

Evolution of Bioequivalence Guidelines in Canada

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[Reference Reading]
Drugs and the Pharmaceutical Sciences
Volume 48: Pharmaceutical Bioequivalence
(1991)
[P.G. Welling, F. L. S. Tse, S. V. Dighe]

- **Part 3: Perspectives on Regulatory Agencies, Worldwide, on Bioequivalence Testing**
  - **Iain J. McGilveray: Bioequivalence: A Canadian Regulatory Perspective (pp 381-418)**

James B. Conant

On Understanding Science ….

"As a first approximation, we may say that science emerges from the other progressive activities of man to the extent that new concepts arise from experiments and observations, and the new concepts in turn lead to further experiments and observations.

The texture of modern science is the result of the interweaving of the fruitful concepts."

An Evolution - Early Developments in B&B History

Overton and Meyer ~ 1900

Indifferent narcotics ….

..narcosis is closely related to the concentration of the active substance in the tissue elements sensitive to it.

and

..all these substances penetrate cells and tissues with ease.

Erik M.P. Widmark ~ 1920

Indifferent narcotics ….

..the percentage of the narcotic substance in the blood, after equilibrium…..is in a definite proportion to the concentration of the substance in the sensitive elements, e.g. the nerve cells.

and

..a knowledge of the percentage of these narcotics in the blood is of the greatest importance for the study of narcosis.

Erik M.P. Widmark ~ 1920

However ….

..determinations of the concentration of these substances in the blood are still comparatively rare. The substances that have been most studied are ethyl- and methyl-alcohol and ether and chloroform.

and

..a micromethod for determining the acetone in the blood further enables us readily to follow the variations in the concentration...in the blood.

EMP Widmark: Acta med. Scand. 52: 88-164 (1920)

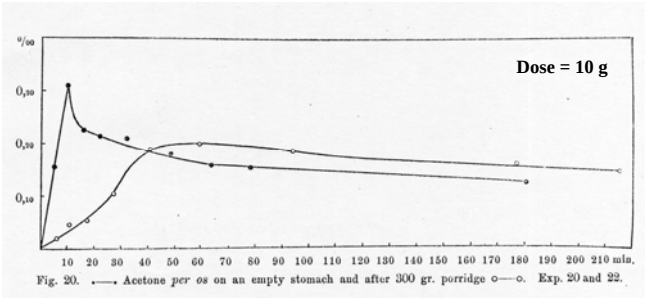


Fig. 20. •—•. Acetone *per os* on an empty stomach and after 300 gr. porridge o—o. Exp. 20 and 22.

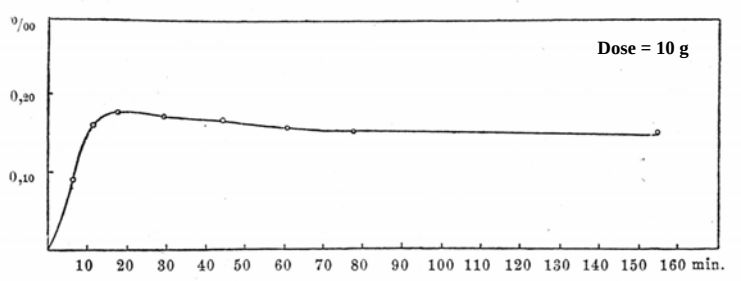


Fig. 21. Acetone *per rectum*. Exp. 23.

EMP Widmark: Acta med. Scand. 52: 88-164 (1920)

Analytical Capabilities Were Scientific Currency

- **H.P. Smith (~1930) – Rochester – dye**
- **Hemingway et al. (~1935) – Minnesota – dyes**
- **T. Teorell (~late 1930's) – Upsala, Sweden**
- **R. Dominguez (~1935+) – Cleveland**
- **Others in Europe**
- **"Bioavailability" first referred to as 'physiologic availability' eg. B.L. Oser – studied vitamins**
- **Post-war – USA moved ahead quickly**

An Evolution - Early Reports in North America

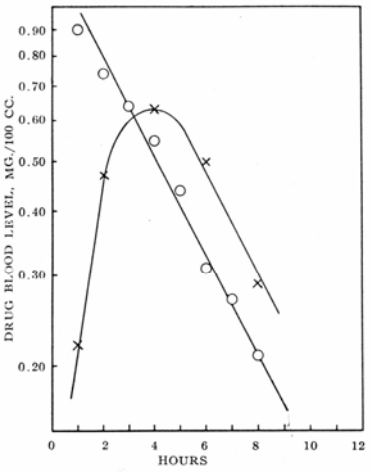


Fig. 3.—Average theophylline blood levels for 11 human subjects receiving 0.5 Gm. intravenous aminophylline, and 1 subject receiving 0.5 Gm. aminophylline orally. Data from reference (6).

