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COMMENTARY

Critical review of European Medicines Agency (EMA) assessment report and related literature on domperidone

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Abstract
European Medicines Agency (EMA) issued a final decision on September 01, 2014 that restricts the maximum daily dose of domperidone to 30 mg and treatment duration to 7 days. This paper presents a critical review of the scientific basis of the literatures having a role in the decision of EMA on domperidone with an approach based on statistical and epidemiological perspective. Although observational studies used by EMA were published, the EMA didn't use an algorithm including "randomized clinical trials" according to evidence-based medicine when presenting their results. In conclusion, the results obtained from published studies are controversial, especially for the bias. From these publications, it cannot be concluded that domperidone exposure definitely increases the risk of "sudden cardiac death", "death associated with ventricular arrhythmia" or "ventricular arrhythmia" The most concrete result of these studies is that the risk is higher with metoclopramide exposure compared to domperidone exposure.

Keywords Critical review · Domperidone · EMA decision · Restriction · Safety

Impacts on Practice

- The decision issued by EMA that restricts the maximum daily dose of domperidone may be disadvantageous for some patients who actually had benefit from the high dose therapy.
- From these publications, it cannot be concluded that domperidone exposure definitely increases the risk of "sudden cardiac death", "death associated with ventricular arrhythmia" or "ventricular arrhythmia".
- Also for the EMA it is important to use the correct and non-biased interpretation of findings obtained via different statistical analysis methods in the epidemiological studies.

Introduction

Domperidone, first marketed in Belgium in 1978, has been withdrawn from the market due to adverse effects of intravenous form in 1986. However, the oral form of domperidone continues to be marketed. On the basis of the domperidone restriction decision issued by European Medicines Agency (EMA), domperidone containing products have been withdrawn from market by Republic of Turkey Ministry of Health on October 3, 2017.

In a review by Rossi and Giorgi [1], two case reports were defined that linked oral domperidone usage with cardiac adverse events. In the meantime, Johannes et al. [2] conducted an observational study on domperidone in September 2010 as followed by another observational study by van Nord et al. [3] published in 2010. On the basis of data from these studies, EMA pharmacovigilance group (PRAC) requested the product information of the drug, which has been on the market for 32 years, to be updated with relevant warnings that reveal the risk of adverse effects.

Upon admission of the licensing company Janssen pharmaceuticals to "RTI Health Solution" for conduction of a post-authorization safety study for domperidone on November 9, 2012, they came to a consensus on performing a study

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in collaboration with Alejandro Arana and Cethrin Johannes from the company [4].

In light of the studies published in 2010, Belgium Medicines Agency asked EMA PRAC's to give its opinion on the benefit-risk benefit ratio of domperidone on March 1, 2013. The review of domperidone was then initiated on March 1, 2013 at the request of the Belgian medicines authority. The assessment report of EMA PRAC including restriction recommendation was published on March 7, 2014 [5].

The CMDh (The Co-ordination Group for Mutual Recognition and Decentralised Procedures—Human) endorsed recommendations to restrict the use of domperidone by EMA/PRAC on April 23, 2014. EMA issued a final decision on 01 September, 2014 that restricts the maximum daily dose of domperidone to 30 mg and treatment duration to 7 days. The decision of EMA was published in the Official Journal of European Union (EU) on September 31, 2014.

This paper presents a critical review of the scientific basis of the literatures having a role in the decision of EMA on domperidone with an approach based on the following criteria.

Estimation of relative risk by using odds ratio in all publications and interpretation of odds ratio

Since the relative risk (RR, risk ratio) cannot be estimated by the statistical model that is mandatory in case–control studies, the odds ratio (OR) is calculated and often interpreted as if it is the RR. In other words, the OR is an estimated value that can be used as an estimate of the RR. If the incidence of > 10% in the population of interest, it is not accurate to use the OR instead of the RR. In that case, the estimate of the RR obtained from the OR would be higher than the true RR [6, 7].

Interpretation of these and similar "parameters" alone is not meaningful, and it is never acceptable by Statistical Science. Therefore, "statistical significance, *p* value" or "confidence interval" is required in order to interpret these parameters.

To be able to say that the risk estimated by the OR is significantly higher within the context of "scientific significance based on statistical methods", the confidence interval (CI) related to this OR is required to be more than "1" range, not including "1".

It is clear that interpretation of the OR should be together with the CI for above mentioned reasons. Concordantly, it was determined that the OR and 95% CI 3.20 (0.59–17.3) for daily dose of more than 30 mg (> 30 mg) domperidone in the result part of Arana's [8] article. Similarly, it was presented that the OR and 95% CI 1.65 (0.89–3.07) for ≥ 60 year-of-age. As is evident from the 95% CI values (because they includes 1), these OR values were not statistically significant for 95% level of significance. Although it is not accurate to expect that the scientific data based on statistical information is significant at the 95% level of significance in such studies evaluating public health related risk, also it would not be correct to conclude a scientific decision with regard to the finding not significant, considering OR more than '1'.

