Provocative Pharmacological Agents for Psychiatric Diagnosis: Methylphenidate, Sodium Amobarbital and Physostigmine

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ABSTRACT

Although sedative and psychostimulant drugs have been used for many years to aid in the diagnostic and prognostic evaluation of psychiatric patients, few controlled studies of their efficacy exist. Recently, we have evaluated three pharmacologic agents, methylphenidate, physostigmine, and amobarbital, to further determine their diagnostic efficacy. This report briefly summarizes our observations concerning the differential effects of these agents in patients with various diagnoses.

INTRAVENOUS METHYLPHENIDATE

As reviewed previously (1) amphetamine-like psychostimulants have been observed to intensify psychotic symptoms in actively ill schizophrenics and to induce catharsis and talkativeness in normals, psychoneurotics and remitted schizophrenics. These observations recently have been extended by administering intravenous methylphenidate (0.5 mg/kg) to a variety of psychiatric patients and evaluating behavioral changes, using clinical ratings, as well as word association and projective psychological tests (1,2,3). Two such experiments are reported in the following paragraphs.

Method

The first set of experiments (1) utilized voluntary male and female psychiatric patients, having a variety of diagnoses, who ranged in age from 16 to 40 years. Diagnostic groups included: a) 22 actively ill schizophrenics, b) 3 remitted schizophrenics, c) 10 acutely ill manics, d) 4 acutely ill depressives, and e) 8 normals Following a series of placebo injections, a single intravenous injection of 0.5 mg/kg methylphenidate was administered to each subject over a 30-60 second period of time. Behavior was rated before and 15 minutes after injection of active methylphenidate. A trained nurse, blind to when and if active drug was being administered, evaluated the patients using a 15-point rating scale in which 0-5 represented mild symptoms, 6-10 represented moderate symptoms, and 11-15 represented extreme symptoms. Global psychosis and interactions were so rated.

A number of patients (13 actively ill schizophrenics, 7 acute manics, and 3 depressives) had the experimental sequence subsequently repeated, receiving a second infusion of methylphenidate after remission had occurred. This second infusion occurred no sooner than four weeks after the initial infusion.

In a second set of experiments (3), psychological tests were used to indirectly evaluate the psychosis activating effects of methylphenidate. This strategy was used to indirectly measure psychosis activation, so as to indicate whether or not "true" psychosis activation occurs following methylphenidate in schizophrenics, or whether patients merely become more trusting and talkative about their existing psychotic symptoms. Two groups, consisting of 16 actively psychotic schizophrenic inpatients, and 18 non-psychotic inpatients were utilized.

A design similar to the above described first set of experiments was used. 20 minutes before intravenous methylphenidate infusion (0.5 mg/kg), 20 minutes after infusion, and 24 hours after infusion, 15 of 16 schizophrenics, and 17 of 18 non-psychotic subjects were given the Kent-Rosanoff word association test(4), a 50 item standardized word association test designed to measure subjects' ability to give common word associations. This test was then scored for the number of common responses, this being defined as one of the five most frequent responses, according to published norms(4).

Furthermore, at 20 minutes before, 20 minutes after, and 24 hours after methylphenidate infusion, each subject was also given 3 different sets of projective ink blot tests, consisting of 5 Holtzman ink blots each(5). For each Holtzman card, each patient was asked to give one response, telling what the blot looked like. The responses to the Holtzman ink blots were then rated blindly by a clinical psychologist (Lowell Storms, Ph.D.) on four dimensions, using a 0-7 point scale. The dimensions were: 1) paranoid trends, 2) autism, 3) inappropriateness to the blot, and 4) thought disorder. The total number of responses given a rating of 6 or 7 (in the pathological range) was used as the pathological response score. All data was analyzed utilizing a Student's T test for paired results.

