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BENZODIAZEPINES IN PSYCHOTIC STATES

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SUMMARY

Benzodiazepines are primarily used for the treatment of generalized anxiety disorder, insomnia and status epilepticus. These drugs can also be useful in hyperaroused states, catatonic stupor, manic episodes, and akathisia. This paper will review indications for their use in various psychotic conditions.

INTRODUCTION

Benzodiazepines are the most prescribed drugs for the past two decades. They act by binding to a specific receptor complex that includes a GABA receptor (Bowery et al, 1984; Gallager, 1978). Functional synergy exists between benzodiazepine and GABA receptors (Iversen, 1983; Richards & Moeler, 1984; Haefely et al, 1983), and in the central nervous system, benzodiazepines inhibit neuronal firing (Laurant et al, 1983). It appears that benzodiazepine/GABA receptor complexes in different areas of the central nervous system mediate their anxiolytic, anticonvulsant, muscle relaxant and hypnotic effects (Neihoff & Kuhar, 1983).

In addition to the above mentioned indications, benzodiazepines are also used to treat acute psychotic states with the possibility of rapid amelioration of agitated and disruptive behavior. In combination with neuroleptics, they may help in lowering the neuroleptic dosage and decrease the occurrence of serious side effects. In this review, the rationale, clinical indications and guidelines for the use of benzodiazepines in the treatment of psychotic states and related disorders will be explored.

CLINICAL APPLICATION IN PSYCHOTIC STATES

I. Catatonic Stupor

Catatonia is a syndrome characterized by varying degrees of mutism and akinesia with a clear state of consciousness (Morrison, 1978). Various psychiatric, neurologic, metabolic or toxic disorders may present with catatonic features (Stoudemire, 1982; Fricchione, 1985). Neuroleptic administration, even though beneficial in a majority of cases, may worsen catatonia in some instances. Hence alternate and effective treatment is needed. Biochemically, benzodiazepines increase GABAergic transmission, decrease dopamine release and enhance motor activity. Similarly, Mucimol, a GABA agonist increases motor activity, aggression, and food intake in rats (Fricchione, 1985; Garbutt & Van Kammen, 1983) which can be blocked by haloperidol. These findings suggest both psychogenic and haloperidol induced catatonia may respond to benzodiazepines.

Recently there are a number of case reports which suggest that catatonic stupor (Salam et al, 1987; Greenfeld et al, 1987; McEvoy & Lohr, 1984; Casey, 1987; Greenberg et al, 1986; Harris & Menza, 1989; Heuser & Benkert, 1986; Ripley & Millson, 1988; Vinogradov & Reiss, 1986; Walter-Ryan, 1985; Wetzel, 1987) neuroleptic induced catatonia (Fricchione et al, 1983), and organic stupor (Sheline & Miller, 1986) responds dramatically, some times as quickly as one hour after the administration of benzodiazepines. Most often lorazepam and occasionally other preparations such as diazepam (McEvoy & Lohr, 1984; Sheline & Miller, 1986) and clonazepam (Martenyi et al, 1986) have been employed. In a literature review, Salam and Kilzeih (1988) emphasized that 1 to 4 mg of lorazepam was beneficial in 22 out of 24 catatonic patients. Rosenbush et al (1990) described that 12 of the 15 episodes of catatonic stupor encountered in one year, including stupor with affective disorder, drug induced psychosis, atypical psychosis and organic conditions improved with lorazepam. As the drug effect wears off the patient may revert to stupor again (Wetzel et al, 1987).

The current data indicate that benzodiazepines are useful in alleviating stupor caused by divergent conditions. This effect is only symptomatic and nonspecific. Therefore, treatment of the primary disorder has to be aggressively sought to prevent reversion to stupor.

