Utrecht WHO Winter Meeting 2011

6 - 7 January 2011

Utrecht - WHO Collaborating Centre

for Pharmacoepidemiology and

Pharmaceutical Policy Analysis

Utrecht, The Netherlands

Location: Faculty Club Helios, Utrecht

Programme Meeting report

World Health Organization

Universiteit Utrecht

Foto cover: Michael Kooren

Programme Meeting report

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Programme

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Welcome

We are very pleased to welcome all of you in Utrecht for the third edition of the Utrecht - WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis Winter Meeting.

The successful format of last year's edition – a plenary programme with key note speakers on Thursday and parallel discussion sessions on Friday – has been maintained this year. Again, we have chosen a hot topic in the pharmaceutical field as central theme for the plenary day: "International variability in regulatory decision making: a window for insight and learning". Policy implications of regulatory decisions, e.g. in pharmacovigilance, may vary across different countries or regions of the world as a result of different circumstances; differences in local needs, local absence of alternatives and many other reasons. The invited speakers will present studies, experiences and views on these and other policy challenges that are faced by decision makers, industry, health care professionals and academia. Lessons learned from three case examples will be discussed by an expert panel.

Researchers from different backgrounds – both in terms of professional as well as geographical background – will be given the floor on Friday to discuss their ongoing work. We sincerely hope that these discussions will contribute to bringing evidence-based policy making on pharmaceuticals to a higher level.

The meeting brings together a mixture of established and young researchers who are committed to make a difference in measuring and evaluating policy initiatives by sharing and discussing their experiences. We hope that this meeting will result in exciting discussions and inspiring new thoughts.

May you all enjoy!

On behalf of the Organizing Committee,

Bert Leufkens and Aukje Mantel

General Information

Location

Faculty Club
Achter de Dom 7
3512 JN Utrecht
Phone: +31 (0)30 253 99 11

Date

Thursday, 6 January – Friday, 7 January, 2011

For all practical matters during the meeting, please contact:

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Organizing Committee

Utrecht - WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis

- Bert Leufkens
- Aukje Mantel
- Niesanne ten Cate

Department of Essential Medicines and Pharmaceutical Policies, World Health Organization

- Richard Laing
- Shanthi Pal

Time schedule

Thursday 6 January
International variability in regulatory decision making: a window for insight and learning

09:00 – 10:00	Registration, coffee and tea	
10:00-10:15	Welcome	**Bert Leufkens (UU) + Richard Laing (WHO)**
10:15-11:00	Regulatory Diversity versus Monoculture	**Miles Braun (University of Pennsylvania, UU)**
11:00-11:15	Tea / Coffee	
11:15-12:00	Pharmacovigilance in public health programmes: a need and an opportunity for best practice	**Shanthi Pal (WHO)**
12:00-12:45	Regulatory decisions will always differ. What is the problem?	**Bert Leufkens (UU)**
12:45-14:00	Lunch	
14:00-17:00	Expert panel discussion – lessons learned	
	Moderators:	**Hans Hogerzeil (WHO) + Bert Leufkens (UU)**
	Panel members (besides key note speakers):	**Kees de Joncheere (WHO EURO), Aginus Kalis (HMA/EMA Management Board)**
14:00-14:45	The evaluation of oncology drugs at the EMA and FDA: when differences impact on clinical practice	**Giovanni Tafuri (AIFA, UU)**
14:45-15:30	Marketing authorization of orphan drugs at FDA & EMA: challenging issues + panel discussion	**Michelle Putzeist (UU)**
15:30-16:00	Tea / Coffee	
16:00-16:45	International responses to emerging safety concerns of Erythropoiesis Stimulating Agents + panel discussion	**Hans Ebbers (UU)**
16:45-17:00	Day closure	**Richard Laing (WHO) + Bert Leufkens (UU)**
17:00-18:00	Drinks	

Friday 7 January
Presentations of ongoing pharmaceutical policy analyses

From 08:30	Coffee
09:00-10:30	Paper discussion - 2 parallel sessions 1a: Policy issues and challenges 1b: Regulatory issues and challenges
10:30-11:30	Coffee break with poster session
11:30-13:00	Paper discussion - 2 parallel sessions 2a: Benefit-risk assessment 2b: Rational use of medicines
13:00-13:15	Wrap up and concluding remarks **Bert Leufkens (UU) + Richard Laing (WHO)**
13:15-14:00	Lunch

Presentations of ongoing pharmaceutical policy analyses

Session 1a – Friday 7 January

09:00 – 10:30 - parallel session -

Policy issues and challenges
Session Chairs: Kees de Joncheere + Douglas Ball

Nr	Author	Title
1	**Ziganshina**	Medicines lists as policy instruments in Tatarstan
2	**Leopold**	How much of the price variance of medicines can be explained by external price referencing? – A price comparison among 15 European countries
3	**Cameron**	Promoting increased uptake of generic medicines: an investigation into the potential cost savings of switching private sector consumption from originator brand medicines to generic equivalents
4	**Hoebert**	Contributions to the EU regulatory network and the uptake of new medicines

Session 1b - Friday 7 January

09:00 – 10:30 - parallel session -

Regulatory issues and challenges
Session Chairs: Aukje Mantel

Nr	Author	Title
5	**Hernandez**	Divergence between reports in scientific journals and news media on the role of SSRIs in suicide risk: a longitudinal study in the Netherlands (NL) and United Kingdom (UK) – 2000-2009
6	**Zomerdijk**	Risk minimisation activities of centrally authorised products in the European Union: a descriptive study
7	**Crijns**	Contraception with isotretinoin: a drug utilisation study
8	**Willemen**	Reasons for and time to discontinuation of rimonabant therapy

Session 2a - Friday 7 January

11:00 – 13:00 - parallel session -

Benefit-risk assessment
Session Chairs: Marieke de Bruin + Shanthi Pal

Nr	Author	Title
9	**Caster**	Decision-analytical benefit-risk assessment allowing for qualitatively related clinical outcomes
10	**Ankrah**	H1N1 vaccine adverse events monitoring at the Korle-Bu teaching hospital: an outcome of mass staff immunisation program
11	**Sagwa**	Prevalence and risk factors of adverse effects of second line anti-tuberculosis medicines in a treatment facility in Namibia: 2009-2010
12	**Irunde**	The Cohort Event Monitoring studies in Tanzania: a pro-active medicines safety surveillance

Session 2b - Friday 7 January

11:00 – 13:00 - parallel session -

Rational use of medicines
Session Chairs: Klara Tisocki

Nr	Author	Title
13	**Abuabker**	New policy for antibiotics used for surgical prophylaxis: influence on patients' clinical outcomes
14	**Oliveira Martins**	Off label use of anti-epileptic drugs: a community pharmacy based study
15	**De Bie**	Utilisation of gastro-intestinal drugs in children: cohort study in three European countries
16	**Tetteh**	Outcomes of a post-exposure prophylaxis (PEP) to HIV exposure at the Korle-Bu Teaching hospital (KBTH) in Accra, Ghana
17	**Luiza**	Remedies at home: evaluating an innovative medicines provision program

Posters session Friday 7 January

10.30 – 11.30

Nr	Author	Title
18	**Crijns**	Pregnancy prevention programme of isotretinoin and the adherence of dermatologists
19	**Liang**	The access to expensive biologicals in the Netherlands and Taiwan: a cross-national policy analysis on therapeutic monoclonal antibodies
20	**Bouvy**	The cost-effectiveness of drug regulation: rationale and methods
21	**Moura**	Risk factors in type 2 diabetes: a cross sectional study in Portuguese patients
22	**Ziganshina**	Problem-based teaching and clinical pharmacology services in improving medicine use in children
23	**Santos**	Strategies to improve pharmacist's involvement in pharmacovigilance system
24	**Arnardottir**	Stakeholders' requirements, facilitators and barriers in the uptake of new glucose lowering drugs
25	**Habarugira**	Mapping European activities on HIV/AIDs, malaria and tuberculosis in sub-Saharan Africa
26	**Spiliotopoulou**	Supply chain and resistance implications of drug variety

