Evaluation of a Computerized Tool allowing Retrospective Detection of Potential Vitamin K Antagonist Overdoses in Complex Contexts

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Introduction

- Vitamin K antagonists (VKA):
  - Anticoagulants
  - Widely used (Deep veinous thrombosis, pulmonary embolism, cardiac arrhythmia)
  - Overdose: bleeding risk
  - Biological monitoring: INR (International Normalized Ratio)
    → dose adaptation

- Numerous drug-drug interactions and clinical interactions
- VKA: 31%-37% of serious adverse events. [1]
- VKA: 12.3% of adverse drug event related hospitalizations. [2]
- Warfarin: major bleeding in 0% to 16% of patients. [3]

Definitions

- **Adverse Drug Reaction (ADR):** "noxious and unintended response to a drug, which occurs at doses normally used in man [...]." [4]
  
  *Ex: VKA imbalance: INR > 5*

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  Ex: VKA imbalance: INR > 5

- **Adverse Drug Event (ADE):** "damage occurring to the patient, related to his drug therapy, and as a result of proper care, inappropriate care, or care deficit.” [5], [6]
  
  Ex: VKA imbalance with bleeding

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Objective

- Evaluate the precision of the detection of risk factors for ADR and ADE by the “ADE-Scorecards” tool.

- “ADE Scorecards”: software, retrospective detection of ADR/ADE and their risk factors, presentation to physicians and pharmacists.[7]

Materials and methods

Structure of ADR/ADE detection rules:
Conditions (C) potentially leading to an outcome (O)

\[ C_1 \cap C_2 \cap \ldots \cap C_k \Rightarrow O \]

Conditions:
• drug (ex: paracetamol),
• abnormal laboratory result (ex: anemia),
• diagnosis (ex: renal insufficiency),
• administrative data (ex: age)

Outcome:
INR > 5

International Normalized Ratio: measure of blood viscosity.
Materials and methods

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\[ C_1 \cap C_2 \cap \ldots \cap C_k \rightarrow O \]

- Conditions: VKA & Risk factors for imbalance
  - drug (ex: paracetamol),
  - abnormal laboratory result (ex: anemia),
  - diagnosis (ex: renal insufficiency),
  - administrative data (ex: age)
Materials and methods

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  - drug (ex: paracetamol),
  - abnormal laboratory result (ex: anemia),
  - diagnosis (ex: renal insufficiency),
  - administrative data (ex: age)

- Outcome: **INR > 5***

*International Normalized Ratio: measure of blood viscosity.*
Materials and methods

○ Example:

\[ \text{VKA} \cap \text{Amiodarone} \cap \text{Age} \geq 70 \implies \text{INR} > 5 \]
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○ Chronology:

• Conditions: coexist within the five days preceding the adverse reaction.

• Outcome \geq 2 \text{ days.}
Materials and methods

- Example:
  \[ \text{VKA} \cap \text{Amiodarone} \cap \text{Age} \geq 70 \implies \text{INR} > 5 \]

- Chronology:
  - Conditions: coexist within the five days preceding the adverse reaction.
  - Outcome \( \geq 2 \) days.

- 16 rules: VKA imbalance.
Materials and methods

- Example:
  \[ VKA \cap Amiodarone \cap \text{Age} \geq 70 \Rightarrow \text{INR} > 5 \]

- Chronology:
  - Conditions: coexist within the five days preceding the adverse reaction.
  - Outcome \( \geq 2 \) days.

- 16 rules: VKA imbalance.

- 2010 data of Denain hospital: 14,747 stays.
Materials and methods

Structure of a rule: \( C_1 \cap C_2 \cap \ldots \cap C_k \rightarrow O \)

Confidence = \( P(O/C_1 \cap C_2 \ldots nC_k) \)
Materials and methods

Structure of a rule: $C_1 \cap C_2 \cap \ldots \cap C_k \rightarrow O$

Confidence = $\frac{\text{Nb stays with } C \& O}{\text{Nb stays with } C}$
Materials and methods

Structure of a rule: \( C_1 \cap C_2 \cap ... \cap C_k \rightarrow O \)

Confidence = \( \frac{\text{Nb stays with } C \& O}{\text{Nb stays with } C} \)

Precision = \( \text{PPV}^* = P(O \cap ADE/C_1 \cap C_2 \ldots C_k) \)

*PPV: Predictive Positive Value
Materials and methods

Structure of a rule: $C_1 \cap C_2 \cap \ldots \cap C_k \Rightarrow O$

Confidence = $\frac{\text{Nb stays with } C \& O}{\text{Nb stays with } C}$

Precision = $\text{PPV}^* = \frac{\text{Nb stays with } C \& O \& \text{validated contribution of the imbalance risk factors}}{\text{Nb stays with } C \& O}$

*PPV: Predictive Positive Value
Materials and methods

Patients receiving VKA

718
Materials and methods

Patients receiving VKA

718

INR > 5

85
Materials and methods

Patients receiving VKA

- 718 total patients
- 85 with INR > 5
- 49 detected by ADE Scorecards
Patients receiving VKA

- 718 total patients
- 85 INR > 5
- 49 detected by the ADE Scorecards

Potential ADEs
Materials and methods

Expert review of the 49 detected ADRs:

