Neuroleptic-Induced Supersensitivity Psychosis

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Dopamine receptor binding sites have been reported to increase in the neostriatum after chronic treatment with neuroleptics, which could account for the dopamine hypersensitivity that induces tardive dyskinesia (1). We propose that similar changes may occur in the mesolimbic region in response to the chronic dopamine blockade of these drugs. Three kinds of clinical evidence are compatible with this hypothesis: 1) central nervous system (CNS) drug tolerance; 2) psychosis following neuroleptic withdrawal, which is correlated with signs of dopamine supersensitivity and which we would therefore term "supersensitivity psychosis"; and 3) psychosis associated with a sudden decrease in prolactin levels following neuroleptic withdrawal.

Study Reports

CNS drug tolerance. In a double-blind controlled study we compared fluphenazine enanthate given every 2 weeks with fluphenazine decanoate given every 4 weeks in the maintenance treatment of 48 schizophrenic outpatients (2). Before entering the trial, patients had received fluphenazine enanthate routinely for periods of 1 to 42 months (median = 14). All patients underwent a further 1-month period of stabilization with fluphenazine enanthate. The bimonthly dosages of the fluphenazine enanthate-treated patients on entering the trial ranged from 2.5 to 125 mg (median = 25 mg, mean = 39.3 mg) and after 7 months of treatment ranged from 2.5 to 325 mg (median = 50 mg, mean = 69.1 mg). Thus, substantial increases in dosage were required to maintain the mean therapeutic effect at the same level. In animal studies, prolonged exposure to neuroleptics leads to increased dosage requirements to block the behavioral effects of apomorphine (3, 4).

Psychosis associated with signs of dopamine supersensitivity. In a 6-week double-blind trial of triptophan-benserazide we studied the relationship between tardive dyskinesia and psychotc relapse in 32 patients with process schizophrenia (5). Half of the subjects received triptophan-benserazide instead of their regular neuroleptic medication and half received chlorpromazine. In the triptophan group, the severity of tardive dyskinesia (assessed on a 9-point clinical impression scale of the Extrapyramidal Symptom Rating Scale (2)) tended to be greater in the 8 patients who deteriorated than in the 6 patients who did not (means ± SD = 5.4 ± 1.4 and 3.8 ± 1.7, respectively, t = 1.85, p < .10). However, there was no difference in severity of tardive dyskinesia between the deteriorated (N = 2) and nondeteriorated (N = 14) chlorpromazine patients (means ± SD = 3.5 ± 0.7 and 3.6 ± 0.7, respectively, t = 0.38, p > .70).

REFERENCES

2. Weinstock FJ: Dilated fixed pupils from atropine (1r to ed). JAMA 229:267-268, 1974

1A more complete bibliography is available on request from the authors.
3.9±1.9, respectively) or between the nondeteriorated pa-
tients in the two drug groups.

These results are consistent with the hypothesis that the
relationship between severity of tardive dyskinesia and psy-
chotic decompensation may be due to a common underlying
mechanism of increased dopaminergic function covertly in-
duced by long-term use of neuroleptics and made overt by
drug discontinuation. There was no evidence that increased
agitation caused a worsening of tardive dyskinesia, since the
2 deteriorated chlorpromazine patients did not show signs of
having more severe tardive dyskinesia than the nondeterio-
rated tryptophan-benserazide patients.

Psychosis associated with sudden decline in prolactin lev-
eels. In a pilot study designed to test whether penicillin has an
antipsychotic effect, 10 hospitalized schizophrenic patients
chronically treated with neuroleptics had their medication
withdrawn and replaced with oral penicillin for 6 weeks (6).
Greater decreases in prolactin (geometric mean = 22.6 ng/ml,
range = 11.7–51.7 ng/ml on day 0; geometric mean = 6.0 ng/
ml, range = 3.7–10.3 ng/ml on day 42) tended to be associated
(r = .62, df = 6, p < .10) with symptomatic deterioration (mean
BPRS total scores ± SD = 37.5 ± 8.8 on day 0 and 46.1 ± 13.2
on day 42), and increased severity of tardive dyskinesia was
significantly correlated with decreases in prolactin (r = .85,
df = 6, p < .01).

