Individual patient risk management

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Minimization of risk
(ADR, DI, CI, medication errors, medication non adherence)

• a suspicion on risk which
  • is theoretical
  • makes any potential harm to patient
• a judgment of clinical significance
• a management of risk
  • **Risk was not manifested - prevention**
    • a monitoring
    • a diminishing of influence of risk factors
    • a preventive treatment
    • a shift to medication without particular risk
  • **Risk was manifested**
    • A compensation of ADR with pharmacotherapy
    • A treatment of complications of risk
    • A shift to medications without risk
Algorithm of three pillars - solution of ADR

• Theoretical pillars
  • 1st p.......risk factors for occurrence and complication of ADR (rating of individual risk)
  • 2nd p.......What, when and how long to monitor ADR and risk factors from 1st p (possibility to monitor risk)

• True management of risk minimization
  • 3rd p (proper risk management)

  • tools:
    a way of administration, medication adherence,
    monitoring, food, hydration,
    live style, medication audit
Algorithm SAFE – complete risk minimization (RM) activity

• Population risk - signal of risk
  symptoms and lab of ADR, pharmacology of medicines, not usual strategy (incl. dosage scheme and monitoring)

• Individual risk - Analysis of risk
  risk factors of ADR, risk factors of complication, level of safety culture in particular surrounding

• Judgement of individual risk - Founding of ways of risk measurement
  risk/benefit,
  control of occurrence of risk factors
  control of clinical manifestation of risk (dechallange/rechallange)

• How to manage risk - Elimination of risk
  • tools: a way of administration, medication adherence, monitoring,
    food, hydration, live style, medication audit
Role of various health care professionals (care givers) in risk management: attending physicians (APhy), clinical pharmacist (CPh); nurse (N), clinical pharmacologist (CPhcol) algoritmus SAFE

<table>
<thead>
<tr>
<th>Role</th>
<th>Signal</th>
<th>Theory of Risk</th>
<th>Risk/Benefit</th>
<th>Elimination</th>
<th>Rate</th>
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</thead>
<tbody>
<tr>
<td>Attending physician</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>16</td>
</tr>
<tr>
<td>APhy + CPh</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>18</td>
</tr>
<tr>
<td>Aphy + Cphcol</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Clinical pharmacist</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>15</td>
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<tr>
<td>Clinical pharmacologist</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>14</td>
</tr>
<tr>
<td>Pharmacists by dispensation</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>7</td>
</tr>
<tr>
<td>APHY + N</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>patient</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3</td>
</tr>
</tbody>
</table>
Example 1 corticosteroids
glucocorticoids - therapeutic use

substitution

immunosuppression

control of inflammation non-infection /infection origin
effect on macrophages and 1st type of cell immunity

anti edematous and symptomatic treatment by emergency
effect (therapeutic/non required)

- Pleiotropic effect
- Effect on all cells
- receptor
  - intracellular - genomic effect
    - transactivation
    - trans repression
    - GKR $\alpha$ (GKR$\beta$)
  - membrane – non genomic
  - aldosterone

- Glucocorticoid effect
  - ↓ anabolism
  - ↑ catabolism
  - ↑ glycaemia, lipids, appetite
  - depression, insomnia, cataract
  - ↓ calcium absorption
  - bradyarrytmia

- Mineralocorticoid effect
  - ↑ blood pressure, developing of glaucoma
  - ↑ blood volume
  - hypokalemia
Type of ADR of glucocorticoids according WHO

- A........dose dependent
- B.........hypersensitivity - rare
- C........dose/duration of exposition dependent
- D........teratogenicity – theoretical significant, clinically not so significant
- E........syndrome of withdrawn by long exposition of larger dosages
- F........corticoresistance
factors influencing effect

- way of administration
  - Local, inhalation, p.o.; intravenous
- daily dose
  - < 5mg
  - 5 – 40mg
  - > 40mg
    - pulses parenteral: 125mg a 1000mg
- genomics
  - expression of GCRβ
  - ABCB1/MDR1 gen – P-glycoprotein
- dosage scheme (1-0-0; 1-1-0; 0-0-1)
  - circadian rhythm
  - clearance of glucocorticoids
- duration of treatment
- age
- polymorbidity - contraindications
- polypharmacotherapy drug/drug interaction
- Medication adherence
- Information – SPC – syndrom of leaflet
Type A and C (risk factors and monitoring)

**Type A**
- arterial hypertension
- hypercholesterolemia
- dyspepsia
- ↑ appetite
- insomnia
- dysrhythmia

**Type C**
- hyperglycemia
- hypertriglyceridemia
- hypokalemia
- osteoporosis (mainly cord)
- Moon face
- Skin thickness
- ↑ blood coaguability
- manifestation of latent infection disease
- candidiasis and pneumonia
- glaucoma; cataract
Osteoporosis – rheumatoid arthritis (RA); COPD

