PHARMACOVIGILANCE RESEARCH APPLIED IN PROMOTION OF RATIONAL AND SAFE USE OF MEDICINES: EXPERIENCE FROM RESOURCE LIMITED SITUATION IN VIETNAM

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Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

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Abstract

Objective To ascertain the current burden of adverse drug reactions (ADRs) through a prospective analysis of all admissions to hospital.

Design Prospective observational study.

Setting Two large general hospitals in Merseyside, England.

Participants 18 820 patients aged >16 years admitted over six months and assessed for cause of admission.

Main outcome measures Prevalence of admissions due to an ADR, length of stay, avoidability, and outcome.

Results There were 1225 admissions related to an ADR, giving a prevalence of 6.5%, with the ADR directly leading to the admission in 80% of cases. The median bed stay was eight days, accounting for 4% of the hospital bed capacity. The projected annual cost of such admissions to the NHS is £469m ($706m, $847m). The overall fatality was 0.15%. Most reactions were either definable or possibly avoidable. Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and others than asp gastrointestinal.

Conclusion It accounting for extra costs, ADRs have proved be possible place to reduce further improve.

Methods

The study was conducted from November 2004 to April 2002 in two NHS hospitals in Merseyside: hospital A—a teaching hospital serving a population of 300 000—and hospital B—a district general hospital, serving a population of 330 000. To ensure that there

18 820 patients required hospitalization

1225 (6.5%) caused by ADRs; 0.15% fatal cases

Most of cases were preventable

ADR by either SM (in hospital A) or SJ (in hospital B) if the cause of admission was consistent with the known adverse effect profile of the drug (according to the British National Formulary), if there was temporal relation with the start of drug therapy, and if, after appropriate investigations, other causes were excluded. When the drug history was unclear, we interviewed the patients or relatives or obtained further details from the general practitioner. All patients initially categorised as having an ADR were assessed again by two or
MEDICATION ERRORS IN HOSPITALS

1. Adverse events that are not reactions to the medicines
2. ADRs (not from errors)
3. ADRs (from medication errors)
4. Medication errors that cause harms that are not ADRs
5. Medication errors that don’t cause adverse events

- 5.7% administrations were erroneous
- 1.07 errors/100 patient - days
- 6% hospitalized patients

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Objectives of Pharmacovigilance (EU Good Vigilance Practice 2014):

- Preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure

- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.
PHARMACOVIGILANCE PRACTICE IN VIETNAM
SOME IMPORTANCE DATES

1994: Foundation of Hanoi ADR center

1999: Became full member of WHO monitoring program

3/2009: Foundation of The National DI & ADR Center at Hanoi University of Pharmacy

3/2011: Foundation of the Regional Southern DI & ADR Center at Cho ray hospital, HCM city

06/2015: Issue of the first National Guidelines for Pharmacovigilance

01/2017: New law on Pharmacy
GENERAL GOALS

Building up a comprehensive DI & PV system to ensure drug safety all over the country

Towards a Comprehensive DI and Pharmacovigilance system

Health care system

- Risk management
- Signal evaluation
- Signal establishment

WHO
- Global initiatives
- Financial supporting systems
- Ministerial agencies
- Donors

Business Sector
- Manufacturers
- Exporters
- Wholesalers
- Hospitals
- Clinics
- Pharmacies
- NGOs

Public sector
- Vietnam Drug Administration
- Medical Services Administration
- Regional and Local DI - ADR centers
- Quality control agencies
- Institutions
- Hospitals
- Clinics
- Research and training establishments
- Medical professional associations
- Community organizations
- Press organizations

Usage

unknown side-effect
sub-quality product
medication error
Community

Risk management
Signal evaluation
Signal establishment

Usage
SYSTEM OBJECTIVES

Strengthening and developing a comprehensive Pharmacovigilance System to ensure drug safety in Vietnam

Specific objectives

1. Improve patient care and safety in relation to the use of medicines

2. Detect problems related to the use of medicines and communicate the findings in a timely manner

3. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit

4. Encourage the safe, rational and more effective (including cost-effective) use of medicines

5. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public
PHARMACOVIGILANCE SYSTEM IN VIETNAM
Cycle of processing and information feedback

Safety of medicines
- Quality defects
- ADRs
- Medication errors

National Network
Public Health Programmes,
Hospitals, Pharmacies,
Industry and Consumers

