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Dystonic Reactions following Neuroleptics: Time Course and Proposed Mechanisms

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Abstract. The occurrence of acute dystonic reactions was studied relative to drug pharmacokinetic parameters following a single dose of the phenothiazine, butaperazine. Dystonias occurred more than one half-life from peak butaperazine levels, 23 to 56 h after drug administration. The authors postulate that the appearance of dystonias on falling plasma concentrations may be due to disruption of dopaminergic-cholinergic balance caused by differential antidopaminergic and anticholinergic potencies of the drug.

Key words: Dystonia – Pharmacokinetics – Neuroleptics – Dopamine – Acetylcholine – Neurotransmitter balance.

Since Curry et al. (1970) demonstrated that plasma phenothiazine levels parallel brain concentrations of the drug over time, there has been interest in relating plasma phenothiazine levels with therapeutic and side effects observed clinically. It has generally been assumed that therapeutic effects of a phenothiazine would appear when plasma and brain concentrations of the drug are optimal. Side effects have been expected to occur along a dose-response continuum, with maximal side effects at maximal brain and plasma phenothiazine levels.

It might be expected, therefore, that side effects, such as dystonic reactions[1] would appear at plasma concentrations above a threshold value. They would be expected to persist, with maximal degree of severity at maximal phenothiazine plasma concentration, until the concentration of drug in plasma drops below the dystonia threshold or until such threshold is raised pharmacologically by the introduction of antiparkinsonian agents.

The delayed time course of the acute dystonic reactions following phenothiazine administration prompted speculation that these dramatic side effects of neuroleptics may not be related to maximal concentrations of the agent. To explore this possibility, we undertook the study of these phenomena clinically by relating the time of onset of the dystonic reactions with the plasma pharmacokinetics of the piperazine phenothiazine, butaperazine (BPZ) following single dose administration.

METHODS

Schizophrenic subjects who had previously been drug-free for at least two weeks were given a single oral dose of 40 mg BPZ. Blood samples were collected for plasma BPZ determinations at 0, 2, 4, 8, 15, 36, 48, and 72 h after the single oral dose. Plasma was immediately separated from the cells and was frozen until fluorometrically assayed according to the method of Davis, et al. (1974) for BPZ. The specificity of the BPZ method was investigated in three ways. First, thin layer chromatographs of the drug in the final extraction were developed on three systems of liquid using: (a) isopropanol: NH_4OH (4:1); (b) butanol: acetic acid: water (4:1:1); and (c) butanol: ethanol: water (4:1:1). The extracted drug had the same Rf value as BPZ and no other fluorescence could be detected on the chromatograms. Second, the extraction of the final organic phase with buffers of pH 11 and 5.2 did not remove any fluorescent material that might have interfered with the assay method. Finally, the absorption and excitation spectra of the extracted drug from whole blood are identical to authentic BPZ.

BPZ curves for each patient in whom dystonias appeared were based on the reported values of plasma BPZ from 0 to 72 h. Inspection of the BPZ curves after a single oral dose of BPZ indicated a reasonable fit with a two compartment, open model. Assuming a two pool kinetic system, the (β) half-lives of BPZ in plasma was computed by the method of least squares using values from 8 to 72 h after BPZ administration. The value of plasma BPZ at the time of dystonia was estimated from these curves. Mean peak height, mean slope, and y intercept were used to derive the mean plasma curve for this group of dystonic patients.

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[1] Dystonic reactions include: torticollis, retrocollis, opisthotonus and oculogyrus.

Table 1. Time course of plasma peaks, half-lives and dystonias following butaperazine (BPZ)[a]

Patient	BPZ peak		β-Half-life h	Dystonias	
	h/BPZ	value ng/ml		h/BPZ	est. value ng/ml
1	4	70	8.4	23	9
2	2	320	6.3	25	27
3	4	345	9.2	26	49
4	4	260	26.6	27	45
5	4	690	16.0	27	231
6	2	310	9.0	27	34
7	8	120	11.5	28	36
8	4	119	12.1	56	4

[a] Patients received a single oral dose of 40 mg BPZ.