II. Hyperaroused and Agitated States.

The need for medication to provide rapid control of agitated and potentially violent patients in the emergency settings cannot be overemphasized. Rapid tranquilization with neuroleptics, an important tool in the management of such patients, may induce severe side effects. Furthermore, neuroleptic induced akathisia may mimic an exacerbation of excitatory symptoms and akinetic mutism may be mistaken for a psychogenic catatonic state leading to administration of more medication with disastrous results. Benzodiazepines have a distinct advantage in treating acute psychotic patients who are unwilling or unable to provide a proper and reliable history thereby posing a problem in making a proper diagnosis.

Intramuscular injection of 2.5 mg of midazolam (Mendoza et al, 1987) and 1 to 2 mg of lorazepam (Dubin, 1987) were found to be beneficial within two to four hours in patients exhibiting acute hyper-arousal and violent behavior, respectively. While antipsychotic medications still remain the preferred method of achieving rapid tranquilization in patients with a verified diagnosis of schizophrenia, poor self care, malnutrition and usage of street drugs and alcohol in these patients make them susceptible to side effects. Therefore, addition of benzodiazepines might serve to lower the dosage of neuroleptics and thereby decrease side effects (Dubin, 1987; Bick & Hannah, 1986).

Retrospective chart reviews have revealed that a decrease in neuroleptic dose to 47 percent (Arana et al,

1986; Busch et al, 1989) and 50 percent (Salzman et al, 1986) of the original dose occurs in patients receiving the combination of benzodiazepines and neuroleptics. In addition, the combination decreased restraints (Busch et al, 1989) and provided a more rapid therapeutic response (Garza-Trevino et al, 1989). Lorazepam alone has been found to be as effective as haloperidol in psychotic agitation (Arana et al, 1986).

It is our hypothesis that agitated and violent patients have two kinds of psychopathology, an anxiety-arousal related disruption and an autonomous psychosis. Clinically, it is not possible to delineate these two groups. Actually, disturbed patients may manifest arousal related disruption as a result of an exacerbation of psychosis and conversely, arousal related disruptions may in turn enhance the preexisting autonomous thought disorder. Benzodiazepine administration to these patients improves arousal related disruptions, while their effect on psychosis is uncertain. Furthermore, the onset of action of neuroleptics and benzodiazepines are different. The latter improves the arousal related psychopathology as early as one to two hours after administration and the former improves psychosis as late as a few days to weeks after administration. In support of this hypothesis, are the findings of Lerner and coworkers (1979) who noted that benzodiazepines can improve symptoms within four hours and neuroleptics after 24 hours in acute psychotic patients. It is likely that both drugs improve different groups of symptoms. Our study (Mendoza et al, 1987) indicates that hyper-aroused patients improve within one to four hours. If a patient does not improve in four hours, it is unlikely that he has arousal related symptoms and further use of benzodiazepines may not be of much use. Intramuscular medication is needed only in patients who refuse oral medication.

III. Acute and chronic schizophrenic states

In general, benzodiazepines are not as effective as antipsychotic drugs in treating psychotic disorders, but they may be very useful especially during the initial phase of psychotic illness. Cohen et al (1987) reported that more than 2mg of lorazepam per day when used in combination with moderate doses of neuroleptic leads to greater improvement in the first four days of acute exacerbation of schizophrenia in comparison to those treated with neuroleptics alone. There are anecdotal reports of improvement of acute schizophrenia with chlorazepate (Joseph, 1987), clonazepam (Raines & Greenspan, 1987) and diazepam. Of the nine studies comparing the effect of neuroleptics with that of neuroleptic- benzodiazepine combination, four reported positive (Guz et al, 1972; Kellener et al, 1975; Lingjaerde, 1979; Lingjaerde et al, 1982) while the other five reported negatively (Hanlon et al, 1969 & 1970; Holden et al, 1968; Karson et al, 1982; Michaux et al, 1969). These discrepancies may well reflect differences in the population studied. The fact that more recent studies reveal positive results indicate the possibility that the earlier studies might have been conducted on chronic institutionalized patients who were unable to report improvement or had very little anxiety-arousal related symptoms, thus making them inaccessible to benzodiazepines. Kirkpatrick (1989), on the assumption that early symptoms of schizophrenic relapse are related to environmental stress, treated such patients with only diazepam and reported positive results. This area needs to be further evaluated.

