ADR surveillance in Hospital

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Adverse Drug Reaction (ADR)

Definition by WHO

“A response to a drug that is noxious and unintended and occurs at doses normally used in man”

Serious ADR

- Death
- Hospitalisation
- Life-threatening
- Disability/incapacity
- Congenital abnormality/birth defect
- Important medical event/medical intervention

Death
Hospitalisation
Life-threatening
Disability/incapacity
Congenital abnormality/birth defect
Important medical event/medical intervention
# Classification of ADR

<table>
<thead>
<tr>
<th>Types of Reactions</th>
<th>Character</th>
<th>Features</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Dose-related</td>
<td>Augmented</td>
<td>Common, &amp; Predictable</td>
<td>Toxic effects, Side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low mortality</td>
<td></td>
</tr>
<tr>
<td>B: Non-dose-related</td>
<td>Bizzare</td>
<td>Uncommon, &amp; Unpredictable</td>
<td>Immunol. R. Idiosyncracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High mortality</td>
<td></td>
</tr>
<tr>
<td>C: Dose-related &amp; Time-related</td>
<td>Chronic</td>
<td>Uncommon</td>
<td>HPA axis sup. by steroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Related to the cumulative dose</td>
<td></td>
</tr>
<tr>
<td>D: Time-related</td>
<td>Delayed</td>
<td>Uncommon</td>
<td>Teratogenic Carcinogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually dose-related</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacovigilance (PV)

- **Definition**
  
  “The science of collecting, monitoring, researching, and evaluating information from health care providers and patients regarding **ADRs**”

- **PV includes...**
  - Post-marketing survey (PMS), Active surveillance...

Post-marketing PV in Korea

의약품 재심사
- 1995년 도입
- 신약 또는 일부 전문의약품 대상
- 품목허가 시점부터 4년-6년

의약품 재평가
- 1975년 도입
- 허가된 모든 의약품 대상

의약품 부작용 모니터링
- 1988년부터 실시
- 2004년 제약사 의무 보고
- 중대한 유해사례 및 이미 알려진 부작용 모두 보고
<table>
<thead>
<tr>
<th>Year</th>
<th>PV Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>자발적 부작용 보고 제도 도입</td>
</tr>
<tr>
<td>1990.8</td>
<td>의약품등안전성정보관리규정 제정</td>
</tr>
</tbody>
</table>
| 2000 | 부작용 보고 식약청 홈페이지 통해 반기 시작  
| | 우수보고자 포상 시작 |
| 1999~2001 | 유해사례 모니터링기관제도 시행 |
| 2006.5 | 의약품부작용 보고 활성화 조치 (분기보고 도입) |
| 2006.5~2008.11 | 지역약물감시센터 지정사업 |
| 2007.10 | 약사법 개정-‘안전관리책임자 지정’ 의무화 |
| 2009~2011 | 약물감시사업단 연구사업 |
ADR collection of Regional PV Centers

2010년도: 36,456 건
Collected ADRs in KFDA

100 ADRs/100,000 people

20 regional PV centres
1. Spontaneous Reporting

2. Stimulated Reporting

3. Active Surveillance
Spontaneous Reporting (1)

- Basic but important method for PV

- Reporting sources
  - Physicians
  - Pharmacists
  - Nurses
  - Patients and their family
  - Pharmaceutical company
Spontaneous Reporting (2)

- Signal detection after marketing
- Rare ADR detection
- Serious ADRs in specific groups
  - Old age/Childhood/Pregnant women
- Limitations
  - ADR recognition and assessment
  - Under reporting due to ignorance
  - Bias
  - Drug exposure level
  - Quality of report
Specified risk management (RM) program

- All patients who prescribed specific drug
- All vs. specified ADRs

Incidence of ADR

Limitations

- Well designed RM program
- Manpower, time, other investments
>5% admissions were associated with ADRs

Increased risk of death (OR 1.208) and length of hospital stay (8.25%)

Significant cause of death in infants and children aged ≤2 years


Bond CA et al. Pharmacotherapy. 2006

Limitations of Pre-marketing Clinical Trial

- Strict exclusion criteria
  - Elderly, Pregnant women
  - Liver/Kidney disease patients
  - Co-morbid patient
  - Other drug usage
- Limited number of patient
Hospital Setting

Diagnosis
Prescription

Preparation

Administration
- IV/IM
- Oral

CT or MRI
Using RCM
Hospital Setting

Monitoring

Monitoring

Monitoring

Monitoring

Monitoring
Hospital Setting

Reporting

ADRs
의사·치과의사, 한의사, 간호사 및 약사·한약사 … 는 의약품 등의 투여·사용 중 발생하였거나 알게 된 유해사례나 약물 유해반응에 대하여 … 이를 식품의약품안전청장 또는 의약품 등의 제조업자 등에게 보고할 수 있다.

