

Etizolam: Use and safety profile in children and adolescent

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Abstract: *Introduction:* Etizolam is a benzodiazepine that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties. It is used in adults with anxiety, depressive, somatization symptoms, generalized anxiety disorder, and panic disorder. *Aims:* The aim of the study was to chart review the use and safety of Etizolam in children and adolescents. *Settings and Design:* This study was a retrospective chart review. *Methods:* Patients who are on Etizolam and had at least 2 weeks follow-up were included for the study. The indications, effectiveness, and adverse effects were noted. *Statistical analysis used:* Data was analysed using Epi Info 7. Descriptive statistics were used. *Results:* 57 (38.51%) patients had been treated with Etizolam. The mean age of children was 13.59 years (7-18 years). Amongst the patients prescribed Etizolam, 37 (64.91%) had a data of follow-up of at least 2 weeks. 25 (67.57%) patients had moderate to complete improvement, 5 (13.51%) had mild improvement and 7 (18.92%) had no improvement. The adverse events were noted only in 3 (8.11%) patients. *Conclusions:* Etizolam is effective in treating common psychiatric symptoms and disorders in children and adolescents and is well tolerated with minimal adverse effects.

Keywords: Benzodiazepine, Etizolam, Children, Adolescents

Introduction

Etizolam is a theinodiazepine, structurally different but pharmacologically similar to benzodiazepines with gamma-amino-butyric acid type A receptor agonism [1]. It was developed in Japan and, at present, it is registered for use as a medicine in Japan, Italy, and India [2]. Etizolam is a benzodiazepine that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties. Alpha-hydroxyetizolam is an active metabolite of Etizolam that is eliminated more slowly with an half-life of 8 hours [3]. Etizolam differs from other benzodiazepines in that the molecules possess a thiophene ring instead of a benzene ring. In an animal study Etizolam had a reduced liability to induce tolerance and dependence compared with classical benzodiazepines [4].

Etizolam is used in adults with generalized anxiety disorder [5], panic disorder [6] and is also helpful in reducing overall anxiety, depressive and somatization symptoms [7]. The most frequent adverse effects in adults are drowsiness and muscle weakness; and it rarely causes

paradoxical excitation. Rebound insomnia is noted with Etizolam in an animal study [8] and no reports on human beings. It may not cause cognitive disturbances [9]. Evidence bearing on its safety in children and adolescents is not available. However, there is a single case report where child accidentally took a single dose of Etizolam, approximately the same as a therapeutic dose for adults, and who showed paradoxical excitation and muscle weakness [10]. Although there are no studies of use and safety of Etizolam in children and adolescents, but off-label use of Etizolam is common in India because of its low side-effect profile.

Material and Methods

This study was a retrospective chart review. It was carried out at the Department of psychiatry in a tertiary care hospital. All age groups of population are attended to at this department for evaluation and management of behavioral or psychiatric illnesses. The children and adolescents who were prescribed benzodiazepines during 2011 to 2013 were

screened for in the charts reviewed. Amongst this the charts of patients who were prescribed Etizolam were assessed. All the patients enrolled were seen by qualified psychiatrists. Patients who had at least 2 weeks of continual follow-up were finally included for the study. The indications, effectiveness and adverse effects were noted using a specially designed proforma. The effectiveness was scored as ‘not effective, mild improvement, moderate improvement, complete improvement and worsening’. These were derived based on psychiatrists’ notes in the case sheets/charts. The statistical analyses were done by using Epi-info 7 software.

Results

A total of 685 children and adolescents visited Department of Psychiatry during the year 2011 to 2013. Among them 148 (21.61%) patients received benzodiazepine (BZD) drugs. Within the BZD group 57 (38.51%) patients received Etizolam drug. None of the children were on combination of BZD drugs. The mean age of children was 13.59 years (range 7-18 years). There were 27 boys and 30 girls. Mean Dose of Etizolam used was 0.67±0.25mg (0.25 to 1 mg)/day. Among the patients prescribed Etizolam 37 (64.91%) had a follow-up data of at least 2 weeks. These patients were included to note the indications, possible efficacy and adverse events. Among boys 20 (74.07 %) had follow-up while among girls 17 (56.67%). Of the 57 patients, 26 had adjunct medications while 31 received Etizolam alone. However, among 37 who followed up 21 (56.76 %) were on adjuncts where as among 20 who did not follow-up only 5 (25%) were on adjunct medications.

