How do you “re-develop” an old antibiotic: experience from AIDA

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Reviving old antibiotics
Reviving old antibiotics: how old?

A COMPARISON OF EIGHT ANTIBIOTIC AGENTS, IN VIVO AND IN VITRO

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During the past year a number of new antibiotic agents have been studied by members of this department. Some of the observations, on separate agents, have already been published (Bliss et al., 1948; Schoenbach et al., 1948; Breyer et al., 1948; Bliss and Chandler, 1948; Chandler and Bliss, 1948). In the present report, comparisons of the agents with respect to antibacterial activity, in vitro and in experimental infections in mice, are presented.

MATERIALS AND METHODS

Agents. Polymyxin D and aureomycin were received through the courtesy of the American Cyanamid Company and the Lederle Laboratories, Inc., during the fall of 1947. Polymyxin D, first described by Benedict and Langlykke (1947) and Stanly, Shepherd, and White (1947), is derived from filtrates of cultures of Bacillus polymyx. The material used here is the hydrochloride, Lederle lot nos. 2-3204 and 2-5314.

Aureomycin is produced from Streptomyces aureofaciens. Its antibiotic properties were discovered by Dr. B. M. Dugur (1948) of the Lederle Laboratories and were first publicly described at a meeting in July, 1948. Lots 7-8020 A, 7-8071 A, 7-8254, and 7-8411 of the dried hydrochloride of this agent were used for the work that will be described. These lots were about 80 per cent pure aureomycin, according to a note from the manufacturer.

We are indebted to Burroughs Wellcome and Company for a supply of polymyxin B. The vials are labeled "Aerobin-Brand." The history of the polymyxins is somewhat confusing. The one that was first described by Benedict and Langlykke and by Stanly, Shepherd, and White was derived, as mentioned above, from an organism identified as B. polymyx. It is now known as polymyxin B. Almost simultaneously with its discovery, Alnsworth, Reiss, and Brownlee (1947) announced that extracts of Bacillus aerogenes (Green) had antibacterial activity. They named this product aerobin but noted that "aerobin" was a nonstandard, Americanism. Buchanan, Subsequent at least finding academic meeting time

Approved in
- Japan 1951
- Europe 1959

(France, Laboratories Roger Bellon → Rhône-Poulenc+Hoechst=Aventis+Sanofi-Synthélabo → SanofiAventis)
- US 1962
(1) improving our surveillance of the rise of antibiotic-resistant bacteria to enable effective response, stop outbreaks, and limit the spread of antibiotic-resistant organisms, and acting on surveillance data to implement appropriate infection control;

(2) increasing the longevity of current antibiotics, by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics;

(3) increasing the rate at which new antibiotics, as well as other interventions, are discovered and developed.
Reviving old antibiotics

1912 - Paul Ehrlich
Paul Ehrlich discovers the first specific chemotherapeutic agent for a bacterial disease: Salvarsan for syphilis

1950 - Colistin
First usage of colistin

1967 - Rifamycin
Rifamycin approved

1972 - Minocycline
Minocycline approved

2012 - AIDA
AIDA starts the project to revive old but still effective antibiotics

1929 - Alexander
Alexander Fleming

1953 - Nitrofurantoin
Nitrofurantoin became an antibiotic

1971 - Fosfomycin
Clinical usage of fosfomycin

1996 - KPC Carbapenemase described
First KPC-carbapenemase described. The beginning of the worldwide resistance threat in Gram-negative bacteria
Why revive old antibiotics?

- Extensively resistant Gram-negatives
- Carbapenem-sparing treatment, i.v., oral
- MRSA – alternative to linezolid oral
Revived old antibiotics – knowledge

- Dose finding
- PK
- PK/PD – exposure-effect relationships
- Clinical efficacy
- Safety

- 1962 FDA approves the marketing application
- 1981 FDA requires preclinical testing before clinical trials
- National agencies
- EMA since 1995
“Re-developing” of old antibiotics

14 partners from 11 different countries
Complimentary expertise

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"Re-developing" of old antibiotics

Example AIDA:
• critically ill patients
• outpatients
• nursing home patients

Colistin
Nitrofurantoin
Fosfomycin trometamol
Rifampicin
Minocycline oral
“Re-developing” of old antibiotics: first step

- Systematic review
- Assess the quality of information
- Identify the information gaps

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“Re-developing” of old antibiotics: principles

**Aims:**
- Dosing recommendations
- Efficacy (superiority, non-inferiority)
- PK
- Safety
- Combination therapy
- Emergence of resistance
- Breakpoints
- Valid comparators for new antibiotics

**Non-clinical**
- **Single drugs, combinations**
  - PK/PD index magnitude exposure-res
  - population PK exposure relationships
    - exposure-clinical outcome
    - exposure-safety
    - exposure-res
  - MCS, PTA

**RCT**
- PK
  - sparse sampling
- endpoints
  - microbiol
  - clinical
    - efficacy
    - safety
    - res
- microbiol
  - res mechan
  - colonisation

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Prior knowledge <2004

2010

Non-clinical studies

Optimised usage

Randomised controlled clinical trial in critically ill patients

PK

microbiology

outcome

Prior knowledge >2004

Current evolving knowledge

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“Re-developing” of old antibiotics: colistin

Non-clinical studies
- Kill dynamics
- Single drug, combination, synergy, res. analysis
- Protein binding
- Population PK
- PK/PD modeling + simulation

RCT
- Colistin alone vs. colistin + carbapenem
- Carbapenem resistant Gram-negative inf.

<table>
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<th>Superiority</th>
<th>Safety</th>
<th>Emergence of resistance</th>
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<td>Microbiology: - MIC, synergy, - colonisation; - res. mechan.</td>
<td>Exposure: - efficacy - toxicity - resistance relationship</td>
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PK
Sparse sampling

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“Re-developing” of old antibiotics: nitrofurantoin, fosfomycin or...
“Re-developing” of old antibiotics: minocycline, rifampicin

Prior knowledge

2010

Non-clinical studies

PK/PD combination testing

PK/PD modelling of combination

Gaps in knowledge

• PK
• PK/PD
• Dosing
• Efficacy vs linezolid
• Combinations
• Breakpoints

PK
• sparse sampling

RCT
minocycline+rifampicin vs linezolid
MRSA SSTI, oral – non-inferiority

endpoints
• microbiol
• clinical
  ➢ efficacy
  ➢ safety
  ➢ res

Current knowledge
in acute infections
~ 1970s-1980s

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“Re-developing” of old antibiotics for today’s use

Update knowledge with today’s methods

- Integrating in vitro, in vivo, in silico, and clinical studies
- Exposure-effect relationships to optimise dosing strategies
- Clinical studies: RCTs, superiority, non-inferiority, combination therapy
- Risk assessment for emergence of resistance
- Clinical breakpoints

Pool expertise and efforts

Communicate results

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Access to clinical trial data
- Open data strategies for clinical trial results to calculate PK/PD relationships

Numerous small observational studies do not provide the needed evidence
- Worldwide coordination of clinical trial protocols to pool data and create evidence

Provide funding for multidisciplinary and multinational teams

Update of knowledge in SPCs
- Share knowledge with regulatory agencies
- Discuss acceptable protocols with agencies