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Apomorphine and psychopathology[1]

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SYNOPSIS Forty men, mainly alcoholics, were administered either the dopamine receptor agonist, apomorphine HCl (1 mg), or distilled water subcutaneously three times a day for 14 days in a double blind study. None of the subjects developed an endogenous depression or schizophrenic symptoms. Scores on the Hamilton Rating Scale, Zung Self Rating Scale, and Brief Psychiatric Rating Scale showed improvement with both apomorphine and placebo. There were no significant differences between the two treatments on these rating scales. A significant incidence of spontaneous penile erections occurred after apomorphine treatment compared with placebo. Both treatments eliminated subjective craving for alcohol. Acute administration of apomorphine had no effect on psychomotor retardation or depressed mood in two patients with endogenous depression.

L-Dopa, the precursor of dopamine and noradrenaline, has been shown to induce a variety of psychiatric symptoms including those of depression (Cherington, 1970; Jenkins and Groh, 1970; Goodwin, 1971). In a series of articles, Tesařová and colleagues have reported the induction of a depressive state resembling an endogenous depression in mentally healthy individuals and in neurotic subjects after the administration of apomorphine (Tesařová and Molčan, 1966; Tesařová, 1968, 1972). Apomorphine, a dopamine analogue, directly stimulates dopamine receptors without affecting noradrenaline receptors (Andén *et al.*, 1967; Ernst, 1967; Roos, 1969) or cerebral levels of 5-hydroxyindoleacetic acid (Tagliamonte *et al.*, 1971; Lal *et al.*, 1972), an index of serotonin turnover. Thus, these clinical observations on the effect of L-dopa and apomorphine may have important implications with respect to the role of an increase in dopaminergic function in the genesis of endogenous depression. However, the studies of Tesařová (1968, 1972), Tesařová and Molčan (1966) were uncontrolled trials. Also, L-dopa has been shown to have an antidepressant effect in some patients (Goodwin *et al.*, 1970) and even to induce hypomania (Murphy *et al.*, 1971). Further, van Praag and Korf (1971) have found a decrease in dopamine turnover in retarded depressions. This latter fact suggests that apomorphine might be a potential antidepressant agent.

The present study was undertaken to replicate the findings of Tesařová in a double-blind study and, in view of the postulated role of an overactivity of dopaminergic mechanisms in schizophrenia (Randrup and Munkvad, 1970; Angrist *et al.*, 1973), to assess the effect of apomorphine on the induction of schizophreniform symptoms. In addition, a pilot study of the effect of apomorphine on psychomotor retardation in depressed patients was undertaken. Also, in view of previous observations of the effect of apomorphine on induction of spontaneous penile erections (Schlatter and Lal, 1972) and references in the literature to an anticraving effect of apomorphine in alcoholics (Dent, 1955), these two phenomena have also been studied after administration of apomorphine.

METHODS

Forty male veterans who were admitted to the Department of Psychiatry at the Queen Mary Veterans' Hospital and who signed a consent form served as subjects. The patients were in good physical

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health and without evidence of psychosis or organic brain disease. Subjects were randomly assigned to treatment with apomorphine hydrochloride (1 mg subcutaneously three times a day for 14 days) or placebo injections of distilled water by a nurse drawing a piece of paper from a box containing the written treatment orders. Apart from this same nurse who prepared the apomorphine solution and administered the injections, no one else was aware of the treatment assignments. The apomorphine was freshly prepared before each injection by dissolving a 6 mg tablet apomorphine HCl in 1.8 ml distilled water.