List of participants UU-WHO winter meeting 6 + 7 January 2011

(as of 20 December 2011)

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- **Arjet Borger**
  Access to Medicine Foundation, the Netherlands
- **Arna Hrund Arnadottir**
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- **Gudrún Stefánsdóttir**
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- **Hans Ebbers**
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- **Marieke De Bruin**
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- **Marjolein Willemen**
  Utrecht University, the Netherlands and Medicines Evaluation Board, the Netherlands
- **Martine van Eijk**
  Instituut voor Verantwoord Medicijngebruik, the Netherlands
- **Michelle Putzeist**
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- **Miles Braun**
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- **Suzanne Edwards**
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- **Tafuri Giovanni**
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- **Toine Pieters**
  Utrecht University, the Netherlands
- **Vera Lucia Luiza**
  National School of Public Health (ENSP), Brazil
- **Yang (Abby) Yu**
  Medicines Evaluation Board, the Netherlands

Overview abstracts 6 January 2011

The evaluation of oncology drugs at the EMA and FDA: when differences impact on clinical practice

Giovanni Tafuri[1,2], Francesco Trotta[1], Jan H. M. Schellens[2,3,4], Richard Laing[5], Hubert G. M. Leufkens[2,3]

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5. Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, CH-1211 Geneva 27, Switzerland.

Background

Different decisions about the same application for marketing approval between leading regulatory agencies may have a strong impact on individual patients and public health. This has paved the way for an increased need for cooperation between drug agencies to optimize harmonization processes and to learn from each other experiences.

Objectives

The aims of this study were to compare the EMA and the FDA approach in the evaluation and approval of new anticancer indications and to identify possible clinical implications associated with these differences.

Methods

Information on the European Union (EU) therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Report (EPAR), publicly available on the EMA website. The information on the therapeutic indications approved in the United States (US) was retrieved from FDA review reports, also available at the FDA website. The following associations with possible regulatory restrictions in indications were evaluated: i) the fact that one agency came first in the approval of the same indication; ii) the use of the same pivotal trial; iii) the robustness of the pivotal study design.

Results

Overall, 42 anticancer drugs were approved by EMA between 1995 and 2008, corresponding to a total of 100 indications. In 57 out of 100 cases the EMA and the FDA based the approval on the same pivotal study. The primary analysis regarding differences between indications approved at the EMA and FDA level revealed that in 52 cases there were no differences between the two regulatory agencies. Only in a single case (i.e. cladribine), a valid comparison was not possible due to a lack of public information on the US label. Therefore, in 47 cases the therapeutic indications as approved by the two agencies showed a difference. For 19 out of these 47 indications, the difference consisted of the fact that one agency approved an indication while the other did not. The remaining 28 cases were further evaluated through an algorithm, highlighting 10 cases where discrepancies in thera peutic indications between EMA and FDA were considered clinically relevant. The dates of appro val in the US and EU were used to calculate which agency came first in the approval of a specific indication. The majority of indications (69%) were firstly approved by the FDA, although a trend shows that there is a continuous increase of first approvals by the EMA. There is a trend (RR=1.71; CI 95%: 0.81-3.62) showing that when the FDA comes first in approving an indication, it is more likely that the same indication will be approved by the EMA with restrictions. Similarly, when the EMA approved first, FDA tended to be more restrictive (RR=2.04; CI 95%: 0.78-5.31).

DISCUSSION

Our analysis shows that differences in approved indications for the same oncology product occurred in about 60% (28 out of 47) of those indications approved by both EMA and FDA. However, neither of the agencies seems to have a prevailing restrictive behaviour over the other. Furthermore, in 21% (10 out of 47) these differences were considered as having a major impact on clinical practice. These different regulatory decisions on the same indication can result in a different place in therapy for the same drug product and/or may exclude a patient subgroup from a treatment. These decisions were taken by the EMA and the FDA on the basis of the same pivotal trials, making these findings relevant for further investigations. Our analysis suggests that decisions taken firstly by an agency may influence the subsequent decision making process at the other agency. Other predicting factors, such as the quality of the study design or the evaluation based on the same pivotal trial, seem not to be associated with more homogeneity between the EU and the US approvals.

CONCLUSIONS

Differences in regulatory decision-making pose various questions on why such differences exist and what consequences these may have for treatment of individual patients and public health. There is no single truth about making complex decisions on the benefit-risk of pharmaceuticals, in this case oncology products. Therefore, regulatory variability may also fuel useful learning across dossiers, thera peutic areas and regulatory systems.

Marketing authorization of orphan drugs at FDA & EMA: challenging issues

M. Putzeist

Rationale

Both FDA and EMA facilitate research and development of orphan drugs by specific orphan legislation. The FDA introduced the Orphan Drug Act in 1983. From 1983-2008 326 ODs received market approval in the US. Since the European Orphan legislation came into force in 2000, 59 new orphan drugs (ODs) have received marketing authorization in the EU, whereas 38 ODs were withdrawn or not approved. In particular in orphan drug development, complying with all regulatory requirements is more challenging for pharmaceutical companies, due to small and heterogeneous patient populations. Consequently, regulators balance benefits and risks of new orphan drugs, taking into account limitations of clinical research and unmet medical needs. Differences in marketing authorization procedures exist between FDA and EMA which may lead to differences in marketing authorization decisions.

Objective

To assess differences in marketing authorization decisions of orphan drugs by EMA and FDA.

Method

(All) marketing authorization applications of orphan drugs at the European Medicines Agency will be compared with their outcome at FDA, if applicable. Inconsistencies in marketing authorization procedure outcomes will be identified and studied in more detail with a focus on characteristics of the orphan drugs and their clinical study design.

Results

Vidaza, Iplex and Vorinostat are examples of orphan drugs that were withdrawn from the EU marketing authorization procedure, while previously authorized by the FDA.

Regulatory responses to emerging safety concerns of Erythropoiesis Stimulating Agents

H.C. Ebbers,[1] A.K. Mantel-Teeuwisse,[1] E.H.M. Moors,[2] H. Schellekens,[2,3] H.G.M. Leufkens[1,4]

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4. Medicines Evaluation Board, The Hague, the Netherlands

Background

Erythropoiesis Stimulating Agents (ESAs) were approved for the treatment and prevention of anemia in patients undergoing chemotherapy in 1993. Over the period 2004-2008, the use of all ESAs for the treatment of chemotherapy-induced anemia has been restricted both in the US and the EU. These restrictions followed (interim) results of post approval clinical trials that indicated increased mortality and tumor progression in patients receiving ESAs compared with patients receiving placebo.

Objective

To assess differences between regulatory actions taken in the US and the EU to restrict the use of ESAs in oncology.

Methods

A descriptive case study of the events leading regulatory actions in the US and the EU was performed. We created an overview of the scientific and regulatory events leading to the restrictions of ESAs.

Results

The safety signal arose from clinical trials and meta-analyses, very few cases were received through spontaneous reporting. The timing and the extent of regulatory actions differed agencies in the US and the EU. The first warnings were issued in the US in 2004, one year earlier than in the EU. The first studies that indicated an increased risk in mortality were performed using off-label treatment targets, leaving controversy on how to interpret this for approved targets. The use of ESA was incrementally restricted following the emergence of new data. In addition, the beneficial effects of ESA treatment were increasingly questioned, while the safety of alternative treatments (blood transfusions) improved. In both regions, the use of ESA is now severely limited, favoring transfusions in some cancer patients undergoing curative treatment.

Conclusions

The benefit/risk ratio of a product changes throughout its life cycle, but the outcome of benefit/risk assessments following emerging safety issues differs across countries. The outcome of the regulatory process may be dependent on less tangible factors.