NTP, HIV, malaria,
immunization

National/Regional
DI&ADR Centers

Pharmacovigilance

Drug Information

Analysis

Feedback

UMC database

Regulatory action

Regulatory agencies: DAV, MSA
Other stakeholders: NIDQC

DAV: Drug Administration of Vietnam
NIDQC: National Institute for Drug Quality Control
MSA: Medical Service Administration
ADR DATABASE: IMPORTANT SOURCE FOR RESEARCH

Number of ADR reports received from spontaneous system

ADR Reports cumulative by year
- With SIDCA support
- Under DAV
- Controlled by NDIADRMC

Report number by year

Number of ADR reports
PHARMACOVIGILANCE STUDIES APPLIED IN PROMOTION OF RATIONAL AND SAFE USE OF MEDICINES

PHARMACOVIGILANCE PROCESS

Risk detection
- Spontaneous reporting
- Drug information inquiries
- Evaluation of drug usage/drug utilization

Risk assessment
- Assessing benefit-risk profile

Risk minimisation and communication
- Minimising risk by appropriate regulatory actions including communicating to optimize safe & effective use

Evaluation of taken actions

Data collection
- ADR report
- Drug Information enquiries
- Drug use evaluation (DUE)

Methodology
- Pharmacoepidemiology
- Clinical Pharmacology
SEVERE CUTANEOUS ADVERSE REACTIONS (SCAR) RELATED TO ALLOPURINOL: FROM ADR REPORTS TO RISK COMMUNICATION
A 85 year-old male patient with hyperuricemia, prescribed allopurinol 300 mg/day

After 3 months of administration, patients suffered from:

- Skin exfoliation
- Blisters/ulceration on the mucous membranes
- Fever

⇒ Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)

From a report on a clinical case from The Center of Allergy – Clinical Immunology, Bach Mai Hospital
Detection of allopurinol-SCAR

- 56 cases of SCAR related to allopurinol (2006-2013).

- Risk of SCAR related to allopurinol: PRR = 45.3 (CI95%: 33.9 - 60.6) - highest PRR in the national database.

- Irrational use: Inappropriate prescription: High level of acid uric without clinical symptoms/Tuberculosis (43%), the initial dosage was too high (≥ 300 mg/day: 95.2%). A number of old patients with renal failure were not rationally adjusted dosage.

- Pharmacogenomics: HLA-B 1502
Co-operating with clinical department to collect SCAR cases: the model of Pharmacy Department - The Center of Allergy – Clinical Immunology, Bach Mai Hospital and The National DI&ADR Center

Clinical pharmacist co-operated with resident doctors and staffs from the National DI & ADR Center: detecting and reporting SCAR related to medicines: during the last 6 months of 2013

- Using simple reporting form.
- Training for resident doctors, unifying the process of exchanging information.
- Causality assessment and feedback to reporters
- Periodical review and draw experiences from collected cases

PROMOTING SIGNAL DETECTION BY ENCOURAGING HEALTHCARE WORKERS TO REPORT ADRs
Detected the following type of SCARs: DRESS, SJS/TEN, AGEP: 132 cases

Popularly suspected drug: allopurinol (21 cases)
MANAGEMENT OF HIGH RISK MEDICINES:
CONTRAST MEDIA
Suspended the use of Xenetix 300mg/50ml

CV 14212/QLD-CL dated 30/08/2013
Suspended the use of Xenetix 300mg/50ml
Lot No. 12WC034A and 12WC027C.

CONNECTION OF ADR REPORTING AND RATIONAL USE OF MEDICINES: MANAGEMENT OF HIGH RISK MEDICINES

BỘ Y TẾ
CỤC QUẢN LÝ DƯỢC
Số A/12/QLD - CL
V/v tạm ngừng sử dụng các lô thuốc căn quan Xenetix 300mg/50ml

Kính gửi: - Sở Y tế các tỉnh, thành phố trực thuộc Trung ương;
- VPĐD công ty Hyphens Marketing & Technical Service Pte. Ltd.

