectively examined the records of 28 patients with Parkinson's disease who participated in

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Supported by a grant from the National Institutes of Health (AG 02802) and the Parkinson's Disease Foundation. The work was completed in the Clinical Research Center of the Presbyterian Hospital, New York, and data were stored and analyzed in the CLINFO system, both supported by a grant from the National Institutes of Health (RR 00645).

Presented in part at the 37th annual meeting of the American Academy of Neurology, Dallas, 1985.

a 10-day drug holiday for another study. We compared these data with the records of 30 randomly chosen patients with Parkinson's disease who continued to take levodopa during the same period, to evaluate the efficacy of complete levodopa withdrawal.

Methods

Subject Selection

The patients were drawn from a study of serotonin metobolism that began on April 1, 1981, and lasted until March 31, 1984. Fifty-six consecutive patients with Parkinson's disease participated in that study, which included 10 days without levodopa or dopamine agonists.[9] In accordance with the literature, patients were told that these drugs would be discontinued for 10 days and that drug-related complications might improve, that they might require less levodopa, or that they might experience an enhanced response to levodopa lasting as long as a year. Forty-nine patients completed the first study. However, for the present study, we analyzed only the records of the 30 subjects examined repeatedly during the follow-up period by two of us (R.M. and L.C.). Two patients were later excluded because they had postencephalitic parkinsonism; all other patients had idiopathic Parkinson's disease.

Thirty controls, regularly examined by the same two investigators, were selected from a larger group of patients with idiopathic Parkinson's disease who had not participated in the previous study. The records of these control patients were selected randomly from nearly 200 records of patients with Parkinson's disease by one of us (K.M.), who had not participated in the original study or in the care of any patient in the current analysis. The controls were chosen by an alphabetical match to the last name of each patient in the drug-holiday group. The sole criterion was that controls had to have taken levodopa during the one-year period beginning at the entry date of the patient in the drug-holiday group to whom they were matched. Choices were made without knowledge of the clinical course during that period. The two groups were then retrospectively compared on measures of disease severity, the quantity of levodopa or other dopamine agonists taken, independence in daily living, and the appearance of adverse effects of dopamine agonists.

Drug Holiday

The 28 patients entered the Clinical Research Center after giving informed consent. On the second day, all dopamine agonists were discontinued (including levodopa, levodopa–carbidopa, and bromocriptine), but anticholinergic agents were continued, without any changes, in six patients who had been taking them. All patients received vigorous nursing care and daily physical therapy. Parkinsonian signs and symptoms (see below), mood, and cognition were assessed and rated daily.

Quantification of Levodopa

A levodopa-equivalence score was calculated for each dopamine agonist used. For levodopa–carbidopa, the total dose of levodopa per day was multiplied by four. The levodopa-equivalence score was determined using a ratio of 1:10 for bromocriptine[10]and 1:150 for pergolide.[11]

Neurologic Examination

Twenty-two signs and symptoms of Parkinson's disease were ranked daily on a Parkinson's disease evaluation scale (PDE)[12] and recorded at each measurement point. Independence in the activities of daily living (ADL)[13] was estimated daily for patients during the drug holiday, and at each observation point for all subjects.

Adverse Experiences

Adverse effects included all psychiatric and motor manifestations not considered typical of Parkinson's disease. We included thrombophlebitis, hallucinations, confusion, and dyskinesias.

Data Collection

In both groups, the period of observation was one year. The date of admission was used as the point of entry or base line for the patients in the drug-holiday group. For control patients, a date between April 1, 1981, and March 31, 1983, was chosen as the baseline entry point.

Scores for each variable were derived at five different times for the drug-holiday group: at base line (the day before levodopa withdrawal), on Day 7 during the drug holiday, at discharge, and at 6 and 12 months. For control patients, data from base line to subsequent evaluations at 6 and 12 months were used.

All data for the drug-holiday and control groups were abstracted and compiled by the same blinded investigator (K.M.). He reviewed records of subjects to determine PDE scores, levodopa-equivalence scores, and adverse experiences at each observation point.

Statistical Analysis

Student's t-test was used to examine differences in various group means; two-tailed t-tests were used exclusively. Chi-square analysis was used to examine any difference in the incidence of disease-severity changes between groups. Split-plot analysis of variance with repeated measures[14] was used to analyze longitudinal aspects of the study. The mean levodopa-equivalence, ADL, and PDE scores for the two groups were compared at base line, six months, and one year, yielding group, time, and interaction effects.

