

Immediate Effects of Droperidol

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The subjective and behavioural responses of 20 healthy volunteers taking droperidol 5 mg as part of a cognitive challenge programme were catalogued. Some form of akathisia was universally experienced. Half of the subjects were dysphoric, but there appeared to be a number of different inputs to their dysphoria and a range of other effects were noted, including sedation, dissociative experiences, alterations in sensation and subtle changes in physiognomy. The duration of these effects varied from a few hours to over a week. In the acute phase, insight as to the origin of what was happening was mixed. The results have implications for the interpretation of cognitive challenge tests, the nature of akathisia, clinical therapeutics and drug development. © 1998 John Wiley & Sons, Ltd.

Hum. Psychopharmacol. Clin. Exp. 13: 113–120, 1998.

KEY WORDS — droperidol; healthy volunteers; akathisia; dysphoria

INTRODUCTION

The challenge faced by clinicians and drug developers in the field of psychiatry is to produce pharmaceutical compounds that do something useful which leads on to therapeutic success. Asking a clinician what that something useful could be will often only lead to the answer that they would like the drug to 'make the patient well'. Commonly there is no specification of what they would wish the drug to do in order to make the patient well (Cook and Healy, 1998). This focusing on long-term outcomes, such as discharge from hospital or prevention of relapse, has led to a neglect of intermediate-term outcomes that might predict the likely success of particular therapeutic strategies in individual patients. Such intermediate-term outcomes might include effects on a biochemical or neurophysiological marker or on a cognitive function test (Fear and Healy, 1996). An alternative might be sought in the reports of patients who take neuroleptics. In 1976, May and colleagues reported that patients who found the initial (within 24 h) effects of a neuroleptic to be beneficial did well with subsequent treatment on that compound, whereas those who found the initial effects to be dysphoric had longer hospital stays (May *et al.*, 1976). While there may be ambiguities as regards the motivation prompting

an individual patient's report, there is a larger problem with relying on patients self-reports which is that to date there are no generally accepted descriptions of the early effects of neuroleptic interventions. In the course of a study investigating negative priming in healthy volunteers and psychotic patients in response to droperidol, lorazepam or placebo, an opportunity arose to investigate the early effects of droperidol on 20 healthy volunteers. The range of experiences and the complications of some of these experiences form the subject matter of this paper.

METHODS

The observations reported arose in the course of a study conducted in the Department of Psychological Medicine in North Wales on the effects of negative priming in psychotic subjects and in healthy controls following droperidol, lorazepam and placebo. The volunteers were drawn from members of the nursing and medical staff in the Hergest Unit in Bangor, as well as members of the clinical and experimental psychology departments and other university research workers. The age span was from 23 to 48 years. None had a history of treatment for psychiatric problems. None were on concurrent medication.

Volunteers were randomised to either droperidol 5 mg, lorazepam 1 mg or placebo. Subjects were blind to the medication they took, but the

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supervisor of the negative priming session was not. None of the subjects identified with confidence the compound they had had during the testing session, although nine of those who took droperidol expressed a belief before the end of the session that they had had something. Instructions to the subjects both before and after testing were that they might have had any of the three compounds and that because they might have had a benzodiazepine they should avoid alcohol that evening. All subjects were given 4 × procyclidine 5 mg pills regardless of whether they had had droperidol, lorazepam or placebo and told they could use these if it seemed appropriate and that they could contact the investigators, whose phone numbers they were given, should they experience undue difficulties (only one availed of this option). No subjects were told what compound they had had until all subjects had completed the experimental protocol, except for one subject who because of ongoing effects it was decided to break the blind 24 h later.

The trial protocol involved 30 min spent at three negative priming tests delivered by computer on the day prior to the administration of the compound. The following day the compound was administered in orange juice. On the day of testing, the subjects repeated the battery of three tests 1 h after drug intake and subsequently 3 h after intake.

