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End of the barbexaclone era: an experience of treatment withdrawal

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ABSTRACT – Barbexaclone is a salt compound of phenobarbital and propylhexedrine (a drug with indirect sympathomimetic properties). Due to the presence of the psychostimulating agent, propylhexedrine, this drug has less of a sedative effect and is well tolerated, compared to phenobarbital. Barbexaclone was widely used in Turkey until 2009 when its production ended, however, it gave rise to an epidemic for which we were not prepared. Since then, no standardised management protocol has been developed and each patient has been evaluated individually, thereby creating tailor-made solutions based on the extent of each patient's supply of remaining drug (from a few tablets to a stock which might last for six months). The rate of seizure freedom was 37.7% under barbexaclone treatment and dropped to 32.2% in the follow-up period after discontinuation of the drug. In the majority of cases, a new antiepileptic drug was added and this was commonly levetiracetam, a more expensive drug. In this article, we share our experiences of a general problem: the withdrawal of an antiepileptic drug from the market. Although there was prior notification regarding barbexaclone withdrawal, it was not possible to contact all patients since such a database is not available in Turkey. Although no conclusions regarding the efficacy of the drug or comparison of efficacy with other antiepileptic drugs is provided, it is nonetheless noteworthy to share these experiences since some patients had lost seizure control for reasons that could not be explained.

Key words: barbexaclone, epilepsy, antiepileptic drug, phenobarbital, propylhexedrine

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Barbexaclone is a salt compound of phenobarbital and propylhexedrine (a drug with indirect sympathomimetic properties) (Iven and Feldbusch, 1983). The drug was first released in 1983 and was reported to be well tolerated and as effective as phenobarbital (Visintini *et al*., 1981; Borromei *et al*., 1987). A dosage of 100 mg barbexaclone is considered to be equivalent to 60 mg of phenobarbital (Perucca *et al*., 1986). The purpose of bonding the levoisomer form of propylhexedrine to phenobarbital was to eliminate the sedative side effect (Visintini *et al*., 1981). Barbexaclone was previously a widely used anti-convulsive drug in Turkey.

Case studies

When barbexaclone production stopped in 2009, patients who

were treated with barbexaclone for many years rushed to the epilepsy outpatient clinics. It was an epidemic for which we were not prepared. No standardised management protocol was developed and each patient was evaluated individually, thereby creating tailor-made solutions; discontinuation of the drug was managed according to the extent of supply of remaining drug (from a few tablets to a stock which might last for six months) of each patient.

We retrospectively analysed this group of patients. We recorded demographic features, seizure type, imaging findings if present, EEG features, and seizure frequency during and after barbexaclone treatment. The preferred method of management (starting treatment with a new antiepileptic drug, cessation of all antiepileptic drugs, increasing the dose of current antiepileptics, *etc*.) and seizure frequency in the following year was documented. Keeping a seizure diary was not common among our patients and only the approximate number of seizures was available, therefore, we grouped patients according to seizure frequency as follows: a) seizure on a daily basis; b) ≥1 seizure per month; c) ≤1 seizure per month; and d) seizure free. For descriptive statistical calculations such as mean values, standard deviation, percentages and frequency distribution, SPSS Statistics version 15.0 software (2006, Chicago, USA) was used. For the reasons discussed above, these data have a low scientific value, thus it is our intention to share these observations and experience without making any further implications.

In total, 64 patients were investigated, 3 of whom were still under barbexaclone treatment. Thirty-four of the patients (53.1%) were female. The mean age of the patients was 40.77±12.23 years and the mean age at seizure onset was 13.7±11.1 years. Most of the patients had focal epilepsy (82.8%; *n*=53). Mean disease duration was 27.32±10.61 years. Mean duration under barbexaclone was 17.01±8.88 years. The final dose of barbexaclone was found to be 164.34±58.17 mg. Only 4.6% of the patients received monotherapy, while 54.6% received two, 35.9% received three, and 4.6% received four drugs. Twenty-three (37.7%) patients were seizure-free with barbexaclone for 4.9 years (2-10). The follow-up period after discontinuation of the drug was 21.28 (2-53) months. The distribution of patients according to approximate seizure frequencies before and after barbexaclone is shown in *table 1*.

After discontinuation of barbexaclone, the most common treatment approach was to replace barbexaclone with a new drug (70.5%) and the most frequently preferred drug was levetiracetam (*n*=28).

According to ILAE treatment guidelines (2006), there was a lack of sufficient data regarding the efficacy of barbexaclone as monotheraphy either for partial or generalised epilepsy for all age groups (Glauser *et al*., 2006). Since it was considered to be effective and well tolerated, barbexaclone was a widely used antiepileptic drug in Turkey. It was also cheap. Before its production ended, the cost of a 50-tablet pack was reported to be 7.85 Turkish Liras (Ommaty, 2009). Another advantage of barbexaclone was easy prescription, compared to phenobarbital which is a controlled substance and available in Turkey only on special prescription.

Table 1. Comparison of approximate seizure frequencies with and after barbexaclone treatment.

Seizure frequency	With barbexaclone (%)	After barbexaclone (%)
Daily	4.9	15.3
≥1/month	26.2	40.7*
≤1/month	31.1	11.9
Seizure-free	37.7	32.2

*p=0.15

The rate of seizure freedom was 37.7% under barbexaclone treatment and dropped to 32.2% in the follow-up period after discontinuation of the drug. In the majority of cases, a new antiepileptic drug was added and this was commonly levetiracetam. At the same time, in 2009, the price of 500 mg, a 50-tablet pack of levetiracetam, was 109.41 Turkish Liras (nearly 14 times more expensive than barbexaclone).

Discussion

Regarding the active substance of barbexaclone, a recent review on the present and future use of phenobarbital in epilepsy came to our attention. In this review, it was pointed out that over the last decade, no major efficacy study had been conducted with phenobarbital and the authors concluded that phenobarbital was found to be the most cost-effective pharmacological treatment for epilepsy (Brodie and Kwan, 2012). This result would appear to be important, particularly for low and middle-income countries. If we extrapolate this discussion to barbexaclone, which may exhibit a better profile (less of a sedative side effect and probably a similar efficacy compared to phenobarbital), it may have been more advantageous to use barbexaclone than phenobarbital.

It is our intention to share these experiences in the light of such a general problem; withdrawal of an antiepileptic drug from the market. Although there was prior notification of withdrawal made by the pharmaceutical company providing barbexaclone, it was not possible to contact all patients since such a database is not available in Turkey. Although no conclusions regarding the efficacy of the drug or comparison of

efficacy with other antiepileptic drugs is provided, it is nonetheless noteworthy to share these experiences since some patients had lost seizure control for reasons that could not be explained. Another important point is that the most frequent approach was to replace barbexaclone with levetiracetam, which is 14 times more expensive. This issue needs to be discussed by health authorities since it raises the issue of increasing health expenses.

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