Impact of European Medicines Agency regulatory action on hydroxyzine initiation, discontinuation and switching to other medicines in Scotland, England, Denmark and The Netherlands: an interrupted time series regression analysis

Morales DR[1], Flynn R[1], MacDonald TM[1], Morant S[1] Mackenzie IS[1], Doney ASF[1], Mitchell L[1], Hallas J[2], Pottegard A[2], Ernst MT[2], Smits E[3], Herings RMC[3,4], Overbeek JA[3], Bennie M[5] , Robertson C[5], Wei L[6], Nicholson L[7], Macfarlane TV[1]

[1]University of Dundee, [2]University of Southern Denmark, [3]PHARMO Institute for Drug Outcomes Research, Utrecht, NL,[4]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands [5]University of Strathclyde, [6]University College London, [7]National Services Scotland.

Background: Antihistamines such as hydroxyzine, are commonly prescribed across Europe for the management of skin disorders, sleep disorders and anxiety. In February 2015, a European Medicines Agency (EMA) safety review concluded that hydroxyzine was pro-arrhythmogenic and that new changes to the product information were required to be implemented and communicated across Europe via a direct healthcare professional communication (DHPC).

Objectives: The aim of the study was to evaluate the impact of the risk minimisation measures following the 2015 review to manage the pro-arrhythmogenic risks of hydroxyzine in Denmark, Netherlands, England and Scotland.

Method: Drug utilisation studies assessing hydroxyzine prescribing or dispensing spanning the regulatory intervention date (February 2015). Quarterly time series analyses was performed measuring the rate of hydroxyzine initiation and discontinuation, and switching to other antihistamines, benzodiazepines and/or antidepressant medications (tricyclic antidepressants, mirtazapine, selective serotonin reuptake inhibitors) in patients who discontinued hydroxyzine. Statistical significance testing was performed using interrupted time series regression.

Results: The 2015 EMA regulatory action had no significant impact on overall hydroxyzine initiation in Denmark or the Netherlands. It was associated with a significant: immediate fall in hydroxyzine initiation per 100,000 in England (-12.05, 95%CI -18.47 to -5.63) and Scotland (19.01, 95%CI -26.99 to -11.02); and change to a negative trend in hydroxyzine initiation per 100,000/quarter in England (-1.72, 95%CI -2.69 to -0.75) and Scotland (-2.38, 95%CI -3.32 to -1.44). The EMA regulatory action was associated with a significant: immediate rise in hydroxyzine discontinuation per 100,000 in England (3850.0, 95%CI 440.0 to 7240.0). The regulatory action was associated with no significant switching to other antihistamines, benzodiazepines or other antidepressant medicines following hydroxyzine discontinuation.

Conclusion: The 2015 Europe-wide regulatory intervention was associated with heterogeneous impact, with significant reductions in overall hydroxyzine initiation observed in England and Scotland only. There was limited impact on discontinuation in all countries but no evidence to suggest unintended consequences of switching to other antihistamines, benzodiazepines or other antidepressant medicines overall.

Impact of European Medicines Agency regulatory action for hydroxyzine initiation in people with contraindications in Scotland, England, Denmark and The Netherlands: an interrupted time series regression analysis

Morales DR[1], Flynn R[1], MacDonald TM[1], Morant S[1] Mackenzie IS[1], Doney ASF[1], Mitchell L[1], Hallas J[2], Pottegard A[2], Ernst MT[2], Smits E[3], Herings RMC[3,4], Overbeek JA[3], Bennie M[5] , Robertson C[5], Wei L[6], Nicholson L[7], Macfarlane TV[1]

[1]University of Dundee, [2]University of Southern Denmark, [3]PHARMO Institute for Drug Outcomes Research, Utrecht, NL, [4]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands [5]University of Strathclyde, [6]University College London, [7]National Services Scotland.

Background: Hydroxyzine is widely used across Europe for the management of skin disorders, sleep disorders and anxiety. Due to pro-arrhythmogenic safety concerns, the European Medicines Agency (EMA) recommended contraindications and changes to the product information for hydroxyzine across Europe in 2015.

Objective: To measure its impact of the regulatory action among contraindicated populations.

Method: Quarterly interrupted time series regression analyses of diclofenac initiation among cohorts with contraindications consisting of 1) people with a history of cardiovascular disease (consisting of ischaemic heart disease, peripheral vascular disease, congestive cardiac failure and/or cerebrovascular disease) and 2) concomitant use of drugs known to prolong the QT interval) from Denmark, The Netherlands, England and Scotland.

Results: The 2015 EMA regulatory action was associated with significant immediate reductions in hydroxyzine initiation in people with cardiovascular disease per 100,000 in Scotland (-46.16, 95%CI -69.98 to -22.34) and England (-36.47, 95%CI -59.42 to -13.51) but not Denmark and the Netherlands. Significant negative changes in post-intention trend per 100,000/quarter were also observed in Scotland (-3.79, 95%CI -6.60 to -0.98) and England (-3.20, 95%CI -6.75 to -0.36) but not in Denmark and the Netherlands. For concomitant use of drugs known to prolong the QT interval, regulatory action was associated with significant immediate reductions per 100,000 in Scotland (-57.06, 95%CI -84.69 to -29.44) and England (-50.10, 95%CI -71.07 to -29.12), with significant negative change in post-intervention trend per 100,000/quarter in Scotland (-7.45, 95%CI -9.92 to -4.98), England (-8.51, 95%CI -16.24 to -0.77) and Denmark (-1.69, 95%CI -3.36 to -0.02), but not in the Netherlands.

Conclusion: Although EMA regulatory action was associated with significant reductions in hydroxyzine initiation apart from in the Netherlands. Some patients with contraindications continued to be prescribed hydroxyzine, the extent of which varied by country and target condition. Further research understanding reasons for such variation may help to guide the design or dissemination of future safety warnings.