Vital role of the clinical pharmacist in the management of adverse drug reactions

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23 October 2008
Who are we?

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Objectives

- To describe and identify the role of the clinical pharmacist in all aspects of the management of adverse drug reactions (ADRs). These include
  - Prevention (& patient counseling)
  - Detection
  - Treatment
  - Reporting
  - Alerting health care providers and patients
Outline of this session

• Intro
  - Definitions
  - ADR statistics
  - ADRs within the healthcare system
• Small groups to evaluate patient profiles and focus on ADR related aspects (1)
• Qs about ADR reporting
• Small groups to evaluate patient profiles and focus on ADR related aspects (2)
• Pharmacovigilance
• Conclusion

ADVERSE DRUG REACTIONS

Definition

“Any noxious, unintended, and undesired effect of a drug that occurs at doses used in man for prevention, diagnosis, or treatment of disease, or modification of physiological function”

WHO, 1966

⇒ Any unwanted effect
ADVERSE DRUG REACTIONS

Terminology

Side effect (beneficial or unwanted):
via same or other mechanism
dose-related or not

Toxic effect: “increase” of the desired therapeutic effect = dose-related

Adverse effect: all unwanted effects
Adverse event: adverse outcome not necessarily related to drug

ADVERSE DRUG REACTIONS

But Doctor,......

I’m allergic

I don’t tolerate

I react

......
ADVERSE DRUG REACTIONS

Classification

**Type A reactions:** pharmacological ADR
- related to the pharmacological actions of the drug
- predictable, dose-related
- low mortality
- usually identified before drug is marketed
  - Examples: Toxicity or overdose
  - Secondary pharmacological effect
  - Drug interaction

Predisposing factors to type A ADRs
- drug formulation
- drug dose
- multiple drug therapy (drug-drug interactions)
- gender: females >> males
- age: altered pharmacokinetics
  - altered pharmacodynamic sensitivity
- underlying disease
- genetic polymorphism
ADVERSE DRUG REACTIONS

Type B reactions:

- uncommon, unpredictable, non-dose-related
- not related to the pharmacological actions of the drug
- high mortality

Importance

- account for 2 - 6% of all hospital admissions
- occur in 10 - 20% of hospital inpatients
- cause death: in 0.1% medical inpatients, in 0.01% surgical inpatients

Manasse HR. Am J Health Sys Pharm 1989
Lazarou J. JAMA 1998
ADVERSE DRUG REACTIONS

Importance

- affect patient quality of life
- cause patients to lose confidence in health care providers
- may mimic disease (unnecessary investigations and delay in treatment)
- increase cost of patient care

➤ BURDEN ON HEALTH CARE BUDGET

ADVERSE DRUG REACTIONS

Diagnosis

Timing
dose-related reaction interacting drug previous exposure
ADVERSE DRUG REACTIONS

Diagnosis

Use of Algorithm

The Naranjo Algorithm

10 Questions with scoring system

-1, 0, +1 and +2

Score of 9-10 → “definitely” ADR

5-8 → “probable” ADR

1-4 → “possible” ADR

< 1 → “doubtful”

ADVERSE DRUG REACTIONS

→ Growing rate of introduction of new pharmaceuticals

→ Early recognition of potential ADRs is critical

Reporting of ADRs is an essential part of medical practice
ADR Workshop

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Case 1

• 52 yr old M, smoker, business man
• Chronic medication: bisoprolol 5 mg (1x/d); Aspirin EC 80 mg (1x/d);
• New prescription: simvastatine 40 mg (1x/d); indapamide 2.5 mg (1x/d)
• Patient is discouraged he has to take even more medication
• Patient asks for Na-naproxen (seen on TV) for back-ache
• A few weeks later, patient enters with complaint of pain in toes.
Case 1 - Qs

- Likely causes?
- Action to be taken?
- Investigations needed?
- Management?
- Further assessment?

Case 1 - Qs

- **Action to be taken?**
  - Medication evaluation
  - Assess patient's expectations/experiences of therapy
  - Patient counselling
  - Contact GP?
Case 1 - Qs

• Action to be taken?
• **Management**?
• Further assessment?

