A novel method to estimate the minimum effective dose for monotone and non-monotone dose-response relationships

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Introduction

• Minimum effective dose (MED): smallest dose producing a clinically important response that can be declared statistically significant different from zero dose

• Minimum detectable dose (MDD): smallest dose statistically significant different from zero dose

• Estimation can be performed by modeling approach or multiple comparison procedures

Outline

1 Introduction
2 Model
3 Procedure
4 Simulations
5 Discussion and Conclusion

Multiple comparison procedures:

• Performance of methods depends on the underlying - a-priori unknown - dose-response shape

• Assumptions about the dose response shape often difficult to elicit and hard to justify
**Assumptions**

Set of increasing dose levels $i = 0, 1, 2, \ldots, k$ with a-priori unknown monotone or unimodal dose-response relationship, where the $j$-th observation in the $i$-th group is distributed according to

$$X_{ij} = \mu_i + \varepsilon_{ij} \quad i = 0, 1, \ldots, k \text{ and } j = 1, 2, \ldots, n,$$

where $\varepsilon_{ij}$ are i.i.d. normally distributed with zero mean and a common $\sigma^2$.

**Control of the type I error**

Control of the error rate for underestimating the true MED

$$P(M < m) \leq \alpha$$

Under weak monotonicity the FWE is also controlled if the error rate of underestimating the true MED is controlled.

**Minimum effective dose**

Let $m$ denote the minimal effective dose so that

$$m = \min \{ i : \mu_i > \Delta + \mu_0 \},$$

for some threshold $\Delta > 0$, and let $M$ denote the smallest dose that is rejected by a hypothesis testing approach.

**Procedure**

1. Perform all $k$ one-sided comparisons with the zero dose and use single step Dunnett’s procedure to adjust for multiplicity.
   - If no dose can be declared significantly superior to the zero dose, then no dose level is declared as MDD and the procedure stops.
   - If one or more test statistics exceed Dunnett’s critical value, let $\ell$ denote the largest index of such test statistic.
2. Perform the following sequential procedure.
   - Set $\ell = \ell - 1$.
   - If $\ell > 0$ and if an unadjusted one-sided two-sample t-test rejects $\mu_0 \geq \mu_\ell$, then go to (2a).
   - Otherwise, go to (3).
3. Set the minimal identified effective dose $M$ to $\ell + 1$. 
**Procedure**

It can be shown that the error rate of underestimating the true MED is controlled strongly for monotone or unimodal shapes.

**Proposition**

\[ P(M < m) \leq \alpha \text{ for monotone or unimodal shapes} \]

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**Simulations**

- Simulation study for 30 scenarios based on 1E6 runs
- Data generated to follow a normal distribution with \( n_i = 10 \) for \( k = 5 \) positive dose levels with \( \sigma = \sqrt{n} \)
- Introduced approach (SD3PC) compared with
  - Step-down version of Dunnett’s procedure (SD1PC)
  - Step-down application of two-sample t-tests (SD2PC)
Discussion and Conclusion

- Novel method combines the advantages of two other methods
- Not applicable to multi-modal dose-response relationships
- Controls the probability in underestimating the true MED
- Best or almost always close second in terms of power
- Advantage to interpret the results from a clinical point of view