UNRESOLVED GUSTATORY, OLFACTORY AND AUDITORY ADVERSE DRUG REACTIONS TO ANTIBIOTIC DRUGS: A SURVEY OF SPONTANEOUS REPORTING TO EUDRAVIGILANCE

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Introduction: Irreversible or persistent mild to moderate disabilities can be an important consequence of adverse drug reactions (ADRs) that hardly affect the quality of life. In 2017, the European Medicine Agency started a review of the safety of fluoroquinolone and quinolone antibiotics with a particular focus on disabling and potentially permanent ADRs including sensory ADRs. In 2018, the Pharmacovigilance Risk Assessment Committee recommended to suspend the marketing authorization of medicines containing quinolones and to restrict the use of fluoroquinolones. Although some sensory alterations are generally labelled for several antibiotic drugs, these reactions are expected to be transient in nature. However, based on current literature, the majority of reports describes these reactions as long lasting or unresolved. In this study, we have reviewed publicly accessible data collected in the Eudravigilance (EV) database to describe the extent and expectedness of unresolved outcomes for gustatory, olfactory and auditory (GOA) suspected ADRs reported for antibiotics drugs.

Methods: We created a dictionary of GOA ADRs through the selection of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) referring to sensory adverse reactions related to GOA alterations. The antibiotics of interest (137) included every drug listed in the Anatomical Therapeutic Chemical (ATC) class J01(antibacterial drugs for systemic use) and available in EV. The total number of "overall" and "GOA" suspected ADRs was extracted from the EV database of spontaneously reported suspected ADRs up to February 2019. GOA suspected ADRs were classified according to their outcome (definite, persistent/permanent and undetermined). The extracted data were organized according to ATC level 3and 4, and the distribution of outcomes among overall, and the GOA suspected ADRs was analyzed. Then, we identified the substances (ATC level 5) that contributed to at least 15% of all GOA reactions extracted from the ATC level 4class. For these substances, we finally evaluated the expectedness of the extracted suspected GOA ADRs.

Results: We extracted 748,798suspected overall ADRs. Nine ATC level 4groups were associated with more than 300 GOA reactions: tetracyclines; penicillins with extended spectrum; combinations of penicillins including βlactamase inhibitors; macrolides; lincosamides; aminoglycosides; fluoroquinolones; glycopeptide antibacterials; imidazole derivatives. Among these groups, persistent/permanent outcomes were generally lower for the overall reactions (21-29%) as compared to GOA (40-56%), and undetermined ADRs are distributed similarly (differences < 10%). Sixteen antibiotics were selected for the expectedness assessment of the suspected GOA ADRs extracted from EV, and we found that unexpected gustatory, olfactory and auditory reactions have been reported in EV for 9, 10 and 9antibiotic drugs, respectively.

Discussion ad conclusions: In the present analysis, several persistent/permanent GOA reactions could met the criteria for being classified as serious and unexpected. The distribution of such outcomes is undoubtedly higher for GOA ADRs, as compared to the overall ones across the different antibiotic classes. This could mean that these reactions are frequently irreversible for several antibiotics, however it might reflect also an intrinsic difficulty in assessing the resolution of these events as compared to other kinds. Further studies should be implemented to clarify this point. The extent of unresolved and undetermined outcomes for GOA ADRs reported for antibacterial drugs in EV might hide a large number of events with underestimated clinical consequences. In general, when assessing the expectedness of a reported ADR, the persistence of signs and symptoms should be always carefully evaluated by follow-up. Improving the collaboration with patients in this process is essential, particularly with subjective ADRs.