Three methods of data collection were employed. First, notes were kept of all adverse experiences reported by all subjects to the experimenter in response to direct questioning during the testing sessions. Second, all subjects were interviewed individually in the weeks following the testing session. They were each encouraged to write a report of their experiences; these are available for inspection. Third, two focus groups were convened in which 12 of the 20 affected subjects participated. These groups were aimed at isolating common elements to the experience. All findings discussed here had been reported during the blind phase of the study. The focus groups were used to achieve some consensus on appropriate descriptors of the states described. No states are described that occurred in one subject only.

RESULTS

None of the 20 subjects who had droperidol had a neutral or pleasant experience. None of those who had either lorazepam or placebo had an adverse experience, apart from sedation in the case of lorazepam. There were both short and longer-term

effects of droperidol, which will be considered together, with the issue of the mean duration of effects being discussed separately.

Akathisia

Droperidol, in this dose under these circumstances, induced restlessness in all 20 subjects. All subjects reported great difficulties with the completion of the tests. The tests it should be noted are boring. The levels of impatience experienced, however, were marked with some subjects remarking that they became belligerent or felt like putting a boot through the computer screen. Such reactions were out of character and were not reported in either the placebo or lorazepam groups. Fifteen of the 20 tested reported a mixture of reassurance by and irritation with the presence of the experimenter.

The restlessness had both clear motor and other components. Six of 20 subjects had what appeared to the experimenter to be visibly observable mild motor restlessness. One subject had to leave the experimental situation, although he did not attribute this at the time to the experimental compound. In contrast, all volunteers subjectively felt impatient and restless such that they wanted to get up and walk out of the testing room. When out of the room, however, either between sessions or after the testing session was over this restlessness continued for all subjects until at least that evening. The experience inhibited their ability to engage in normal social interactions. They felt there was a loss of composure in such situations, stemming in part from a sense of impatience with normal social interactions. Fifteen of the 20 found themselves to be irritable and belligerent.

Ten subjects felt that going to bed and remaining still might be a means to cope with the restlessness they were otherwise experiencing. This appeared to be an effort to manage restlessness by reducing stimulation. One of the subjects compared the predicament to that experienced by someone who might be sea-sick — in both cases there was switch to monitoring and attempting to manage internal stimuli rather the more usual focus on external stimuli. Six subjects, however, when in bed felt too restless to stay there. A feeling that a number of subjects had while snoozing or sleeping was that if they moved something would happen or would go wrong.

The experience of akathisia lasted until the evening of the day of testing for all subjects. For seven it had cleared up by the following morning

or was only mildly present. Five subjects took procyclidine but none found that it substantially alleviated the experience. Seven took alcohol and these seven reported what appeared to be better effects from the alcohol than procyclidine. Two subjects took both procyclidine and alcohol and both claimed that the alcohol was more helpful. For the remaining 13 subjects the experience lasted at least through the following day and for eight, although waxing and waning during subsequent days, the problem lasted even longer regardless of the measures taken to alleviate it.

Sedation

Seventeen of the 20 subjects felt, in their words, sedated. Seven snoozed during the breaks between testing sessions, some feeling unable not to. Ten went to bed immediately on returning home that afternoon or early evening. Some slept successfully at that point, but others, owing to restlessness, did not. It was difficult to tease apart a proper sedative effect of the droperidol from the feeling of boredom in the test situation, but also from the feeling that things had become more effortful. Some subjects felt tired at the prospect of doing things and felt that they might not have been feeling sedated if the sense of effortfulness were lifted. There is a question, therefore, about the nature of this 'sedative' effect or the number of its component parts.

Dysphoria

Eleven subjects reported dysphoria while the other nine were quite sure that although akathistic, they were not dysphoric in any meaningful sense of that word. The onset of dysphoria in most cases was relatively immediate with one subject breaking down in tears within an hour of having droperidol. In part dysphoria appeared to mean an experience during the testing session that personal horizons were closing in. Another component appeared to stem from an anxiety that the state was likely to go on forever. Yet another component seemed to stem from the effort they were now having to make even to do the most simple things; they found this tremendously dispiriting and worried that everything would take a comparable effort in the future. Some of these subjects found themselves remembering some of the unhappiest moments in their life, perhaps owing to state dependent effects. There was a feeling of the return of mood-dependent

memories, of having fallen back into traps they had been in the past. This, in some instances, was accompanied by an evocation of imagery from the past, on others it simply appeared to be an evocation of feelings. Suicidal feelings emerged acutely in two subjects and were entertained in two more subjects whose reactions continued over succeeding days.

