CAPRA APRIL 2005

DIABETES: Current Practice, Future Trends

The Impact of Guidelines and Recently Completed Studies on Clinical Trial Design

INSULIN

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Overview

- Expectations for all clinical trials:
- Insulin - General
- Hypoglycemia
- Efficacy and safety issues for recently Completed Studies with Inhaled/oral insulin
- Conclusions

Clinical Trial Design Issues for Insulin:

- In general as for other biologic products
- different than for oral hypoglycemic agents
  - Rx effects are more direct and evident
  - Hence better understood

Clinical Trial Design Expectations:

- subjects should receive:
  - adequate dietary and lifestyle counselling
  - adequate treatment for concurrent conditions
- subjects should self-monitor blood glucose daily or as directed and self-monitor body weight at frequent intervals
- monitoring during the trial should conform to the CDA guidelines

Clinical Trial Design
CDA Glucose Monitoring Targets:

- Improved glucose control = reduced risk of morbidity (less macro- and micro-vascular disease) & mortality
- short-term hyperglycemia has impact
- HbA1c <7% or FPG = 4.0–7.0 mmol/L
- target HbA1c attainable 6 to 12 months for Type 2
  - HbA1c >9% considered marked hyperglycemia and the recommended treatment includes 2 antihyperglycemic agents or insulin

clinical trials must be designed within this context

i.e. current standards of care (practice guidelines) are applicable when "proving" efficacy or collecting safety data

Insulin Therapy:

- Insulin mostly now recombinant
- Analogues designed to improve pharmacokinetics
- Classified by duration, onset and peak action times
- Premixed insulin used alone more frequently in Type 2 but can be part of therapy in type 1 as well
- Inhaled/oral insulin in the pipeline – may be others… e.g. Patch

Animal vs. human insulin:
(according to the CDA practice guidelines)

- No significant clinical difference wrt
  - symptomatic response
  - frequency of hypoglycemia
- no proof animal insulin afford advantages regarding hypoglycemia awareness
  - Perhaps the contrary

Insulin regiments:

- Requirements tend to increase with time (after initial 'honeymoon' period)
- Basal bolus over longer acting (once or twice daily) + shorter acting insulin for food intake

Hypoglycemia recommendations:

- Early identification of risk factors and strategies
- Hypoglycemia unawareness:
  - more frequent monitoring,
  - less stringent controls,
  - > freq. of injections
- Awareness of Somogyi Effect:
  - Caused by the release of stress hormones
  - high FPG level from an extremely low level
    - (usually occurring after an untreated insulin reaction during the night)
  - Subjects with high FPG levels may need to test PG in the night.
- Insulin glargine or detemir
  - should be considered when there is difficulty with FPG
  - or overnight hypoglycaemia

Targets for Glycemic Control:

For most / (and when tighter controls are deemed safe):

- HgA1C: ≤ 7 / (6)
- FPG: 4-7 / (4-6)
- 2hr PPG: 5-10 / (5-8)

Insulin Glargine:

- insulin analog indicated for o.d. SC administration
- Type 1 or Type 2 DM who require basal insulin for the control of hyperglycemia
- NOC: April 3, 2002

Insulin Applications to BGTD:
(Biologic and Genetic Therapies Directorate)

- CTA's:
  - 6 products
  - ~ 45 trials over past 5 years
- NDS's:
  - insulin detemir
  - insulin aspart and insulin glargine approved

General Recommendations; Insulin Type 2 DM:

- Multiple daily injections (3 or 4 per day)
- Combinations of:
  - Long and short acting regimes preferred to regular insulin alone for 'smoother control'
- Continuous Subcutaneous Insulin Pumps
  - Long acting insulin should be used in addition to the insulin in the pump

Clinical Trials; Insulin Type 2 DM:

- Sample regimes in the Canadian Practice Guidelines include:
  - 100% long acting insulin at bedtime
  - 2 insulin injections premixed (2/3 in am 1/3 in pm)
  - Intensive regimes (40% long acting at baseline, 20% of total at mealtimes – inhaled/oral insulin formulations fit in here in Type 2)
- typically treatment naïve or poorly controlled diabetes
  - HbA1c of 6.5–10.0%
  - generally for whom two oral agents are not providing tight enough controls as per guidelines.
  - This is beginning to change with newer longer acting insulins.

Clinical Trials; Type 2 Diabetes Phase 2 trials

- typically placebo-controlled proof-of-concept dose ranging studies
- 12-24 weeks duration
- add-on to oral therapy
- objective is to demonstrate (E10 – ICH);
  - non inferiority
  - or superiority to comparable alternatives
  - and choose dose for phase 3 studies

Clinical Trials; Type 2 Diabetes
Phase 3 trials (Confirmatory)

- typically 1-2 years duration
- objective is to demonstrate efficacy and safety
- efficacy:
  - non-inferiority or equivalence to an accepted treatment
  - for new insulin (including inhaled/oral insulin – 1 year minimum for filing)

Clinical Trials: inhaled / oral insulin
New efficacy/quality and safety issues

Efficacy/quality issues

- Potential issues of;
  - dose delivery
  - Variability
  - Consistency
  - new devices associated with products
- Optimization of therapies in each arm of CT
  - compared (sc insulin vs. oral/inhaled) must be consistent
  - Very important for both non inferiority and superiority designs

Safety issues inhaled/oral insulin

- New route of administration,
  - Variability of absorption – pattern hypoglycemia
  - Different theoretical concerns for autoimmunity
  - new devices associated with products
- Monitoring Pulmonary Function: PFT
  - Significant cough
  - short and long term studies
    - special populations
    - (COPD, Asthmatics, elderly, paediatric, etc.)
- Others yet to be identified

Conclusions

- Old guidelines vs. new
  - not as much of a problem for interpretation/review as with oral agents
- Regulatory approval of Insulin Studies
  - evidence-based with case-by-case adjustment
- review is aimed at safeguarding clinical trial participants

- Sponsor's obligation to follow Good Clinical Practices Under Division 5 (C.05.010):
  - includes current practice guidelines
  - Where Rx guidelines do not exist – consensus statements should be taken into account

- well presented functional outcomes more easily analyzed
- facilitate review
  - ultimately assist in bringing new and better Insulins to the market