All subjects were told they would receive apomorphine to study the effect of the drug 'on the nerves' and that this might make them worse or better. This was considered ethically acceptable as apomorphine has been found to have an antianxiety effect in alcoholics (Dent, 1955) and also to be an effective tranquilliser in a variety of psychiatric and neuropsychiatric disorders (Feldman *et al.*, 1945). In addition, the dopamine receptor agonistic effect of apomorphine suggested that this drug might have an antidepressant effect. Subjects were advised to remain recumbent for 20 minutes after each injection to avoid nauseating effects of the drug (Isaacs and Macarthur, 1954). Seven of the patients in the apomorphine group and five in the control group were suffering from a neurosis; of these, six and four respectively also had a significant drinking problem. The remaining subjects in each group were chronic alcoholics. None of the subjects had been on a course of neuroleptics or antidepressant drugs for at least two months before the trial. Most subjects were receiving benzodiazepine medication and various hypnotic agents before the study. Forty-eight hours before the investigation all medications were discontinued and during the study only methyprylon (300 mg) or dichloralphenazone (650 mg) were permitted as hypnotics if necessary.

The age of the experimental group was 52 ± 1 years (mean $\pm$ standard error) and the control group 49 ± 1 years. The interval (days) between admission to hospital and commencement of the trial was 15.7 ± 2.5 and 14.4 ± 1.6 for the two groups respectively. Subjects were rated by two independent raters using the Hamilton Rating Scale (HRS) (Hamilton, 1960) and the extended form of the Brief Psychiatric Rating Scale (BPRS) (Ban, 1969) just before commencement of the treatment and also at the end of the trial. In addition, the patients completed the Zung Self Rating Scale (ZSRS) (Zung, 1965) at both these times.

Subjective craving for alcohol was assessed before and at the completion of the trial, using a four point rating scale: 0 = no desire for alcohol; 1 = occasional desire for alcohol; 2 = frequent desire for alcohol; 3 = continuous desire for alcohol. Only subjects in category 2 and 3 were considered to have craving. At the termination of the trial each patient was assessed for side-effects of treatment by a check list which included data on the development of spontaneous penile erections.

Two male patients aged 54 and 48 years, with a history of manic-depressive psychosis of unipolar depressed type, were admitted for their second and third depressive episode respectively. Both patients had signs of retardation of movement and speech and a depressed mood. The patients were administered, in an uncontrolled study, three injections of apomorphine HCl (0.5, 1.0, and 1.5 mg) with an interval of four hours between each injection. The patients were rated by two evaluators at 30 minute intervals for two hours after each injection on retardation of speech, retardation of movement, and depressed mood. A scale of 0–4 for each symptom was used; 0 = absent; 1 = mild, 2 = mild–moderate; 3 = moderate; 4 = severe. The score for each subject on the three items was seven out of 12.

RESULTS

Three of the 20 patients treated with distilled water withdrew from the trial because of side-effects: one patient complained of anorexia, anergia, and an itchy face; another felt depressed and was afraid he was becoming worse; and the third complained of increasing anxiety. All three patients showed rapid symptomatic improvement on discontinuing the placebo injections. One of the 20 subjects receiving apomorphine withdrew from the study because of frequent emesis and epigastric distress.

Of the subjects completing the trial, five receiving apomorphine vomited on one to five occasions during the study; six additional subjects experienced occasional nausea. Other side effects with apomorphine were: dizziness (six), drowsiness (five), burning at the site of injection (three), feelings of anxiety (two), palpitations (one), and anorexia (one). In contrast, none of the patients receiving placebo experienced emesis, two felt nauseated, four had dizzy spells, two experienced drowsiness, 11 burning at the site of injection, two headaches, one constipation, and one an unpleasant odour. Three subjects experienced a sense of well being after apomorphine and one after placebo injection.