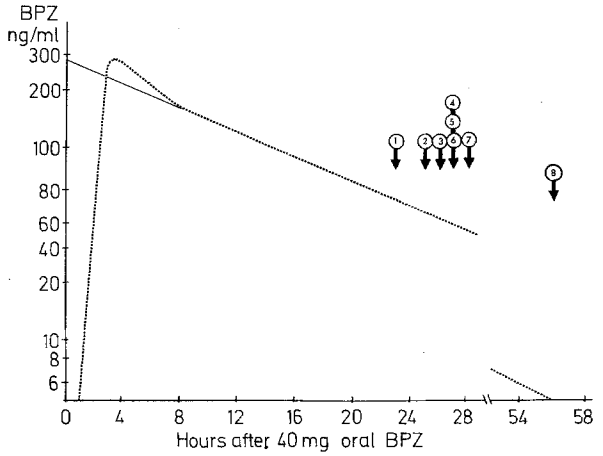

Fig. 1. Mean plasma BPZ and dystonic reaction following 40 mg oral BPZ

RESULTS

Following the single oral 40 mg dose of BPZ, 8 of 13 schizophrenic patients experienced acute dystonic reactions, including torticollis and/or opisthotonus in three cases, oculogyric crisis in four cases, and jaw extension, i.e. open mouth (an element of oculogyric crisis), in one case.

Table 1 indicates pharmacokinetic parameters for each of the 8 schizophrenic subjects who experienced dystonias. Figure 1 shows the mean pharmacokinetic curve for this group of patients. As shown in Table 1 and summarized in Figure 1, peak plasma BPZ occurred within 2 to 8 h following a single oral 40 mg dose of BPZ. In contrast, acute dystonic reactions occurred 23 to 56 h after the single dose, when plasma levels had fallen to between 3 and 33% of the initial peak levels. Moreover, all but one of the dystonic patients had dystonic reactions occurring in the 23 to 28-h interval after BPZ. The exception was a single patient who experienced even further delay of onset of dystonic reaction at 56 h.

DISCUSSION

Dystonias appeared with remarkable regularity 23 to 28 h after the single dose of BPZ. They appeared during falling plasma concentrations, when mean plasma levels had fallen 84% from their peaks. It is clear that such dystonic reactions are not a pharmacologic response to post-synaptic dopaminergic blockade produced directly by the drug at peak concentrations, but rather are a phenomena in some way related casually to events which take place later in time: to compensatory processes or to falling brain phenothiazine concentrations itself.

The dystonic reactions caused by neuroleptics are known to be modulated both by dopaminergic and cholinergic factors. While they can be relieved by methylphenidate (Davis and Cole, 1975), whose principal mode of action is release and inhibition of reuptake of dopamine (Ferris et al., 1972), they are commonly treated by anticholinergic agents.

Perhaps the most likely explanation for the delayed onset of acute dystonic reactions concerns the role of anticholinergic properties of BPZ. Extrapyramidal side effects of neuroleptics have been shown to be related to anticholinergic activity; drugs which have the least such side effects have greater anticholinergic properties (Snyder et al., 1974). More recently comparisons have been made between anticholinergic and antidopaminergic potencies of the neuroleptics. Drugs such as thioridazine and clozapine have anticholinergic potency in excess of antidopaminergic potency as determined by activity of dopamine sensitive adenyl cyclase (Iversen, 1975), and these drugs have few extrapyramidal effects. Drugs such as chlorpromazine and especially pimozide and trifluoperazine have antidopaminergic potency in excess of anticholinergic potency and have a high incidence of extrapyramidal disorders (Iversen, 1975).

Disruption of dopaminergic-cholinergic balance in favor of cholinergic dominance may underlie the occurrence of acute dystonic reactions during falling drug concentrations in the group of neuroleptics which have antidopaminergic in excess of anticholinergic potency. At higher BPZ concentrations both anticholinergic and antidopaminergic effects of the drug maintain the system in balance. As BPZ concentrations fall, an interval is reached during which dopamine blockade is maintained at a drug concentration insufficient to exert anticholinergic effects. Under these circumstances a state of cholinergic dominance may emerge accompanied by the display of dystonic symptomatology. Subsequently, as BPZ levels fall beneath the threshold for dopaminergic blockade, dystonias abate as dopaminergic-cholinergic balance returns.

If such mechanisms underlie the occurrence of acute dystonic reactions on falling blood levels, we would also expect to see a short-lived dystonic reaction during rising neuroleptic levels. It is of interest that patient No. 4 was observed to have short-lived, mild dystonic reaction beginning 90 min after the administration of BPZ which cleared spontaneously to reappear 26 h later on the falling neuroleptic curve.

We have postulated that the regular occurrence of dystonic reactions, which appear many hours after peak levels and on falling plasma and presumably brain concentrations of drug, may be result of a temporary disruption of cholinergic-dopaminergic balance in the direction of cholinergic dominance. There is as yet no direct evidence to favor this hypothesis rather than alternate hypotheses concerning, for example, temporary overshooting by compensatory mechanisms following dopaminergic blockade. However, a period of temporary cholinergic dominance accompanied by a display of extrapyramidal symptoms on falling drug concentrations might be predicted from knowledge of relative antidopaminergic and anticholinergic potencies of this group of neuroleptics.

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