Results

In the 22 actively ill schizophrenic patients, there was a statistically significant and clinically dramatic intensification of pre-existing psychotic symptoms, including hallucinations, delusions, bizarre thinking and behavior, and catatonic posturing (baseline global psychosis score = 6.5 ± 0.4; + 15 minutes post-methylphenidate psychosis score = 10.5 ± 0.7, $p<.003$, students T test for paired results). Most schizophrenics changed from having active symptoms to moderate control to manifesting severe, florid psychotic symptoms. In most cases, symptom activation occurred within one or two minutes of injection and intensified to a peak within 15 to 30 minutes. Symptoms spontaneously decreased to their baseline level after a one to four hour period of time, as did increases in pulse rate and blood pressure. Interaction ratings also increased significantly after methylphenidate infusion in the actively ill schizophrenic patient group as a whole, although this phenomena did not occur in every patient(1).

For the 13 schizophrenic patients who had a second methylphenidate infusion, receiving a methylphenidate infusion while actively ill and later while in remission, methylphenidate increased psychosis ratings only while the patients were actively psychotic, but not while they were in remission. In contrast, methylphenidate increased the interaction ratings of these patients while they were actively psychotic, as well as after they had remitted.

Among both actively ill and remitted schizophrenic patients, no changes in global psychosis, or interaction ratings, depression or anxiety occurred following placebo administration during the baseline phase.

In the acutely ill manic patient group, as with the schizophrenics, interaction scores increased significantly following administration of methylphenidate. In addition, four of the ten manic patients showed obviously increased psychosis

ratings after methylphenidate infusion. In these, the content of the psychotic material generally was grandiose, elated, or paranoid in nature. Overall, psychosis ratings did not increase significantly in the manic patient group.

In addition, of the ten acutely ill manic patients, 5 showed increased manic symptoms, 3 showed no change, and 2 showed decreased manic symptoms after receiving methylphenidate.

Furthermore, methylphenidate did not increase psychosis scores in any of those 7 manic patients given methylphenidate a second time after remission had occurred, although interaction scores again were significantly increased following the second methylphenidate infusion.

The depressed patient group showed no significant increase in psychosis scores following methylphenidate administration. Interaction scores consistently and significantly increased in these four cases. In two cases, depression was significantly and dramatically alleviated, and the patients entered a euphoric, hyperverbal state, which lasted from one to two hours. In the other two cases, dramatic catharsis, increased interactions, and increased talkativeness occurred.

The reaction of the 12 normal controls to methylphenidate infusion was similar to that of the remitted manic and schizophrenic patients and the depressives. No increase in psychosis ratings occurred. Most subjects showed increased talkativeness, catharsis, interactions, and thoughts.

For the second set of experiments(3) a significant decrease over baseline ($p<.05$) in common word associations occurred 20 minutes after, but not 24 hours after, methylphenidate infusion in the schizophrenic group only. This effect was not found for the non-psychotic patient group (mean number of appropriate responses: Schizophrenics-baseline = 23.8 ± 2.1, + 20 minutes = 18.3 ± 3.0, + 24 hours = 22.2 ± 2.0; Non-psychotics-baseline = 32.9 ± 1.3, + 20 minutes = 32.6 ± 2.1, + 24 hours = 34.0 ± 1.9). Furthermore, a significantly lower number of common word associations occurred overall at baseline, + 20 minutes, and + 24 hours after methylphenidate infusion, in the psychotic patients as compared to the non-psychotic patients.

A significant increase over baseline in pathologic projective responses to the Holtzman ink blot test occurred in the schizophrenic group 20 minutes after ($p<.05$), but not 24 hours after, methylphenidate intoxication (number of pathologic responses: Schizophrenics-baseline = 2.3 ± 0.5, + 20 minutes + 4.4 ± 0.9, + 24 hours = 2.2 ± 0.4). This statistically significant increase did not occur in the non-psychotic group of patients, although a slight increase in pathologic responses did occur.

Discussion

The above data are consistent with the assumption that methylphenidate significantly intensifies schizophrenic symptoms and activates the schizophrenic thought process in actively ill schizophrenic patients, but not in remitted or non-schizophrenic subjects; and that methylphenidate generally increases interactions, talkativeness, and catharsis in most subjects. The fact that the word association test scores of the schizophrenic patient group showed less commonality after methylphenidate infusion suggests that methylphenidate causes a loosening of associations in schizophrenic patients. The projective test results parallel the above observations, and indicate that the autistic and projective components of schizophrenic thinking are increased by methylphenidate. Since both of these tests are indirect measures of psychotic thinking, it is likely that methylphenidate increases psychotic symptoms, and it is unlikely that methylphenidate merely makes patients more trusting or talkative.