Trong thời gian vừa qua, đã xảy ra một số trường hợp phản ứng có hại liên quan đến việc sử dụng các lô thuốc căn quan XENETIC 300 mg/50ml - Số lô: 12WC034A và 12WC027C; SDK: VN-4976-07 do Công ty Guerbet - Pháp sản xuất, Công ty Hyphens Marketing & Technical Service Pte. Ltd đăng ký. Để đảm bảo an toàn cho người sử dụng, Cục Quản lý được thông báo:

1. Tạm ngừng việc sử dụng đối với các lô thuốc căn quan XENETIC 300 mg/50ml - Số lô: 12WC034A và 12WC027C; SDK: VN-4976-07 do Công ty Guerbet - Pháp sản xuất, Công ty Hyphens Marketing & Technical Service Pte. Ltd đăng ký.
# ADR REPORTS RELATED TO CONTRAST MEDIA IN THE NATIONAL DATABASE

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of ICSRs related to contrast media</th>
<th>Total No. of ICSRs in the database</th>
<th>No. of ADR related to contrast media</th>
<th>Percentage of ICSRs related to contrast media /Total No. of ICSRs (%)</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>18</td>
<td>704</td>
<td>44</td>
<td>2.56</td>
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<tr>
<td>2007</td>
<td>29</td>
<td>1328</td>
<td>82</td>
<td>2.18</td>
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<tr>
<td>2008</td>
<td>26</td>
<td>2032</td>
<td>52</td>
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</tr>
<tr>
<td>2009</td>
<td>16</td>
<td>2499</td>
<td>35</td>
<td>0.64</td>
</tr>
<tr>
<td>2010</td>
<td>11</td>
<td>1807</td>
<td>21</td>
<td>0.61</td>
</tr>
<tr>
<td>2011</td>
<td>35</td>
<td>2407</td>
<td>48</td>
<td>1.45</td>
</tr>
<tr>
<td>2012</td>
<td>55</td>
<td>3024</td>
<td>75</td>
<td>1.82</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>13801</td>
<td>357</td>
<td>1.4</td>
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</table>

**Contrast media which were reported in ICSRs:**
- iobitriol (Xenetic), ioxithalamat (Telebrix), ipromid (Ultravist), iopamidol (Pamiray và Iopramio)

*Nguyễn Phương Thúy et al. Pharmaceutical Journal No. 2/2014*
## ADR RELATED TO CONTRAST MEDIA

<table>
<thead>
<tr>
<th></th>
<th>2006 n=18</th>
<th>2007 n=29</th>
<th>2008 n=26</th>
<th>2009 n=16</th>
<th>2010 n=11</th>
<th>2011 n=35</th>
<th>2012 n=55</th>
<th>Total</th>
<th>Percentage % n=190</th>
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<td>Anaphylactic reactions/shock</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>14</td>
<td>31</td>
<td>58</td>
<td>30,5</td>
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<tr>
<td>Fatal cases</td>
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<td>0</td>
<td>1</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>7</td>
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CLEAR SIGNAL OF ANAPHYLACTIC REACTIONS RELATED TO CONTRAST MEDIA IN THE NATIONAL DATABASE