Oral Presentations

1

MEDICINES LISTS AS POLICY INSTRUMENTS IN TATARSTAN

LE Ziganshina, VN Khaziakhmetova, EG Alexandrova, and TR Abakumova
Kazan State Medical Academy, Russia

Rationale:

Pharmaceutical situation in Russia changed dramatically since 90th. The number of registered medicines kept increasing with over 19000 products by 2010. The new time required re-evaluation of strategic approaches to health and adoption of Essential medicines concept. Governmental project of Supplementary medicines provision for selected patients has been initiated with introduction of corresponding medicines lists.

Objectives:

To compare medicine lists, effective in Tatarstan and Russia, with WHO Model List of Essential Medicines (EML) and identify problems in medicine selection.

Methods:

We analyzed increments in numbers on the lists as compared to WHO EML from 2000. We compared medicines lists effective in Tatarstan in 2009 with the 16th WHO Model List of Essential Medicines, WHO EML: Russian Essential Medicines List, REML (2009), Russian Supplementary Medicines Lists, RSML (2008), Tatarstan Supplementary Medicines List, TSML (2009), Tatarstan Formulary List, TFL (2009).
We used Microsoft Access for list comparisons and developed a database of lists. We calculated portions (percentages) of coincidences and discrepancies. We performed quality analysis of discrepancies according to WHO Essential Medicines Concept.

Results:

The expansion rates exceeded WHO EML expansion rate by 3 times (TFL), by 8 times (REML), and by 10 times (RSML). TSML had the highest percentage of WHO essential medicines and the TFL had the broadest EML coverage. The RSML had the lowest indices for both WHO essential medicines inclusion and the EML coverage. Comparison of listed medicine numbers revealed discrepancies. The discrepancies were uniform through the lists with RSML being the most problematic and reflected vulnerability to pharmaceutical promotion.

Conclusions:

Development of national pharmaceutical policy was urgently needed to further implement the WHO Essential Medicines Concept.

2

How much of the price variance of medicines can be explained by external price referencing? – A price comparison among 15 European countries

C. Leopold[1, 2], L. Seyfang[1], S. Vogler[1], A.K. Mantel-Teeuwisse[2], K. de Joncheere[3], H.G.M. Leufkens[2], R. Laing[4]

(1) Austrian Health Institute (2) Utrecht Institute for Pharmaceutical Sciences
(3) WHO Regional Office for Europe (4) WHO Department of Essential Medicines and Pharmaceutical Policies

Problem statement:

Regulating medicine prices by the implementation of pricing policies such as external price referencing (EPR) is widespread in Europe. The assumption is that countries which apply EPR have lower medicine prices as countries without EPR.

Objectives:

To examine the impact of EPR on the average price level of 15 European countries in 2007 and 2008.

Design:

Cross-country volume-weighted price analysis of a basket with 20 products in 15 countries in 2007 and 2008. Multivariable analysis was performed to account for differences on the gross domestic product, total pharmaceutical expenditure and the national employment in the pharmaceutical industry.

Setting/study population:

A total of 20 products in 15 countries (11 applying EPR and 4 countries without EPR) in 2007 and 2008. The unit ex-factory prices of each product were weighted according to their sales volume. The prices were compared between the two groups of countries with and without EPR as well as over time. For some countries, such as the United Kingdom, the prices were adjusted to exchange rate fluctuations.

Interventions: not applicable

Policy:

External price referencing, a policy where the price(s) of a medicine in one or several countries is used to set or negotiate the price of the product in a given country, is in the majority of EU countries only applicable for prescription-only or reimbursable medicines.

Outcome measure: The average price level in the countries with and without EPR.

Results:

Data will be presented showing that in principle the average prices were lower in countries with EPR. This outcome was especially true for on-patent reimbursable products, which showed a less erratic picture. However, considerable variation was observed between individual products and countries. Regulatory safety discussion (e.g. for Avandia and Actos) had also an influence on the price development of the products. Products which already had generic alternatives on the market had in general lower prices in all countries despite of applying EPR or not.

Conclusions:

Countries with EPR seemed to have more erratic prices. More specific EPR seemed to be a reasonable pricing policy for on-patent reimbursable medicines to have moderate prices.

Key words:

Pharmaceutical policy, price comparison, external price referencing, Europe

Funding Sources:

This study was written as part of a professional PhD programme at the Utrecht Institute for Pharmaceutical Sciences.

3

Promoting increased uptake of generic medicines: An investigation into the potential cost savings of switching private sector consumption from originator brand medicines to generic equivalents

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2 Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

ABSTRACT

Objectives

In low- and middle-income countries, patients purchasing medicines in the private sector pay substantially more for originator brands when generic equivalents exist. When generic medicines are of assured quality there is a potential for patients and health systems to achieve equivalent health outcomes at a lower cost. The potential savings that could be obtained from a hypothetical switch in private sector purchases from originator brand medicines to lowest-priced generic equivalents was estimated for a selection of medicines in low- and middle-income countries.

Methods

The prices of originator brands and their lowest-priced generic equivalents were obtained from facility-based surveys conducted using a standard methodology developed by WHO and Health Action International (HAI). The 15 medicines most commonly included in WHO/HAI surveys, plus 3 statins, were included in the analysis. For each medicine, the volume of private sector consumption of the originator brand product was obtained from IMS Health. Volumes were applied to the median unit prices for both originator brands and their lowest-priced generics to estimate cost savings. Prices were adjusted to 2008 using Consumer Price Index (CPI) data for each individual country.

Findings

Across the countries studied, an average of 9%to 89% could be saved by individual medicine from a switch in private sector purchases from originator brands to lowest-priced generic equivalents. In public hospitals in China, over US 86 million (2008 dollars) could be saved from switching only 4 medicines, saving patients an average of 65%. Across individual medicines, average savings range from 11% for beclometasone 50mcg/dose inhaler to 73% for ceftriaxone 1g/vial injection.

Conclusion

Significant savings could be achieved from switching private sector purchases from originator brand medicines to lowest-priced generic equivalents. Investments in the promotion of quality assured generic medicines are therefore warranted. Strategies include fast-tracking regulatory approval of generic medicines, generic substitution and increasing confidence in generics by professionals and the public.

4

Contributions to the EU regulatory network and uptake of new medicines

J.M. Hoebert[1], A.K. Mantel-Teeuwisse[1], L. van Dijk[2], H.G.M. Leufkens[1]

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2 NIVEL, Netherlands institute for health services research, Utrecht, the Netherlands

Introduction

Governments have various manners to protect, maintain and restore public health and to influence the type and amount of medicines consumed in a country. One way is to contribute to decision making in the market approval procedures by acting as a (co-)rapporteur within the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). This study explores whether countries with a low uptake of newly approved medicines in terms of consumption by volume contribute as individual member states, to the EU regulatory system in terms of the number of (co-) rapporteurships.

Methods

The total number of (co-)rapporteurships of each EU member state between 2004 and 2009 was determined using the European Public Assessment Reports of all centrally authorised medicines. All medicines that received a central market authorisation by EMA in 2004 were selected and data on medicines usage by volume in various EU member states were collected using IMS data. Countries were ranked according to their consumption, defined per 1000 inhabitants/day. Finally, the average ranking per country was set out against the number of (co-)rapporteurships.

Results

The outcome showed no relation between the number of (co-)rapporteurships and the uptake of medicines. Nevertheless, a distinction was seen between the newer and older EU member states. Newer EU member states showed almost no variation in their (low) contribution to the regulatory system but did show large variation in the uptake of new medicines. Older EU member states showed large variation in their contributions but almost no variation in the uptake of these medicines.

Conclusion

There is a clear distinction between the number of contributions to regulatory system between older and newer EU member states. Nevertheless, this does not seem to exert an effect on the uptake of medicines. This study opens the discussion about what the future role of regulatory agencies in the central market authorization should be.

5

Divergences between reports in scientific journals and news media on the role of SSRIs in suicide risk: A longitudinal study in the Netherlands (NL) and United Kingdom (UK) - 2000-2009

J.F. Hernandez[1], A.K. Mantel-Teeuwisse[1], G.J.M.W. van Thiel[2], J.A.M. Raaijmakers[1], T. Pieters[1]

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Background:

SSRIs have improved the treatment of depression in terms of efficacy and safety. However, scientific, regulatory, and, news media scrutiny on the possible risks of suicidality during SSRIs treatment started to escalate since last millennium. Consequently, several regulatory warnings, documentaries, and large numbers of scientific and newspaper articles were issued.