Twelve of the 19 subjects completing the apo-

TABLE

EFFECT OF APOMORPHINE ON VARIOUS PSYCHIATRIC RATING SCALES*

Treatment	Rating Scales					
	HRS		ZSRS		BPRS	
	Outset	Termination	Outset	Termination	Outset	Termination
Distilled water (n=17)	10.00±1.08	6.47±0.88	38.41±2.16	31.23±1.78	27.62±0.97	24.50±0.90
P‡	<0.001		<0.02		<0.01	
Apomorphine† (n=19)	10.26±0.89	6.23±0.78	42.31±2.02	32.89±2.45	26.73±0.80	23.95±0.90
P‡	<0.001		<0.001		<0.01	
P§	NS	NS	NS	NS	NS	NS

* HRS = Hamilton Rating Scale; ZSRS = Zung Self Rating Scale; BPRS = Brief Psychiatric Rating Scale. Values represent the mean ± standard error. The individual values on the HRS and the BPRS were taken as the mean of the two independent raters. Scores for the ZSRS refer to the raw scores.
† Apomorphine HCl (1 mg) was injected subcutaneously three times a day for 14 days; controls received distilled water injections.
‡ Significance of differences between values at the outset and those at termination using the paired *t* test.
§ Significance of differences between patients treated with distilled water and those treated with apomorphine using Student's *t* test.

morphine treatment experienced spontaneous penile erections at least once within 10 to 20 minutes of injection and lasting two to five minutes; in six of these subjects the erection occurred after each injection. In contrast, only three out of 17 control subjects experienced a spontaneous erection (Chi square, using Yates' correction for continuity, 5.88, df=1, $P<0.02$) and in only one subject did it occur more than once.

There was a high degree of inter-rater reliability on the HRS and BPRS: the correlation coefficients were 0.65 and 0.53 respectively. There were no significant differences in the scores on the HRS, ZSRS, or BPRS between the apomorphine and control groups at the outset of the trial or at the completion of treatment (Table). There was a significant decrease in scores on the HRS, ZSRS, and BPRS at the termination of treatment compared with pretreatment scores both for subjects receiving apomorphine and those receiving placebo. None of the subjects developed a clinical picture of an endogenous depression or schizophrenic symptomatology.

At the outset, five of the apomorphine group and four of the controls were in the minimal–moderate range of depression on the ZSRS—that is, a score of 40–47 (Zung, 1968) and eight and four respectively in the moderate–severe range (48–55). The remaining subjects were in the normal–borderline range. At the termination of the trial one of the apomorphine group (score unchanged during the trial) and none of the control group were in the moderate–severe range on the ZSRS and two of the subjects in each treatment group were in the minimal–moderate range; the remaining subjects in both treatment groups were in the normal–borderline range of depression. On the HRS, four of the patients in the apomorphine group and three in the control group were in the range of the mildly depressed—that is, 15–20 (Mowbray, 1972)—and one of the controls in the moderately depressed range (20–25) at the commencement of the trial; the remaining patients were in the normal to borderline range. At the completion of the study none of the subjects in either group had a score of more than 14 on the HRS.

On the 10 items of the BPRS commonly associated with schizophrenia—namely, emotional withdrawal, conceptual disorganization, mannerisms and posturing, grandiosity, hostility, suspiciousness, hallucinatory behaviour, uncooperativeness, unusual thought content, and blunted affect—which are rated on a score of 1–7 (1=absent; 2=mildly present), the mean score before treatment was 11.3±0.4 and 10.6±0.3 and after treatment 10.4±0.2 and 10.4±0.2 for

the control and experimental group respectively.

Eight of the control and 15 of the experimental subjects experienced craving for alcohol at the outset of treatment. At the termination, subjective craving was eliminated in all subjects.

After apomorphine administration, both patients with psychomotor retardation started yawning and became drowsy within 10 minutes of each injection. In neither subject was there a change in retardation of motor activity or speech or change in mood.

