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Letter to the Editor

Reply to the article "Management of status epilepticus in adults. Position paper of the Italian League against Epilepsy"

To The Editor

We would like to comment on the review article entitled "Management of status epilepticus in adults. Position paper of the Italian League against Epilepsy" [1]. This article updates the previous article published by the same Italian League against Epilepsy in 2006. In particular, the updating regards some drugs (levetiracetam, lacosamide, midazolam, etc.) that were not available at that time, even if some of these have not yet obtained the specific indication to treat status epilepticus (SE) and their use is considered off-label. The use of one of them (midazolam) is not correctly reported in the article. Indeed, in Section 4.1 "*Prehospital management*", the sentence "not approved for this indication in Italy" does not reflect the present regulatory scenario, since the use of oral midazolam has been allowed in Italy also in adults who started taking the drug before the age of 18 years. In fact, this authorization has been granted by the Italian Medicines Agency via a special law (the so-called 648/96) and dates back to 2014 [2]. The official Journal of the Italian Government (Gazzetta Ufficiale) [3] has subsequently published that midazolam can be prescribed compiling a form for a specific therapeutic plan [4,66,page]. Following these restrictions and indications, along these years, oral Buccolam has been prescribed by the majority of the Italian Epilepsy centers also in adults. This point is very important, and the article is already creating confusion and concern among epileptologists and the people with epilepsy (PWE) and their families. The second critical point regards the point in Section 4.2, the intrahospital management of ES. On the other hand, the use of intravenous midazolam to treat ES is allowed, in Italy, for pediatric patients only. The authorization has been granted by the Italian Medicines Agency via a special law (the so-called 648/96) and dates back to 2012 [5], and was then updated in 2016. It has also been published in the official Journal of the Italian Government (Gazzetta Ufficiale) [6]. But the use of midazolam is again off-label to treat SE in adults, and this should be clearly stated in the article for the possible legal consequences. Another minor point in the article, in Section 4.1, is the lack of the indication of a maximum dose for rectal diazepam, as 0.5 mg in an adult of 80 kg means 40 mg, a potentially toxic dose if used off-label. It is also in contrast with the Summary of Product Characteristics (SmPC) of rectal diazepam, where a maximum dose of 10 mg is recommended also in adults, as reported in the Recommendations of the Italian League against Epilepsy for the treatment of convulsive ES in childhood [7]. Finally, few words should be spent on the dose of nasal midazolam. This preparation is on the market in the Netherlands as midazolam 2,5 mg unit dose or midazolam 5 mg unit dose, and the Food and Drug Administration (FDA) has granted the orphan designation in the US for the treatment of repetitive seizures for the unit dose of 5 mg. So, in general, the two recommended doses in the article seem anyway excessive in general but, in particular, in the group with an extreme low weight. In conclusion, even if this article contains some useful information, we think that it should be revised according to the Italian regulatory scenario and the current scientific data. The ultimate goal is to allow patients to benefit from standard of care avoiding both the inappropriate use of medicines and unjustified concerns in PWE.

References

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