Thus, the administration of psychologic tests, plus a psychostimulant may have clinical usefulness in the rapid differential diagnosis of psychiatric patients beyond that of conventional interviewing or psychodiagnostic tests used alone. In addition, use of a methylphenidate interview at the end of a hospitalization may allow a clinician to tell whether the schizophrenic patient is clinically remitted and free of psychotic symptoms, or is merely withholding or suppressing information concerning his symptoms.

PHYSOSTIGMINE

Various cholinesterase inhibitors have been shown to induce depression, antagonize manic symptoms, and cause anergic effects in psychiatric patients, presumably by increasing central acetylcholine levels(6,7,8). The current study was conducted to determine whether or not physostigmine has a differential effect in causing depressive symptoms in groups of patients with and without affective symptoms respectively(6).

Method

Subjects studied consisted of: a) 8 floridly ill schizophrenic patients without marked affective symptoms, b) 6 acutely ill schizo-affective patients with notable affective symptoms, c) 8 manic-depressive patients, manic type, and d) 2 depressed patients, suffering from unipolar depression.

As described elsewhere(6), each patient participating in the study was pretreated with methscopolamine (0.75 - 1.0 mg, I.M.), so as to partially block peripheral cholinomimetic effects. A varying number of placebo injections were given, followed by intravenous injection of up to a total of 3.0 mg physostigmine or 1.5 neostigmine. Subjects were rated on a 0–5 point continuum scale for global depression and on a 0–5 point continuum scale for sadness by a nurse-rater who was blind to the type of drug infused and the timing of when active drug was infused. Increases over placebo-baseline scores for the sadness and global depression ratings in the manic depressive and schizo-affective groups were compared with increases in these variables in the schizophrenic group of patients who did not have significant affective symptoms. Comparison of groups occurred, using the Student T-Test (one tailed) for unpaired results.

Results

Most patients who received physostigmine exhibited symptoms of psychomotor retardation, similar to those observed in patients with retarded depression. Physostigmine did not produce marked sedation, slurred speech, or ataxia, although some patients became nauseated and/or vomited. Decreases in the subjects' levels of cheerfulness, friendliness, interactions, and talkativeness occurred. In contrast, neostigmine did not cause a significant change in behavior.

Physostigmine, appeared capable of inducing depressed mood and sadness in patients with an affective component to their illness. Six of the 8 manics and both depressives showed increased depressed mood after receiving physostigmine (manic group's increase in depression rating from baseline = $0.79 \pm .27$, significance = $p<0.02$; manics increase in sadness rating = $0.81 \pm .26$, significance = $p<0.01$). Likewise, 5 of the 6 schizo-affective patients showed depression after physostigmine infusion ($1.60 \pm .39$ = increase in depression rating, significance = $p<0.005$; increase in sadness rating = $1.48 \pm .40$, significance = $p<0.007$).

In contrast, physostigmine caused depression in only 1 of the 8 schizophrenics who did not show an affective component to their symptoms, and the increase in sadness and depression for this group was not significant. (Both sadness and depression increases = $0.23 \pm .48$).

Discussion

More recently, K.L. Davis, et al(8) administered physostigmine to 13 normal volunteers. Although a physostigmine inhibitory syndrome occurred frequently, depression was noted in only two subjects. Thus, there is evidence from the work of Davis et al(9), and Janowsky et al(6,7,8) to support the hypothesis that physostigmine may selectively cause a depressed mood in subjects with pre-existing affective disorder, in contrast to non-affective disorder patients.

Given that the above differentiation between physostigmine's effects on mood in patients with and without affective symptoms proves valid in larger samples, it is at least possible that physostigmine infusions might have some diagnostic potential.

AMOBARBITAL

There have been no placebo-controlled, double-blind studies evaluating the usefulness of barbituates, such as sodium amobarbital in uncovering schizophrenic or depressive symptoms, or indicating that barbituates improve diagnostic potential(10,11,12). The purpose of the present study is to compare sodium amobarbital and saline interviews in psychiatric inpatients to determine if this barbituate is effective in differentiating depressive from schizophrenic symptoms.