EB Truitt et al: J. Pharmacol. Exp. Ther. 100: 309 (1950)

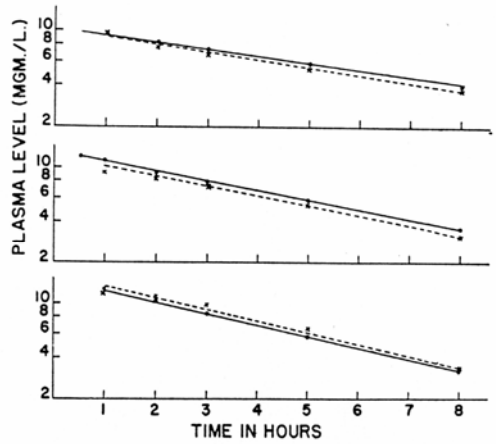


FIG. 1. Plasma levels of caffeine after the oral (solid line) and intravenous (dashed line) administration of 7 mgm. per kgm. of caffeine to three subjects.

J Axelrod, J Reichenthal: J. Pharmacol. Exp. Ther. 107: 519 (1953)

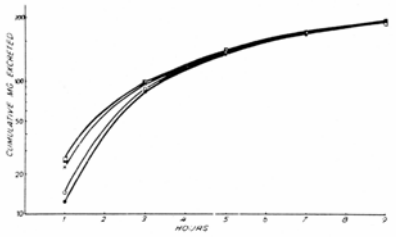


Fig. 1.—Cumulative amounts of apparent salicylate excreted after ingestion of 0.65 g. of aspirin or equivalent (average of 12 subjects). □ Choline salicylate solution, ■ Sodium salicylate solution, × Aspirin solution, ● Aspirin tablets, Brand A, ○ Aspirin tablets, Brand B.

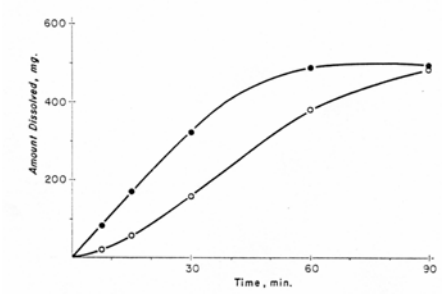


Fig. 1.—Dissolution of tolbutamide from compressed tablets as a function of time. ● Clinically effective tablets, ○ clinically ineffective tablets.

G Levy: Can. Med. Assoc J. 85: 414 (1961).

G Levy: Can. Med. Assoc J. 90: 978 (1964).

Bioavailability and Bioequivalence

Analytical

Experimentation

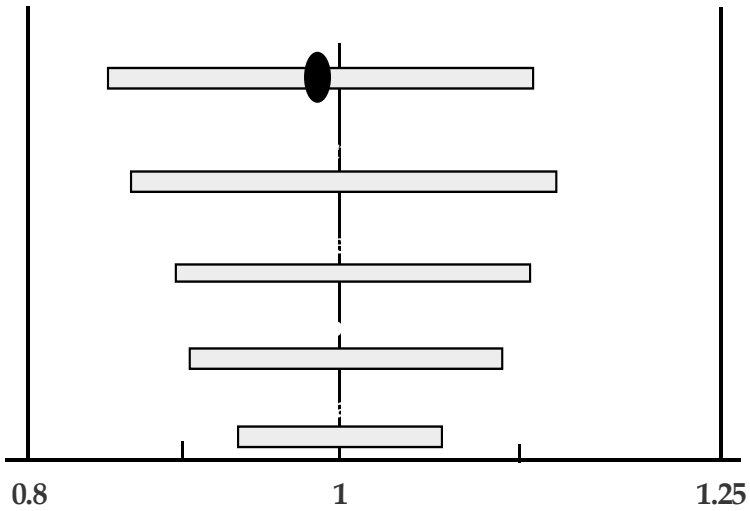
Statistics

Bioavailability: Statistical Highlights

Basis: 20% variability could be tolerated clinically

- ***Mean AUC and Cmax within 20% of reference***
- ***Null hypothesis and power approach (80/20), ~1977***
- ***75/75 (or 75/75-125) rule, 1978 – stopped 1986***
- ***Confidence limits – eg. Westlake (1979), 1986***
- ***Log transformation of data ~ 1993***
- ***Individual bioequivalence – eg. Anderson and Hauck, 1990 …..~1997/1999***
- ***Population bioequivalence ~1997/1999***