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<td>Cephalosporins</td>
<td>Cefotaxime</td>
<td>403</td>
<td>2337</td>
<td>1.9 [1.2-3.0]</td>
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<td>Ceftriaxone</td>
<td>214</td>
<td>1190</td>
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<td>1.7 [1.4-2.1]</td>
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<td>Ceftazidime</td>
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<td>869</td>
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<td>4.2 [2.9-6.1]</td>
<td>3.2 [2.4-4.4]</td>
<td>2.7 [2.2-3.3]</td>
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<tr>
<td></td>
<td>Cefoperazone</td>
<td>83</td>
<td>388</td>
<td>1.3 [0.4-3.7]</td>
<td>1.8 [0.9-3.1]</td>
<td>1.9 [1.2-3.0]</td>
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<td>Cefalexin</td>
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<td>312</td>
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<td>0.9 [0.5-1.9]</td>
<td>1.0 [0.6-1.7]</td>
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<td>Cefepime</td>
<td>20</td>
<td>111</td>
<td>---</td>
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<td>2.0 [0.7-5.4]</td>
<td>1.6 [0.8-3.2]</td>
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<tr>
<td></td>
<td>Cefazolin</td>
<td>19</td>
<td>113</td>
<td>0.9 [0.1-7.1]</td>
<td>1.1 [0.3-3.7]</td>
<td>1.4 [0.6-3.3]</td>
<td>1.4 [0.7-2.7]</td>
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<td>Cefitoxime</td>
<td>18</td>
<td>91</td>
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<td>8.8 [1.2-63.1]</td>
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<td>2.1 [0.8-5.1]</td>
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<tr>
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<td>Cefadroxil</td>
<td>16</td>
<td>69</td>
<td>---</td>
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<td>5.0 [2.1-12.0]</td>
<td>3.1 [1.5-6.1]</td>
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<td>Penicillins</td>
<td>Ampicillin</td>
<td>56</td>
<td>382</td>
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<td>1.8 [1.0-3.2]</td>
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<td>Phenoxybenzylpenicillin</td>
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<td>47</td>
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<td>4.3 [1.5-12.8]</td>
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<td>Benzylpenicillin</td>
<td>15</td>
<td>83</td>
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<td>Aminoglycosides</td>
<td>Gentamicin</td>
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<td>1.9 [0.9-3.9]</td>
<td>1.6 [0.9-2.9]</td>
<td>1.7 [1.1-2.7]</td>
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<td>Amphenicols</td>
<td>Chloramphenicol</td>
<td>17</td>
<td>82</td>
<td>4.4 [1.5-13.0]</td>
<td>2.1 [0.8-5.5]</td>
<td>2.6 [1.2-5.5]</td>
<td>1.8 [0.9-3.7]</td>
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<td>Anesthetics</td>
<td>Lidocaine</td>
<td>42</td>
<td>144</td>
<td>3.4 [0.9-12.7]</td>
<td>2.7 [1.1-6.8]</td>
<td>3.8 [2.1-6.7]</td>
<td>4.3 [2.8-6.5]</td>
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<td>Propofol</td>
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<td>54</td>
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<td>2.9 [1.3-6.5]</td>
<td>4.3 [2.5-7.7]</td>
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<td>Bupivacaine</td>
<td>17</td>
<td>67</td>
<td>2.4 [0.3-21.8]</td>
<td>1.0 [0.1-8.3]</td>
<td>1.9 [0.5-6.6]</td>
<td>2.0 [0.9-4.4]</td>
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<tr>
<td></td>
<td>Fentanyl</td>
<td>11</td>
<td>62</td>
<td>---</td>
<td>2.3 [0.6-9.0]</td>
<td>2.7 [1.3-5.4]</td>
<td>2.6 [1.4-4.7]</td>
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<tr>
<td>Contrast media</td>
<td>Iobitridol</td>
<td>30</td>
<td>122</td>
<td>---</td>
<td>2.8 [0.7-10.3]</td>
<td>1.2 [0.4-3.6]</td>
<td>2.2 [1.3-3.8]</td>
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<tr>
<td></td>
<td>Ioxitalamic acid</td>
<td>26</td>
<td>80</td>
<td>9.9 [1.4-70.9]</td>
<td>12.5 [3.9-39.6]</td>
<td>2.7 [1.2-6.1]</td>
<td>2.6 [1.4-5.0]</td>
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<tr>
<td></td>
<td>Iopromide</td>
<td>25</td>
<td>78</td>
<td>---</td>
<td>3.8 [1.3-11.1]</td>
<td>2.1 [0.8-5.8]</td>
<td>3.4 [1.9-6.2]</td>
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<tr>
<td>Antacid</td>
<td>Omeprazole</td>
<td>15</td>
<td>81</td>
<td>3.7 [0.4-36.3]</td>
<td>3.9 [1.4-11.3]</td>
<td>2.4 [1.0-5.6]</td>
<td>1.6 [0.8-3.3]</td>
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<tr>
<td>Solution additives</td>
<td>Amino acid</td>
<td>18</td>
<td>86</td>
<td>4.3 [1.1-17.7]</td>
<td>3.5 [1.4-8.4]</td>
<td>2.9 [1.3-6.1]</td>
<td>2.0 [1.0-3.8]</td>
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<tr>
<td>Hematological agents (enzymes)</td>
<td>Chymotrypsin</td>
<td>36</td>
<td>175</td>
<td>3.7 [0.9-14.1]</td>
<td>2.0 [0.7-5.3]</td>
<td>2.3 [1.2-4.2]</td>
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<td>Antifibrinolics</td>
<td>Tranexamic acid</td>
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<td>33</td>
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<td>8.6 [1.7-43.0]</td>
<td>9.7 [3.5-27.0]</td>
<td>9.3 [3.9-21.0]</td>
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<td>Muscle relaxants</td>
<td>Atracurium</td>
<td>16</td>
<td>23</td>
<td>---</td>
<td>9.0 [0.6-159.1]</td>
<td>20.5 [3.7-112.3]</td>
<td>21.2 [6.5-69.0]</td>
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<tr>
<td>System hormonal preparation</td>
<td>Oxytocin</td>
<td>18</td>
<td>125</td>
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<td>1.8 [0.5-6.2]</td>
<td>2.7 [1.2-6.0]</td>
<td>2.6 [1.4-4.7]</td>
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<tr>
<td>Antineoplastic agents</td>
<td>Oxaliplatin</td>
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<td>9.4 [0.6-151.2]</td>
<td>1.7 [0.2-14.9]</td>
<td>0.9 [0.1-6.8]</td>
<td>2.6 [0.9-7.2]</td>
</tr>
</tbody>
</table>