Results

Subjects

The mean age (± S.D.) of the drug-holiday group was 66.5±9.3 years. The average duration of illness was 10.4±8.5 years, and the duration of levodopa therapy was 5.8±3.8 years. The 30 control patients had a mean age of 65.0±8.9 years, with a disease duration of 8.3±4.8 years; the duration of levodopa therapy was 6.5±3.9 years. The mean time before the initiation of levodopa therapy in the drug-holiday group was 3.1±5.4 years, whereas in the control group it was 1.8±2.1 years. This difference was not significant, nor were the differences in age at the onset of Parkinson's disease and duration of parkinsonism or levodopa therapy. Fourteen men and 14 women were in the drug-holiday group; 19 men and 11 women were in the control group.

Drug Holiday

The PDE scores indicated much more severe disability during the period of levodopa withdrawal, and ADL scores dropped precipitously. The amount of levodopa taken at the time of discharge from the hospital, based on the levodopa-equivalence score, was reduced by about 50 per cent. PDE scores and ADL ratings at the time of discharge were similar to those at base line (Table 1).

Longitudinal Studies

PDE

The severity of parkinsonism increased for both groups over the year of observation ($F = 12.06$, $P<0.01$). The severity at base line was similar in the two groups, and an analysis of variance revealed no

Table 1. Progression of Parkinson's Disease in Patients on a "Drug Holiday" and Controls.*

Disease Progression	Base Line	Drug Withdrawal	Discharge	6 Months	12 Months
			mean ±S.D.		
PDE score					
Drug-holiday group (n = 28)	35.9±16.2	52.8±19.9	38.4±20.2	38.4±14.0	44.8±20.9†
Controls (n = 30)	36.6±16.2	—	—	35.8±19.7	37.3±20.1
ADL score (%)					
Drug-holiday group (n = 28)	69±13	60±15	68±14	67±16	62±21†
Controls (n = 30)	67±21	—	—	66±22	62±22

*PDE denotes Parkinson's disease evaluation, and ADL activities of daily living.

†N = 26.

difference between the groups at six months or one year (Table 1).

ADL

Independence in daily living also deteriorated significantly for both groups over time ($F = 6.4$, $P<0.01$). ADL scores, which were comparable in the two groups at base line, were also similar at six months and one year (Table 1).

Levodopa Equivalence

Patients in the drug-holiday group took smaller amounts of levodopa and other dopamine agonists immediately after the period of levodopa withdrawal, but levodopa-equivalence scores were comparable in the two groups at base line and at 6 and 12 months (Table 2). The amount of anticholinergic agents used was the same in the two groups.

Change in Severity

The frequency of change in the severity of disease over time was also examined. We arbitrarily chose a change of five points in the base-line PDE score as indicative of increased severity (increased score) or decreased severity (decreased score). In the drug-holiday group, severity increased in nine patients and decreased in seven; severity remained unchanged in the others. Among controls, severity increased in 12, decreased in 4, and was unchanged in the others. Chi-square analysis revealed no statistically significant difference in the incidence of these changes between groups. If only the patients who experienced a change in severity are considered, the calculated odds ratio is 2.3 in favor of the drug holiday. Although this difference is not statistically significant, it is possible that in a larger study a clearer benefit might have been observed. However, the odds ratio is based on the "arbitrary" criterion (a change of five points in the PDE score); the actual PDE comparisons revealed no significant differences between the groups. One patient in the drug-holiday group died from a myocardial infarction before the last examination, and another had a stroke; both were excluded from this analysis.

Adverse Experiences

Drug Holiday

Two patients became so rigid that parenteral nutrition was required. Other medical complications were observed; one patient had a pulmonary embolus, two experienced severe rigidity, another had a urinary tract infection, one became hypotensive, one had transient psychosis, one had dystonic leg cramps, and one experienced repeated falls. No similar medical complications were noted in the records of the controls at any point in the study period.

