

Commentary

Clobazam: The phoenix drug (from the very old to the brand new)

In Greek mythology, a phoenix is a long-lived bird that is cyclically regenerated or reborn. Clobazam (CLB) a 1,5-benzodiazepine, has been used as an anticonvulsant for children and adults for almost four decades and is available in over 100 countries¹. It has been considered a safe and efficacious drug for focal and generalized epilepsy in combination as well in monotherapy. Clobazam acts as a gamma-aminobutyric acid alpha ($GABA_A$) receptor agonist. It is primarily metabolized in the liver by cytochrome P450 (CYP)3A4, producing an active metabolite, N-desmethyloclobazam, which has a long half-life of 30-65 h and is metabolized by CYP2C19².

Joshi and colleagues³ in this issue studied a group of 417 epilepsy patients (3-66 yr old, mean age 22 yr) treated with CLB in addition to other antiepileptic drugs (AEDs). They utilized several clinical parameters, such as retention rate over a long-range and seizure-free period, and found 151 seizure-free patients (36.2%) after 12 months. The average number of adverse effects was 3.3 per patient. The most frequent adverse events were somnolence (39.1%), fatigue or tiredness (34.1%), irritability (33.4%), poor memory (36.2%), headache (30.2%) and loss of appetite (17.3%). The majority of these adverse events were self-limiting and resolved after adjustment of the CLB dosage. Clobazam treatment was discontinued in only a few patients. They concluded that CLB is a broad-spectrum antiepileptic drug for both generalized and focal seizures. They also found, as expected, that in first and second add-on therapy with CLB, freedom from seizures was more likely to be achieved. They also suggested CLB as an efficacious, relatively well tolerated and inexpensive medication. The strength of this study was the number of patients and long follow up period.

On October 21, 2011, the US Food and Drug Administration (FDA) approved CLB as an adjunctive

treatment for seizures associated with Lennox-Gastaut syndrome in adults and children aged two years and older¹. On December 3, 2013, the FDA issued a drug safety communication warning of “rare but serious” skin reactions from the antiseizure drug CLB⁴. These included Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The FDA identified 20 cases of SJS and TEN associated with CLB⁴. Approximately 31,000 patients have received CLB since its approval in 2011 in the USA, which suggests a rate of SJS or TEN of at least 20 cases per 31,000 users, or six cases per 10,000 users. Because not all cases may have been reported to the FDA, this figure is probably underestimated. Two deaths occurred, one of which was “possibly” related to CLB. One patient developed blindness, and all required hospitalization. Although nearly all patients (19 of 20) had taken other drugs associated with SJS or TEN, such as other AEDs (n = 18), antibiotics (n = 3), or sulphasalazine (n = 2), there was a strong temporal relationship (within two months) for 14 of the 17 cases that strongly implicated CLB. One patient developed TEN with CLB monotherapy. Many patients improved after CLB was stopped⁵.

According to this warning, we should be cautious and vigilant with the use of CLB, particularly in the first eight weeks or when stopping or starting therapy. Unless clearly shown due to another cause, the development of a rash should trigger immediate discontinuation of CLB, albeit with alternate provisions for seizure control and possible withdrawal symptoms. The fact that CLB has been in use for so many years without recognition of these dramatic skin rashes defies ready explanation. Does the current formulation of CLB contain another ingredient that induces rash? Or could it be that the FDA’s assiduous collection of adverse events through its Medwatch program and vigilant analysis surpasses the efficacy of all other

postmarketing reporting systems worldwide?⁵. Many epileptologists (opinion leaders) in Brazil, as well in many other parts of the world, have never seen a case of idiosyncratic reaction to CLB. In Brazil CLB is mainly used as add-on therapy for focal and generalized seizures but also for catamenial epilepsy, for risky situations such as sleep deprivation seizures, for avoiding prolonged seizures or status epilepticus and, ironically, for abrupt discontinuation of any AED after a skin or idiosyncratic reaction. It is known that there is a higher probability of a secondary idiopathic reaction after a rash-anticonvulsant hypersensitivity syndrome (AHS)-with carbamazepine, phenytoin or phenobarbital after the prior use of any of these. An important issue regarding AHS is the cross-sensitivity among aromatic AEDs, which has been reported to be 40-80 per cent. This means that patients with a history of AHS should immediately avoid further use of any aromatic AED⁶. Idiopathic reactions occur around 10 per cent in patients using carbamazepine, phenytoin and phenobarbital. Even so, we have never diagnosed a simple rash after CLB use in Brazil⁷.

Are our pharmacovigilance systems so ineffective that these are not recognizing SJS or TEN? One pertinent question is: what about all the components of the American preparation versus the cheaper version of CLB, widely used all over the world? Are these the same? Are the vehicles the same? What about the combination of drugs used in polytherapy for Lennox-Gastaut in USA? Were most patients using tablets or oral suspension? In Brazil, only tablets are used. We would like to emphasize the potential synergistic action between carbamazepine and CLB. The same observation has been reported in the study by Joshi *et al*³ when they pointed out that most seizure-free patients were taking the combination of both AEDs. This was also the most effective regimen in a specific epilepsy syndrome –mesial temporal lobe epilepsy⁷. On the other hand, one side effect that has to be considered in the treatment with a combination of carbamazepine and CLB is weight gain⁸.

In general, higher doses of CLB are usually prescribed than those used in this study by Joshi and colleagues³. However, a response at a lower dose is probably a predictor of a good response to CLB, as suggested by the authors³. According to Joshi's study, CLB is an important AED available in our armamentarium for the medical treatment of epilepsies.

The phoenix is generally believed to be a colourful and vibrant bird. So is CLB.

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