---: anaphylaxis signal was not detected

MANAGEMENT APPROACH: DEVELOP AND A STANDARD GUIDELINE ON CONTRAST MEDIA USAGE IN CLINICAL PRACTICE

Based on ESUR Guidelines on Contrast Media

Bảng 4: Các yếu tố nguy cơ có thể gây phản ứng tương tự điều ống với thuốc cần quang

1. Phản ứng với thuốc cần quang trước đó
2. Tiền sử dị ứng
3. Bệnh tim mạch
4. Mất nước
5. Bệnh thận
6. Tuổi: trẻ sơ sinh/ người cao tuổi
7. Bệnh về huyết học/ chuyển hóa (vd: hồng cầu linh liem, đa hồng cầu)
8. Lo áu/ trầm cảm
9. Thuốc: thuốc chẹn beta, interleukin-2, aspirin, NSAID
10. Mùa: thời kỳ điều ống phán hoạ

Bảng 5: Hướng dẫn xử trí sốc phản vệ của ESUR năm 2004

1. Gọi nhôm hô sức
2. Đất nội khí quản nếu cần thiết
3. Nắng cạo chân bệnh nhân nếu bị hạ huyết áp
4. Thở oxy (6-10 L/ phút)
5. Tiêm bắp adrenalin (epinephrine) [1:1000], 0,5ml (0,5mg) với người lớn, nhắc lại nếu cần. Đối với trẻ nhỏ: 0,01mg/kg đến lớn tối đa 0,3mg
6. Truyền dung dịch tĩnh mạch (ví dụ: dung dịch mui, dung dịch Ringer Lactat)
7. Thuốc kháng histamine H_{1} (ví dụ: tiêm tĩnh mạch diphenhydramin 25-50mg)
MANAGEMENT APPROACH: DEVELOP AND A STANDARD GUIDELINE ON CONTRAST MEDIA USAGE IN CLINICAL PRACTICE

SOPs and form to control the usage of Contrast Media

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Evaluate usage of contrast media</td>
</tr>
<tr>
<td>2.</td>
<td>Monitor adverse reactions (ADRs) related to contrast media</td>
</tr>
<tr>
<td>3.</td>
<td>Control the usage of contrast media</td>
</tr>
</tbody>
</table>

**Standard Operation Procedure**

To monitor ADRs related to Contrast Media
PROMOTING SIGNAL DETECTION BY TARGETED REPORTING

Working group: clinical pharmacists + radiologists
- Simple form
- Training and regular meeting
- Causality assessment and feedback

Targeted reporting form for contrast media products at Bachmai hospital (Hanoi) and impact on number of ADR report
Management of high risk medicines: Assessing the risk of Contrast-induced nephropathy (CIN)

- Cohort on patients prescribed contrast media
- 40 patients experienced CIN (7.1%), in which 6 cases (1.1%) were clinically significant contrast induced nephropathy (CSCIN)

Risk factors:
- Age > 70: OR = 2.28 (1.11-4.68)
- Low renal clearance (< 30 ml/min): OR = 7.97 (2.49-25.57),
- High Volume of IV injection (> 200 ml): OR = 3.12 (1.12-8.68)
LIVER INJURY RELATED TO MEDICINES:
FROM ADR reports, COHORT, ACTIVELY SCREENING TO RISK COMMUNICATION
DILI: serious reactions, life-threatening, needing to identify exactly suspected medicines to stop the administration.