Objectives:

To investigate and compare the nature (positive/negative evaluation) of the articles discussing SSRIs and suicidality in scientific journals and newspapers in NL and UK.

Methods:

We analyzed all articles (2000-2009) from Embase, LexisNexis NL and UK dailies on content. Articles were extracted using keywords and categorized according the type of message, article, and age group mentioned. The articles' positive/negative content message ratio was determined.

Results:

A total of 1736 articles were successfully analyzed: 474 scientific (27.3%), 270 Dutch (15.5%), and 992 British newspaper (57.2%) articles. Scientific articles were predominantly positive (ratio=3.4) and on research (59%, followed by 34%-opinion). Age group distribution in the scientific literature was nearly equally distributed (31%-paediatrics, 25%-adults, 23%-both, and 21%-unspecified). Dutch and British newspaper articles were negative (ratio=0.7 and 0.9, respectively). The majority of type of articles in newspapers was reports (49%-NL and 51%-UK). Other types of articles were science journalism (18%-NL and 14%-UK), interviews (17%-NL and 14%-UK), and opinion (11%-NL and 19%-UK). Newspaper articles reported more on adults (57%-NL and 55%-UK to 14%-NL and 16%-UK on paediatrics). The positive/negative ratios of articles on adults were overall higher (ratio=10-scientific, 1.0-NL, and 1.7-UK) than on paediatrics (ratio=2.3-scientific, 0.2-NL, and 0.2-UK). Newspaper reporting trends were similar in both countries. In all databases, publication peaks coincided with regulatory interventions.

Conclusion:

Newspaper reporting trends were significantly at odds regarding the evaluation of the role of SSRIs in suicide risk with those in scientific journals. Regulatory actions may influence publication patterns in science and news media and vice versa.

6

Risk Minimisation Activities of Centrally Authorised Products in the European Union: A descriptive study

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Keywords

Centrally Authorised Products, drug safety, pharmacovigilance, risk management plan, risk minimisation.

Background

Since the new legislation on Risk Management of November 2005, a Risk Management Plan (EU-RMP) is a required part of the authorisation dossier of innovative drugs licensed in the European Union. The EU-RMP can include additional risk minimisation activities (RMAs) to strengthen the benefit-risk balance of a drug. This study describes the additional RMAs of centrally authorised medicinal products authorised between 1st January 1995 and 1st January 2010.

Methods

The European Public Assessment Reports (EPARs) of all centrally authorised products were analysed to identify characteristics of the product (active substance, the authorisation date, ATC-classification, EU member state acting as Rapporteur), the additional RMAs and the corresponding safety concerns (classified at MedDRA System Organ Class (SOC) level).

Results

Additional RMAs were identified for 57 of the 391 active substances that were authorised during the study period. The proportion of active substances with additional RMAs increased from 4% before to 29% after the new Risk Management legislation. Product classes most frequently concerned blood products and anti-neoplastic and immunodulating products. Additional RMAs always included the provision of educational material, most frequently involving the health care professionals (n=55). Thirty-three active substances required additional RMAs on top of provision of educational material, including patient monitoring most frequently (n=11).

Conclusion

Since the EU-RMP is a legal obligation, the proportion of active substances with additional RMAs has increased substantially. The provision of educational material is the primary additional risk minimisation strategy in the EU. Detailed public information on additional RMAs was limited. Easy access to comprehensive information and transparency might facilitate implementation of additional RMAs.

7

Contraception with isotretinoin: a drug utilisation study

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Background

For a teratogenic drug as isotretinoin a worldwide Pregnancy Prevention Programme (PPP) was implemented. However, still pregnancy cases with in utero exposure to isotretinoin occur. We performed a drug utilisation study to investigate compliance with the isotretinoin PPP by the use of contraceptives.

Materials and Methods

Data from a drug prescription database (containing Dutch community pharmacy data) were used covering a population of 500,000. Contraceptive use in isotretinoin users and in a reference group of non-isotretinoin users (aged 15-49 years) was compared using data from 1999 until 2006.

Results

There were 1825 (651 female, 1171 male) isotretinoin users identified, aged 15-49, during the study period 1999-2006. Of the female isotretinoin users 52-54% used prescribed contraceptives according to the PPP compared to 39-46% in the reference group, which was statistically higher. Similar patterns were seen broken down in age groups. A better compliance was seen for the innovator product compared with generics, for women in rural versus urban areas and in women with preceding therapy of conventional anti-acne treatment compared with no preceding therapy of these treatments. Furthermore, general practioners prescribers had a better performance compared to specialists.

Conclusion

Compliance to risk minimisation measures such as a PPP for teratogenic drugs is lower than intended. Reasons for this low compliance will need to be clarified before further measures can be taken.

8

Reasons for and time to discontinuation of rimonabant therapy

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Abstract

Objective

To explore relations between patient characteristics and reasons for and time to discontinuation. The focus of the study is on psychiatric events, because these were the main area of concern for rimonabant.

Methods

A Modified Prescription Event Monitoring (M-PEM) study was conducted for rimonabant. Descriptive statistics were used to describe the patient population; and relative risks (RR) with 95% confidence intervals (95%CI) were calculated to explore associations between patient characteristics and reasons for stopping (RfS). Kaplan Meier curves were constructed to analyse time to discontinuation.

Results

The cohort comprised 10,008 users of rimonabant. A total of 7,204 patients (72.0%) stopped using rimonabant. Female patients discontinued treatment more frequently than males, independent of the reason for stopping. Patients with a history of psychiatric events stopped treatment more frequently (RfS inefficacy: RR 1.13 (95%CI 1.02-1.26, RfS any safety-related event: RR 1.32 (95% CI 1.17-1.48); RfS psychiatric event 1.79 (95CI% 1.54-2.09)). Patients with cardiovascular disease and type 2 diabetes mellitus discontinued treatment less frequently, independent of the reason for stopping. For patients who discontinued treatment due to inefficacy, the median time to stop was 95 day. For patients discontinuing treatment due to any safety related events and due to psychiatric events, the median times to stop were 62 days and 73 days, respectively

Conclusions

Although in June 2008 the marketing authorisation for rimonabant was suspended, the information on patient characteristics and reasons for discontinuation can be used for the identification and characterisation of the early discontinuers and ultimately may add to further improvement of adherence to therapy and thus to optimalisation of treatment benefits and drug safety.

9

Decision-analytical benefit-risk assessment allowing for qualitatively related clinical outcomes

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Background

Whether in the context of regulatory decisions on initial or sustained marketing, or in the guidance of an individual patient's therapy, the assessment of the benefit-to-risk balance of drugs remains a fundamental challenge. To date a variety of different methods have been proposed, of which none has achieved general acceptance. Whereas decision analysis is a sound general methodology, previous applications in this area have required strictly numerical input regarding the utilities of clinical outcomes. Commonly, data to reliably derive such estimates is unattainable, which forces such approaches to rely on far-reaching assumptions whose validity cannot be determined.

Objective

To demonstrate how decision analysis allowing for qualitative information on the utilities of clinical outcomes can be used for robust benefit-risk assessment.

Method

Our proposed methodology is based on the analysis of clinical decisions, modelled as decision trees and evaluated with respect to expected utility. We make use of computational developments that allow combining belief distributions over the utilities of the outcomes with qualitative relations between these utilities. An example of such a relation is 'successful treatment without adverse effects › unsuccessful treatment without adverse effects › unsuccessful treatment with adverse effects'. We demonstrate how such relations combined with appropriately vague belief distributions, in conjunction with extensive sensitivity analysis, provides for robust benefit-risk assessment whose results can be probabilistically interpreted.

Results

We present reassessments of real examples from the scientific literature. Reassuringly, preliminary results indicate that our approach will in general provide similar results as the original analyses, with the added benefit of better control over utility input. Further, our approach should be more widely applicable since it allows for impreciseness, which is common in practice.

