Transient psychological syndrome following diazepam therapy for tetanus

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Summary

Two cases of transitory reversible pathopsychological changes associated with diazepam therapy in tetanus are described. The psychopathology developed owing to an abrupt discontinuance of diazepam or to a sudden reduction of its dosage. The reinstitution of diazepam in low doses and the administration of regulators of cerebral metabolism resulted in a progressive normalization of the psychological state.

It is suggested that the described syndrome was caused by two aetiological factors; the toxoinfectious factor giving rise to the primary cerebral dysfunction, and the prolonged action of high doses of diazepam with a sudden withdrawal, playing a role as precipitating factor.

EEG findings showed widespread abnormality which corresponded with the clinical diagnosis. Even the normalization in EEG correlated well with the disappearance of psychiatric symptomatology.

To avoid such undesirable psychic side effects, a gradual discontinuance of the drug is recommended.

Introduction

The importance of diazepam treatment in tetanus is widely recognized. Although occasional unexpected reactions to diazepam have been reported including a sudden cardiorespiratory depression (Rollason, 1968), prolonged unconsciousness (Kendall and Clarke, 1972) and even death resulting from withdrawal of diazepam (Relkin, 1966), the benefits of the drug outweigh the potential hazards.

Psychiatric disorders associated with long-term diazepam treatment for tetanus occur relatively often, but as yet they have been reported not to be alarming or deleterious (Kloetzel, 1963; Femi-Pearse, 1966). Haider and Tschakaloff (1970)

observed psychic changes following long-term diazepam therapy in 90% of their surviving tetanus patients. These included psychic retardation, indolence, motor restlessness, tremor, confusion, disorientation and paranoid pictures.

The authors observed temporary psychiatric changes after diazepam treatment in tetanus in two out of five surviving patients who had overcome moderate and severe tetanus.

Case 1

A 66-year-old man with moderate tetanus was admitted to the I.C.U. Artificial ventilation with muscle paralysis was not applied throughout. The diazepam course was started immediately on admission. At the outset it was given i.v., later orally, in daily doses averaging 86.5 mg. The total dose achieved was 950 mg. Pentobarbitone was administered for a few days at the beginning, the first daily dose of 600 mg being reduced to 200 mg/24 hr. The diazepam was completely withdrawn from 80 mg/24 hr on the eleventh day. As a result, mental disorders emerged: delirium with visual illusions and hallucinations, confusion, motor restlessness, disorientation of time, place and persons, as well as memory defects and a pronounced irritability and emotional instability. The episodic psychosis was ascribed to tetanus toxin aetiology. After an interval of a few days a four-day diazepam treatment was reinstituted in a low dosage of 10-20 mg/24 hr, as the patient became more agitated, hostile and resistive. In parallel a twelve day therapy course of meprobamate 1000 mg/24 hr with vitamins was started.

The EEG record at that time showed an irregular background activity and signs of deep-stem structures disturbance—intermittent delta rhythm bilaterally, predominantly in anterior regions (Fig. 1).

On stopping the low-dose diazepam course, only a partial disorientation of time, distractibility, wandering of attention and inability to concentrate

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Case reports

FIG. 1 Irregular background activity of lower amplitude, involving some dispersed theta waves. Bursts of delta waves bilaterally, predominantly in anterior regions.

FIG. 2. Generalized fast activity as a dominant feature. The bursts of delta waves disappeared.

persisted. The psychomotor restlessness disappeared. The normalization of mental state progressed further, and 2 weeks after the drug was stopped no mental abnormalities were present at all. The EEG correlated with the clinical improvement and at that time the EEG tracing was at the borderline of normal (Fig. 2).

Case 2

A 60-year-old man suffering from severe tetanus was admitted to the I.C.U. Diazepam therapy was commenced on admission and continued for 34 days,

the total dose amounting to 4570 mg. Except for the first i.v. dose it was given orally in an average daily dose of 134 mg. In addition, during the first 3 days pentobarbitone 300 mg/24 hr was given orally. During these days, while the patient breathed spontaneously, psychic retardation was revealed. Then the patient had to be tracheostomized, paralysed with pancuronium and ventilated artificially for 18 days in total. On terminating the period of muscle paralysis he was able to obey verbal commands. On the 11th day the dosage was suddenly reduced from 120 mg/24 hr to 30 mg/24 hr. The change resulted in a

psychological and behavioural syndrome, with negativism and mutism as dominant features. The daily dosage of 30 mg diazepam remained unchanged. Therapy with pyritinol was instituted on the seventeenth day and supported with vitamins. On the twentieth day, the dose of diazepam was reduced to 20 mg/24 hr and afterwards to 10 mg/24 hr until the thirty-fourth day.

