Requiem for tetrazepam

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In recent months, as healthcare professionals, we have been witness to the emergence of a rather surprising subject of debate, namely the possible withdrawal of pharmaceutical products that contain tetrazepam as one of their active ingredients (Clinoxan ®, Epsipam ®, Myolastan ®, Musaril ®, Relaxam ® and Spasmorelax ®). The reason for this withdrawal is the negative benefit/risk balance resulting from the possible appearance of adverse skin reactions, which in some cases may be severe [1]. The Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh) of the European Medicines Agency [1] recommended suspending the marketing authorisations of those preparations across all member countries of the European Community. Finally, on 7th June the Spanish Agency for Medicines and Healthcare Products published a safety note in which it stated that marketing of Myolastan ® would be suspended as of 1st July 2013.

Tetrazepam was first introduced onto the Spanish market in 1978 and in other countries, such as France, in 1967. The reader will recall that tetrazepam is included within the group of muscle-relaxant drugs (ATC code: M03BX 07). Its mechanism of action is associated with presynaptic inhibition of the mono- and poly-synaptic reflex arc, and with supraspinal inhibiting activity. It also acts as an anxiolytic and is a hypnotic, anticonvulsive and amnesic sedative, as is to be expected of a benzodiazepine [2].

We conducted a thorough electronic search for the term 'tetrazepam' in the different databases available from our healthcare centres and universities, including pharmaceutical product datasheets and the PubMed, Cochrane, DARE, EMBASE or IME databases.

As can be seen in the figure, a total of 35 studies referring to some kind of side effects produced by tetrazepam were found. Surprisingly, we have not found any significant increase in the number of scientific publications that could be taken as a turning point that underpins this recommendation. Moreover, a systematic review of the literature did not reveal any clinical trials that were conducted to evaluate the safety and tolerability of tetrazepam.

The total number of cases reported in the 30 publications that were analysed (five were excluded from the study because no abstract or information was available in the databases) amounted to 72 subjects. This fact contrasts with the data provided by the French National Pharmacovigilance System, which refer to a total of 1616 cases, of which 648 have been classified as severe (including 11 deaths) [3], and with the data from the Spanish Pharmacovigilance System, which has recorded 545 cases, 82 of which are severe [4].

We have analysed the type of side effects presented in the cases that have been published and one of the most notable features is the appearance of skin conditions due to allergic reactions. These data are not new, since its product datasheet describes conditions affecting the skin and subcutaneous tissue that may be both mild (erythematous and pruriginous maculopapular skin rash or eczema) and more severe (erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, although no date of appearance is stated) [5]. Our study reveals that this side-effect is typical of the tetrazepam molecule, since in the vast majority of patients there is no cross-reaction with other benzodiazepines, such as diazepam, lorazepam or clorazepate.

On analysing the publications our attention was drawn to the fact that almost 38% of the 72 subjects were not patients, but instead professionals who had been in contact with tetrazepam (23 nurses and three laboratory workers). This means that those publications could be considered as referring to cases belonging to the area of work safety rather

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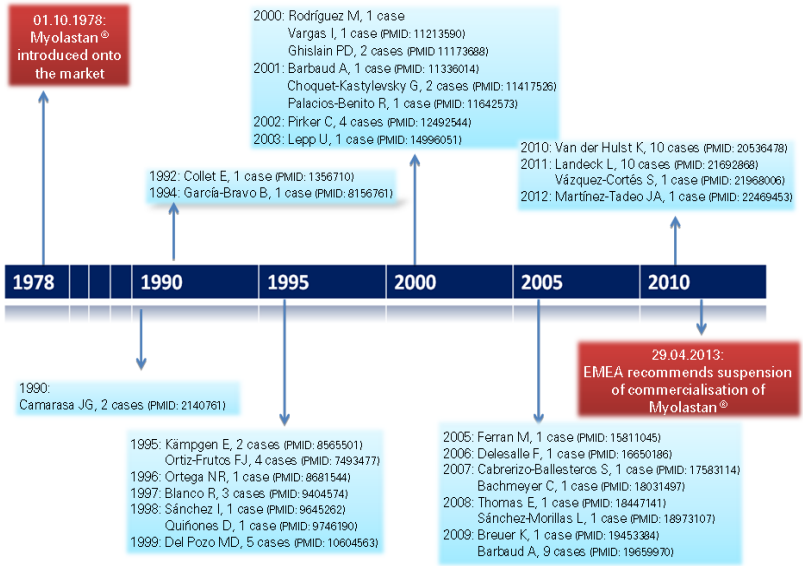
Figure. Studies referring to some kind of side-effect produced by tetrazepam.



than a side-effect following correct administration of the drug.

Tetrazepam offers an intense hepatic metabolism with a metabolic profile that is unlike that of the other benzodiazepines. Notable features include its hydroxylation in position 3 or the substitution of the typical phenyl moiety in position 5 by a cyclohexenyl ring. In blood, nortetrazepam or N-desmethyltetrazepam, the active metabolite, represents only a small proportion (3%) of the circulating tetrazepam. A possible explanation could be the existence of a subpopulation of fast-metabolising subjects in whom there might be an exceptional transient increase in plasma concentration levels. This would lead to a pharmacogenetically interesting case. Variations in a single nucleotide (SNP) are responsible for up to 90% of all human genomic variations, and appear once every 1300 nucleotides on average, along the human genome. More specifically, SNP can have a significant influence on both the pharmacokinetic and pharmacodynamic properties [6,7]. Today we have access to fast, readily-available sequencing techniques, which would make it possible to conduct a study of the patients who have already presented such side-effects.

Hence, we wish to draw attention to the importance of ensuring a greater interconnection between pharmacovigilance agencies, scientific literature and doctors so that the cases of side-effects that do appear can be made known. It should be remembered that even reporting single cases is relevant. This greater exchange of information would make it possible to avoid the 'surprise' withdrawal of active ingredients that have been used apparently quite safely for years. We are aware that all this entails an extra workload on healthcare services, but we believe that it would lead to a better reasoning and understanding of the underlying causes.

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