Discussion

One ever-present challenge to be discussed is the definition of what constitutes generally agreeable statements regarding the utilities in a given assessment.

10

H1N1 VACCINE ADVERSE EVENT MONITORING AT THE KORLE-BU TEACHING HOSPITAL: AN OUTCOME OF MASS STAFF IMMUNISATION PROGRAM.

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Introduction

The new swine-origin influenza virus, A(H1N1) originated in Mexico in March 2009. Within months, it was present in almost all the WHO regions and WHO declared a pandemic alert (level 6) on the 11th June, 2009. Because of the limited amount of vaccines received in Ghana, there was a need for prioritization for vaccination. This study reports on vaccine adverse events recorded after vaccination of healthcare workers.

Method

Trained community health nurses were used for the immunization. Five vaccination centers were set up and all workers of the Korle-Bu Teaching Hospital (KBTH) were eligible. Those who have had the infection previously and have been treated were excluded. Injection was given intramuscularly and vaccinees were advised to fill vaccine adverse event forms and return these to specific places or call designated staff members of the Public Health Unit of the KBTH for assistance should they experience any adverse events. Vaccination was done over a period of one week (14th-18th June, 2010) and adverse events were monitored until the end of the next week. The Pandemrix® vaccine with batch number A81CA656A was used.

Results

In all 5870 people were vaccinated. There were 140 reports of vaccine adverse events. Vacinees reported multiple events with an average of four per person. A total of three people were admitted during the period, however, there were no reported fatalities. Overall, the incidence rate of reported cases was 0.024 (95% CI 0.020, 0.028).

Discussion

Most of the adverse effects reported were classified as very common. There were a few common and uncommon vaccine adverse events too. It is important that information on both the benefits and the risks of the vaccine should be made available to the public to improve awareness.

11

PREVALENCE AND RISK FACTORS OF ADVERSE EFFECTS OF SECOND LINE ANTI-TUBERCULOUS MEDICINES IN A TREATMENT FACILITY IN NAMIBIA: 2009-10

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Problem Statement

Namibia reported 286 cases of drug resistant TB in 2007. Second line TB medicines have more frequent and serious adverse effects than first line regimen. The high TB/HIV co-infection is a further complicating factor. With little documented information on the profile, frequency, characteristics and risk factors of these ADRs, managers of tuberculosis control programs, clinicians and patients face challenges in optimizing treatment outcomes.

Objectives

1) To determine the types and frequency of adverse reactions to second-line anti-TB medicines in a selected MDR-TB treatment facility; 2) Identify risk factors for these adverse reactions

Design and Methods

Retrospective cross-sectional design. Data were collected from treatment records of all patients treated for MDR-TB at the study facility between 01-Jan-2008 and 24-Feb-2010 using a structured data collection form. OR and RR (95% CI) were calculated. Logistic regression models were used to calculate the OR for multiple risk factors.

Results

Male (M) 65.5%; Age (mean years ± SD), 36.9 ± 8.4 (M), 31 ± 10.2 (F); Initial weight (mean kgs ± SD), 53.6 ± 7.8 (M) and 49.8 ± 16.4 (F)

Prevalence of ADRs was 90% (53/59 patients). Hearing loss was 47%; GIT events 39%; joint pain 31%; fatigue 19%; headache 19%; dizziness 14% and rash 12%.

73% of the moderate and severe ADRs lasted › 3 months; while 60% of the mild ADRs resolved in ‹ 3 months. ADRs in 53% of patients resolved within 3 months, while 47% suffered ADRs that persisted › 3 months.

In 15% of patients, ADRs were severe and offending drug was discontinued. 9% of patients recovered from their adverse reactions with sequelae.

Risk-factor analysis

OR (95% CI)

Univariate Analysis

Cycloserine regimens and risk of joint pain-6.4 (1.55-26.48); Levofloxacin regimens and risk of hearing loss-0.24 (0.08-0.76); Ethambutol regimens and risk of dizziness- 0.17 (0.03-0.91); Rifampicin regimes and risk of mild ADRs-0.21 (0.05-0.81); Females and risk of skin rash-15.86 (1.75-143.70)

Multivariate Analysis

Age and risk of mild ADRs -1.14 (1.02-1.27); Females and risk of mild ADRs-7.26 (1.00-52.50); HIV status and risk of ADRs-2.99 (0.50-17.89); Initial patient weight and risk of ADRs-0.99 (0.93-1.06)

Conclusions

Although ADRs were highly prevalent in MDR-TB chemotherapy, 85% of the patients tolerated them. Hearing loss was commonest. Findings of risk-factor analysis are statistically imprecise, inconclusive and require further study.

Key Words

Pharmacovigilance; Adverse Drug Reactions (ADRs); Drug-resistant (MDR) TB; Second line anti-TB medicines; Medicine safety

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The Cohort Event Monitoring Studies in Tanzania; a Pro-active Medicines Safety Surveillance

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Abstract

Purpose

The purpose of this paper is to describe the novel method of medicines safety surveillance introduced recently in Tanzania; the Cohort Event Monitoring (CEM) programme.

Rationale

Policy changes in treatment of malaria has lead to introduction of Artemether-Lumefantrine (ALu) as the first line antimalarial drug in Tanzania. Similarly drugs such as tenofovir are being introduced in management of HIV/AIDS, and older medicines such as stavudine are being phased out. The spontaneous adverse drug reaction reporting system alone is inadequate in monitoring safety of medicines hence need of a complementary method. To date, little is known of safety of new medicines used by Tanzania National Malaria Control Programme(NMCP) and National AIDs Control Programme (NACP).

Method

The Tanzania Food and Drugs Authority (TFDA) in collaboration with the World Health Organisation (WHO) undertake prospective observational cohort studies of selected new drugs. Patient cohorts are established from the structured CEM pre-treatment questionnaire filled by healthcare providers at selected CEM sites. Adverse events are reported by healthcare providers using post-treatment or a follow-up questionnaire. Completeness and accuracy of data is performed at TFDA before data entry into the CEMflow database. The method of signal generation is done with particular emphasis on the review of individual event reports and their relationship to the medicine. Signals reported under CEM programme are assessed for the purpose of advising the Ministry of Health and a specific public health programme.

Results

A total of 18 CEM sites in four regions are now collating safety information of antimalarial Artemether-Lumefantrine (Coartem®). Ninety nine staffs have been trained on CEM techniques and are participating in the programme. Six sites have passed feasibility study to participate in CEM of antiretrovirals (ARVs) and data collection will commence soon. To date, 4,000 (target is 10,000) questionnaires on safety of ALu have been collated and 60% entered into the CEMflow database.

Conclusion

CEM type methodology of pro-active safety surveillance is doable in Resource Limited Settings (RSLs), is effective and cost-efficient method though labour intensive.

Key words

adverse drug reactions, adverse events, cohort event monitoring, observational cohort studies, post-marketing surveillance, signal detection, spontaneous adverse drug reaction reporting

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New policy for antibiotics used for surgical prophylaxis: Influence on patients' clinical outcomes.

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Background

Absence of antibiotics policies result in misuse of these agents which contribute significantly to the increase prevalence of antibiotics resistance. In Sudan at different health care levels absence of such policies to govern the use of these agents is a health problem of concern.

Objectives

This study main aim is to identify the influence of a new policy for antibiotics use on surgical prophylaxis on patients' clinical outcome.

Design

Time series, with a baseline phase, interventional phase and monitoring one.

Settings

Khartoum Teaching Hospital – Sudan.

Study population

All adult patients scheduled for elective clean and clean –contaminated surgical procedures will be recruited in the study. Interventions: The interventional phase involves the development of treatment guidelines, distribution and implementation. The development of guidelines involves the adaptation of international guidelines regarding the scientific evidences and selection of specific regimens for the specified surgical procedures based on the local resistance patterns. The distribution involves academic detailing conducted by clinical pharmacists, distribution of printed materials monthly audit and feedback.

