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Case Report

Flumazenil Reversal of Benzodiazepine-Induced Sedation for a Patient with Severe Pre-ECT Anxiety

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Summary: We describe various measures to reduce severe anxiety that interfered with much-needed maintenance electroconvulsive therapy in a 32-year-old man. Treatment with ketamine met with moderate success, and then large doses of lorazepam and midazalam were used. The potential anticonvulsant effect of these drugs was successfully reversed by the administration of intravenous flumazenil just prior to the treatments.

Many patients who might otherwise benefit from electroconvulsive therapy (ECT) are not able to avail themselves of this treatment due to the very severe anxiety that they experience just prior to the treatment (Gallinek, 1956; Hastings, 1961; Freeman and Kendell, 1980, 1986; Hughes et al., 1981; Freeman and Cheshire, 1986). Because of this, it is not uncommon for patients who have agreed to have the treatment, and who have signed informed consent, to be so overwhelmed by anxiety that they leave without being treated. Fox (1993) reported several cases in which patients who were benefiting from treatment developed a pathological fear of further treatment. He noted that this fear may be particularly problematic for patients receiving long or repeated courses of ECT.

Pre-ECT anxiety can be reduced to a manageable level by the administration of a benzodiazepine, but a dose that is adequate to sufficiently lower the patient's anxiety may also manifest an anticonvulsant effect that interferes with the development of an adequate seizure.

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We were confronted by this problem in the treatment of the following case. After trying to induce sedation prior to treatment with intramuscular and intravenous ketamine, we decided to try to use an intravenous benzodiazepine followed by intravenous flumazenil, a short-acting benzodiazepine antagonist, to reverse the expected anticonvulsant effect of the benzodiazepine.

CASE REPORT

Mr. A, a 32-year-old man with a *DSM-IIIR* diagnosis of schizophrenia, chronic undifferentiated type, with acute exacerbation, was readmitted to the hospital after decompensating while living in a residence for psychiatric patients. At the time of relapse, he was taking clozapine (300 mg b.i.d.) and was scheduled for weekly maintenance ECT. He had been compliant with his medication, but had missed two scheduled ECTs because he became too anxious to proceed with the treatment after arriving at the ECT treatment suite. Two prior decompensations had occurred following his inability to proceed with the prescribed course of maintenance ECT.

As in prior admissions, Mr. A was guarded and suspicious and admitted to auditory hallucinations and thought broadcasting. He had a blunted affect and poverty of speech. On the unit, he was apathetic and uninvolved. Clozapine (300 mg b.i.d.) was continued and further ECT prescribed. Mr. A said that he was too fearful of ECT to agree to restart it. Fluoxetine was added, and the dose was gradually increased to 40 mg b.i.d. This resulted in some improvement in his mood, but he remained very psychotic and withdrawn. We asked him if he would agree to resume ECT if he were sedated in his room prior to going to the ECT area. Although he was very fearful, with encouragement from the staff and his parents, he agreed to try.

We decided to use ketamine for sedation and anxiolysis in the patient's room just prior to ECT. As his unit was in the same building, just across the hall from the ECT area, we planned to wheel him in a chair into the ECT area as soon as he was adequately sedated.

Treatment was scheduled on a three times per week basis. For the first treatment, Mr. A was given ketamine (100 mg i.m.) in his room. This made him drowsy, but he was still awake, with his anxiety reduced just enough that he would accept the treatment. He was given methohexital (50 mg) and succinylcholine (50 mg) prior to treatment and had a well-modified 33-s grand mal (GM) motor seizure. This treatment (and all subsequent treatments) was given with bilateral electrode placement using the MECTA SR-1 brief pulse ECT device at maximum settings. The next treatment was done without any change in the technique.

Treatment no. 3 was given without sedation in the patient's room prior to treatment. He had a well-modified 29-s GM motor seizure, but subsequently complained of increased anxiety about continuing treatment. For the next two ECT, intravenous ketamine (120 mg) was given prior to treatment. This dose was determined by slowly administering the drug up to the point that the patient became very drowsy. The motor seizures at these two treatments were 20 and 34 s.