Benzodiazepines have been employed in the treatment of neuroleptic resistant chronic schizophrenic patients having hallucinations, delusions, and paranoid ideation. The rationale is that, in animal studies, diazepam in high doses acts like the neuroleptic clozapine and inhibits central dopaminergic systems (Bunney & Aghajanian, 1974). As benzodiazepines are GABAergic, they may also alleviate postulated GABA deficiency in schizophrenia (Tallman et al, 1980; Van Kammen, 1979). Two uncontrolled studies with 18 patients have reported that diazepam alone improved schizophrenic psychosis (Nesteros et al, 1982; Beckman & Haas, 1980). Contrary to these, Jimmerson et al (1982) treated five patients with diazepam without any significant clinical effect. While the use of benzodiazepines as the sole medication has not been proven to be effective, Estazolam, a triazolo benzodiazepine has been reported to be useful in schizophrenic patients, particularly in chronic hallucinatory psychosis (Astrup & Vatten, 1984). Currently, long term, double blind and controlled studies are needed to establish benzodiazepines in the treatment of chronic schizophrenic states and it may not be wise to use these as the sole medication in treating schizophrenic patients.

IV. Negative Symptoms

The relatively large number of treatment resistant schizophrenic patients with negative symptoms have prompted efforts to augment the therapeutic effects of conventional neuroleptics. To this end, benzodiazepines have been tries as adjuncts in the treatment of schizophrenia (Wolkowitz et al, 1986; Csernansky et al, 1984 & 1988). Wolkowitz et al (1988) noted that in 12 hospitalized schizophrenic patients meeting the RDC criteria and initially treated with fluphenazine hydrochloride for at least two weeks, the addition of alprazolam resulted in significant improvement in psychosis, notably positive symptoms. A nonsignificant decrease in negative symptoms in patients who showed an overall favorable response was also observed.

Those patients who were more psychotic and more anxious during fluphenazine therapy than before showed the greatest improvement when alprazolam was added. However, the improvement observed during the second two weeks could be due to neuroleptics alone rather than the combination or due to the reduction of subclinical akathisia or other extrapyramidal symptoms. Csernansky et al (1984) in a double blind comparison of alprazolam, diazepam, and placebo concluded that alprazolam had no significant effect on negative symptoms of schizophrenia. The limitation of the study was the degree of compliance to therapy of the exclusive outpatient population in their sample. To date, there are only three studies with a small

number of patients. The benefit reported can be due to a diminution of anxiety, depression, extrapyramidal symptoms or mild disinhibition. A careful analysis of the above mentioned variables in patients receiving benzodiazepines, specifically alprazolam, is necessary to understand their clinical effects on negative symptoms.

V. Mania

Benzodiazepines have been administered to manic patients because of their relatively benign side effect profile associated with possible therapeutic efficacy. Lenox et al (1986) found that lorazepam administration to acute manic patients during the initial phases of lithium therapy produced sedation as well as control of excitability and psychomotor activity to a degree that patients were manageable within the first two days of treatment. Psychotic symptoms on the other hand, improved within five to ten days, during which time plasma lithium levels ranged between 0.4 and 1.0 mEq/L. Peak lorazepam dosage averaged about 20 mg a day and the most significant side effect was mild to moderate ataxia during the early phase of treatment.