DILI is drawn less attention and less reported.
Screening drug-induced liver injury in the database of laboratory tests at Huu Nghi Hospital

1. All of AST & ALT tests at the Biochemical Department
   - Selection criteria

2. AST & ALT tests met the selection criteria
   - Definition of Liver Injury

3. Patients met the definition of Liver Injury
   - Additional criteria

4. Patients met the additional criteria
   - Collecting patient information

5. Assess liver injury by RUCAM scale
Screening drug-induced liver injury in the database of laboratory tests at Huu Nghi Hospital

- Screening 36771 ALT test and 881 ALP test (11809 in-patient entries in 2015)
- Detected 37 suspected cases in which 22 cases were DILI.
- Estimating the incidence of DILI: 0.11% in-patient, 6% patients with abnormal liver function tests
- Most of liver injury was severe and able to recover after 1 week to 1 month since drug withdraw
- Antibiotic (fluoroquinolone, amoxiclav) were the most frequently detected group

Case series from Department of Infectious Diseases, Bach Mai Hospital

National guideline of diagnosis, treatment and prevention of Tuberculosis

(Ban hành kèm theo Quyết định số: 4263/QĐ-BYT ngày 13 tháng 10 năm 2015 của Bộ trưởng Bộ Y tế)

2.2.2. Điều trị lao tiêm ẩn bằng INH:

- Đối tượng:

  + Tất cả những người nhiễm HIV (người lớn) đã được sàng lọc hiện không mắc bệnh lao.

  + Trẻ em dưới 5 tuổi và trẻ 0-14 tuổi có HIV sống cùng nhà với người bệnh lao phổi, những trẻ này được xác định không mắc lao.

vs. the opposite opinion from literature …

Isoniazid-associated hepatitis in HIV-infected adults receiving thirty-six months isoniazid prophylaxis in Botswana

LIVER TOXICITY IN HIV-INFECTED PATIENTS USED ISONIAZID PREVENTIVE THERAPY HIV/AIDS OUT-PATIENT CLINICS, DEPARTMENT OF INFECTIOUS DISEASES, BACH MAI HOSPITAL

- Retrospective cohort: 833 patients
- No. of patients experienced liver injury: 29 (3.5%).
- Average onset time of liver injury: 11.4 ± 9.4 (months)
- 25 patients required drug withdrawal. 100% patients recovered.
- Independent risk factor (multivariate analysis): ALT baseline: OR = 1.02 (1.00-1.03), p=0.043 and HCV co-infection: OR = 3.82 (1.59-9.18), p= 0.003
- Adherence to the National guideline is highly recommended, closely monitoring high risk patients

Cumulative incidence of liver toxicity during the administration of isoniazid preventive therapy

COLISTIN DOSAGE REGIMEN: BALANCE OF EFFECTIVENESS AND TOXICITY
Colistin is a re-emerging antibiotic used as the last resort for multi-resistant Gram (-) bacterial infections.

Identifying rational colistin dosage regimen in critically ill patients is a huge challenges in clinical practice.

Balance of effectiveness (depended on dose) and nephrotoxicity (also dose-dependent).
Assessing effectiveness/safety of colistin low-dose regimen (Hospital guideline 2012)

- Prospective cohort in 28 critically patients with severe nosocomial infections from at the Department of Intensive Care unit, Bach Mai hospital.
- Average dose of colistin $4.1 \pm 1.6$ MIU/day
- Microbiological cure (day 5): 62.5%.
- Mortality (day 14): 28.6%.
- Nephrotoxicity: 21.4%
- However, the group of failure cure had higher MIC than the group of bacterial cure ($0.38$ vs $0.125$, $p = 0.022$)
Changes of MIC of colistin for *Acinetobacter baumanii*: signal for dosage revision?
### Assessing effectiveness/safety of colistin high-dose regimen (recommended by EMA based on PK/PD data) (2015)

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Dose</th>
<th>Time of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital – acquired infection</td>
<td>Loading: 9 MUI (applied to all patients)</td>
<td>90 min (in 250ml)</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 3 MUI every 8h</td>
<td>60 min (in 100ml)</td>
</tr>
</tbody>
</table>

