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Treatment of Mania with the Cholinomimetic Agent RS 86

SIR: According to observations that cholinomimetic agents such as physostigmine may counteract mania and can cause depression, Janowsky (1972) formulated the cholinergic-adrenergic imbalance hypothesis of affective disorders. It postulates that depression is due to a central nervous hyperactivity of the cholinergic system in relation to the adrenergic system and that the opposite is the case for mania. In contrast to physostigmine, which has a half-life of only 10–20 minutes and the injection of which is frequently accompanied by unpleasant vegetative side-effects requiring the application of the peripherally acting antidote methscopolamin, the spiroperidyl derivative RS 86 is a more suitable drug for studying the question of whether cholinomimetic agents possess an anti-manic effect. RS 86 is a direct muscarinic agonist, passes the blood brain barrier, has a half-life of six to eight hours and because of the drug's minor peripheral side-effects its combination with an antidote is not necessary (Spiegel, 1984).

In a double-blind study, using a placebo-drug-placebo-drug design, RS 86 was given to six female and four male patients aged between 19 and 52 years (mean = 35.6, SD = 10.6); nine patients fulfilled the RDC for mania, one for hypomania. The length of the placebo phases varied from two to seven days; the drug phases lasted six days with a successive increase of the doses generally up to 4 mg RS 86 per day. If clinically necessary, chloral hydrate, paraldehyde or levopromazine (maximally 400 mg per day) were administered. The degree of mania was assessed daily by two independent raters using the Inpatient Multidimensional Psychiatric Scale (IMPS) (Lorr, 1974).

Three patients did not show any improvement in their manic syndrome after the intake of RS 86. In one of them, even the increase of the dosage up to 6 mg had no effect on the psychopathology but caused nausea. Two patients displayed a marked improvement of the manic disorder during the drug phase, a relapse during the following placebo phase, and once again an improvement in the second drug phase. Five patients experienced a continuous improvement in their manic symptomatology which also lasted throughout the following placebo phase. As indicated by the relevant IMPS items, the

improvement of the manic symptoms, which was observed two to four days after RS 86 intake, included not only psychomotor disturbances but also euphoria, grandiosity and superiority. Except for the nausea reported by the one patient who did not even respond to the 6 mg RS 86 dose, only minor side-effects such as increased salivation or sweating were reported.

Our study confirms former findings that cholinomimetic agents possess antimanic properties. The lack of effectiveness of RS 86 in three of the ten patients cannot be explained by the fact that the non-responders suffered from a more severe manic psychopathology than the responders, as this was not the case. A different pathogenetic mechanism, not influenced by the muscarinic agonist, or individual differences in the bioavailability of RS 86 might be responsible for the varied clinical responses. Surprisingly, five of the seven RS 86 responders did not show a relapse during the second placebo phase. As a spontaneous remission occurring in each of these patients during the first days of RS 86 medication seems to be rather unlikely, a RS 86 induced "switch process" terminating the manic episode has to be considered.

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Is Mania Really Incompatible with Down's Syndrome?

SIR: As we were already surveying the Down's syndrome population of our hospital, for psychiatric illness, we were very interested in the observation of Sovner *et al* (*Journal*, March 1985, *146*, 319–320). Their hypothesis that Down's Syndrome precludes the development of mania enhances our understanding of the aetiology of psychosis.

We identified 60 cases of Down's syndrome from among a hospital population of 1014. Apart from the Standard Psychiatric Interview we used Feigner's criteria and ward staff's observations in