DISCUSSION

Tesařová and Molčan (1966) and Tesařová (1968, 1972) reported that administration of 0.5–1.0 mg apomorphine subcutaneously three times a day for 12–14 days induced experimental depression of psychotic depth resembling 'melancholia simplex' in 64% of neurotics and 37.2% of mentally healthy individuals. A large sample was investigated—that is, 78 subjects in each group. Unfortunately, controls receiving placebo were not included in their studies. In the present investigation, using a double-blind technique, none of the subjects receiving apomorphine or placebo injection developed a clinical picture of an endogenous depression. Three of the subjects receiving placebo withdrew because of psychiatric side-effects. Both apomorphine and placebo resulted in a significant decrease in depression scores on the ZSRS and HRS. At the termination of the trial there was no significant difference on these two scores between experimental and control groups. After treatment none of the subjects was depressed on the HRS; on the ZSRS one of the apomorphine treated subjects was in the moderate–severe range of depression and two in each treatment group in the minimal–moderate range. Tesařová (1972) found that there was a significant correlation between a latent predisposition to depression, as revealed by psychological testing, and those subjects who became depressed after apomorphine. It is possible that the population investigated in the present study, which consisted predominantly of alcoholics, lacked the premorbid personality necessary for induction of apomorphine-induced depression.

In the present study some of the apomorphine-treated patients vomited on one or more occasions and several experienced transient nausea, though not consistently so, so that it is possible that the differences in side-effects unblinded the study. However, a significant incidence of side-effects did occur among the placebo-treated individuals leading, in three cases, to withdrawal from the study thus making it difficult to differentiate the experimental from the control group on the basis of side-effects.

Apomorphine is a central dopamine receptor agonist without affecting noradrenergic receptors (Andén *et al.*, 1967; Ernst, 1967; Roos, 1969) or cerebral levels of 5-hydroxyindoleacetic acid levels (Tagliamonte *et al.*, 1971; Lal *et al.*, 1972), an index of serotonin turnover. In a dose of 1 mg subcutaneously, apomorphine HCl is capable of reversing the symptoms of Parkinsonism (Cotzias *et al.*, 1970), a condition associated with a deficiency of striatal dopamine (Ehringer and Hornykiewicz, 1960). Thus, the findings of Tesařová might point to the role of hyperactivity of dopaminergic mechanisms in the genesis of endogenous depression. The present study, however, fails to reveal a depressogenic effect of apomorphine and this failure suggests that a hyperactivity of dopaminergic mechanisms is insufficient in itself to induce depression. Also, the failure of apomorphine to induce schizophrenic symptoms would suggest that hyperactivity of dopaminergic mechanism is also inadequate by itself to induce schizophrenia. The failure of apomorphine to induce significant psychopathology is in keeping with the absence of recorded psychiatric side-effects of apomorphine in the extensive literature on the clinical use of this drug, even after prolonged treatment at high dosage. In fact, before the neuroleptic era, apomorphine was found to be a very useful agent in the management of a variety of psychiatric and neuropsychiatric diseases (Feldman *et al.*, 1945). Recently, Strian *et al.* (1972) noted paranoid symptoms with sexual colouring in a patient with Parkinsonism and slight euphoria with sexually coloured behavioural patterns in others who were receiving oral apomorphine. However, the patients were also receiving L-dopa and a dopa decarboxylase inhibitor. The presence of co-existing disorientation in their patient with paranoid symptoms suggests more a picture of an organic confusional state than a schizophrenic picture.

Van Praag and Korf (1970) have postulated

that a deficiency of dopamine may subserve the symptom of psychomotor retardation in depressed patients. In the present pilot study, apomorphine had no acute effect on this symptom or on the depressed mood.

L-Dopa causes spontaneous penile erections in man (Yaryura-Tobias *et al.*, 1970). L-Dopa is a precursor of dopamine and noradrenaline and, in addition, decreases the turnover of serotonin (Goodwin *et al.*, 1971) so that the mechanism underlying the development of L-dopa-induced spontaneous erections is unclear. The present findings with apomorphine confirm our previous observations (Schlatter and Lal, 1972) and point to a dopaminergic basis for this response.

Both placebo and apomorphine eliminated subjective craving for alcohol. This points to the difficulty in evaluating the anti-craving effects of drugs in the absence of objective criteria of craving.

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