Author’s response to reviews

Title: A Serious Adverse Drug Reaction Probably Induced by Clonazepam: a case report of Myotoxicity

Authors:

Xiaonian Han (xjtuhxn@126.com)

Jinpeng Wang (184232699@qq.com)

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you very much for your letter and for the reviewers’ comments concerning our manuscript entitled "A Serious Adverse Drug Reaction—Myotoxicity Probably Induced by Clonazepam" (ID: PHAT-D-19-00193). Those comments are all valuable and very helpful for revising and improving our paper. We have studied the comments carefully and have made correction which we hope meet with approval.

The point by point responses to the reviewer’s comments are as following:

Reviewer #1: While I thought this was an interesting account, though necessarily lacking in some desirable details because of circumstances outside the authors’ control, I felt that it might be safer to relate the problem encountered to the use of clonazepam in the presence of valproate, since clonazepam was never the only drug present when the probable adverse reaction occurred, and to put less emphasis on the speculative nature of the muscle pathology presumed to present. No description is provided of the neurological findings at the time the patient’s epilepsy was investigated before any treatment commenced, and also no details of the clinical findings during the presumed adverse reaction. Partly because of the lack of this information a number of questions need to be raised in the Discussion section of the paper, and answers provided. Thus *how certain is the diagnosis of early-life poliomyelitis? Could this young woman really have had some very slowly progressive early-onset type of muscle wasting disease of neurological or myopathic origin, and the epilepsy treatment simply accelerated its progress? A long-standing myopathic disorder might be more likely in view of the high creatine kinase level during the adverse reaction.

Response: Thanks for the constructive suggestion. Some early laboratory examinations data including poliovirus was unavailable because of the long history of polio. At present, the diagnosis of poliomyelitis can only be based on the sequelae of polio. It might be that the young woman really had some very slowly progressive early-onset type of muscle wasting disease of
neurological or myopathic origin, which was possibly accelerated by the epilepsy treatment, causing the clinical manifestations. But anyway, the probable myotoxicity varied with clonazepam intake. So, clonazepam was probably related to the myotoxicity. We have added this point to paragraph 2 of the discussion section (Discussion section, paragraph 2, page 3) and changed Naranjo ADR probability scale score from 9 to 7 (Discussion section, page 4).

*Because the patient was always taking valproate, even though the probable myopathy seemed to vary with clonazepam intake, could it be that there was a metabolic interaction between valproate and clonazepam leading to the presence of a myotoxic valproate metabolite. Valproate has a considerable number of known metabolites and the formation of some of them has been related to occasional but serious liver toxicity, though reports of this have largely ceased to occur in recent years. At the least, I think it might be wise to bring out the point that clonazepam was never the sole antiepileptic drug present.

Response: Thanks for the constructive suggestion. We have added the potential drug interaction between sodium valproate and clonazepam (Discussion section, paragraph 2, page 5).

*A post-polio syndrome has been described on a number of occasions, though as far as I can make out its exact spectrum of manifestations and cause remain unclear, but it might be worth mentioning this though I think the high creatine kinase level makes it likely that you are correct in believing that the issue is muscle toxicity, though the detail of its pathogenesis has to be speculative.

Without some mention of matter such as the above I suspect your confidence that clonazepam by itself was the cause of the muscle problem, and your ideas of the nature of the muscle microscopic pathology may be questioned by some readers.

Response: Thanks. We have deleted the mechanism of drug-induced myopathy by clonazepam in the discussion section (Discussion section, page 5) and emphasized that the detail of its pathogenesis was only speculated (Discussion section, line 8-9, page 5).

Reviewer #2: The case report of the authors highlights a very rare adverse effect of clonazepam. The only concern I have is about the strength of association between the clonazepam absorption and a Myopathy. Actually authors did not report any electrophysiological examination, biopsy or detailed neurological examination supporting a primitive myopathic damage. I mean that it could be also mediated by nerve injury or by a neuromuscular plaque disorder. In this light, the association is Probable and thus authors should add the term probable all along the manuscript and in the title and the above reported limitations.

Response: Thanks for the constructive suggestion. I have added the term “probable” all along the manuscript and in the title and added the limitation of this article in the discussion section (Discussion section, line 7-8, page 5).

If you have any question about this paper, please don’t hesitate to let me know. Once again, thank you very much for your comments and suggestion.

Best regards,
Jinping Wang