**Dose modification in renal failure patients**

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>3 MUI every 8h</td>
</tr>
<tr>
<td>30 – 50</td>
<td>4 MUI every 12h</td>
</tr>
<tr>
<td>10 – 30</td>
<td>3 MUI every 12h</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>2 MUI every 12h</td>
</tr>
</tbody>
</table>

- **Hemodialysis HD**
  - Day of no HD: 1 MUI every 12h.
  - Day of HD: 1 MUI every 12h + 1MUI right after HD

- **CVVH**
  - 3 MUI every 8h
Assessing effectiveness/safety of colistin high-dose regimen (2015)

- Prospective cohort on 44 infectious patients at ICU, Bạch mai Hospital
- Colistin high-dose regimen, average dose 8.3 MIU/day.
- Factor affecting on treatment outcome: age, severity (SOFA, APACHE II score, renal failure at baseline). MIC of colistin does not affect.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response, n (%)</td>
<td>31 (70.5)</td>
</tr>
<tr>
<td>Microbacterial response, n (%)</td>
<td>31 (70.5)</td>
</tr>
<tr>
<td>Both clinical and microbacterial response</td>
<td>23 (52.3)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
</tr>
<tr>
<td>In Day 14</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>In Day 28</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>During the time hospitalized in ICU</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td><strong>Incidence of nephrotoxicity</strong></td>
<td>14 (31.8)</td>
</tr>
</tbody>
</table>
Develop a new dosage regimen of colistin to balance efficacy-toxicity

Nephrotoxicity related to colistin

Risk factors (cox regression multivariate analysis)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Theo thời gian dùng thuốc</th>
<th>Theo liều colistin tích lũy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR hiệu chỉnh CI 95%</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>1,03 (1,01 – 1,05)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1,05 (1,01 – 1,09)</td>
<td>0,009</td>
</tr>
<tr>
<td>Sepsis shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin increases</td>
<td>4,14 (0,90 – 19,06)</td>
<td>0,068</td>
</tr>
<tr>
<td>Colistin ≥4mg/kg/day</td>
<td>3,10 (1,41 – 6,81)</td>
<td>0,005</td>
</tr>
<tr>
<td>Co-administration of furosemid</td>
<td>2,54 (0,92 – 7,00)</td>
<td>0,072</td>
</tr>
<tr>
<td>Co-administration of inotropic drugs</td>
<td>2,65 (1,21 - 5,80)</td>
<td>0,015</td>
</tr>
</tbody>
</table>

- Retrospective cohort in 131 patients used colistin. 30 (22.9%) patients experienced nephrotoxicity
- Independent factors were age, weight and high dosage of colistin

Protocol 2016: Balance efficacy and toxicity of colistin

The new protocol was implemented in ICU-Bach Mai hospital based on Garonzik calculation (2011) with weight adjustment, $C_{\text{target}} = 2 \, \mu\text{g/ml}$ (MIC$_{90}$ of colistin with multi-resistant Gram (-) from 2012-2015 was 0.5 \(\mu\text{g/ml}\))

<table>
<thead>
<tr>
<th>WEIGHT-BASED LOADING DOSE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30kg</td>
<td>4 MUI</td>
</tr>
<tr>
<td>&gt; 30 – 40kg</td>
<td>5MUI</td>
</tr>
<tr>
<td>&lt; 40- 50kg</td>
<td>6MUI</td>
</tr>
<tr>
<td>&gt; 50- 60 kg</td>
<td>7MUI</td>
</tr>
<tr>
<td>&gt; 60- 70kg</td>
<td>8MUI</td>
</tr>
<tr>
<td>Trên 70kg</td>
<td>9 MUI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MAINTENANCE DOSE BASED ON RENAL FUNCTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCr &lt; 15m/phút</td>
<td>3 MUI mỗi 24 giờ</td>
</tr>
<tr>
<td>ClCr: từ 15 - 30ml/phút</td>
<td>2 MUI mỗi 12 giờ</td>
</tr>
<tr>
<td>ClCr: từ 30 - 50ml/phút</td>
<td>3 MUI mỗi 12 giờ</td>
</tr>
<tr>
<td>ClCr: từ 50 - 80ml/phút</td>
<td>4 MUI mỗi 12 giờ</td>
</tr>
<tr>
<td>ClCr: ≥ 80ml/phút</td>
<td>3 MUI mỗi 8 giờ</td>
</tr>
<tr>
<td>Lọc máu ngắn quãng (HD)</td>
<td>2 MUI mỗi 24 giờ, bổ sung 1 MUI sau lọc</td>
</tr>
<tr>
<td>Lọc máu liên tục(CVVH)</td>
<td>3MUI mỗi 8 giờ</td>
</tr>
</tbody>
</table>
Pharmacovigilance: ensuring the safe use of medicines