There was a growing element of anxiety for a number of subjects when the condition appeared to persist. Some had expected that when they got home and back into their normal routine that they would feel well and they were alarmed when they did not feel well. Others wondered whether they had done some irreversible damage to their brains — this was particularly the case for those subjects for whom the effects lasted more than 24 h. Even when the condition began to ameliorate, four of the subjects with longer lasting reactions described feeling vulnerable as though they were standing on the edge of a possible relapse.

Other experiences reported

Among other experiences reported were skin hypersensitivity, which was reported by five subjects. This was an odd feeling of either fleeting tingling or painful sensations in arms or legs or in the trunk. One subject found the seat belt of her car very uncomfortable. It can be noted that sensations of this sort are a commonly unrecognised, but not infrequent, occurrence in neuroleptic induced extrapyramidal syndromes (Decina *et al.*, 1992).

One subject had very marked rhinorrhoea. This is listed in the datasheet for droperidol as a possibility. Six subjects reported an aching feeling in their muscles as though they were on the verge of the onset of a flu. One subject reported a wheezing that was consistent with a respiratory dyskinesia, another reported a change in voice quality and ability to speak that might have been consistent with a laryngeal dyskinesia and one subject reported word finding difficulties that lasted for several days.

Six subjects had very obvious 'freezing' responses during the course of the testing sessions. Images would flash up on the computer screen that required a response, but the subject was left looking at the screen and did not respond. This immobility was experienced by subjects as a lack of caring about the outcome. There was a general feeling common to all subjects to some

extent of disengagement — a feeling of uninvolved with tasks in hand. While feeling disengaged and uninterested, a number of subjects reported what appeared to be a paradoxical heightening of visual or auditory perceptions.

Mental effort appeared to be difficult, with all subjects reporting some problems with concentration. Apparently simple tasks, such as obtaining a sandwich from a sandwich machine, proved too difficult for some people, which contributed in turn to the dysphoria mentioned above.

There were subtle changes in physiognomy in some subjects, noticeable to the observing experimenter, which in some cases were later remarked on independently by relatives of the participants. These appeared to involve changes to skin and hair as well as a 'shrunk' appearance, that to the observing experimenter had the appearances of an incipient influenzal infection. Changes of this sort led to one of the participants being later described, by a team member unaware of their participation in the study, as looking like a chronic schizophrenic.

Duration

The duration of adverse effects varied markedly. Four subjects essentially had recovered that night or following their sleep that night. A further three subjects reported feeling somewhat flat or hung-over the next day, but otherwise little the worse for wear. Five subjects remained intensely restless the following day, but the problem cleared toward the end of the second day. Of the remaining eight subjects, three were restless into their third day, but the problem cleared up then. Five subjects were restless and/or dysphoric for more than three days. Of these, three remained unwell for a week after the initial testing session. In the case of two of those three subjects, the effects subsided very gradually across the week, but in the case of one the effects escalated from the first day to reach a peak on the third day and only subsided slowly thereafter. All subjects had recovered fully after a week and none have had subsequent sequelae.

Insight

Only two of those who took droperidol reported discomfort during the testing session. Although some subjects were observably more impatient, even these did not report a clear recognition at the time that they had had droperidol. Five subjects felt that they must have had something owing to the

sedative effects, two because of their dysphoria and two owing to a prior familiarity with alterations in the experience of the self under the influence of psychoactive agents. Of the remaining eleven, a number left the final testing session still not certain that they had had an active agent.

When challenged on the discrepancy between their reports of no undue discomfort at the time of testing and subsequent reports of extreme distress all subjects recognised a paradox. The 18 subjects who had not reported distress at the time of testing subsequently reported that even when they were denying discomfort they had been acutely restless, impatient or dysphoric. One explanation for this dissociation was an unwillingness to report these subjective effects in case they indicated they had been taken in by the experimental protocol. There was also a feeling that they didn't want to be affected and that not acknowledging a problem might help it to go away. There was a disbelief that a small dose of a psychotropic agent in common use not noted to produce severe problems could be causing such discomfort. Thus there appeared to be some awareness of an altered state, but an unwillingness or inability to admit to this altered state, owing in part to the rapidity of its onset and in part to a more general difficulty in pinpointing the distinctive features of an unusual experience.