Clonazepam has been reported to have a specific antimanic property. This effect may be due to the potentiation of 5HT synthesis (Browne, 1978; Jenner et al, 1975) in addition to its well established GABAergic effect. As synthesis of 5HT has been hypothesized to be low in manic patients (Murphy et al, 1974 & 1978), clonazepam administration may correct this deficiency (Schildkraut, 1974; Wise et al, 1972) with a resultant antimanic effect. Chouinard (1985, 1987a & 1987b) found that clonazepam was effective in the treatment of mania with a number of distinct advantages. He concluded from his study of 12 acutely manic patients that clonazepam was more effective and faster acting than lithium in the first few days of therapy and there was a decreased need for neuroleptics which in turn diminished extrapyramidal side effects. He, therefore, suggested that 1 mg of clonazepam was equivalent to 2.5 mg of haloperidol. Even complicated (Victor et al, 1984), atypical (Pande, 1988), rapid cycling (Freinhar & Alvarez, 1985) or mixed (Adler, 1986) manic states have been reported to respond to clonazepam.

The efficacy of clonazepam as a prophylactic agent has been investigated. In a retrospective study (Sachs et al, 1990) of 20 patients, 13 were receiving lithium and an adjunctive neuroleptic and six were receiving lithium and clonazepam combinations. In the clonazepam group, an average of 2.2 cycles during the year preceding clonazepam was decreased to 0.94 cycles during the year on clonazepam. As the assignment was not random, the results are inconclusive. On the other hand, Aronson et al (1989) noted their patients became worse when they were switched from neuroleptic to clonazepam. There was a recurrence of affective episodes in all five patients within 12 weeks. Hence, the specificity of clonazepam in acute mania appears promising, at least in the first week prior to the onset of action of lithium. Definitive conclusions can be derived following well designed, placebo controlled prospective studies. Sufficient evidence regarding its prophylactic action in bipolar disorders is not yet available.

VI. Tardive Dyskinesia

Tardive dyskinesia is associated with the long term administration of neuroleptics (Jeste et al, 1976; Jus et al, 1976; Simpson et al, 1981; De Veaugh-Geiss, 1982; Hanlon et al, 1969; Holden et al, 1968; Michaux et al, 1966; Kirkpatrick, 1989). As the pathophysiology of this condition is still elusive, treatment of this condition has not been rewarding (Ananth, 1982; Gerlach et al, 1974). Benzodiazepines have been reported to be beneficial in the treatment of this condition (Goodwin-Austin & Clark, 1971; Jus et al, 1974; O'Flanagan, 1975; Singh, 1976; Jeste & Wyatt, 1979 & 1982). GABAergic action of benzodiazepines is implicated in this therapeutic action (Johnson, 1976; Singh et al, 1980). Diazepam (Singh, 1976) and clonazepam (O'Flanagan, 1975; Thaker et al, 1990) have been found to be beneficial in neuroleptic induced and tricyclic induced (Deckret et al, 1977; Fann et al, 1976; Sedivec et al, 1970; Woogen et al, 1981) tardive dyskinesia, respectively. However, tricyclic induced tardive dyskinesia is infrequent and may constitute a different subgroup. In contrast, in one study (Rosenbaum & De la Fluente, 1979), diazepam aggravated tardive dyskinesia while in another, clonazepam was found to be no better than phenobarbital in reducing tardive dyskinesia (Bobruff et al, 1981). Therefore, the therapeutic effects of benzodiazepines in tardive dyskinesia, if any, may simply be due to a nonspecific sedative effect. With the available evidence, it appears that benzodiazepines may not have any specific effect on tardive dyskinesia.

VII. Akathisia

Akathisia, an extrapyramidal side effect (Barels et al, 1981; Braude et al, 1983; Delay & Deniker, 1968; Marsden & Jenner, 1980), may occur in twenty percent of neuroleptic treated patients. This condition is difficult to diagnose (Raskin, 1972; Donlon, 1973). because of its subtle manifestation and resemblance to other syndromes. The inner disquiet, anxiety, restlessness and the subjective need or desire to move exhibited by these patients can be mistaken for exacerbation of psychosis leading to the inadvertent increase in the dose of antipsychotics; consequently, the patients' condition may worsen. As a side effect, it is the most frequently cited reason for stopping neuroleptic medication by the patient (Van Putten, 1974). Discontinuation of the drug or a reduction of its dosage, administration of anticholinergics and antihistamines do not always provide prompt relief. Therefore, alternative treatments including the use of benzodiazepines are being explored. Diazepam was reported to be effective within three days in 13 akathisic patients (Donlon, 1973). Gagrat et al (1975) indicated that intravenous diazepam was as effective as anticholinergic drugs. Even dystonia associated with akathisia, previously unresponsive to standard treatment, improved with diazepam administration (Director & Munitz, 1982). Kutcher et al (1987) reported an open trial of clonazepam in 10 psychotic patients who