Pharmacovigilance (PV) is defined as the *science and activities* relating to the *detection, assessment, understanding and prevention* of adverse effects or any other drug-related problem.

**Objectives of Pharmacovigilance** (EU Good Vigilance Practice 2014):

- **Preventing harm from adverse reactions** in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure
- **Promoting the safe and effective use of medicinal products**, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.
Lesson learnt…

- Pharmacovigilance was born in clinical practice context, aimed at managing drug related problems.
- Clinical practice serves as an important/critical resource for development of research question, hypothesis, hypothesis confirmation, for implementation interventions as well as impact evaluation
- Pharmacovigilance through pharmacoepidemiological, clinical pharmacology and clinical pharmacy approaches could help step by step the detection, evaluation, understanding and prevention of drug related problems in daily practice.
Acknowledgments

Hospitals and healthcare professionals

NGOs

PV team
Acknowledgments to ASEAN PharmNet

2015

BUILDING UP A SUSTAINED AND PRO-ACTIVE PHARMACOVIGILANCE SYSTEM IN A RESOURCE-RESTRICTED COUNTRY: EXPERIENCES FROM VIETNAM

Hoang Anh NGUYEN, Dang Hoa NGUYEN
National Center for Drug Information and ADR monitoring
& Hanoi University of Pharmacy
Hanoi, Vietnam

The 1st International Conference on Pharmacy Education and Research Network of ASEAN “Harmonizing the Diversity of Pharmacy Profession in the Era of AEC”, December 2-4th, 2015, Bangkok, Thailand

Overview of Pharmacovigilance System in Vietnam: Lessons Learned in a Resource-Restricted Country

Khac-Dung Nguyen1,2 † Phuong-Thuy Nguyen1 † Hoang-Anh Nguyen1 † Anne Roussein1 † Jean-Louis Montastruc1,3 † Haldh Bagheri1,3 † Sten Olsson1

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Abstract Drug safety issues in developing countries are complex and sensitive, and health authorities cannot always simply implement decisions from developed countries because the health system, disease patterns, and lists of marketed drugs all differ. A system for proactive and effective surveillance of drugs in each nation is needed to identify and manage the exact drug-related problems faced by patients in these countries. Vietnam launched its university-based National Drug Information and Adverse Drug Reaction Monitoring Centre (NDIADRMC) in 2009, a significant step towards catching up with international trends. Although the center is still in its infancy and has limited resources, it has attained some achievements and largely met the minimum World Health Organization requirements for a functional pharmacovigilance center.

The number of reports has increased rapidly, with some important signals generated from the national database leading to regulatory actions at a national level. In addition, this system can help detect drug-quality problems that are less common in developed countries. The success of the quantity and quality of reporting, risk assessment, and communication is still limited compared with more developed systems. A number of opportunities remain to enhance the system, particularly in risk communication and evaluation of the impact of pharmacovigilance, and to apply reporting outcomes to reduce drug-related risks throughout the country. More internal and external support is needed to develop a stronger and more comprehensive pharmacovigilance system.

Key Points

As an independent university-based center, the National Drug Information and Adverse Drug Reaction Monitoring Centre (NDIADRMC) in Vietnam has benefited from the well-educated human resources and research capacities of the Hanoi University of Pharmacy and close coordination with the drug regulatory authority in managing all pharmacovigilance activities.

With national and international support (from the Global Fund) and increasing participation from clinical pharmacists in reporting adverse drug reactions, the NDIADRMC has been able to solve drug safety problems to some extent, especially the detection of drug-quality signals.

An interactive two-way mechanism between the NDIADRMC and healthcare units has been created to enhance the quality of the pharmacovigilance process, from signal detection to risk management.
THANKS FOR YOUR ATTENTION