There are a number of other features to the issue of insight and dissociation. Some subjects were later that day reported by co-habitees to look more than ordinarily calm and relaxed, who at the same time described themselves as internally seething. There can therefore be a substantial lack of insight on the part of external observers, misled perhaps by possible early Parkinsonian signs in the features of those affected. Of those who experienced dysphoria, half clearly blamed the drug and recruited no 'depressive' responses. The other half, while aware the drug had triggered the dysphoria, believed the experience revealed something about them — what may be depressive responses appear to have been mobilised.

Finally five subjects reported 'flashback akathisia'. In two of those with the longest lasting reactions, there was an initial concern that these heralded yet further episodes of restlessness and irritability. A more general impression among the five subjects reporting these effects, however, was that sensitised by their experience they were now more aware of minor levels of irritability or 'naturally occurring akathisia' or restlessness that had gone unnoticed previously.

Context

Aspects to the experiences appeared to be constrained by context. Part of the difficulty initially may have stemmed from having to do the tests, which perhaps because of their boring and repetitive nature, contributed to the stimulation of impatience and discomfort (although this did not happen in the placebo and lorazepam groups). A number of subjects reported that while they became more irritable in the testing situation, at other times when they were more likely to be irritable, such as when driving their car, their normal levels of irritability were reduced. Other subjects reported that when they resigned themselves to doing nothing, such as when they were lying in bed, that the experience of detachment and disengagement was not unpleasant. The problems started when there was a perceived requirement to perform.

DISCUSSION

These results have implications for a number of different areas of research in psychopharmacology. One area concerns the reports of depression and suicidal behavior induced by reserpine, which began appearing shortly after its use in the treatment of hypertension in the 1950s (Wallace, 1955). Reserpine is a neuroleptic and accordingly one possibility is that the mechanism by which the changes in state were brought about may be somewhat similar to that by which droperidol induced dysphoria, restlessness and possible suicidality in this study. Such effects may happen even though neuroleptics are effective drugs in the treatment of both anxiety and depressive states. Indeed, the first randomised controlled trial of reserpine in psychiatry showed it to be effective in the treatment of anxious and depressive states (Davies and Shepherd, 1955). There would seem to be implications from this for a whole generation of theories which have directly or indirectly been associated with the supposed 'depressing' effects of reserpine and an association of those effects with monoamine-amine depletion. An alternative is that abrupt changes in monoamine states may produce dysphoria and akathisia rather than depression *per se*.

In a similar manner, there would appear to be implications for current research on the effects of tryptophan depletion. A proportion of both healthy volunteers and subjects who have been previously depressed appear to become dysphoric following the administration of cocktails deficient

in tryptophan (Delgado *et al.*, 1990). It would be of some interest to know whether there is any overlap between individuals who become dysphoric in response to tryptophan depletion and individuals who become dysphoric on droperidol. If there is minimal overlap this might point to a number of different physiological susceptibilities to depressive disorders which could be mapped using cognitive challenge and neuroendocrine strategies. Alternatively, if there is a large overlap, this might point to the role that a number of different provocative stimuli may have in mobilising depressive responses as a final common pathway. This possibility could be investigated by means of attributional style questionnaires and instruments to probe latent self descriptors (Williams *et al.*, 1990). Work in this area to date has used tasks such as the attempted solution of unsolvable anagrams to generate 'helplessness'. A dysphoria-inducing psychotropic challenge test, however, would appear to have much greater ecological validity for this work (see also Adeniran *et al.*, 1996).

At present there is an almost complete lack of knowledge on the phenomenology of subjective states such as dysphoria and akathisia. From our data, in line with proposals from King *et al.* (1995), it would appear that there was some dissociation between these two conditions, in that all subjects recognised an inner restlessness, whereas only half the sample reported dysphoria. In addition, among subjects reporting dysphoria there appeared to be a number of different processes leading to what may be substantially different experiences coded under a common rubric.

