Market Safety Evaluations

The diabetic population as a focus & as a challenge

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Introduction

- Approval of a drug on the Canadian market is on:
  - the evidence of its efficacy
    - pcb vs active comparator (std medical practice)
  - the hypothesis of its safety

- Marketing of a drug is only the beginning of its safety assessment

Pharmacovigilance

- Tools / Stakeholders
  - Spontaneous adverse event (AE) reporting
    - MAHs (PSURs - Periodic Safety Update Reports)
    - health care providers (HCPs)
    - public
    - international databases (WHO, US-FDA, HC)
  - Scientific literature
    (case reports, case series, cohort studies)

Canadian Adverse Drug Reaction Monitoring Program

CARDMP

- only domestic 'events' (clinical vs WHO definitions)

- Rate of reporting: +++ confounders 👎
  - duration on the Canadian market
  - level of awareness
  - share of the market
  - drug given to patients with adv dz or +++ co-morbidities
    - 2nd line Tx (has to fail 1st line to qualify)
  - under-reporting not necessarily uniform amg drugs
  - sub-pop at risk (♀, elderly, diabetics)
  - background noise

CARDMP data

- Caveat
- Does it fit with other sources of data ?
  - MAH's (PSURs)
  - literature
  - *etc*
- Purposes:
  - signal generation
  - monitoring of the domestic situation
    - trends in reporting

ADR Reports

- Processing
  - adv event →→→→ adv rxn
  - in blinded clinical trials, 5% of people on pcb
  - adv rxn ≠ side effects (type A vs type B ADRs)
- Causality algorithm
  - WHO (definite, probable, possible, unlikely, unassessible)

ADR Reports

- Cornerstones:
  - Description / qlty of the report
    - id of the reporter / id of the pt
    - dose, duration of Tx, dates of start of Tx, date of ADR
  - Likelihood (includes differential diagnosis)
    - background noise
  - Seriousness
    - WHO, FDA, Food & Drugs Reg's

Signal Identification

- Signal generation from diff sources:
  - CARDMP
  - regulatory agencies (international data)
  - scientific literature
  - pre-marketing directorate (TPD) / Clinical Trials
  - industry (PSURs)

- From collation of data: is there a signal ??

Signal Prioritization

- Standard Operating Procedure
  - major vs minor criteria
- High, medium, or low priority

Signal Processing

- Identification of a risk factor:
  - co-med's (PD / PK interactions)
  - duration of exposure
  - dose (O/D)
  - age, gender, vulnerable sub-pop's
  - genetics (family clusters)
  - underlying dz
- Identification of a RF makes a risk mitigatable

Signal Processing (cont'd)

- Processing → → → Recommendations
  - labeling changes
  - risk communications
  - contact MAH for safety data

- International collaboration
  - MOU (Memorandum of understanding)
    - signals, pending regulatory actions
  - PSURs (Periodic Safety Update Reports)
    - MAH must declare if any regulatory action has been taken anywhere around the world against their product

Signal Assessment

- Is the risk acceptable ?
  - unacceptable benefit / risk ratio
    - consider risk of not treating underlying dz
  - available alternative Tx for less risk
- Timing: depends on the health hazard
  - very rare, very serious events
  - very common, very non-specific events

Risk Communications

- no regulatory authority to force a MAH to issue a risk communication

- Types
  - Dear Health Care Professional Letter
    - targeted
    - wide distribution
  - Dear Pharmacist / Retailer Letter
    - recall issues
  - Public Advisory (web posting)
    - Q & A
    - position statement
  - Note to hospitals

Diabetic Population

Vulnerable population: ↗ risk of serious AE's

- underlying disease (complications / co-morbidities)
  - high background noise for adverse events
- polypharmacy
  - risk for drug-host + drug-drug interactions
  - difficulty for identification of culprit drug
- hemodialysis (abrupt volume shifts, E^+ abN)
- ↗ risk of infections: +++ need for ABTx
- pediatric / elderly / pregnant segments
- ↗ prevalence in Canada

Diabetic Population (cont'd)

- Difficulty to reach ☹
  - coordination of multiple health care providers
    - follow-up by fam MD's vs endocrinologists
    - ambulatory care vs hospital settings
  - limits of communication tools: public advisories
    - pediatric vs elderly segments →→ access ??
- Signal prioritization: major criterion for high priority

Diabetic Population (cont'd)

- Poor qlty data / complex cases
  - decision by health care provider
    - individualized benefit-risk assessment
  - decision by regulator
    - intensified monitoring
      - international collaboration
      - interaction with pharmaceutical companies
    - strengthening of labelling →making info available
    - raising awareness for risk →stimulating reporting
    - risk communications