**Management**?
- Re-assure patient:
  - propose medication scheme
  - Explain purpose of therapy + emphasize compliance/concordance to medication
- First delivery:
  - Explain possible side effects of simvastatin
- Counselling:
  - Stop smoking (suggest to help)
  - Motivate to adjust life style
  - Explain main aspects of each medication
  - Written information
- **Na-naproxen**?
  - Assess back ache by questioning
  - If NSAID relevant, restrict to 1 week max (other NSAID?)

**Further assessment and follow-up**?
Case 1 - Qs

• Action to be taken?
  - Medication evaluation
  - Assess patient’s expectations/experiences to therapy
  - Patient counselling
  - Contact GP?

• Management?
  - Re-assure patient:
    • propose medication scheme
    • Explain purpose of therapy + emphasize compliance/concordance to medication
  - First delivery:
    • Explain possible side effects of simvastatin
  - Counselling:
    • Stop smoking (suggest to help)
    • Motivate to adjust life style
    • Explain main aspects of each medication
    • Written information
  - No naproxen?
    • Assess back ache by questioning
    • If NSAID relevant, restrict to 1 week max (other NSAID?)

• Further assessment and follow-up?

Case 1 - follow-up

• Pain in toes:
  - assess uric acid levels in blood via GP (possible side effect of indapamide)

• Next visit to pharmacy:
  - Check for any complaints with simvastatin
  - Check for any effects on blood pressure due to NSAIDs (if chronic treatment)
  - Check compliance
  - Motivate patient to take medication
  - Life style? Stopped smoking?

• Later visit:
  - Ask how cholesterol levels are?
Case 2

• 22 yr old M, RTA/HI and Abd I
• Meds upon admission
  - Ranitidine 50 mg q8h iv
  - Phenytoin 1 gram over 30 min IV + 300 mg HS
  - Paracetamol 1G q6H IV, morphine 5-15 mg IV PRN
• Day 2 – nausea & vomiting, blurred vision
Case 2 - Qs

- Likely causes?
- Action to be taken?
- Investigations needed?
- Management?
- Further assessment?

Case 2 - Qs

- Likely causes
  - Head Injury itself - patient deterioration?
  - Drug induced?
  - Other??
Case 2 - Qs

- Likely causes?
- **Action to be taken?**
- Investigations needed?
- Management?
- Further assessment?

Case 2 - Qs

- **Likely causes**
  - Head Injury itself - patient deterioration?
  - Drug induced?

- **Action to be taken?**
  - CT scan head
  - Assessment of drug related problem
Case 2 - Qs

- Likely causes?
- Action to be taken?
- **Investigations needed?**
- Management?
- Further assessment?

**Likely causes**
- Head Injury itself - patient deterioration?
- Drug induced?

**Action to be taken?**
- CT scan head
- Assessment of drug related problem

**Investigations needed?**
- Phenytoin level, also renal parameters, LFTs, albumin
Case 2 - Qs

- Likely causes?
  - Head injury itself - patient deterioration?
  - Drug induced?
- Action to be taken?
  - CT scan head
  - Assessment of drug related problem
- Investigations needed?
  - Phenytoin level, also renal parameters, LFTs, albumin
  - Phenytoin level = 102 (N: 40-80)
- Management?
  - Hold phenytoin
  - Re-assess levels
  - Re-introduce phenytoin at lower dose?
- Further assessment and follow-up?
Case 2 - Qs

- Likely causes
  - Head Injury itself - patient deterioration?
  - Drug induced?

- Action to be taken?
  - CT scan head
  - Assessment of drug related problem

- Investigations needed?
  - Phenytoin level, also renal parameters, LFTs, albumin

- Management?

- Further assessment and follow-up?

Case 2 - preventive measures

to avoid phenytoin toxicity

-->Take care of the challenges
Challenges for phenytoin

Mode of administration

IV  dilution rate in line filter complications
IM  ? slow & erratic absorption
“PO” capsules & suspension

Challenges for phenytoin

Phenytoin plasma conc. (microM)

Narrow Therapeutic Window

Therapeutic range

Daily dose (mg)
Challenges for phenytoin

some guidance ...

• Level within 24 hrs after loading dose
• Albumin < 30 g/L (N 35-50) → also free level
• Monitor: efficacy side effects need drug levels (total vs free)
• Discuss adjustment & changes with prescriber

Outline of this session

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  - ADRs within the healthcare system
• Small groups to evaluate patient profiles and focus on ADR related aspects (1)
• Qs about ADR reporting
• Small groups to evaluate patient profiles and focus on ADR related aspects (2)
• Pharmacovigilance
• Conclusion
Qs related to ADR reporting

• Why?
• What?
• How?
• Who?
• What happens to the ADR report?