- reduced mobility (RA, arthritis, muscle failure); COPD), osteoporosis on the base of inflammation (RA)
- absorption of calcium and vit D (RA: bowel disease, problems with swallowing)
- Co-medications:
  - SSRI,
  - loop diuretics,
  - PPI?
    - Some longitudinal analysis: no association between PPI and BMD

- Inhaled corticoids – association with osteoporosis development in elderly

Glucocorticoids and peptic ulcer disease

• No association.................................................................1976

• 2times increased risk RR = 2..................................................1983

• No risk except of cases contemporary using of NSAIDs..........1991

• Meta-analysis – no risk..........................................................1994
Type E – „end of therapy“

• 1.p: RF: long term use of dosages > as 5mg,
  - atrophy of cortex of adrenal gland
  - not enough corticoids by stress situation

• 2.p.: medication adherence

• 3.p: not to stop therapy immediately
  - to administer morning
  - patient should to store enough amount of glucocorticoid pills in his/her cabinet
Women 72 year, steroid DM, RA; in 2015 new Dg: glaucoma

- **FA 2014:**
  - methylprednisolone 15mg, metformin 1000 1-0-0, glimepiride 1 1-0-0, nimesulide 100 according the need; Ca 1000mg, vitamin D, ibandronate 150 once a week, sertraline 50 1-0-1

- **FA 2015:**
  - metformin 1000 1-0-0, glimepiride 1 1-0-0, nimesulide 100 according the need; Ca 1000mg, vitamin D, ibandronate 150 once a week, sertraline 50 1-0-1
  - *Methyprednisolone was stopped by patient – the fear of loss of vision*

- **What are the drug related problems (DRP)? How to measure it? How to manage it.**
Example 2: coagulation management
case 2 men *1941

- Arterial hypertension; Parkinson disease (2010)
- STEMI - PCI (2012) vertebrogenic algic syndrome; osteochondrosis
- Pulmonary emphysema, state after spontaneous pneumothorax (2012),
- Log term epistaxis

- Recent heath state: dyspnea, fever (39.2°C), hypotension, palpitation - tachycardia (106/ min), diarrhea

- TROMBEX 75mg (clopidogrel) 1-0-0  
  Aspirin 100mg 0-1-0
- BETALOC ZOK (metoprolol) 50mg 1-0-0  
  SORTIS 20mg 0-0-1
- HYDROCHLOROTHIAZID 25mg 1/2-0-0 every other day  
  ISICOM 100mg 1,5-1,5-1,5 (levodopa/carbidopa)
- REQUIP MODUTAB (ropirinol) 2mg 1-1-1-1 each 6 hours  
  NEUPRO emp 8mg/24 hod 1 after launch (roligotin)

- Thrombocytopenia 108; hypokalemia 3,7mmol/l;

- Why dual therapy? Can we shift antiplatelet agents to LMWH?
Case 3 men 85 year old; atrial fibrillation (FiS), arterial hypertension, BHP, chronic pain of joint tissues; 3 times TEP

- betaxolol 20 1-0-0
tamsulosine 0,4 0-0-1 ramipril 5 1-0-0 finasterid 5 1-0-0
- methylprednisolone 5 1-0-0 hydroxychloroquine 200 1-0-0
- Ibuprofen 600 1-0-0 according the need
- Warfarin 2 a 5mg ...labile INR
- easy wound of skin + bleeding; frequent falls; bleeding from nose frequent in past
- risk minimization: shift to rivaroxaban 20 1-0-0 (medication audit); to stand-up slowly, enough hydration
- complicated tooth extraction – rivaroxaban was not use during a day of a tooth extraction
- In 5th day: bleeding – was stopped with gelaspon (local gelatine)
- In one weak by a biting of bread – again bleeding – intervention on stomatology clinic – INR 5,5,
- risk minimization: To stop rivaroxaban 20 1-0-0 (medication audit), look for adherence to all medicines
Case 3 men 85 year old; atrial fibrillation (FiS), arterial hypertension, BHP, chronic pain of joint tissues; 3times TEP

- betaxolol 20 1-0-0  tamsulozine 0,4  0-0-1  ramipril 5 1-0-0  finasterid 5 1-0-0
- methylprednisolone 5  1-0-0  hydroxychloroquine  200 1-0-0  Ibuprofen 600 1-0-0 according the need
- Warfarin 2 a 5mg ...labile INR
- easy wound of skin and riks of bleeding; ; frequent falls and a nosebleed

- risk minimization: shift to rivaroxaban20 0-1-0 (medication audit); to stand-up slowly, enough hydration
- To stop rivaroxabam 20 1-0-0 (medication audit), look for adherence to all medicine

