TITLE

Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal

1. ABSTRACT

1.1 Title

Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside-containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal

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1.2 Keywords

Thiocolchicoside-containing Medicinal Products for Systemic Use, Safety, Dear healthcare professional communication, Educational Materials, Risk minimization measures.

1.3 Rationale and background

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity, used in the management of non-specific low back pain. TCC is indicated as adjuvant treatment of painful muscular contractures in acute spinal pathology, in adults and adolescents from 16 years onwards.

An Article 31 referral on thiocolchicoside-containing medicinal products for systemic use was initiated in February 2013. The CHMP had concerns with regard to the potential genotoxicity of thiocolchicoside (TCC)-containing medicinal products for systemic use.
As per European Commission decision dated 17 January 2014, risk minimization measures (RMMs) were implemented including a Dear Healthcare Professional Communication (DHPC), changes to the Summary of product characteristics (SmPC) and Package Leaflet and Educational Materials (EM) for Health Care Professionals (HCP) and patients. A Drug Utilisation Study (DUS) was also requested to assess the effectiveness of the imposed risk minimisation measures and to further characterise the prescribing patterns for TCC-containing medicinal products for systemic use.

On 8 October 2015, following the DUS protocol review (ENCePP registration number EUPAS11081), EMA requested to complete it with the present survey to evaluate the effectiveness of the RMMs and assess HCP knowledge and attitudes on prescribing conditions of TCC-containing medicinal products for systemic use.

1.4 Research question and objectives

Research question: whether the DHPC and EM, implemented as risk minimization measures, were effective to ensure:

• correct knowledge of physicians about prescribing conditions and safe use when prescribing systemic thiocolchicoside
• appropriate attitude when prescribing systemic thiocolchicoside, in particular as concerns pregnancy, lactation and contraception.

Objective: to measure the effectiveness of the DHPC and EM, by ascertaining the proportion of targeted physicians who understood and implemented the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EM.

Specific objectives were to evaluate the proportion of physicians who:

- Prescribe systemic thiocolchicoside only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- Do not prescribe systemic thiocolchicoside for long-term treatment of chronic conditions.
- Follow the recommendations regarding the doses and duration restriction:
  - For oral forms: the recommended and maximal dose is 8 mg every 12 hours, i.e. 16 mg per day. The treatment duration is limited to 7 consecutive days.
  - For IM forms: the recommended and maximal dose is 4 mg every 12 hours, i.e. 8 mg per day. The treatment duration is limited to 5 consecutive days.
- Do not prescribe systemic thiocolchicoside during pregnancy and lactation.
- Do not prescribe systemic thiocolchicoside in women of childbearing potential not using adequate contraception.

1.5 Study design

Cross-sectional, multinational and non-interventional survey conducted through a web questionnaire in an anonymous way among physicians in 4 selected European countries (France, Greece, Italy and Portugal).

1.6 Setting

The survey was conducted during 01st February 2017 to 10th March 2017 through a web questionnaire among prescribers of systemic thiocolchicoside in settings of 4 European countries.

1.7 Subjects and study size, including dropouts

Among a total of 651 physicians who completed the questionnaire, 200 were from France, 124 were from Greece, 203 were from Italy and 124 were from Portugal.

1.8 Variables and Data sources

The primary data on physician's demographics and practice information, knowledge, awareness about and attitude towards prescribing conditions and safety information/warnings and prescriptions records were collected.

1.9 Results

The results of the survey questionnaire indicate that 63.2% of the physicians had knowledge of the approved indication (adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards). This results varied across countries from 39% in Greece to 69.2% in France. Overall, 24.2% of physicians reported prescribing TCC for acute painful muscle contractures conditions. This rates were heterogeneous across countries (from 17.9% for France to 48.6% for Greece). Only 6.5% of the physicians responded that the indication was long term treatment of chronic conditions. A majority of physicians known the recommended dose and duration for oral form (78.9%) and to a lesser extent (55.4%) for intramuscular form of systemic TCC. Concerning contraindications, the majority (85.0%) of physicians reported not prescribing systemic thiocolchicoside to patients under 16 years old. A majority of them deemed the use of systemic TCC containing medical products to be contraindicated for pregnant women (87.6%), and for breastfeeding women (80.3%). However, less