Statistics and Study Design Issues



An Evolution – Canadian B&B Regulatory Developments

- **1969 Amendments to Patent Act with compulsory licensing enabled many drugs to be available as generics (amended 1988 to afford longer (eg 20 year) protection)**
- **Concern about so-called "critical" 'old' drugs**

  ***e.g.* digoxin, phenytoin, quinidine and warfarin. HPB bioequivalence studies began in 1970**

B&B Regulatory Developments

- **1971 HPB study of 17 Digoxin products**
- ***ad hoc* External Advisory Committee (EAC) struck**
- **6 of 17 products declared unacceptable Dr John Ruedy was on the committee -- invited to chair the "Permanent" EAC on Bioavailability in 1973**

B&B Regulatory Developments

- HPB, 4 product Warfarin bioequivalence study, 1975
  - AUC ratios: 97.3, 86.6 and 100.5%
  - Peak ratios: 89, 78 and 86%
- EAC -- "products considered to have satisfactory, though different" BA should not be substituted without re-titrating the patient (prothrombin time)

B&B Regulatory Developments

- EAC looked at many BA studies,e.g. phenytoin and also consulted for NDS
- Late 80s began work on "guidelines"
- Produced as reports A, B and C '90-92
- "A" became Guideline A, 1995.
  - General guidance for BA and BE for 'uncomplicated' drugs. Complicated drugs defined.
- "B" became Guideline B, 1996
  - A guidance for modified release formulations

B&B Regulatory Developments

- Report C: Specialized cases never converted into a Guideline although it served as a basis for decisions.
- Normalize comparative bioavailability information for drug content (dose)
- Study designs; logarithmic transformations
- Evolution of hypothesis testing and confidence intervals beginning with W. J. Westlake (1972)
- Development of the Add-on Study Design
- Geometric means and the 80-125% window for both means and confidence intervals

2001 EAC Mandate

- Bioavailability and bioequivalence
  - Medical, scientific and clinical advice
    - Current and emerging issues
- Recommendations on questions like:
  - Pharmaceuticals and biologicals
    - Outcome: new guidances (ANDS and NDS)
  - Interactions: drugs, foods, natural products, environmental contaminants

EAC Mandate (cont'd)

- Methods of assessing population and individual bioequivalence
- Special populations (age, genetic, gender, etc.)
- Guidances for products where bioavailability determination is not suitable
- Alternative dosage forms

Other issues identified by the committee

The TPD: Recent, Present and Activities

Report C drugs – No general guideline; individual issues

- **Bioequivalence Requirements for Combination Drug Products**
- **Bioequivalence Requirements for Long Half-life Drugs**
- **Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs)**
- **Bioequivalence Requirements: Critical Dose Drugs**

Other Issues

- **Removal of Requirement for 15% Random Replicate Samples**
- **Use of Metabolite Data in Comparative Bioavailability Studies**
- **Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State**

The TPD: Future Activities?

- ***Is there room for reduction/minimalism of criteria?***
  - The development of the Biopharmaceutical Classification System (BCS); reduced bioequivalence requirements (Europe – 1998; USA – 1999)
  - Fixed maximum subject numbers, mean ratio, dispersion
- ***Is this the time for Guidelines A and B to be updated?***
- ***Is there a need to move ahead with biologic products?***

B&B -- Fruitful Concepts??

- ***An engine for science and education:***
  - Research and method developments
  - Statistical developments/illustrations
  - Education, degrees, teaching/courses
- ***An engine for commerce:***
  - Pharmaceutical manufacturers and products
  - Clinical researchers and CRO's
  - Laboratories
  - Legal specialists
  - Advertising, marketing, etc.

Fruitful Concepts, and B&B??

- ***An engine for governments and agencies:***
  - Regulatory departments and criteria for approvals
  - Laboratory testing
  - Drug budget savings
- ***Patients:***
  - Product safety and efficacy
  - More affordable choices??