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Antipsychotic Drug-Induced Dysphoria

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Background. Dysphoric reactions to antipsychotic medication are well recognised in association with akathisia, but can also occur independently.
Method. Fifty-one healthy volunteers were given haloperidol 5 mg in two consecutive pharmacokinetic studies.
Results. Dysphoria occurred in about 40% of the subjects on both occasions, but akathisia was only detected in 8% (first study) and 16% (second study). All adverse effects were transient and were abolished in nine of the ten subjects given procyclidine.
Conclusions. While dysphoria is a well-recognised reaction in healthy volunteers, it is probably insufficiently recognised in patients, particularly if it occurs in the absence of akathisia. Better detection could improve compliance in patients.

The adverse effects of antipsychotic drugs continue to be a major problem in the management of schizophrenia and an important reason for non-compliance (van Putten, 1974), which in turn undermines the successful management of schizophrenic patients. One of the commonest adverse effects is akathisia, which has been associated with suicide and violent behaviour (van Putten, 1974; Drake & Ehrlich, 1985). An important aspect of the akathisia syndrome, dysphoria (a subjective, unpleasant mood) (Halstead *et al*, 1994), is, however, often unrecognised (van Putten, 1975). Therefore, patients who are irritable or complain of tension or panic can be given excessive treatment rather than dose reduction.

Dysphoria has long been recognised in non-psychotic subjects given antipsychotic drugs (Hollister, 1992), and indeed one such report (Anderson *et al*, 1981) was influential in deterring many investigators from the use of antipsychotic drugs in normal, healthy volunteer studies. This was partly due to the long duration of adverse effects described in three subjects who allegedly had symptoms which persisted for up to 6 weeks. This was an unfortunate consequence since such studies are important in order to delineate the neuropsychological, cognitive and psychomotor effects of these drugs from the psychopathological effects of illness in patients. We therefore report our experience in a large series of volunteers given haloperidol.

Method

In a pharmacokinetic study of haloperidol, we gave two groups of healthy volunteers (26 and 25 subjects; 51 in total) a single, oral dose of haloperidol 5 mg on two separate days. The total drop-out rate of 40–50% was largely due to adverse effects (Table 1). These were most frequently subjective complaints of dysphoria or agitation, while objective signs of akathisia (motor restlessness) were much less evident.

Table 1
Adverse drug effects following haloperidol 5 mg in healthy volunteers[1]

	Study I	Study II
Number of volunteers	26	25
Sedation	17 (65)	19 (76)
Dysphoria	10 (38)	10 (40)
Akathisia Probable	2 (8)	4 (16)
Definite	0 (0)	4 (16)
Dystonia	1[2] (4)	0 (0)
Total drop-outs	1[3] (50)	10 (40)

1. Percentages shown in parentheses.
2. 14 hours after dosage.
3. One volunteer did not attend the blood test 72 hours after dosage.

Results

Every subject who dropped out was examined by the principal investigator (DJK) who was experienced in diagnosing akathisia in psychiatric patients. Since the principal aim of the study was an investigation of pharmacokinetic variables, no formal rating scales for adverse drug reactions were used. As shown in Table 1, however, the investigator's index of suspicion for akathisia was markedly increased on the second study day. This was because a similar number of drop-outs due to identical *subjective* complaints began to be made after a similar 3-hour time interval after dosing to the first study day. Typical comments were: "I'll have to get out of