- Risk minimization: what to do: again rivoroxabam 20 1-0-0 or 15 1-0-0, warfarin small dose (INR will not reach 2) warfarin full therapeutic dose, apixabam 2,5 1-0-1
HAS-BLED score

- Hypertension STK $>160$ mmHg 1
- Abnormal function 1 or 2
  - kidney (dialysis; Kr $\geq 200$ umol/l);
  - liver ALT/AST $>3$ times
- Stroke 1
- Bleeding 1
- Labile – nonstabile value of INR 1
- Elderly – >65 year old 1
- Drugs - antipatelet, NSAID; abusus of alcohol 1 or 2
- score $>3$....higher risk of bleeding 3
comparision of NOAC with warfarin

<table>
<thead>
<tr>
<th>vs warfarin atrial fibrilation</th>
<th>Stokecs + embolisation HR (95%KI)</th>
<th>Clinically significant bleeding HR (95%KI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>0.79 (0.66 - 0.95)</td>
<td>0.69 (0.60 - 0.80)</td>
</tr>
<tr>
<td>Dabigatran (RE-LY)</td>
<td>0.65 (0.52 - 0.81)</td>
<td>0.93 (0.81 - 1.07)</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET AF)</td>
<td>0.88 (0.75 - 1.03)</td>
<td>1.04 (0.90 - 1.20)</td>
</tr>
</tbody>
</table>
## Basic coagulation tests by NOAC

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban*</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma peak level</strong></td>
<td>2 h after ingestion</td>
<td>1–4 h after ingestion</td>
<td>1–2 h after ingestion</td>
<td>2–4 h after ingestion</td>
</tr>
<tr>
<td><strong>Plasma trough level</strong></td>
<td>12–24 h after ingestion</td>
<td>12–24 h after ingestion</td>
<td>12–24 h after ingestion</td>
<td>16–24 h after ingestion</td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Prolonged but no known relation with bleeding risk</td>
<td>Prolonged: may indicate excess bleeding risk but local calibration required</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>aPTT</strong></td>
<td>At trough: &gt;2x ULN suggests excess bleeding risk</td>
<td>Cannot be used</td>
<td>Prolonged but no known relation with bleeding risk</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>dTT</strong></td>
<td>At trough: &gt;200 ng/ml or &gt;65 s: excess bleeding risk</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>Anti-FXa chromogenic assays</strong></td>
<td>Not applicable</td>
<td>No data yet</td>
<td>Quantitative; no data on threshold values for bleeding or thrombosis</td>
<td>Quantitative; no data on threshold values for bleeding or thrombosis</td>
</tr>
<tr>
<td><strong>ECT</strong></td>
<td>At trough: ≥3× ULN: excess bleeding risk</td>
<td>No data</td>
<td>No data</td>
<td>Not affected</td>
</tr>
</tbody>
</table>

*: no EMA approval yet. Needs update after finalisation of SmPC
### 6 most important possibilities of monitoring s NOAC

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 1 | Compliance        | Each visit • Instruct patient to bring remaining medication: note and calculate average adherence  
|   |                   | • Re-educate on importance of strict intake schedule  
|   |                   | • Inform about compliance aids (special boxes; smartphone applications; … )                                                                                                                                |
| 2 | Thrombo-embolism  | Each visit • Systemic circulation (TIA, stroke, peripheral)  
|   |                   | • Pulmonary circulation                                                                                                                                                                                   |
| 3 | Bleeding          | Each visit • ‘Nuisance’ bleeding: preventive measures possible? (PPI; haemorrhoidectomy; … ). Motivate patient to diligently continue anticoagulation  
|   |                   | • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?                                                                     |
| 4 | Other side effects| Each visit • Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.                                              |
| 5 | Co-medications    | Each visit • Prescription drugs; over-the-counter drugs (see Section 4)  
|   |                   | • Careful interval history: also temporary use can be risk!                                                                                                                                               |
| 6 | Blood sampling    | Yearly 6 monthly 3 monthly On indication • Haemoglobin, renal and liver function  
|   |                   | • Renal function if CrCl 30–60 ml/min, or if on dabigatran and >75 years or fragile  
|   |                   | • If CrCl 15–30 ml/min  
|   |                   | • If intercurring condition that may impact renal or hepatic function                                                                       |
conclusion

• Individual risk minimization requires
  • knowledge and skills (algorithm of three pillars) + safety culture problems
  • critical appraisal of information from SPC, papers etc.
  • To focus on risk/benefit ratio by particular patient—algorithm SAFE
  • team work of all health care workers including clinical pharmacist
  • cooperation with patient
  • denveloping of safety culture on all level of health care

• Missing of monitoring of risk factors adverse drug reaction occurrence, risk factors; prescribers and/or patients behavior regarding the treatment wrong risk minimization process

• By individuals is challenging to manage clinical significance of benefit and medication errors (drug related problems) and look for best way

Thank you