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

Masarykovou náměstí s pomníkem TGM (pomník presidenta a úprava náměstí, 1930)

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,
      monitoring,
      live style,
      medication adherence,
      food, hydration,
      medication audit

Algorithm SAFE – complete risk minimization (RM) activity

- Population risk - **s**ignal of risk no….stop/yes↓

  symptoms and lab of ADR, pharmacology of medicines, not usual strategy (incl. dosage scheme and monitoring)

- Individual risk - Analysis of risk no…..stop/yes↓

  risk factors of ADR, risk factors of complication, level of safety culture in particular surrounding

- Judgement of individual risk - **F**ounding **of ways** of risk measurement no…stop/yes↓

  risk/benefit,

  control of occurrence of risk factors

  control of clinical manifestation of risk (dechallange/rechallange)

- How to manage risk -**E**limination 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

	level				
		population	individual		
	signal	theory of risk	risk/benefit	elimination	rate
Attending physician	**+++**	**++++**	**+++++**	**++++**	**16**
APhy +CPh	+++++	++++	++++	+++++	18
Aphy + Cphcol	++++	++++	+++++	++++	17
Clinical pharmacist	+++++	++++	++	++++	15
Clinical pharmacologist	++++	++++	++	++++	14
Pharmacists by dispensation	+++	++	+	++	7
APHY + N	++	+	+	+	5
patient	+	+		+	3

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 α (GKRβ)
  - 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 coaguabilty
- 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-medication:
- SSRI,
- loop diuretics,
- PPI?
  - Some longitudinal analysis: no association between PPI and ↓ BMD

- Inhaled corticoids – association with osteoporosis development in elderly

Suzuki A, et al. On "2015 Guidelines for Prevention and Treatment of Osteoporosis" . Medication-related osteoporosis : others]. Clin Calcium. 2015;25(9):1367-72.

Solomon DH, et al. Bone mineral density changes among women initiating proton pump inhibitors or H2 receptor antagonists: a SWAN cohort study. J Bone Miner Res. 2015 Feb;30(2):232-9.

Glucocorticoids and peptic ulcer disease

- No association……1976

Conn HO, et al. L. N Eng J Med 1976;294:473–9.

- 2times increased risk RR = 2……..1983

Messer J, et al. N Eng J Med 1983;309:21–4.

- No risk except of cases contemporary using of NSAIDs……1991

Piper JM, et al. Ann Intern Med 1991;114:735–40.

- Meta-analysis – no risk……..1994

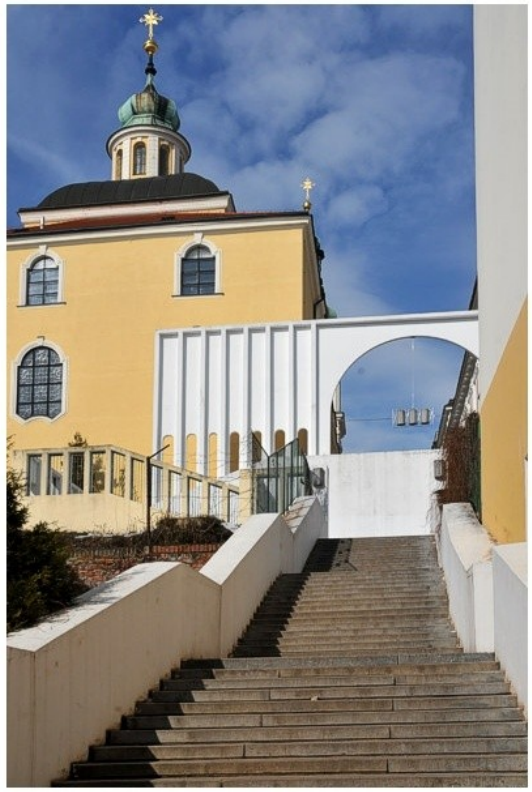
Conn HO, et al. J Int Med 1994; 236:619–32.

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



Gočárovo schodiště (schodiště u kostela Panny Marie, 1909-10)

- 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;
- STEMI - PCI (2012)
- Pulmonary emphysema,
- Log term epistaxis

Parkinson disease (2010)
vertebrogenic algic syndrome; osteochondrosis
state after spontaneous pneumothorax (2012),

- Recent heath state: dyspnea, fever (39,2◦C), hypotension, palpitation - tachycardia (106/ min), diarrhea

- TROMBEX 75mg (clopidogrel)1-0-0
- BETALOC ZOK (metoprolol) 50mg 1-0-0
- HYDROCHLOROTHIAZID 25mg 1/2-0-0 every other day
- REQUIP MODUTAB (ropirinol) 2mg 1-1-1-1 each 6 hours

Aspirin 100mg 0-1-0
SORTIS 20mg 0-0-1
ISICOM 100mg 1,5-1,5-1,5 (levodopa/carbidopa)
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 85year old; atrial fibrilation (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 + bleeding; ; frequent falls; bleeding from nose frequent in past

- risk minimization: shift to rivaroxaban20 0-1-0 (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 rivaroxabam 20 1-0-0 (medication audit), look for adherence to all medicines

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- **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

• **H**ypertension STK>160mmHg	1	
• **A**bnormal function	1 or 2	
• kidney (dialysis; Kr >=200umol/l);		
• liver ALT/AST >3times		
• **S**troke	1	
• **B**leeding	1	←
• **L**abile – nonstabile value of INR	1	
• **E**lderly – >65year old	1	←
• **D**rugs - antipatelet, NSAID; abusus of alcohol	1 or 2	←
• score >3….higher risk of bleeding		**3**

comparition of NOAC with warfarin

vs warfarin atrial fibrilation	Stokecs + embolisation HR (95%KI)	Clinically significant bleeding HR (95%KI)
Apixaban (ARISTOTLE)	0.79 (0.66 - 0.95)	0.69 (0.60 - 0.80)
Dabigatran (RE-LY)	0.65 (0.52 - 0.81)	0.93 (0.81 - 1.07)
Rivaroxaban (ROCKET AF)	0.88 (0.75 - 1.03)	1.04 (0.90 - 1.20)

Basic coagulation tests by NOAC

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

**: no EMA approval yet. Needs update after finalisation of SmPC*

6 most important possibilities of monitoring s NOAC

	Interval	Comments
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