Table-1: List of indications for which Etizolam was used (N=57)

Sl. No.	Diagnosis	n (%)
1	Dissociative Disorder	24 (42.11%)
2	Anxiety Disorder	18 (31.58%)
3	Depressive Disorder	12 (21.05%)
4	Adjustment Disorder	05 (08.77%)
5	Sleep Disorder	02 (03.51%)
6	Behavioral Problems	03 (05.26%)
7	Psychosis	01 (01.75%)
8	Medical Condition	08 (14.04%)

Table No. 1 describes list of indications for which Etizolam was used. Some patients did have dual diagnoses like Depressive disorder and Dissociative disorder which were counted separately. Behavioural problems group involved children with MR or ADHD with behavioural problems. ‘Medical condition’ group involved epilepsy, headache, and premenstrual syndrome. There was no significant difference in follow up rates among all disorders. Table No. 2 describes effectiveness of Etizolam during 2 weeks follow-up. 25 (67.57%) patients had moderate to complete improvement, 5 (13.51%) had mild improvement and 7 (18.92%) had no improvement. The adverse events were noted only in 3 (8.11%) patients. Two patients had sedation and one patient had gastro-intestinal side effects.

Table No. 2: Effectiveness of Etizolam during 2 weeks follow-up (N=37)

Sl.No	Effectiveness	n (%)
1	Worsening	00(00.00)
2	No Improvement	07 (18.92%)
3	Mild Improvement	05 (13.51%)
4	Moderate Improvement	18 (48.65%)
5	Near complete Improvement	07 (18.92%)

Discussion

The current study is an initial observation of Etizolam in children and adolescents. Etizolam was developed in 1978 [1]. The literature about its use and efficacy profile is minimal even in adults, so it is not included in most of the guidelines for treatment of psychiatric symptoms and disorders. The available literature points to be helpful in reducing anxiety, depressive, and somatization symptoms. The animal studies have shown that Etizolam has a reduced liability to induce tolerance and dependence as against classical benzodiazepines [4].

However, there are a couple of reports of Etizolam dependence from India [11], Japan [12] and USA [13]. It is difficult to comment on Etizolam dependence in the current study because of the short follow-up period of only

two weeks. Death by Etizolam is rare. Only two cases have been reported in which the concentration of Etizolam in post-mortem blood indicated that Etizolam may have contributed to death or was the likely cause of death [14].

Etizolam acts on benzodiazepine receptor like other BZD's, it may also has action over 5-HT and NE systems which may explain additional benefits of reducing depressive and somatic symptoms [3]. It is mainly metabolized in liver and its metabolism is unaffected even in severe hepatic impairment. There is no literature on use of Etizolam in children and adolescents except one case report of adverse event in a child with accidental consumption of Etizolam [10].

Etizolam was first launched in Japan in 1983 and later in Europe. In India it was launched in 2007, and since then it is been widely used in treatment of patients. Considering its efficacy and safety profile in adults, psychiatrists at our tertiary hospital used it as off-label medicine in children and adolescents for treating psychiatric symptoms. The main reason for prescribing of Etizolam in the study population was for its ability to cause less day time sedation, as per the literature and clinical observation; most children were school-going and classical BZDs are likely to cause day time sedation. Most of the study population was also on concurrent psychotropic medicines like antidepressants. Around 68% of the patients had shown moderate to near complete

improvement in 2 weeks time. Reasons for rapid improvement could be because of Etizolam itself, as concurrent medications like antidepressants have a longer duration to effect changes.. Similar to other BZDs which usually has rapid onset of action could be a reason. Majority of the sample consisted of patients with Dissociative disorder, psycho-education and psychological interventions which are instituted to all the patients attending our hospital may also have helped these patients for rapid improvement in their symptoms. Only 3 (8.11%) patients had side effects with Etizolam. There was a drop out of 20 (35%) patients in the follow-up; some of them may also have had side effects.

Limitations: It is a retrospective observational study. Sample size was small and many dropouts were noted. All the patients treated with Etizolam were included irrespective of diagnosis. No formal scales used assess efficacy, hence it would be difficult to measure and generalize findings related to efficacy.

Conclusions

Etizolam is effective in treating common psychiatric symptoms in children and adolescents and is well tolerated with minimal adverse effects.

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