Outcomes measures

(1) improvement of performance outcome measures related to the use and administration of antibiotics namely, proper antibiotic selection, proper timing of first preoperative dose and proper discontinuation of antibiotics. (2) Decrease in the rate of surgical infection.

Results

(baseline phase finished; March-October 2010; data under processing), but generally the results showed marked increase in both second generation (cefuroxime) and third generation (ceftriaxone) and co amoxiclav, antibiotics was unnecessary used in clean surgeries, antibiotic first dose was administered in a very narrow time frame before incision made which was not sufficient to allow tissue penetration and finally antibiotics used for a prolonged period range from 5-7 days and more. The rate of infection was ranged between 9-10%, which was high when compared with the rate of infection in such type of surgical procedures in the international publications.

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OFF-LABEL USE OF ANTI-EPILEPTIC DRUGS: A COMMUNITY PHARMACY BASED STUDY

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Rationale

According to the Portuguese Medicines Authority, the use of antiepileptic drugs has grown in the last years, eventually as a result of an off-label use (outside the terms of its Marketing Authorization). This can be harmful for the patients and also increases costs for the Health System as these drugs are reimbursed in Portugal at the maximum level (95% at the time of the study implementation).
Therefore, this study aims to analyse the current pattern of prescription and use of these drugs.

Setting

17 community pharmacies in Lisbon area.

Methods

Cross sectional survey, carried out from Sept. 2009 to Feb. 2010. Inclusion criteria: users with a prescription including at least 1 prescribed antiepileptic drug (all the medicines that have epilepsy approved in the SmPC as main indication).
Information was collected by interview, conducted by trained pharmacy students based on self-reported data.

Preliminary Results

We analyzed data from 481 patients (63.6% females), age range 2-94 years (mean: 52.2). The main consumed antiepileptic drugs were topiramat (16.9%), pregabalin (16.0%) valproic acid (15.6%) and carbamazepine (14.0%). The first prescriber was in 35.0% of the cases a neurologist and in 32.2% a psychiatrist. Epilepsy was the indication in 135 patients. 36.1% of the patients used antiepileptic drugs in off-label indications. The main off-label indications were anxiety (26.8%) and pain (14.1%). Topiramat (28.9%), clonazepan (16.3%) and valproic acid (15.1%) was the anticonvulsants most widely used off-label. Psychiatrists (59.4%) and neurologists (16.4%) were more likely to prescribe antiepileptics off-label.

Conclusions and future research

More than 1/3 of the studied sample used antiepileptic medication in off-label indications. Future steps will include the analysis of data from the whole sample (N=554) and an economic study of the off-label use expenditures per molecule and per type of prescriber (general practitioner, neurologist, psychiatrist and others).

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Utilization of gastro-intestinal drugs in children: cohort study in three European countries

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Background

Gastro-intestinal drugs are widely prescribed to children. Especially the use of prokinetics is controversial due to serious adverse drug reactions (ADRs) like extrapyramidal disorders (EPD) and QT prolongation. Little is known on differences of use throughout Europe.

Objectives

Describe time and age-dependent prescription patterns of proton pump inhibitors (PPIs), Histamine-2 receptor antagonists (H2RA), and prokinetics in children in the Netherlands (NL), Italy (IT), and Spain (ES).

Methods

A retrospective population-based study was conducted to describe drug-use using data from 3 primary care databases in NL (IPCI), IT (Pedianet), and ES (BIFAP).
The study period ran from 1996 to 2008 for NL and from 2001 to 2008 for IT and ES. Annual prevalence of use was calculated (users/1000 PY) and stratified by age and gender.

Results

During the study period, prescribing of PPIs and H_2RAs increased in all countries. The prescribing of prokinetics decreased in NL and IT, and increased in ES. An increase in ES is mainly due to prescriptions of metoclopramide, which are rarely used in NL and IT.
H_2RAs are mainly prescribed in children under the age of 2, with an increase again in puberty. PPIs are hardly prescribed until the age of 12 with, especially in ES, a rapid increase from the age of 12 on. Prokinetics are prescribed in all ages, with a peak until the age of 3 and an increase, mainly in ES, from the age of 13 on.

Conclusions

In the study period there was an increasing use of PPIs and H2RAs in NL, IT and ES. The use of PPIs and H2RAs is highest in puberty, with the highest peak in ES. The use of prokinetics in NL and IT decreased. Cisapride prescriptions were rare from 2001 on in all countries.
Overall big differences exist between the prescription rates of gastro-intestinal drugs in children throughout Europe.

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OUTCOMES OF A POST-EXPOSURE PROPHYLAXIS PROGRAM AT THE KORLE-BU TEACHING HOSPITAL (KBTH) IN GHANA

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BACKGROUND

The Korle-Bu Teaching Hospital (KBTH), Ghana's premier Hospital, started providing antiretroviral therapy to patients infected with the Human Immunodeficiency Virus (HIV) in 2003.It is estimated that currently there are over 10,000 registered HIV patients that are receiving clinical care. Accidental exposure from infected blood/body fluids is a risk to Healthcare workers (HCW) and as part of a comprehensive program, a policy on Post-Exposure Prophylaxis (PEP) was adopted not only to offer services to HCW and but clients (general public exposed to rape or armed attack) who encounter accidental exposure.

OBJECTIVES

To determine the incidence and frequency of accidental exposures, time of initiation of antiretroviral medicines, medication safety and outcomes of the Post-Exposure Prophylaxis among the various HCW referred.

METHODS

A retrospective records review study using data captured on HCW and clients who received PEP at the Korle Bu Teaching hospital between the years 2004-2007. Data on demography, clinical, laboratory, drugs used and the side/ adverse events reported were also documented.

RESULTS

There were a total of 172 respondents of which of 133 (77.3%) were HCW, 22 (12.8%) were clients and 17 (9.9%) were Healthcare students (HCS). Of the 96 (56%) respondents who agreed to do the (HIV) test, none of them was positive. However, those who declined were made up of 63 (83%) HCW, 7(9%) HCS and 6 (8%) clients. The HIV status of the source patients of exposure were as follows: 82 (48%) unknown, 49 (28%) positive and 41(24%) negative. The most common type of exposure was by percutaneous, 158 (91.8%) and mucocutaneous, 14 (8.2%). The means of injury exposure were by needle stick 135 (78.5%), canula 14 (8.1%) and others include rape 9 (5.2%), bloody bite 4 (2.3%) and blood splash 3(1.7%).

Of the 111 HCW who reported for PEP with needle stick injuries,58 (41.4%) were nurses, 48(36.9%) were medical doctors, 17(11%)were HCS ,11(8.1%) ward attendants, 10 (9%) were other health workers and 6 (4.5%) were laboratory staff.

The odds ratio (OR) expressed as odds of exposure for some HCW compared to ward attendants were the following: medical doctor {OR 4.25 [2.18-8.28] (p=0.001)}, nurse {OR 2.26 [1.18-4.34] (p=0.012)} and HCS {OR 0.55 [0.25-1.8] (p=0.116)}

There were 110 cases of side/adverse events recorded, 85(77%) were by patients on dual therapy, with nausea 36(36.5%) and weakness 10(11.8%) being the most predominant. 25(4.7%) patients on triple therapy reported 22 cases of adverse reactions, with 7(35%) nausea, 5(25%) diarrhoea and 4(20%) vomiting.

CONCLUSION

Doctors of the KBTH who reported for PEP have 40% greater risk of exposure to injuries as against nurses who have 20% when both categories of staff are compared with ward attendants.

More public health education on efforts aim at reducing occupational exposures to injuries should be strengthen with emphasis on early reporting for PEP in the Hospital.

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Remedies at home: evaluating an innovative medicines provision program

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Background

The municipality of Rio de Janeiro, Brazil, implemented in 2002 a public medicines provision program to hypertension and diabetes patients consisting in delivering, free of charge, medicines directly to their houses. This program is named "Remedies at home" (Remédio em Casa or RECASA)

Objective

Evaluate the RECASA program considering aspects linked to structure, activities and results.