Follow-up Period

During the year of follow-up, the distribution of drug-related dyskinesias, psychiatric symptoms, and fluctuations were comparable in the two patient groups in terms of frequency and severity (Table 3). However, adverse experiences over the study period (including the time of levodopa withdrawal) were significantly more frequent in the drug-holiday group ($P<0.01$; odds ratio, 3.75).

Discussion

Our results do not support the claim that levodopa withdrawal, or a drug holiday, has a long-term benefit in the management of Parkinson's disease. Patients left the hospital taking less levodopa after the drug holiday, but the reduction in dose usually lasted less than six months. Psychiatric symptoms were similar

Table 2. Levodopa-Equivalence Scores.*

Group	Base Line	Drug Withdrawal	Discharge	6 Months	12 Months
			mean ±S.D.		
Drug-holiday group (n = 28)	466.1±656.3	—	216.4±191.2	289.3±287.6	401.5±443.8†
Controls (n = 30)	363.7±251.9	—	—	383.7±275.4	380.5±233.0

*See text for explanation of the calculated score.

†N = 26.

before and after the drug holiday, and hallucinations developed in two patients within six months after levodopa withdrawal. Subsequent dyskinesias and clinical fluctuations ("wearing off") were comparable in the two groups, and the disease progressed similarly in both despite the drug holiday.

Long-term levodopa therapy alters dopamine-receptor sensitivity,[15,16] and withdrawal of levodopa may alleviate that phenomenon. A drug holiday presumably allows resensitization of the striatal dopamine receptors,[2,15,16] improving the response to exogenous levodopa. The lack of a long-term benefit may indicate that the period of drug withdrawal is too brief. However, the discomfort and risks of serious complications probably preclude the continuation of a drug holiday for more than 10 days.

Adverse experiences have been encountered by other investigators, and despite skilled, aggressive nursing care, they occurred during the period of levodopa withdrawal in the patients we studied. The lack of group differences in the frequency of adverse experiences during follow-up also indicates that levodopa withdrawal has no prophylactic benefit.

Our patients were not selected for the presence of complications from levodopa, but the prevalence of such complications in the drug-holiday group was comparable to that reported in previous studies.[2-5] Other studies of a drug holiday in Parkinson's disease have been small and have lacked controls.[1-5] Some studies were also retrospective, but did not report the method of patient selection or data analysis or the period of follow-up.[2,3,5] In one study all but one subject was demented.[3] Koller et al.[5] followed 14 patients for up to a year and reported increased motor responsiveness and reduced side effects of levodopa. However, the only method of data analysis was Student's t-test, which is inappropriate for repeated observations over time,[17] and controls were not studied.

Kofman[8] reported that 9 of 24 patients remained improved for one year after a drug holiday, and 6 of them remained better even longer. Improved motor function was observed, but there were no long-term benefits with regard to fluctuations or drug-induced psychosis. All patients were "helpless" during the period of levodopa withdrawal, and intensive nursing care was required. Rigidity was frequently severe, and thrombophlebitis developed in one patient. Kofman concluded that a drug holiday was of limited value because of the enormous risk and small benefit.

Studies without controls, such as the previous investigations of a drug holiday,[2-8] can be clinically useful when promising results of a new treatment are reported or when successful modifications in an accepted treatment are recognized, but the data are not necessarily universal.[18] Although the attempt to use a drug holiday may have originally been justified by the lack of alternative treatments, our critical examination with a control group suggests a different conclusion.

Table 3. Adverse Experiences during the Follow-up Period.

	Base Line	6 Months	12 Months
		no. of patients	
Dyskinesias			
Drug-holiday group	5	6	5
Controls	11	10	12
Fluctuations			
Drug-holiday group	3	3	3
Controls	4	2	2
Psychosis			
Drug-holiday group	1	3	3
Controls	0	0	3

Complete withdrawal of levodopa only briefly reduces subsequent requirements for the drug, does not reduce the incidence or severity of complications associated with long-term levodopa therapy, and does not alter the subsequent clinical course. It may transiently relieve drug-related probems, such as hallucinations, but does not prevent the later onset of dyskinesias, fluctuations, or psychosis when therapy is resumed. Use of a lower dose of levodopa after the drug holiday may suggest an overdose before drug withdrawal rather than an enhanced response afterward.

There is little doubt that complications occur with long-term levodopa therapy. A transient reduction in the dose may be effective in eliminating some side effects. However, a drug holiday does not enhance the efficacy or prevent the problems of long-term levodopa therapy, and it may engender serious risks.