Mr. A became more ambivalent about continuing treatment. As he had improved considerably, it was decided to hold further ECT until we could determine if he could maintain his gains on fluoxetine and clozapine alone.

When he again showed signs of deterioration, it was decided to restart ECT using a benzodiazepine to control his pretreatment anxiety followed by flumazenil. Flumazenil is a newly marketed short-acting benzodiazepine antagonist with agonist features at high doses (Amrein and Hetzel, 1990). We anticipated that flumazenil would reverse the adverse effects on seizure threshold and/or seizure duration caused by the benzodiazepine.

Prior to the next treatment, the patient was given intravenous lorazepam. A 5-mg dose was slowly administered without effect. This was followed by additional 2-mg doses until the patient was sedated; 17 mg was required. He was then wheeled into the ECT area, where he was given 0.2 mg i.v. of flumazenil, divided into 0.1-mg doses 90 s apart. With this dose, he awakened and appeared anxious. Methohexital (50 mg) was given immediately, followed by succinylcholine (50 mg). After 60 s, a stimulus was given, resulting in a 29-s GM motor seizure. Recovery was uneventful. Mr. A was very sleepy for several hours following the treatment. Later he reported that he did not feel any anxiety during the treatment procedure, and for the first time said he did not dread the next treatment. As lorazepam has a longer half-life and does not have as rapid an onset of action as midazolam, we chose to use midazolam for subsequent treatments. An intravenous line was started in his room and midazolam was slowly administered in 2-mg doses until he was sedated; 20 mg was required. In the ECT area, the same procedures were followed and the patient exhibited a well-modified 21-s GM motor seizure with an uneventful recovery. The patient slept on the unit for ~2 h after the treatment. He again reported no anxiety over continuing ECT. Treatment no. 8 was done using the same procedure and he had a well-modified 30-s GM motor seizure.

Treatment no. 9 was given without using midazolam or flumazenil. The patient was pretreated with 500 mg i.v. of caffeine sodium benzoate followed by methohexital (80 mg) and succinylcholine (60 mg). He had a well-modified 65-s GM motor seizure and an uneventful recovery.

Treatment nos. 10–13 were given using midazolam followed by flumazenil. The doses of midazolam required to induce sedation declined with subsequent treatments, and by treatment no. 13, 7 mg was required. The flumazenil doses varied from 0.2 to 0.5 mg and motor seizure times ranged from 25 to 33 s, with the exception of treatment no. 10. For this treatment the patient was given 10 mg midazolam and 0.5 mg flumazenil and he had a 14-s motor seizure.

During this course Mr. A became much less psychotic and his clinical state improved to the point that his return to the community residence was planned. For his 14th and final inpatient treatment, we decided to give him oral lorazepam (4 mg) 45 min prior to treatment. With this dose, he was awake but calm. He was given flumazenil (0.2 mg) and had a well-modified 27-s GM motor seizure. Recovery was uneventful.

The patient has been discharged from the inpatient service, has continued the same medications, and has returned for weekly maintenance ECT for the last 2

months. Because of the added anxiety associated with the trip to the hospital and potential delays, the oral dose of lorazepam was increased to 6 mg. This dose, followed by 0.2 mg flumazenil, permitted motor seizures of ~30 s in duration without the anxiety and severe panic that had made continuing maintenance impossible in the past.

DISCUSSION

To our knowledge, this is the first report of the use of flumazenil to attempt to reverse the anticonvulsant effect of benzodiazepines in ECT. The many uncontrolled variables in this case (e.g., different types and doses of benzodiazepines, anesthetic agents, etc.) preclude definite conclusions about the efficacy and safety of this novel use of a benzodiazepine antagonist.

However, this experience suggests that flumazenil has the potential to be used to reverse pre-ECT benzodiazepine anticonvulsant effect. It will be crucial to determine in controlled studies whether this use of flumazenil is adequately safe (the main concern being the possibility of inducing a spontaneous seizure) and whether the benzodiazepine-reversing effect is clinically relevant. Further investigation to determine the potential benefits from the use of flumazenil in the treatment of anxious ECT patients is encouraged.

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