Methodology

It was conducted a cross sectional survey. Data collection methods included interviews with managers and health professionals, observation of storage conditions and medical records review. All 88 health facilities operating the program were visited. Patients were approached at household level, for what representative sample of 580 was calculated. Indicators were related to financing, human resources, health care, dispensation, adherence to treatment and patient satisfaction.

Results

Related to structure a specific central distribution facility where prescriptions were prepared for delivery was organized. RECASA could count on a specific budget, information system and human resources. Not all procedures were adequately standardized and communicated to professional involved. Consistency problems between information entered in the computerized system and medical records. Most of patients (91.6%) declared to be satisfied with RECASA but only 1% were found to be totally adherent according to MBG scale.

Conclusions

Some good achievements as the structure established to operate the program and patient satisfaction were found. Failures on the program implementation allied to the magnitude of the challenge to operate it in a city with 6.2 million inhabitants and many clusters of violence resulted some bad health care performance.

Financing

FAPERJ

Poster Presentations

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Pregnancy prevention programme of isotretinoin and the adherence of dermatologists

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Background

Isotretinoin is a Vitamin A derivative registered for the treatment of acne since 1982. Because of its teratogenicity, isotretinoin was contra-indicated for pregnancy at licensing. After identification of the isotretinoin embryopathy1 with a frequency of 30% in exposed patient, a Pregnancy Prevention Programme (PPP) was implemented worldwide. Severe acne occurs in 35% in puberty2.
Prescribers (mostly dermatologists) are one group of stakeholders for the PPP for isotretinoin.

Objective

The aim of this survey was to identify the practice of the PPP among dermatologists and their adherence to the PPP prescribing isotretinoin to female patients.

Materials and methods

A questionnaire related to the execution of PPP of isotretinoin was sent to 564 practicing specialist dermatologists and medical interns registered to the Dutch Association of Dermatology and Venereology (NVDV) through e-mail with a link to an online questionnaire.

Results

Hundred-sixty one out of the 564 (28.5%) surveyed dermatologists and interns completed the questionnaire.
Contraception was prescribed by 105 responders (64%). However, if they checked whether the patient is already on contraception or otherwise would give a prescription or refer these patients to the general practioner, this number would become 140 (88%).
94% of the dermatologists were of the opinion that he/she executed the PPP. The response on execution of separate parts of the PPP identified that only 43 (27%) executed the PPP.

Conclusions

Execution of the PPP of isotretinoin by dermatologists is poor and should draw special attention of the regulatory authorities.

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The Access to Expensive Biologicals in the Netherlands and Taiwan: A Cross-National Policy Analysis on Therapeutic Monoclonal Antibodies

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Backgrounds

With therapeutic advance and costly expenditure, biologicals are exerting their influence pushing pharmaceutical policy boundaries. To harness the explosive expenditures by biologicals, governments have exercised more scrutiny in pharmaceutical policies, while confronting the dilemma of maintaining the access to new expensive medicines, financial sustainability and rewards for innovation.

Objectives

This study aims to 1) illustrate the characteristics of marketing and reimbursement authorisation policies in the Netherlands and Taiwan; 2) describe the current access to and utilisation patterns of the four therapeutic monoclonal antibodies (mAbs) in the two countries; 3) identify and analyze the differences in the access to therapeutic mAbs by comparing the relevant national policies in the two countries, as implications for public health.

Methods

The governmental technical reports and statutory documents issued by healthcare regulators, payers, or statistics organisations were used to demonstrate the legal framework of institutions involved in the policy decision-making process surrounding expensive biologicals. The published scientific articles were retrieved in Pubmed by using the keywords regarding the access to expensive medicines in both countries. Drug utilisation data on mAbs were obtained from Taiwan National Health Insurance Research Database (NHIRD) and the Dutch Foundation for Pharmaceutical Statistics (SFK), complied to present the annual expenditure.

Results

The access to mAbs, namely number of marketing /reimbursement approvals and utilisation of marketed mAbs, in the Netherlands is remarkably higher than that in Taiwan. The less marketing approvals in Taiwan could potentially result from the additional requirements for local clinical trials and the strict reimbursement polices. Furthermore, the enormous differences in the mAb utilisation are likely caused by 1) the stringency of cost-containment (reimbursement restrictions, budgetary control), 2) the intensity of risk-sharing schemes (coverage with evidence development, price-volume agreements) and 3) use of Health Technology Assessment (HTA) in the national reimbursement policies

Conclusion

The access to expensive medicines in a country is directly regulated by its reimbursement policies, which are influenced by a country's medical priorities, financial capacity and infrastructure of pharmacoeconomics and outcome research (HTA). In the long run, to maximize the access to new expensive drugs while dealing with its uncertain effectiveness, more holistic strategies are required for the cost-benefit assessment. Meanwhile, the communication, reconciliation and consensus among all stakeholders need to be reached for the better medical access, financial sustainability and innovation.

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The cost-effectiveness of drug regulation: rationale and methods

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ABSTRACT

Rationale/Objective

The costs of bringing one drug to the market are now being estimated at more than one billion US dollars. Pharmaceutical companies are required to show quality, safety and efficacy of drugs before market approval might be granted. In pharmaceutical policy analysis (unlike in reimbursement decisions), cost-effectiveness of regulatory actions thus far has not been an issue. Health technology assessment (HTA) is a well-developed method to evaluate the cost-effectiveness of medical interventions and is increasingly used to inform reimbursement decisions and could be used to evaluate the cost-effectiveness of pharmaceutical regulatory actions.

Methods

Regulatory actions can be evaluated in terms of their cost-effectiveness. All health effects and costs directly resulting from the regulatory action should be estimated. Health effects should be measured in quality-adjusted life years (QALYs) gained. The QALY (health-related quality of life (HRQL) * remaining life expectancy) is the preferred outcome measure in regulatory cost-effectiveness analysis as it is a generic measure that allows for the comparison of different regulatory actions.

Results

Imagine a regulatory action (ECG monitoring of all patients taking a drug) to prevent a rare (10 per one million users) but fatal adverse drug reaction (ADR). 1 million patients use this drug per year. The ADR can be prevented by performing 2 ECGs in all patients using the drug (ECG cost: €20). Patients who take this drug have a HRQL of 0.70 and life expectancy of 70 years. The average age of a user is about 50 years. This means that a patient experiencing the ADR would lose (70-50)*0.7=14 QALYs and therefore the regulatory action of ECG monitoring of all patients would gain 140 QALYs per year, at total costs of €40 million. The cost-effectiveness of the regulatory action therefore is €4 million per death avoided and €286,000 per QALY gained.

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Risk Factors in Type 2 Diabetes: a Cross Sectional Study in Portuguese Patients

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Background

The Diabetology Portuguese Society Guideline for the treatment of type 2 diabetes established the level of glycohemoglobin (HbA1c) in 6.5% or below as a target for glycemic control and algorithms for the use of anti-diabetic medication. Guideline also established control levels for other risk factors.

Objective

The study was aimed to observe the level of agreement with the determinations of the guideline (control of HbA1c, as well as eight other risk markers). Medications were described in order to establish medication profiles.

Methods

Observational database study. Cases were identified in a database recently built in the field of cardiovascular disease and metabolic syndrome. All the patients with clinic diagnostic of diabetes and with one anti-diabetic prescription, at least, were selected. Diabetics only prescribed with insulin and diabetics with prescriptions not specified were excluded.

Results

Database contains 2434 patients, 51.6% female, 50.1% aged ≥ 65 years and 26.9% with cardiovascular disease (CVD).

Patients had a large range of therapeutic agents instituted (from 1 to 5), of which 31.8% were on monotherapy and 50.9% were on bitherapy. On monotherapy, 72.5% of patients were prescribed metformin. On bitherapy, 31.9% of patients were prescribed metformin and DPP-4 inhibitor. Regardless of the treatment regimen, 88.2% of patients were prescribed metformin and 6.1% insulin.