Method

Twenty psychiatric inpatients, including 11 schizophrenics, 5 affect disorder patients and four subjects with other psychotic and/or character disorder diagnoses, who had difficulty talking to their therapist during psychiatric evaluation, were studied. Subjects served as their own controls and were given two interviews on the same day. Sodium amobarbital was injected at a rate of 25 mg/min, and was stopped when sustained horizontal nystagmus developed (dosage ranged from 150 mg to 350 mg).

An interviewer conducted both sessions on each patient. The first session occurred in the late morning, while the second session occurred at least four hours later. The interviewer randomly administered intravenous saline solution during one session and intravenous sodium amobarbital during the other session. Following each session, the interviewer completed a Hamilton Depression Scale, a New Haven Schizophrenic Index (NHSI) and a Brief Psychiatric Rating Scale (BPRS). All interviews were audio-recorded, and also were rated blindly by another rater on the Hamilton Depression Scale, NHSI, and the BPRS.

In addition, the patient's regular therapist completed a pre-interview and a post-interview questionnaire. The pre-interview questionnaire was designed to measure the therapist's expectations and his diagnosis. The post-interview questionnaire was designed to measure his observation of the usefulness of each of the two interviews with respect to such components as a) new behaviors, b) information elicited, c) increased known information, d) diagnosis, e) treatment options, and f) psychodynamics elicited, on a scale ranging from 0-8. The therapists attended both interviews and were blind to the drug condition.

Results

On the basis of therapist ratings, there was no significant differences between the usefulness of the respective interviews. On the average, the therapists found both sessions moderately useful (range 3-4 out of 8), suggesting that neither the sodium amobarbital nor the interview sequence had a specific effect in facilitating diagnostic interviewing. In terms of eliciting new behaviors, new and known information, and clarifying diagnosis and psychodynamic formulations, there were no significant differences between the active and placebo sessions.

Furthermore, in comparing the Hamilton Depression Scale, the NHSI, and the BPRS for both sessions, no significant differences were found between placebo and active sessions, as noted by either the interviewer or the blind rater. Again, these results suggest that sodium amobarbital had no significant effect in unmasking repressed schizophrenic (psychotic) or affective symptoms.

Discussion

It should be recognized that sodium amobarbital interviews are used for other purposes, beyond those noted above (13,14). It has been reported, for example, that sodium amobarbital causes a lucid interval in catatonic patients (a finding we also observed in one catatonic), and barbituates may also be useful in clarifying a diagnosis of organicity.

However, our findings strongly suggest that sodium amobarbital is no more effective than placebo in eliciting new psychopathologic behaviors, or in eliciting new information or specific symptoms that would help in the differential diagnosis of schizophrenia versus affect disorder. Both the placebo and the active amobarbital condition moderately facilitated the acquisition of new information. Separate studies to verify the usefulness of barbituates in other situations need to be conducted to further explore their efficacy.

CONCLUSION

We have examined the use of physostigmine, methylphenidate and sodium amobarbital as provocative agents with potential to clarify diagnostic issues among hospitalized psychiatric patients. With the exception of catatonic schizophrenia, we conclude that sodium amobarbital does not have a specific pharmacological effect, compared to placebo, in uncovering material that might aid in the differential diagnosis between schizophrenia and depression. On the other hand, physostigmine may have some usefulness in identifying patients who have an affective component to their illness, by virtue of its possible ability to selectively increase depressive symptomatology. More research will have to be carried out before we can be certain that the risk/benefit ratio will justify physostigmine use as a diagnostic procedure in psychiatry, since physostigmine has numerous side effects and countraindications. Finally, methylphenidate administration exacerbates schizophrenic thought processes. This can be valuable in distinguishing schizophrenia (or other psychotic states) from non-psychotic syndromes. However, it must be noted that methylphenidate, like physostigmine, must be carefully evaluated as to its risk/benefit ratio in a given patient, since it also has a variety of side effects and several contraindications.

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