had incomplete relief of their akathisia with benztropine; when clonazepam was used as an adjunct, akathisia reduced significantly. Bartels et al (1987) indicated that complete remission occurred in nine and partial remission in the remaining five akathisic patients treated with lorazepam. On the other hand, Braude et al (1981) found that benzodiazepines did not produce any significant improvement.

Akathisia is proposed to be due to supersensitivity of the noradrenergic neurons in the supraspinal and spinal regions (Barels et al, 1981). GABAergic stimulation produced by benzodiazepines, counterbalancing the noradrenergic overactivity as well as their anxiolytic effects, may be beneficial. As they are safe, they are the drugs of choice in patients who are unable to take anticholinergic drugs.

DISADVANTAGES OF BENZODIAZEPINE THERAPY

High dose therapy in acutely ill patients can cause sedation, memory disorders, disinhibition, ataxia and respiratory depression. Behavioral disinhibition is particularly a serious problem, as this side effect may mimic an exacerbation of psychosis. This has been noted with clonazepam (Karson et al, 1982), alprazolam (Faucett et al, 1987; Feighner et al, 1984; Gardner & Cowdry, 1985; Rosenbaum et al, 1984) and other benzodiazepine preparations as well. Ataxia may lead to fall and fractures in elderly. Excessive use in the hope of achieving a quick response may produce benzodiazepine toxicity. Respiratory depression can occur when combined with other central nervous system depressants. With long term use, dependence, sexual side effects, mania (Bacher et al, 1986) as well as depression have been reported.

CONCLUSION

While neuroleptics remain the cornerstone of treatment of psychotic disorders, especially schizophrenia, their limitations have become apparent after many years of experience with their use. Basically, they do not help every patient and they have a lag period before improvement occurs. In addition to these variables, an acute psychotic process poses problems of a different dimension. The acute patient needs immediate relief to protect him from danger, which the neuroleptic cannot provide. An acutely ill patient may have problems of exhaustion, malnutrition, as well as other medical illnesses all of which predispose the patient to risks if neuroleptized. The psychopathology itself may be hyper-arousal related disruption, for which neuroleptic treatment may be improper.

The need for immediate improvement without major side effects has prompted the investigation of alternatives to neuroleptics in acute psychosis. Of all the alternatives that have been tried, benzodiazepines seem to be the safest and the most effective. They have been proven to effective in both catatonic stupor and excitement. However, their role in the treatment of chronic schizophrenic states as well as tardive dyskinesia has been disappointing. Even the limited use of benzodiazepines in such areas as hyper-arousal states fill a much needed vacuum, with the added advantage of proven safety. When the drug is given in acute states, the patient should be observed for four hours. If no response occurs, this medication should be discontinued. The rationale is that arousal related disruptions are immediately responsive to benzodiazepines and those that do not respond within this time period may not have arousal related psychopathology and hence, not accessible to benzodiazepine treatment. Further research in this area will be of interest to delineate the different psychopathologies.

While the traditional doses of benzodiazepines (when used as the sole agents) have not been noted to be consistently useful in the treatment of psychosis, there has been some suggestion in the literature that higher doses might be effective (Lingjaerde, 1991). The recent benzodiazepines, without significant sedation, may provide definitive answers regarding usefulness in higher doses in the treatment of schizophrenia.

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