On the twenty-fifth day the EEG record revealed a generalized slow activity as well as intermittent delta rhythm in both frontotemporal regions. On the thirty-eighth day EEG was even more improved, attaining the borderline of a normal pattern, and corresponding well with the clinical improvement.

Discussion

In our patients an abrupt withdrawal or a sudden reduction of diazepam dosage was initiated in order to obtain clear information on the actual clinical state (muscular rigidity, tendency to spasms, level of consciousness). Thus, in Case 1 the drug was suddenly withdrawn from 80 mg/24 hr and in Case 2 the dosage was abruptly reduced from 120 mg/24 hr to 30 mg/24 hr, on the eleventh day of diazepam treatment in each instance. The rapid change in dosage was immediately followed by the psychological syndrome described.

The possible relationship between the dosage of diazepam and/or the time duration of its administration on the one hand and the degree of mental disorder on the other hand, has been considered unlikely (Haider and Tschakaloff, 1970) but others found that the impairment of consciousness and EEG alterations are linked with the intensity and the duration of diazepam therapy (Kurtz *et al.*, 1967). Milne (1965) states that disturbances in homeostasis of body fluids (acidosis) can significantly influence the efficacy and the toxicity of diazepam. In our cases, however, impairments of that kind are out of the question as any electrolyte and acid-base shifts were corrected immediately.

The tetanus toxin, fixed as it is to nervous tissue (cellular lipid components, ganglioside and cerebroside), is known to play an important role in damaging the central nervous tissues (Frank, 1956). In particular, ganglioside is accumulated at sites of action of tetanus toxin, i.e. at the synaptic membranes. The high affinity of the drug to lipid tissues (Van der Kleijn, 1969) seems to conform with the Kendall and Clarke case of delayed regaining of consciousness in an obese patient treated with large doses of diazepam for tetanus; this was accounted for by the cumulative body stores (Kendall and Clarke, 1972).

Mental disorders occur rather with severe and moderate tetanus, than with milder degrees. However, Haider and Tschakaloff (1970), classifying tetanus patients in five degrees, observed confusion

and paranoid-hallucinatory picture even with second degree tetanus. In our cases, more severe degrees and higher dosage of diazepam have led to the development of a psychological syndrome, while mild cases remained free of any psychiatric alterations.

The toxoinfectious aetiology has been supported by Kloetzel (1963) who reported on disorientation and hallucinations in moderate and severe tetanus cases treated without diazepam. Even in our Case 2 (severe tetanus), the tetanus toxipathic component was evidenced by initial slowing of psychological process and the later mental normalization during follow-up made it unlikely that altered premorbid personality had played a role.

Barbiturates were supposed to play an adjuvant role. Presumably, diazepam may potentiate the sedative and possibly even the side effects of barbiturates (Haider and Tschakaloff, 1970). Nevertheless, Kurtz *et al.* (1967) found no influence of barbiturates on EEG pattern and ascribed all changes to diazepam. Femi-Pearse (1966), treating patients with diazepam and/or barbiturates, failed to discriminate between these two dosages in respect of patients who developed mental changes. In our cases, it is unlikely that the phenobarbitone, given only at the very outset, contributed significantly to the manifestation of a psychological syndrome at the end of the second week of diazepam therapy.

The age of patients seems not to be of decisive importance but, possible hypoxic cerebral lesions arising during the treatment, as well as potential premorbid changes of personality should also be taken into consideration when assessing the dynamics of psychopathology.

There was a definite relationship between the degree of behavioural changes and EEG abnormalities. Kurtz *et al.* (1967) found changes ranging from slowing of background activity to periodic silences and including delta-activity, either generalized, or with frontal predominance, unstable, often associated with fast rhythms and with unreactive 10–12 c/sec activity. In the present cases, EEG records correlated well with the clinical course and the abnormal EEG pattern improved in parallel with the normalization of mental disorders. The EEG findings are not specific, but are similar to those described with alcohol and drug withdrawal syndromes (Penin, 1971).

Thus, 'withdrawal symptoms' following a long-term diazepam treatment with high doses in tetanus in fact signify a psychological syndrome of complex aetiology, the abrupt withdrawal of the drug being only a precipitating factor leading to cerebral decompensation (Haider and Tschakaloff, 1970).

Psychiatric symptoms in our patients occurring on withdrawal have been suppressed efficiently by a short-term reinstitution of diazepam in low doses

(10–30 mg/24 hr). The disappearance of mental disorder was accelerated by regulators of cerebral metabolism and vitamins.

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