Why to report?

Thalidomide
## What to report?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>dry cough</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>meningitis</td>
</tr>
<tr>
<td>topiramate</td>
<td>confusion, speech problems</td>
</tr>
</tbody>
</table>

## What affects ADR reporting?

Failure of

- patient recognition
- patient communication
- doctor’s recognition
- reporting system
Qs related to ADR reporting

• Why?
• What?
• How?
• Who?
• What happens to the ADR report?
Adverse drug reactions: what happens to a report

All reports are assessed by a health professional and entered into the Australian Adverse Drug Reactions System (ADRS). All reports of serious reactions, reports for vaccines (vaccines and non-vaccines), and reports for complementary medicines (vaccines and non-vaccines) are forwarded to the Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC is composed of independent medical experts who have expertise in areas of importance to the evaluation of medicine safety.

ADRAC may make one of several decisions for a report:

- No further action on the basis that the event is due to a well-known non-serious reaction
- No further action unless additional or similar reports are received
- Request for additional information from the reporter
- Analysis of the ADR database reports to investigate potential safety signals
- Referral for information from the drug sponsor or manufacturer
- Publication in the Australian Adverse Drug Reactions Advisory or medical journals to raise awareness of the reaction
- Referral to other areas of the TGA for further investigation
- Discussion of the reaction with international medicines regulatory agencies
- Recommendation to amend the medicine's product information
- Recommendation to restrict the availability of the medicine
- Recommendation to remove the medicine from the market
Reporting suspected adverse drug reactions

A side effect from a medicine? Report it using Yellow Card.

If you or a member of the public experience a side effect from a medicine, please click on the Yellow Card below to go to the online reporting site. Alternatively, the United Kingdom can report this

Go to the online reporting site for the Yellow Card Scheme (opens in a new window)

The Yellow Card Scheme is run by the MHRA and the Commission on Human Medicines (CHM) and is used to collect information from healthcare professionals and the general public on suspected side effects of adverse drug reactions (ADRs) from medicines.

The continued success of the Yellow Card Scheme depends on the willingness of people to report

Related Information:
- MHRA homepage
- "Medicines Safety News
- Commission on Human Medicines
- Drug Safety Update
- Yellow Card Scheme
ADR Workshop

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Case 3

• 87 yr old M
• Parkinson’s disease
• Light renal dysfunction: GFR = 57, and ureum = 55
• Regular falls
• Patient complains of chronic back pain
• Regular alcohol intake
### Case 3

<table>
<thead>
<tr>
<th>Morning</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin EC 160 mg</td>
<td>Pipamperon 40mg x1/4</td>
<td>Pipamperon 40mg x1/4</td>
<td>Pipamperon 40mg x1/4</td>
</tr>
<tr>
<td></td>
<td>Pipamperon 40mg x1/4</td>
<td>EtilephrinHCl 5mg x2</td>
<td>EtilephrinHCl 5mg x2</td>
<td>EtilephrinHCl 5mg x2</td>
</tr>
<tr>
<td></td>
<td>Pipamperon 40mg x1/4</td>
<td>EtilephrinHCl 5mg x2</td>
<td>EtilephrinHCl 5mg x2</td>
<td>EtilephrinHCl 5mg x2</td>
</tr>
<tr>
<td></td>
<td>Levothyroxin 0.05 x1.5</td>
<td>Pramipexole 0.7 x1</td>
<td>Pramipexole 0.7 x1</td>
<td>Pramipexole 0.7 x1</td>
</tr>
<tr>
<td></td>
<td>Prolopa 250 x1</td>
<td>Prolopa 250 x1</td>
<td>Prolopa 250 x1</td>
<td>Prolopa 250 x1</td>
</tr>
<tr>
<td></td>
<td>Escitalopram 10 x1</td>
<td>Tamsulosine 0.4 x1</td>
<td>Lorazepam 1mg x0.5</td>
<td></td>
</tr>
</tbody>
</table>

### Case 3 - Qs

- Likely causes?
- Action to be taken?
- Investigations needed?
- Management?
- Further assessment?
Case 3 - Qs

• Likely causes
  - Fracture due to fall?
  - General patient deterioration due to disease?
  - Drug related problem?
  - Other??