There are a number of implications for clinical practice. These included alterations in physiognomy such that observers ignorant of the status of the subject could remark over 24 h later that the subject looked like a chronic schizophrenic. Given that Parkinson's Disease can be accompanied by subtle changes to skin and hair, the possibility needs to be borne in mind that some of the agents we use in the treatment of schizophrenia may by altering certain cues lead to a 'sick look' that stigmatises those in treatment. The shuffling gaits and clumsiness more often associated with high dose regimes have commonly been cited in this regard, but the number and subtlety of these changes may be greater than has been previously appreciated.

Another unexpected and interesting finding was that a number of behaviours that are associated with individuals with schizophrenia, that have ordinarily been seen as part of the illness or

otherwise problematic, appeared in a new light following this study. Some could be seen as adaptive strategies to manage side effects. A number of individuals found that the best way to handle their side effects was to disengage from company and take to bed. A number of others found that the most effective antidote to their restlessness was alcohol. This finding has not been reported in the literature. It emerged quite independently from several different volunteers who had been advised as part of the experimental protocol not to take alcohol that evening. Future studies might explore this effect more systematically.

Finally and perhaps most importantly, there is the multi-faceted lack of insight that appears to go with akathisia and dysphoria. A number of observers have drawn attention to the possibility that such effects may lead to suicide or violence (Van Putten, 1974, 1975; Van Putten *et al.*, 1974; Drake and Ehrlich, 1985). These effects may be quite subtle so that nursing staff faced with a patient wishing to leave hospital may not see any reason why such a patient should not be deterred from leaving — they may appear in possession of their faculties or at least in a state where they would ordinarily be deemed responsible for their actions. These results, however, would suggest that in the circumstances when an individual has begun taking an antipsychotic agent or had their treatment changed, situations may develop in which the patient may appear outwardly normal, but where they may pose a substantially greater threat to either themselves or others than would ordinarily be the case.

There are a number of questions as regards dose regimes. One possibility raised by these reports is that low dose neuroleptics might cause a different range of side effects or problems with a different quality than high doses, although it would seem improbable that the side effects in general are more severe given the success of low dose flupenthixol, for instance, in the management of anxiety states. The possibility of a somewhat paradoxical reversal of the normal dose response curve as regards overall clinical utility rather than individual symptoms, however, should not be entirely discounted in that it is still not clear how effects such as akathisia are mediated. It may, therefore, be that an action on some other receptor, such as sigma receptors, might produce a propensity to akathisia, particularly with the butyrophenones, and that where this is not covered by a higher level of a D2

receptor blockade akathisia effects emerge more clearly. In this case, relatively higher doses may be more useful, even though they may make Parkinsonian effects more likely.

The picture indeed may be quite complex. Akathisia may often appear with as little as 1 mg of a butyrophenone. There may be quite different dose response curves, therefore, for the production of Parkinsonian and akathisia effects that could be explored by concomitantly administering tests, such as the Haase hand-writing test (Haase and Janssen, 1985) and monitoring for akathisia. Furthermore, apparent dose response inductions of dysphoria, for instance, may vary depending on the constraints of the experimental situation. Dysphoria may be more likely to happen as the effort to act increases. Such possibilities may underpin effects reported by Hollister that neuroleptics were more likely to induce dysphoria in healthy volunteers than in psychotic subjects or that any dysphoria induced was likely to be found less tolerable by the healthy volunteer (Hollister, 1961, 1992).

King and colleagues (King *et al.*, 1995; Lynch *et al.*, 1996) reported akathisia and dysphoria in healthy volunteers following haloperidol 5 mg. Half of their subjects were affected by what was, in terms of dose equivalents, possibly a somewhat larger dose of neuroleptic than ours. The time course of side effects was comparable to that found in this study — appearing after 3 h and lasting for 8 h or more. They reported no disturbances lasting as long as those found in this study, which may have stemmed from an immediate treatment of unsettled volunteers with intravenous procyclidine, but it is not clear from their reports how long a period of follow-up they employed.