than half of them (49.1%) believed that the use of systemic TCC was contraindicated in women of childbearing potential not using contraception. This rate was even lower for orthopedists (36.7%) versus 50.5% for generalists and 48.5% for rheumatologists. Overall, 68.6% of physicians acknowledged receipt of both or either DHPC and the EM. However, in Greece this rate was lower (51.1%). Physicians recalling having received either or both DHPC and EM had higher rate of success in all single criteria and in aggregated criteria compared to those who mentioned they had received neither the DHPC nor EM. In particular, the acknowledgement of the receipt of either or both DHPC and EM increased the proportion of physicians regarding as contraindicated the prescription of systemic TCC in patients of childbearing potential not using contraception, from 31.9% to 56.9%. One exception was criterion No 2 (Proportion of physicians who do not prescribe systemic thiocolchicoside for long-term treatment of chronic conditions) which did not seem to be influenced by the receipt of RMMs documents. Exactly in the same trend, physicians stating that they were aware that changes had been made to the package leaflet (66.5%) performed better on single criteria (expect No2) and aggregated criteria than physicians who reported not being aware of these changes.

Results of the prescription analysis produced results in agreement with those of the survey. A large majority (72.8%) of prescriptions of systemic TCC containing medicinal products had the indication of adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and in adolescents from 16 years onwards. A majority of prescriptions were of oral TCC (65.3%), with a median daily dose of 16.0 mg/day and a median duration of prescription of 6.0 days. Intramuscular TCC (32.4% of prescriptions) was prescribed with a median daily dose of 8.0 mg/day and a median duration of prescription of 5.0 days.

When addressing to women of childbearing potential, only a minority of physicians reported not asking to the patient if she was using an effective method of contraception (11% of prescriptions) and if she was pregnant (6.8% of prescriptions). In less than 1% of prescriptions to women of childbearing potential, the physicians reported that the female patient was planning to be pregnant or breastfeeding and for 6.8% of prescriptions, they prescribed systemic TCC containing medicinal products to women they know did not use effective methods of contraception.

1.10 Discussion

This study investigated whether the Dear Healthcare Professionals Communication (DHPC) and Educational Materials (EM), implemented as risk minimisation measures (RMM), were effective to ensure correct knowledge of physicians about prescribing conditions and safe use as well as appropriate attitude when prescribing systemic TCC containing medicinal products.

The survey was conducted in 4 European countries. A higher response rate was observed in Italy, Portugal and Greece than in France. The highest percentage of respondent physicians was among GPs in all countries but France, where rheumatologists had the highest response rates.

A majority of physicians had a correct understanding of the approved indication and respected recommended dose and duration for oral form and to a lesser extent for intramuscular form of systemic TCC. This difference in knowledge about the duration and dose of prescription for the 2 forms of systemic TCC could be explained by the fact that a majority of physicians were more used to prescribe the oral form rather than IM form of systemic TCC.

However, it should be highlighted that there was a heterogeneity in the results across countries with lower rates in Greece and higher rates in France. In addition, the percentages differed among specialty with lower rates for orthopedists compared to GPs and rheumatologists.

The majority of physicians surveyed had a correct understanding about most of the contraindications of systemic TCC use, namely a patient's age of less than 16 years, a pregnancy, or a breastfeeding status. They were however, less than half to be aware of the contraindication related to patients of childbearing potential not using contraception. This was in line with their reported advice to a patient of child bearing potential ("use with a reliable method of contraception": 52.3% of responses). When considering the prescription component of this survey, we noted however, that when addressing to women of childbearing potential, only a minority of physicians reported not asking to the patient if she was using an effective method of contraception (11% of prescriptions), while 64.2% reported that the patients was using effective methods of contraception. The percentage of doctors who replied that they had not received DHPC and/or EM

was of 31.4%. However, physicians recalling having received either or both DHPC and EM had higher rate of success in all single criteria and in aggregated criteria compared to those who mentioned they had received neither the DHPC nor EM.
In summary, although there are some limitations and inherent bias in this survey, the result of the study showed that risk minimization measures materials, when their receipt was acknowledged by physicians, improved physicians' knowledge and attitude regarding systemic TCC containing medicinal products. However, this study reveals geographical heterogeneity and across specialty, and differences in the level of understanding of key messages of RMMs, especially the contraindication related to women of childbearing potential non using contraception. These results suggest the need for a re-distribution of existing additional risk minimisation measures ((DHPC, HCP Guide and Patient Card) implemented following the referral in 2014. DHPC and HCP Guide, evaluated through this survey, will be adjusted to be more straightforward and and focused on genotoxic risk. In addition the outcomes of this study will be complemented by the upcoming results from the "Drug Utilisation Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study".

1.11 Marketing Authorisation Holders (MAHs)

Consortium of companies.
The full list of all MAHs (Companies and/or their Affiliates and licensors) and address is provided in Annex 2

1.12 Names and affiliations of principal investigators

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