식품의약품안전청고시 제 2009-208호
의약품 등 안전성 정보관리 규정
What should we report?

1. 중대한 유해사례-약물유해반응
2. 예상하지 못한 약물유해반응
3. 이미 알려진 약물유해반응
4. 오-남용 또는 약물상호작용, 과량투여로 인한 유해사례
5. 의약품에 의하여 발생함 경미한 유해사례
6. 기타 의약품 등의 안전성 관련 정보 (임상검사 치 영향 등)

식품의약품안전청고시 제 2009-208호
의약품 등 안전성 정보관리 규정
Sometimes very difficult to report

Primarily depend on reporter’s opinion

- Indifference
- Ignorance
- Lack of time
- Nuisance

Pushkin R et al. Postgrad Med. 2010
**Underreporting of ADRs**

- **Widespread significant problem**
  - 37 studies from 12 country
  - Median underreporting rate: 94%
  - Lower median rate for serious ADR: 85%
  - 4-10% of TEN was reported (5 yrs)

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**Fig. 1.** The distribution of under-reporting rates across 37 studies.

Hazell L *et al.* *Drug Saf.* 2006
Reporting sources

- **To FDA Most ADR reports from...**
  - Manufacturers (~94%)
  - Health care professionals (~10%)

- **To KFDA Most ADR reports from...**
  - Health care professionals (68%)
  - Manufacturers (32%)
Position to be an integral component of ADR reporting

1. ADR is a cause of admission
   - Ideal opportunity to recognize ADRs and to evaluate their causal relationship

2. New medication started in the hospital
   - Patient was under direct observation
   - Easy to assess causality
     - Temporal relationship/Dechallenge/Rechallenge
Change of reporting culture of institution

- Commitment from hospital administration
- Individual employees to motivate to report
  - ? Rewards

Goal setting

- Broad vs. Specific
- Select department or unit or personnel
Most frequently used method to improve reporting

- Non-punitive approach to ADE (84.6%)
- Using errors as an opportunity to learn (75.7%)
- Communicating improvements resulting from reported events (67.6%)
- Sharing reporting rates with staff (53.5%)

Pedersen CA et al. Am J Health Syst Pharm. 2010
Process of reported ADRs

1. Report
2. Review
3. Assess
4. Feedback

Causal Relationship?
Causality Assessment (TREND)

Temporal relationship: 약물 투여와 ADR 발현간의 시간적 연관성

Rechallenge: 다시 투여했을 때 같은 증상 발현

Exclusion: 약물 이외에 다른 원인의 가능성 - 기저질환, 약물상호작용

Novelty: 이미 보고된 유해반응 여부

Dechallenge: 복용 중단시 증상의 소실
Causality assessment method

- Global Introspection
  - WHO-UMC categories

- Algorithm requires score
  - Naranjo algorithm
  - 한국형 인과성 평가 알고리즘

- Probabilistic methods
Global Introspection Method

Simple to apply
– Dependent to knowledge & experience of assessor

Needs EXPERT
## WHO-UMC Causality categories (2)

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| **Certain**    | • Event or laboratory test abnormality, with plausible time relationship to drug intake  
• Cannot be explained by disease or other drugs  
• Response to withdrawal plausible (pharmacologically, pathologically)  
• Event definitive pharmacologically or phenomenologically  
• Rechallenge satisfactory, if necessary |
| **Probable/likely** | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Unlikely to be attributed to disease or other drugs  
• Response to withdrawal clinically reasonable  
• Rechallenge not required |
| **Possible**   | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Could also be explained by disease or other drugs  
• Information on drug withdrawal may be lacking or unclear |
| **Unlikely**   | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  
• Disease or other drugs provide plausible explanations |
### WHO-UMC Causality Categories (3)