We are indebted to the nursing staff of the Clinical Research Center and Heather Conklin, R.N., who made this study possible; to Mr. Donald McMahon for his assistance in data management; and to Lewis P. Rowland, M.D., for his help on this manuscript.

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SPECIAL ARTICLE

POTENTIAL EPIDEMIC OF CREUTZFELDT–JAKOB DISEASE FROM HUMAN GROWTH HORMONE THERAPY

PAUL BROWN, M.D., D. CARLETON GAJDUSEK, M.D., C.J. GIBBS, JR., PH.D., AND DAVID M. ASHER, M.D.

A DECADE after the demonstration that Creutzfeldt–Jakob disease could be accidentally transmitted from one person to another during brain or eye surgery,[1,2] iatrogenic Creutzfeldt–Jakob disease has reappeared as a result of earlier therapy with human growth hormone, with the ominous possibility of a burgeoning epidemic.

Within just a few months, three young adults in the United States have died from the disease, confirmed neuropathologically in two patients and clinically detected but unconfirmed in one[3]; an additional neuropathologically confirmed case has been identified in Great Britain.[4] Salient data on these four cases are summarized in Table 1. (The details of both confirmed American cases[5,6] are reported in this issue of the *Journal*.)

Four other young adult U.S. growth hormone recipients who later died of chronic neurologic diseases that were not clinically characteristic of Creutzfeldt–Jakob disease are also under investigation. Their antemortem diagnoses were postradiation encephalopathy (two patients), atypical motor neuron disease (one), and atypical multiple sclerosis (one).

Creutzfeldt–Jakob disease has a worldwide yearly incidence of about one case per million population in countries where physicians are fully aware of the diagnosis and where it has been vigorously sought.[7,8] However, only 9 previous cases in patients under 30 years of age[9,10] are known among more than 3000 worldwide cases either reported in the literature or referred to us for experimental transmission studies, and 3 of these cases were iatrogenic.[1,2] The age-specific mortality rate for Creutzfeldt–Jakob disease in the population under 40 years of age is only 0.01 case per million (Brown P, et al.: unpublished data). Since approximately 10,000 Americans, all under 40, have received human growth hormone, the expected incidence of Creutzfeldt–Jakob disease in this group is 0.0001 case per year — i.e., the chance of one case occurring in a given year is 1 in 10^4. The chance of three cases occurring in one year is 1 in 10^{12}, and the chance of six cases occurring in one year is 1 in 10^{24}. Thus, the abrupt appearance of at least three cases of the disease in Americans under the age of 40 who had all been treated with growth hormone derived from pools of human pituitary glands obtained at autopsy strongly incriminates Creutzfeldt–Jakob disease–contaminated growth hormone as the cause.

A potential conflict exists between the legitimate interests of patients, parents, and physicians, many of whom are willing to accept a small risk of iatrogenic Creutzfeldt–Jakob disease rather than relinquish the benefit of therapy with human growth hormone; pharmaceutical firms that make the hormone, which wish both to exonerate their products and continue to market them; and public health officials and scientists, who must decide what degree of risk attends treatment with human growth hormone and formulate a policy that minimizes this risk yet does not ignore the hormonal needs of patients.

From the available data, and allowing for the influence of variables that are less well defined, one can estimate the risk of inadvertent contamination of human growth hormone by Creutzfeldt–Jakob disease virus. The U.S. annual mortality rate from all causes during the 1960-1980 period was approximately 0.9 per cent, or, in the population of 250 million, somewhat fewer than 2.5 million deaths each year. Since the annual mortality rate from Creutzfeldt–Jakob disease is approximately 0.7 to 1.0 per million, or, in the U.S. population, somewhat fewer than 250 deaths per year, it follows that roughly 1 in 10,000 deaths in this country is due to this disease. Because lots of pituitaries used in the preparation of human growth hormone have varied from 500 to nearly 20,000 glands, frequent episodes of contamination can be expected to have occurred, unless patients with Creutzfeldt–Jakob disease were systematically excluded as sources of pituitary glands. Such exclusion was unlikely for at least two reasons: (1) patients with chronic neurologic diseases were not banned from collection, and until the mid-1970s diagnostic awareness

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