Unadjusted OR and misuse of OR

The OR (unadjusted) for the risk of sudden cardiac death (SCD) with domperidone exposure compared to the untreated group was reported as 3.72 in the summary part of Van Noord's [3] study. In the same study, the ORs were also presented for effects of covariates on the occurrence of SCD and severe non-fatal ventricular arrhythmia (VA) in Table 1. As it is understood from this table (Table 1), a large number of covariate variables can lead to statistically significant occurrence of SCD and VA. While there are statistically significant so many covariate variables, It is not accurate to comment on unadjusted (obtained by ignoring these covariate variables) OR for domperidone-related occurrence of SCD and VA. If the adjusted OR is used instead of the unadjusted OR, the OR will decrease from 3.72 to 1.99. Nevertheless, it will also lose the statistical significance [95% CI (0.80–4.96)]. Yet, the author avoided to emphasize this fact by commenting unadjusted OR. In fact, the risk associated with covariate variables demonstrated as if it is related to domperidone exposure.

In addition to the above, a small sample size can always have an impact on the final CI values and therefore these studies/papers should be calculated with a great caution before final conclusions.

Low level of evidence in observational studies

Drug exposure period covered 37 days prior to death in Johannes's study [2], whereas in Arana's study [8] duration of exposure was determined by addition of 7 days to the prescription date. This discrepancy even in the identification of exposure, as the basic part of case–control studies, seems to be a concrete indicator of low level of evidence in observational studies. Similarly Rossi [1] included case reports which are the lowest level of evidence and they have many limitations including question of concomitant medications and therefore drug–drug interaction could not be excluded.

Important outcome discrepancies presented in publications

Bias is defined as "systematic deviation of the results or inferences from truth" [9]. It was encountered a situation in this context, and was described as "protopathic bias" [9] in Arana's [8] study. In other words, the perception management bias has been made. Namely; OR 4.06 and 95% CI (1.55–10.67) was estimated for domperidone exposure period of "< 16 days" in the publication at Table 4. Besides, OR 0.97 and 95% CI (0.42–2.26) was obtained for "> 16 days" exposure. It is clear that these OR scores conflict with one another. It is not possible to interpret the situation logically.

Using the term "protopathic bias" to express the emerging unreasonable condition herein can be seen as the consequence to obtain the results by evaluating a small number of samples (the imperfect data, and the case/control numbers of domperidone exposure of < 16 days, and of > 16 days were 16/14, and 12/38, respectively). However, there is no statistical significance for the OR 0.97 value with regard to domperidone exposure of > 16 days (since the 95% CI contains 1 value).

"Bias" similar to the one in the Arana's [8] publication can be seen in Johannes's [2] publication. The OR score of 1.44 and the 95% CI (1.12–1.86) was estimated for the current (present) domperidone exposure in Table 2. The OR of 0.78, and the 95% CI (0.61–1.00) was calculated for the past exposure. Then; domperidone seems to increase the risk of the occurrence of the event (severe VA/SCD) by having statistically significant higher OR. On the other hand, the past domperidone exposure decreases the event risk by having statistically significant lower OR. It is clear that these two consequences are completely opposite to each other. However, researchers have never mentioned about this.

The molecules having higher odds ratio were not sufficiently addressed

Domperidone was evaluated along with Proton pump inhibitors (PPI), and metoclopramide in Arana's [8] publication. The estimated OR for metoclopramide was ignored, and never mentioned in the result part of the publication. However, the OR, and 95% CI for metoclopramide was 4.31 (2.33–7.98), which could be generalized to the population by having a statistically significant higher OR. Similarly, the OR and 95% CI for PPI was 1.35 (1.21–1.51) in the same publication. Instead of these, the OR and the 95% CI of 3.20 (0.59–17.3) for > 30 mg/day domperidone and the estimated OR and the 95.5% CI of 1.65 (0.89–3.07) for domperidone exposure of ≥ 61 years of age were reported although they were not statistically significant due to the value more than 1. While the findings of PPI and metoclopramide were not discussed, domperidone was interpreted with bias in the conclusion part of the publication. The findings related to metoclopramide were briefly mentioned in the discussion part of the publication (NOTE: the study referred to metoclopramide and PPI as "comparator medication").

Combined usage

Combination therapy was only discussed in Johannes's [2] study. In this study, the combination therapy of domperidone and PPI has been evaluated. The OR and the 95% CI for the combination therapy was 1.39 (0.89–2.16). This value which was not statistically significant could not be judged that the combination therapy increases the risk of SCD or severe VA with regard to OR rate.

Differences between the results of the unpublished study mentioned in EMA report and the results of published study in question

An unpublished pharmaco-epidemiological study [5] that was mentioned in the EMA evaluation report, carried out in 2014, with the support of the sponsor company was published in 2015 [4]. It was seen that the OR in the EMA report are different from those presented in the publication.

Conclusion

The above mentioned domperidone studies are epidemiological observational studies with a low level of evidence addressing domperidone exposure in terms of "SCD", "death associated with VA" or "VA" risks [10]. The results obtained from these studies are controversial, especially for the bias mentioned in detail above. From these publications, it cannot be concluded that domperidone exposure definitely increases the risk of "SCD", "death associated with VA" or "VA".

The most concrete result of these studies is that the risk is higher with metoclopramide exposure compared to domperidone exposure. Even though PPI exposure has lower risk than both drugs, the combination therapy with PPI and domperidone bears no risk compared to domperidone alone.

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Conflicts of interest Authors declare that they have no conflict of interest.

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