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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

here . . . I need to go home . . . I'll be all right outside . . .".

In the first group of 26 subjects, the drop-out times ranged from 3–8 hours after dosing. When these similar events occurred in the second group of 25 subjects, procyclidine 10 mg was given intravenously to all ten subjects with subjective dysphoria, regardless of the presence or absence of objective signs of restlessness. Seven of these had a good response and two were euphoric ("That's wonderful stuff . . . what's it called? . . . where can you get it?"). All dysphoric symptoms resolved completely within 2–3 hours. This was in marked contrast to the report by Anderson *et al* (1981) in which two of the three subjects were not helped by diphenhydramine or benztropine.

Discussion

The importance of this study was the similarity in the nature of the subjective dysphoric complaints to those frequently heard from psychiatric patients given antipsychotic drugs; the response to anticholinergic medication; and the fact that subjective dysphoria can occur as an important adverse effect in the absence of objective signs of akathisia.

We have also reported dose-dependent effects of haloperidol (2, 4 and 6 mg) on eye movements in healthy volunteers which were maximal at 4 mg (King, 1994). This is remarkably similar to the average 'neuroleptic threshold' of 3.7 mg found in schizophrenic patients (McEvoy *et al*, 1991). Thus the widely held view that patients can tolerate much greater doses of neuroleptic drugs than normal healthy subjects (Young *et al*, 1994) may be fallacious and based on an erroneous comparison between the effects of acute and chronic dosing.

Dysphoria has recently been identified as a major factor in the residual psychopathology and poor treatment response in psychotic patients on antipsychotic drugs (Newcomer *et al*, 1994). This should be distinguished from any underlying depressive or other mood disturbances associated with the illness itself.

Although Young *et al*'s (1994) report suggests that antidepressant medication may be beneficial, there might be a reciprocal impairment of antipsychotic efficacy (Kramer *et al*, 1989). Following an earlier demonstration that anticholinergic medication antagonised the antipsychotic effect of flupenthixol (Johnstone *et al*, 1983), it has been customary in the UK, and indeed backed up by a World Health Organization Consensus Statement (1990), to avoid the adjunctive use of anticholinergic drugs if possible. On the other hand, on the basis of their findings in an Italian study, Spina *et al* (1993) have recommended short-term anticholinergic prophylaxis for patients being treated with high-potency antipsychotic drugs. Our experience also suggests that anticholinergic drugs would be effective in the immediate or acute situation. Nevertheless, further, properly designed, placebo-controlled studies will be required to establish whether this is due to a direct effect on dysphoric mood or a non-specific stimulant effect.

Compliance with antipsychotic medication could certainly be improved if dysphoric reactions were detected and effectively treated more often.

References

ANDERSON, B. G., REKER, D. & COOPER, T. B. (1981) Prolonged adverse effects of haloperidol in normal subjects. *New England Journal of Medicine*, **305**, 643–644.

DRAKE, R. E. & EHRLICH, J. (1985) Suicide attempts associated with akathisia. *American Journal of Psychiatry*, **142**, 499–501.

HALSTEAD, S. M., BARNES, T. R. E. & SPELLER, J. C. (1994) Akathisia: prevalence and associated dysphoria in an in-patient population with chronic schizophrenia. *British Journal of Psychiatry*, **164**, 177–183.

HOLLISTER, L. E. (1992) Neuroleptic dysphoria: so what's new? *Biological Psychiatry*, **31**, 531–532.

JOHNSTONE, E. C., CROW, T. J., FERRIER, N., *et al* (1983) Adverse effects of anticholinergic medication on positive schizophrenic symptoms. *Psychological Medicine*, **13**, 513–527.

KING, D. J. (1994) Psychomotor impairment and cognitive disturbances induced by neuroleptics. *Acta Psychiatrica Scandinavica*, **89** (supplement 380), 53–58.

KRAMER, M. S., VOGEL, W. H., DiJOHNSON, C., *et al* (1989) Antidepressants in 'depressed' schizophrenic inpatients. *Archives of General Psychiatry*, **46**, 922–928.

McEVOY, J. P., HOGARTY, G. E. & STEINGARD, S. (1991) Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Archives of General Psychiatry*, **48**, 739–745.

NEWCOMER, J. W., MILLER, L. S., FAUSTMAN, W. O., *et al* (1994) Correlations between akathisia and residual psychopathology: a by-product of neuroleptic-induced dysphoria. *British Journal of Psychiatry*, **164**, 834–838.

SPINA, E., STURIALE, V., VALVO, S., *et al* (1993) Prevalence of acute dystonic reactions associated with neuroleptic treatment with and without anticholinergic prophylaxis. *International Clinical Psychopharmacology*, **8**, 21–24.

van PUTTEN, T. (1974) Why do schizophrenic patients refuse to take their drugs? *Archives of General Psychiatry*, **31**, 67–72.

—— (1975) The many faces of akathisia. *Comprehensive Psychiatry*, **16**, 43–47.

WORLD HEALTH ORGANIZATION CONSENSUS STATEMENT (1990) Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. *British Journal of Psychiatry*, **156**, 412.

YOUNG, C. S., STEWART, J. B. & FENTON, G. W. (1994) Neuroleptic medication for dystonia. Reciprocal relationship between effects on motor function and mood. *British Journal of Psychiatry*, **165**, 384–386.

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