With regard to HbA1c, 30.5% of patients achieved a value ≤ 6.5% (32.3% and 25.6% with or without CVD, respectively). Other risk factors evaluated were smoking, arterial tension, fasting glycemia, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and non-HDL-cholesterol. No one's reached the target of all these nine factors.

Conclusions

We found low levels of glycemic control in these patients as well as an important proportion of patients that were not achieving the target in many others risk factors. Further studies must be developed to correlate type 2 diabetic patient's outcomes and their treatment.

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PROBLEM-BASED TEACHING AND CLINICAL PHARMACOLOGY SERVICES IN IMPROVING MEDICINE USE IN CHILDREN

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Rationale

Prescribing to children remains an important public health problem.

Objectives

To evaluate if problem-based pharmacotherapy in-service teaching by practicing clinical pharmacologists contributes to improvement of medicines use. Reinforcement of clinical pharmacology services in health facilities was intended to improve prescribing and treatment outcomes.

Methods

Intervention non-randomized controlled study was conducted in Tatarstan public primary care facilities and hospitals. Medical records of 920 children with iron-deficiency anemia (2003-2005), with epilepsy - 417 hospitalized and 1266 out-patients (2003-2007), and of 750 hospitalized children with urinary infection (2005-2008) – were randomly selected and studied. Base-line medicine use and treatment outcomes were studied and analyzed. At randomly selected facilities education intervention was carried out by practicing clinical pharmacologists in the problem-based mode with provision of feed-back on medicines use monitoring. Teaching sessions consisted of two week problem-based learning courses and a series of 5 to 7 weekly patient rounds and conferences. Post-education medicine use evaluation was performed within a year - three years after completion of intervention depending on disease. In matching health facilities with the same patient burden medicine use monitoring was performed at the same time intervals (control). Patterns of medicine use were evaluated; the primary study outcome for anemia was recurrence within a year, for epilepsy – remission lasting over one year and over three years, and for urinary infection – clinical and laboratory remission.
Intervention resulted in improvement of prescribing and improved health outcomes of children.

Conclusions

Problem-based pharmacotherapy teaching delivered by clinical pharmacologists needs to be institutionalized and repeated on regular basis for in-service physicians with continuous monitoring of medicine use.

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Strategies to improve pharmacist´s involvement in pharmacovigilance system

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Rational

The national pharmacovigilance system was created in 1992. In 1998, pharmacists were allowed to report adverse drug reactions (ADR) independently.
Although there is relatively little information about the contribution of pharmacists in ADR reporting, they play an important role on drug safety, as they are very sensible for ADR identification.

Objectives

To improve pharmacist´s involvement in pharmacovigilance, particularly increase ADR reporting quality and rate and their collaboration in pharmacovigilance research.

Methods

The study will take place in the Portuguese South regions, in three stages:

1. Characterization of pharmacist´s reports

Analysis of ADR reports based on the national pharmacovigilance database according to the ADR type and severity, medicines most frequently involved and reporting rates from 1998 to 2009. Comparison between hospital and community pharmacist's reports is also performed.

2. Strategies designed

Different approaches were defined according to pharmacist´s environment.
Hospital: focused on pharmacovigilance delegates. A biannual educational program for delegates and encouragement of pharmacist´s collaboration in local pharmacovigilance activities, including drug safety research.
Community pharmacy: periodic distribution of ADR guides, biannual workshops and awareness raising telephone calls.

3. Outcome evaluation

Analysis of trends in the ADR reporting (number and quality of reports) between 2010 and 2011.
Evaluation of pharmacist´s knowledge on pharmacovigilance and their opinion about developed activities.

Early results

The preliminary analysis of the national pharmacovigilance database revealed growing pharmacist´s participation on the pharmacovigilance system. During the studied period, pharmacists reported 2448 ADR. Over two thirds of these reports were made by community pharmacist.
Forty eight per cent of the ADR were classified as serious. The most frequently involved medicines were antiinfectives for systemicuse (21%), central nervous system drugs (16%) and cardiovascular drugs (15%).

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Stakeholders' requirements, facilitators and barriers in the uptake of new glucose lowering drugs

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Background

Increasing demands made by guidelines and regulatory authorities on the requirements for registering new drugs to the market create difficulties in make new drugs available to patients. As a result development costs and times of drugs are increasing. Additionally the number of truly new drugs registered is decreasing each year. It is assumed that the assessors that recommend approval or refusal of marketing authorization base their decision on these guidelines. Which other factors also influence their decision is not yet known.

When a drug reaches the market, doctors will need to make a decision whether they will prescribe the drug to individual patients and the patients will need to make a decision whether they will take the drug. In the case of diabetes a number of different treatment options are available or in the pipeline and different attributes of the drugs may influence the decisions made by the relevant stakeholders. Whether these attributes are similar between the groups is not known.

Study question

What are the stakeholders' requirements, facilitators and barriers in the uptake of new glucose lowering drugs?

Methods

Qualitative study, using open interviews (with cues) with individuals that are representatives of each stakeholder group. Respondents are a purposeful sample of 2 regulators, 10 – 15 health care providers and 8 -10 patients. Interview topics include experience with glucose lowering medication, expectations of a drug that comes new to the market and attitudes towards benefit and risks of drugs that are new to the market. The interviews are recorded and transcribed verbatim. The transcripts are analyzed using the "three-step" method for content analysis. First the transcript is read to familiarize with the content. Secondly statements are coded and thirdly themes from the coding are identified.

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Mapping European Activities on HIV/AIDS, Malaria and Tuberculosis in sub-Saharan Africa

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Abstract

Objectives

The European and Developing Countries Clinical Trials Partnership (EDCTP) is a partnership between 16 European Countries with Sub Saharan African (SSA) countries. EDCTP aims to promote collaboration between European Member States, integrate and coordinate their national research programs, and form research partnership with African researchers in the field of HIV/AIDS, tuberculosis and malaria. The aim of this study was: 1)to provide an overview of key European networks and consortia conducting research activities on the three diseases, 2) to identify where EDCTP Member states are working together with or without the involvement of EDCTP funds.

Methods & findings

We collected data on all recently completed or ongoing clinical trials, capacity building and networking projects in SSA, conducted in partnership with European institutions or agencies. Data were collected from online clinical trials registries, EDCTP database and annual certificates from member states. Were included in the dataset: 254 clinical trials, 92 capacity building and 30 networking projects. Most of the trials are on existing pharmacological products undergoing late phase III or IV. Only a few are investigating new product candidates. On a total of 254 trials, only 69 (including 40 EDCTP-funded trials) are conducted in a collaboration between two or more European countries. We found significant disparities in the distribution of projects in SSA countries, where a country hosts 50 trials sites while its neighboring country hosts no site at all despite similar epidemiological figures in both countries.

Conclusions

The map of European ATM research activities in SSA should be regularly updated, and used to stimulate more collaborations and participation. There is a disparity in distribution of research activities on the continent. The gaps in terms of research and capacity need to be closed. Epidemiological maps of the three PRDs in SSA should be considered before allocating new research funds.

Abbreviations:

- ATM: HIV/AIDS, Tuberculosis and Malaria
- EDCTP: European and Developing Countries Clinical Trials Partnership
- PRDs: Poverty Related Diseases
- SSA: Sub Saharan Africa

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Supply Chain and Resistance Implications of Drug Variety

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Abstract:

Drug efficacy is a public good that is threatened by the emergence and spreadof resistance. Multiple studies show that available drugs should be used in a socially optimal way in order to contain the emergence and spread of resistance. In this paper we quantify the benefits associated with drug variety and compare them against the cost of higher variety in the supply chain.

Extending a simple general disease model to include the emergence and evolution of resistance we show that the percentage of the infected population that cannot be treated is decreasing with the number of available drugs.

Furthermore, we show that drug assortment determines the fraction of the infected population that gets treated.

We compare the benefits of delayed emergence of resistanceand higher treatment seeking with the increase in procurement and safety stock holding costs that result from a wider drug assortment.

Our model lends insights to policy makers into the socially optimal size of the drug assortment.


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