In contrast, Williams and colleagues (Williams *et al.*, 1997) have reported that haloperidol given in a 1 mg i.v. dose to volunteers produced no restlessness or other effects during the subsequent hour and a half as measured using visual analogue rating scales. The differences between their findings and both ours and those of King *et al.* (1995) may stem from a number of sources. One possibility is that intravenous preparations of haloperidol or other compounds might produce a quite different side effect profile to oral preparations; there is some evidence in support of this. Another is their use of a lower dose, although because of the different compounds and different routes of administration it is difficult to be precise about the comparable magnitudes of the doses. Finally, their period of

observation was considerably shorter than ours and during this period even self-report visual analogue scales may be subject to the effects of confounded insight observed in this study.

Another notable aspect of the dosing regime in this study was that the design was an on again–off again design. This may generate both the problems that occur acutely on starting a compound as well as effects that may stem from discontinuation. In clinical practice, clearly in the ordinary course of events a patient would only be exposed to one set of effects at a time and this may be a much more manageable proposition that being exposed to both sets within a short period of time. In addition, in clinical practice the patient has an opportunity to get accustomed to the increased cost in terms of effort required to engage in activities and has the possibility to adjust their expectations accordingly so that there is less of a mismatch between expectations and outcomes and less hopelessness accordingly. Another aspect of the difference between patients and volunteers is that patients on chronic dosing will develop a tolerance to, rather than just an accommodation to, at least some of the adverse effects.

Finally there is the matter of individual responses to the effects of droperidol. In the field of cognitive challenge testing using psychotropic agents, individual differences in responses have long been recognised (Claridge and Healy, 1994; Healy and Watson, 1995). Systematic testing with personality inventories, such as the EPQ or more recently developed measures, might predict which subjects would have dysphoric responses and which would not. Such effects are likely to have a genetic basis. Quite apart from these differences, however, there was the extended duration of the responses in some individuals compared to others. These differences may reflect variations in metabolizer status that have recently been reported with different neuroleptics (Gill *et al.*, 1997), which may underpin the propensity of 10–15 per cent of psychotic subjects to react particularly adversely to neuroleptic treatment (Bowers and Swigar, 1988). The adoption of pharmacogenetic strategies in healthy volunteer studies might permit a better understanding of how particular symptoms, such as dissociative experiences, as well as akathisia, dysphoria and a number of other mental states, relate to underlying neurophysiological functions.

The present study was largely qualitative in nature with some quantitative aspects. This was appropriate in order to establish the issues that

might be suitable for further investigation. Further qualitative studies under different conditions are called for to explore context dependent aspects of the issues touched on here and to permit the development and standardisation of the rating instruments that will be necessary for any future quantification of the frequency with which some of the phenomena described here occur and the extent to which they impinge on daily functioning.

While the volunteers involved underwent considerable discomfort, those working in the mental health services all found the experience illuminating. They expected it to influence their clinical practice and despite their discomfort felt further studies should be undertaken to explore the phenomena further. While such experiences may be educational, there would also seem to be a need to establish safe protocols that expose volunteers to a minimum of discomfort. Subsequent pilot work with lower doses of droperidol (down to 2 mg) and a range of different solutions (blackcurrant or apple juice) did not seem to alleviate the problem. Future studies might consider using another neuroleptic.

This experiment clearly illustrates what the cost in terms of quality of life of some of the older neuroleptics may be. Antipsychotic drugs that do not induce comparable levels of dysphoria or akathisia would seem to be clearly preferable, even if their cost is substantially greater. Unfortunately, at present, the kinds of studies that would establish such findings are not being conducted. In order to tease apart the contribution of the different active principles in any of these cocktail compounds and the interaction of those principles with personality and constitutional profiles as well as the context in which such compounds are given, an ideal experiment would require the availability of several hundred healthy volunteers. The pharmaceutical industry are ideally placed to conduct or support the necessary investigations, but to date the relevance of such studies to drug development has not been clear. Developing pharmaco-economic constraints may alter perceptions in this area.

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