Case 3 - Qs

• Likely causes?
• Action to be taken?
• Investigations needed?
• Management?
• Further assessment?
Case 3 - Qs

• Likely causes
  - Fracture due to fall?
  - General patient deterioration due to disease?
  - Drug related problem?
  - Other ??

• Action to be taken?
  - Consultation for fracture?
  - Assessment of drug related problem
  - Consult family

Case 3 - Qs

• Likely causes?
• Action to be taken?
• Investigations needed?
• Management?
• Further assessment?
Case 3 - Qs

- **Likely causes**
  - Fracture due to fall?
  - General patient deterioration due to disease?
  - Drug related problem?
  - Other??

- **Action to be taken?**
  - Consultation for fracture?
  - Assessment of drug related problem
  - Consult family

- **Investigations needed?**
  - Determination TSH
  - Rx spine
  - Evaluation of medication

Case 3 - Qs

- Likely causes?
- Action to be taken?
- Investigations needed?
- **Management?**
- Further assessment?
Case 3 - Qs

• Likely causes
  – Fracture due to fall?
  – General patient deterioration due to disease?
  – Drug related problem?
  – Other ??
• Action to be taken ?
  – Consultation for fracture?
  – Assessment of drug related problem
  – Consult family
• Investigations needed ?
  – Rx spine
  – Evaluation of medication
• Management ?
  – Stop alcohol
  – Stop Pipamperon: Cl for PD
  – Substitute tamsulosine by Serenoa repens-extract
  – If possible reduce PD medication
  – Pain treatment
  – Adjust levothyroxine if necessary
• Further assessment and follow-up ?
Case 3 - follow-up

- Re-evaluate TSH levels
- Suggest vit D, Calcium, bisphosphonates if necessary (levotyroxine can induce bone loss)
- Inform family of changes in medication

Case 3 - medication scheme

<table>
<thead>
<tr>
<th>Morning</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levotyroxine 0.1mg x1</td>
<td></td>
<td>Aspirin EC 160 x1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pramipexole 0.7 x1</td>
<td></td>
<td>Pramipexole 0.7 x1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolopa 125 x1</td>
<td>Prolopa 125 x1</td>
<td>Prolopa 125 x1</td>
<td>Prolopa 125 x1</td>
</tr>
<tr>
<td></td>
<td>Escitalopram 10 x1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostaserene 320 x1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ Chronic analgesic
(+ Vitamine D / Calcium / Biphosphonates)
Case 4

- 65 yr old F, HTN, DM, high cholesterol
- SAH
- Intubated and ventilated, NGT
- Evacuation of hematoma
- Day 2 – hydrocephalus and EVD* inserted
- Day 10 – thracheostomy
- Day 14 – sputum and blood MRSA

*Extraventricular drain
Case 4

- Rx for 1 gram vancomycin IV q12H

BP from 145/80 to 95/60

Case 4 - Qs

- Likely causes?
- Action to be taken?
- Investigations needed?
- Management?
- Further assessment?
Case 4 - Qs

- Likely causes

  - Patient induced?
  - Drug induced?
  - Other ??

Case 4 - Qs

- Likely causes - drug induced

  - Volume of diluent?
  - Administration “route”?
  - Rate of infusion?
Case 4 - Qs

• Likely causes?
• **Action to be taken?**
• Investigations needed?
• Management?
• Further assessment?

Case 4 - Qs

• **Likely causes**
  - Drug induced – vancomycin dilution?
  "route"?
  rate of infusion?

• **Action to be taken?**
  - Hold infusion
  - Assessment of drug related problem
  - Treat skin and BP problem
  - Adjust rate, volume
  - Reporting?
Case 4 - Qs

- Likely causes?
- Action to be taken?
- **Investigations needed?**
- Management?
- Further assessment?

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Case 4 - Qs

- **Likely causes**
  - Drug induced - vancomycin dilution?
  - Rate of infusion?

- **Action to be taken?**
  - Hold infusion
  - Assessment of drug related problem
  - Treat skin and BP problem
  - Adjust rate, volume
  - Reporting?

- **Investigations needed?**
  - Dermatology assessment?
Case 4 - Qs

- Likely causes?
  - Drug induced – vancomycin dilution?
  - Rate of infusion?