- Physician and pharmacist, double review, consensus.
- Evaluation of the influence of the risk factors indicated by the rules (Kramer’s algorithm).
- Clinical damage
  - Bleeding
  - Transfer to an intensive care unit
  - Transfer to a specialized medical unit
  - Death
- Physicians reactions
Results - validated cases

Detected cases (ADR)

49
Results - validated cases

Detected cases (ADR)

49

2

Poor quality
Results - validated cases

Detected cases (ADR)

- No significantly contributing risk factor
  - Treatment initiation
    - 34

- Poor quality
  - 2

Total: 49
Results - validated cases

- Detected cases (ADR)
  - No significantly contributing risk factor
    - Treatment initiation
      - 34
  - ≥1 significantly contributing risk factor
    - 13
  - Poor quality
    - 2
Results - validated cases

Detected cases (ADR)

- 49 total cases
  - 13 with ≥ 1 significantly contributing risk factor
  - 34 with no significantly contributing risk factor

- 2 cases classified as poor quality

The detected risk factor is/are not the contributing factor(s)
Results - validated cases

Detected cases (ADR) = 49

- 13 ≥ 1 significantly contributing risk factor
- 34 No significantly contributing risk factor

- 2 ≥ 1 detected risk factor contributes significantly
- 11 The detected risk factor is/are not the contributing factor(s)

- 2 Poor quality

PPV risk factors for ADR = 11/49 = 22.4%
Results - validated cases

Detected cases (ADR) = 49

- No significantly contributing risk factor
  - Treatment initiation
    - 34 cases

- \( \geq 1 \) significantly contributing risk factor
  - 13 cases
    - PPV risk factors for ADR = 11/49 = 22.4%

- Poor quality

- The detected risk factor is/are not the contributing factor(s)
  - 2 cases

- \( \geq 1 \) detected risk factor contributes significantly
  - 11 cases
    - Amiodarone initiation
      - 3 cases

- Infection
  - 8 cases
Results – clinical damages

Detected cases (ADR)

- No significantly contributing risk factor: 34
- ≥1 significantly contributing risk factor: 13
  - Poor quality: 2
  - The detected risk factor is/are not the contributing factor(s): 11
    - ≥1 detected risk factor contributes significantly: 2

Detected cases (ADR) = 49
Results – clinical damages

Detected cases (ADR)

- No significantly contributing risk factor
  - Treatment initiation
    - 7 clinical damage
    - 34

- ≥ 1 significantly contributing risk factor
  - The detected risk factor is/are not the contributing factor(s)
    - 2
  - ≥ 1 detected risk factor contributes significantly
    - 13
    - 11

Poor quality

49
Results – clinical damages

Detected cases (ADR)

- No significantly contributing risk factor
  - Treatment initiation
    - 7 clinical damage
      - The detected risk factor is/are not the contributing factor(s)

- ≥ 1 significantly contributing risk factor
  - 49
    - ≥ 1 detected risk factor contributes significantly
      - PPV_{ADE} = 4/49 = 8.1%
    - Poor quality
      - 11
    - 2

- 13
  - 2
  - 2
Results – clinical damages

Detected cases (ADR) 49

- No significantly contributing risk factor
  - Treatment initiation
    - 7 clinical damage 7

- ≥ 1 significantly contributing risk factor 34
  - The detected risk factor is/are not the contributing factor(s) 2
    - PPV_{ADE} = 4/49 = 8.1%
      - ≥ 1 detected risk factor contributes significantly 11
        - 4 clinical damage 4

- Poor quality 2
  - 1 Severe bleeding Medication error 1
Discussion

Rules
Discussion

Pharmacy data

Rules

Drug-drug interactions
Discussion

Pharmacy data

Rules

Drug-allergy contra-indications

Diagnostic data
Discussion

Pharmacy data

Rules

Drug-Lab warnings

Laboratory data
Discussion

Pharmacy data

Rules

Administrative data

Drug-Age warnings
Discussion

- Administrative data
- Pharmacy data
- Lab data
- Diagnostic data

PSIP rules

Rules
- Drug-drug interactions
- Drug-allergy contra-indications
- Drug-Lab warnings
- Drug-Age warnings
Discussion

PSIP rules

Rules
- Drug-drug interactions
- Drug-allergy contra-indications
- Drug-Lab warnings
- Drug-Age warnings

& chronological parameters

Pharmacy data

Diagnostic data

Lab data

Administrative data
Discussion

- Litterature review of detection of vitamin K imbalance:
  - PPV_{ADE} = 8.1%
  - PPV_{risk factors ADR} = 22.4%

- PSIP approach is promising:

Conclusion

- ADE-Scorecards: comprehensive statistics, personal review of the detected inpatient stays
  ➔ Precious tool for physicians and pharmacists to evaluate and adapt their practices.
- Implemented in Denain hospital for 3 years: positive feedback.
- Wide range of possible applications:
  ➔ Integration in decision support systems,
  ➔ Quality of hospital care assessment
  ➔ Drug safety research.
Thank you for your attention

Acknowledgments:
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Further information:
http://psip.univ-lille2.fr/prototypes/public/scorecards.htm