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| Conditional / unclassified   | • Event or laboratory test abnormality  
• More data for proper assessment needed, or  
• Additional data under examination |
| Unassessable / Unclassifiable | • Report suggesting an adverse reaction  
• Cannot be judged because information is insufficient or contradictory  
• Data cannot be supplemented or verified |
## Naranjo Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Previous conclusive reports on this reaction?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Adverse event after the suspected drug?</td>
<td></td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>3. Adverse reaction improve on drug withdrawal (or antagonist)?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Adverse reaction when re-administered?</td>
<td></td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5. Alternative causes?</td>
<td></td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>6. Reaction reappear with a placebo?</td>
<td></td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>7. Drug in body fluid in toxic concentrations?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Dose-related response?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Past Hx. of similar reaction?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. ADR confirmed objectively?</td>
<td></td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Scoring:** >9 definite, 5-8 probable, 1-4 possible, 0 doubtful
Select Causality Assessment Method

- **No gold standard**

- ** Depend on...**
  - Aim of ADR monitoring
    - Research vs. QI
  - Quantity of ADR reports
  - Existence of ADR expert
  - Quantity & quality of clinical information
Feed back!

- **Share ADR information**
  - Health care professionals
  - Hospital administration & management
  - Report to KFDA to generate safety information

- **Very important to QI & patient safety**
  - Prevent same ADR due to same drug
  - Secondary prevention
  - 28-56% of ADRs occurring in hospital are preventable

Bates DW *et al.* *JAMA*. 1995
Other Tools for Searching ADRs

- **Trigger tool analysis**
  - Signal words (or “triggers”) in medical record
  - Using customized software link to hospital system
  - Retrospective focused assessment of ADRs

  Rozich JD et al. *Qual Saf Health Care.* 2003

- **Electronic medical Records (EMR)**
  - Automatized keyword searching vs. manual searching
  - Low sensitivity and moderate positive predictive value


- **Active surveillance**
Major ADR reporting sources

Admission → AE occur! → Discharge

- Spontaneous Reporting (SP)
- EMR manual review (AS)
- CDR Search & Reporting (CDR)

DAEM COMMITTEE

Reported ADRs to DAEM Committee (Cases)

Jan-09 | Feb-09 | Mar-09 | Apr-09 | May-09 | Jun-09 | Jul-09 | Aug-09 | Sep-09 | Oct-09 | Nov-09 | Dec-09 | Jan-10 | Feb-10 | Mar-10

SP: 47, 52, 80, 53, 57, 69, 68, 109, 101, 155, 148, 144, 99, 154
AS: 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0
CDR: 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0
Total: 47, 52, 80, 53, 57, 69, 68, 109, 101, 155, 148, 144, 99, 154

Korea Food & Drug Administration
Characteristics of ADRs – Culprits

Different methods detect Different ADRs
Characteristics of ADRs – Symptoms

- **Generalized Sx**: 10%
- **Skin**: 33%
- **Gastrointestinal**: 31%
- **Neurologic**: 11%
- **Cardiovascular**: 4%
- **Liver & biliary**: 6%
- **Hematologic**: 26%
- **Nephrologic**: 10%
- **Neurologic**: 7%

**Spontaneous Reporting**

- **Serious ADR**: 5%

**EMR review**

- **Serious ADR**: 6%

**CDR Searching**

- **Serious ADR**: 24%

Different methods detects Different ADRs
Spontaneous Reporting vs. Active Surveillance

- **Drug**: Metoclopramide inj.
- **ADR**: All

**Spontaneous reporting**
- Analyze ADR reports for 2 years

**Active surveillance**
- 2 weeks
- 2 Oncology/GI Wards
표 1. 자발적 보고에 의한 Metoclopramide(MCP) 유해반응빈도

<table>
<thead>
<tr>
<th>MCP inj. 유해반응</th>
<th>전체 약물유해 반응</th>
<th>자발적 보고에 의한 MCP ADR Reported incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>유해사례수 (명)</td>
<td>62</td>
<td>1,450</td>
</tr>
<tr>
<td>유해반응 증상수 (건)</td>
<td>120</td>
<td>3,190</td>
</tr>
<tr>
<td>사례당 증상수</td>
<td>1.94</td>
<td>2.20</td>
</tr>
</tbody>
</table>