- Action to be taken?
  - Hold infusion
  - Assessment of drug related problem
  - Treat skin and BP problem
  - Adjust rate, volume
  - Reporting?

- Investigations needed?
  - Dermatology assessment

- Management & Prevention?
  - Further assessment and follow-up?
Case 4 - preventive measures & follow-up

- Ensure correct dilution rate of infusion
- Consider pre-meds
- Desensitization if necessary
- Awareness
ADR Workshop

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Reporting Adverse Drug Reactions (ADRs) Pharmacovigilance (WHO)

To enhance patient care and patient safety through activities related to
  - detection
  - evaluation
  - understanding
  - prevention
of ADR’s or other problems with medicines
Pharmacovigilance
Objectives

• To rapidly detect unknown or less-described ADRs

• To communicate the ADR’s so they occur less frequently

• To evaluate risk-benefit ratio’s

The Rofecoxib story

• 20 May 1999 – FDA Approval
  indications: OA, acute pain &
  dysmenorrhea
  \( \rightarrow \) Vioxx®, Ceoxx®, Ceeoxx®

• 30 Sep 2004 – worldwide withdrawal
  reason - increased risk of heart attack
  and stroke associated with long-term,
  high-dosage use.
The Rofecoxib story

• ... Litigation
• Mar 2006 – more than 10,000 cases filed against Merck

→ The recall and litigation over rofecoxib has provoked debate over drug safety in the United States. Some argue that the FDA does not do enough to monitor product safety.

Pharmacovigilance Problems

• 75% of reporting in EU comes from pharmaceutical industry (mandatory, part of PMS)

• Only 25% from health care professionals

• Need for incentives for more frequent reporting by health care professionals: new project from the Belgian medicines Agency
What to report?
Belgian project

• Each serious, unexpected or suspicious ADR

• All ADR’s observed in:
  - Vulnerable patient groups: children, pregnant or breastfeeding women, elderly)
  - After administration of vaccines
  - First administration of innovative or generic drug
  - Incorrect use of a drug

• Online reporting system to the Belgian centre of pharmacovigilance

ADR reporting

Different formats around the world
➢ Hospital based
➢ MOH based
➢ Paper versus electronic

Common and similar goal
Evaluation criteria

- Clinical assessment of the ADR: symptoms, biochemical data...
- Relationship between time of onset of the ADR and intake of the medication
- Evolution after medication has been stopped
- Absence of any other causes: other medication, co-morbidity, genetic factors, ...
- Pharmacological properties of the drug
- Similar cases described in literature or reported in other centres.
Problems when evaluating

- ADRs mimic symptoms of illnesses also occurring in the absence of the suspect drug.
- ADRs are frequently present in patients with co-morbidities or in patients with predisposing factors.
- Spontaneous background incidence is usually not known.
- Quality of reporting is poor at times.

Figuur 3: Distribution (%) of causal relationship

Distribution (n = 13,515)
Most reported ADRs

Pharmacotherapeutic classes of drugs mostly responsible for ADRs
Data from around the world

- Vigibase = WHO global ICSR database
- 89 full member countries
- 31 associate members

Data from around the world

- In 2008 4 million reports reached!
Data from around the world

Active ADI-reports in Vigibase / 1 million inhabitants
Average during year 2002 - 2006
**ADRs & role of pharmacy staff**

- Identify possible ADR
- Alert doctor/nurse
- Provide extra information to medical staff, nurses AND patients.
- Organize ADR sessions for medical & nursing staff
- Keep updated
- Remind the use of ADR reporting form
- Make sure filled form is sent to relevant body
- Provide summaries and reviews

**ADR Sessions**

- What is an ADR?
- How common are ADRs?
- Types
- Problem?
- What to report?
- Why to report?
- What affects reporting?
- How to report?
- Who can report?
- Whom to give the reports to?
- What happens to my ADR report?
Objectives

- To describe and identify the role of the clinical pharmacist in all aspects of the management of adverse drug reactions (ADRs). These include
  - Prevention (& patient counseling)
  - Detection
  - Treatment
  - Reporting
  - Alerting health care providers and patients
ADRs - Conclusion

• Any unwanted effect

• Importance of ADR reporting

• Pharmacy staff have an active role in preventing, identifying, managing and reporting ADRs