There is evidence to suggest that supersensitivity does not
occur in response to chronic dopamine blockade in the dopa-
mine hypothalaminofundibulum tract (7), so the extent of
prolactin elevation can be seen as a measure of absolute
dopamine blocking. That some patients require more dopa-
mine blocking to control their symptoms, as suggested by
their elevated prolactin levels, and relapse suddenly when
the dopamine blocking is removed is consistent with the hy-
pothesis that these patients have developed a supersensi-
tivity in their mesolimbic dopamine receptor sites as
they have in the neostriatum.

Discussion

The association between dyskinesia and psychotic
relapse has been observed by others (8, 9). The hy-
pothesis that tardive dyskinesia and supersensitivity
psychosis may be caused by a similar mechanism oc-
curring in different areas of the brain is suggested by
the common factors that can alter the clinical picture of
both syndromes: increasing the neuroleptic dosage
decrees the severity of dyskinesia and psychosis,
increasing the dosage makes both worse, stress ex-
acerbates both dyskinetic and psychotic symptoms,
and L-dopa and amphetamine can increase the severity
of both.

We suggest that neuroleptics can produce a dopa-
mine supersensitivity that leads to both dyskinetic and
psychotic symptoms. An implication is that the ten-
dency toward psychotic relapse in a patient who has
developed such a supersensitivity is determined by

more than just the normal course of the illness. This
may explain why Hogarty and associates (10) were un-
able to identify “good prognosis” patients who do not
relapse when maintenance neuroleptics are discon-

Another implication is the possibility that this super-
sensitivity is irreversible. This is accepted to be true of
tardive dyskinesia unless it is diagnosed early and
medication is discontinued. If the same irreversibility is
occurring in the mesolimbic region, the result would be
patients who must remain on neuroleptics for the
rest of their life regardless of the natural course of their
illness. In the studies done by Hogarty’s group, two-
thirds of patients thought to be suitable for drug with-
drawal after 2 years of drug therapy relapsed following
drug discontinuation, causing the authors to state that
“the need for maintenance chemotherapy may be in-
definite” (10). In some of these cases, the need for
continued neuroleptic treatment may itself be drug-in-

REFERENCES

1. Creese J, Burt DR, Snyder SH: Dopamine receptor binding en-
    hancement accompanies lesion-induced behavioral super-
    controlled study of Fluphenazine decanoate and enanthate in
    the maintenance treatment of schizophrenic outpatients, in Depot
    Fluphenazines: Twelve Years of Experience. Edited by Ayd FJ Jr.
    Baltimore: Ayd Medical Communications, 1978
    with neuroleptic catalepsy, amorphomere stereotypies and stra-
    tal dopamine metabolism in the rat after single and repeated ad-
    ministration of loxapine and haloperidol. Eur J Pharmacol
    of neuroleptics upon repeated administration. Psychopharma-
    cologia (Berl) 34:95–104, 1974
    tryptophan-benserazide in schizophrenia. Communications in
6. Chouinard G, Annable L, Horrobin DF: An antipsychotic ac-
    tion of penicillin in schizophrenia. JRCS Medical Science 6:187,
    1978
7. Allen RM: Dopamine hypersensitivity and tardive dyskinesia.
    Am J Psychiatry 134:1154, 1977
8. Degkwitiz VR, Bauer MP, Gruber M, et al: Der zeitliche Zusam-
    menhang zwischen dem Auftreten persistierender extrapyramida-
    ler Hyperkinesen und Psyschosereidiven nach abrupter Unterbrechung
    langfristiger neuroleptischer Behandlung chronisch schizophrener Kranken.
    Arznem Forsch 20:890–893, 1970
9. Crane GE: Pseudoparkinsonism and tardive dyskinesia. Arch
    Neurol 27:426–430, 1972
    tion among long term, successfully maintained schizophrenic out-