2006.8 ~ 2008.7, 2년간
 표 2. 세브란스병원 MCP inj. ADR의 임상적 특징

<table>
<thead>
<tr>
<th>연령, 세(범위)</th>
<th>44.8 (4-76)</th>
<th>성별 (남:여)</th>
<th>25 : 37 (1 : 1.48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>기저 질환, 례(%)</td>
<td>유해사례 증상, 건(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>악성종양</td>
<td>52 (83.9)</td>
<td>신경학적 증상</td>
<td>73 (60.8)</td>
</tr>
<tr>
<td>감염증</td>
<td>1 (1.6)</td>
<td>소화기 증상</td>
<td>21 (17.5)</td>
</tr>
<tr>
<td>심혈관질환</td>
<td>1 (1.6)</td>
<td>심혈관 증상</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>뇌혈관 및 신경질환</td>
<td>1 (1.6)</td>
<td>호흡기 증상</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>소화기질환</td>
<td>3 (4.8)</td>
<td>피부 증상</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>신장질환</td>
<td>1 (1.6)</td>
<td>안증상</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>류마티스질환</td>
<td>2 (3.2)</td>
<td>전신적 증상</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>약물유해반응</td>
<td>1 (1.6)</td>
<td>기타</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>계</td>
<td>62 (100)</td>
<td>계</td>
<td>120 (100)</td>
</tr>
</tbody>
</table>

2006.8 ~ 2008.7, 2년간
Spontaneous Reporting (3)

Possible 이상  87.5%

Certain-확실함
Possible-가능함
Unassessable-평가불가
Probable-상당히 확실함
Unlikely-가능성 적음

그림 1. WHO-UMC 인과성 분석 결과 (총 120 증상)
Active Surveillance

- 전체 대상 환자 - 133명
- 평균연령 - 58.6세 (22-85)
- 성별 - 71 : 62 (1 : 0.87)

- MCP inj. ADR - 3 건

- 능동적 조사를 통한 MCP inj. ADR 발생율 - 2.3% (3 건 / 133 명)
표 3. 조사기간 동안 MCP inj.을 투여받은 환자의 특징

<table>
<thead>
<tr>
<th>기저 질환, 례(%)</th>
<th>악성종양 기타</th>
<th>125 (94%)</th>
<th>8 (6%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MCP inj. 사용이유, 례(%)</th>
<th>항암화학요법/방사선요법 전처치</th>
<th>53 (39.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>오심/구토 증상 조절</td>
<td>61 (45.9%)</td>
</tr>
<tr>
<td></td>
<td>위장관운동 촉진</td>
<td>19 (14.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>조사당시 MCP inj. 투약상태, 명(%)</th>
<th>처음 투약환자</th>
<th>78 (58.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>기투약 환자</td>
<td>55 (41.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>기투약환자의 투여기간, 일(범위)</th>
<th>3.8 (1-36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>기투약환자의 누적용량, mg(범위)</td>
<td>84.4 (10-610)</td>
</tr>
<tr>
<td>사례번호</td>
<td>투약상태</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>1</td>
<td>처음 투약</td>
</tr>
<tr>
<td>2</td>
<td>처음 투약</td>
</tr>
<tr>
<td>3</td>
<td>6일전부터 투약</td>
</tr>
</tbody>
</table>
Feed Back

○ MCP inj.에 의한 약물유해사례 빈도
  - 자발적 보고에 의한 Reported incidence : 4.3%
  - 능동적 조사에 의한 Incidence : 2.3%

○ MCP inj.은 다른 약물의 유해반응 발생 빈도를 고려할 때 비교적 안전한 것으로 판단함
Hospital Physicians Rolls(2)

- **Reporter**
  - Certainty vs. Possibility

- **Assessor**
  - Knowledge & Experience

- **Educator**

- **Organizer**
Conclusions

○ PV in Hospital
  - Important as “Hand Washing”
  - Important to protect patients’ safety
    ▪ Spontaneous Reporting
    ▪ Active Surveillance
  - Easy to report by all employee
    ▪ Reporting culture
    ▪ Will of Hospital administration

○ Physician have to play central role...
  - ADR experts
Thank you for your attention!