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

U. Theuretzbacher
Center for Anti-Infective Agents, Vienna, Austria
Reviving old antibiotics: how old?

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

ELEANOR A. BLISS AND H. PATRICIA TODD
Department of Preventive Medicine, The Johns Hopkins University, School of Medicine, Baltimore, Maryland.

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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; Bryer 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 Stanaly, Shepherd, and White (1947), is derived from filtrates of cultures of Bacillus polymyx. The material used here is the hydrochloride, Lederle lot nos. 7-2206 and 7-2214.

Aureomycin is produced from Streptomyces aureofaciens. Its antibiotic properties were discovered by Dr. B. M. Dugger (1948) of the Lederle Laboratories and were first publicly described at a meeting in July, 1948. Lots 7-8202 A, 7-8207 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 “Aeropin-Brand.” The history of the polymyxin is somewhat confusing. The one that was first described by Benedict and Langlykke and by Stanaly, Shepherd, and White was derived, as mentioned above, from an organism identified as B. polymyx. It is the one now known as polymyxin D. Almost simultaneously with its discovery, Amsworth, Brown, and Brownlee (1947) announced that extracts of Bacillus aequorae (Green) had antibacterial activity. They named this product aeropin but noted that it was not comparable to the agent investigated by Benedict and Langlykke.

Approved in

• Japan 1951
• Europe 1959
(France, Laboratories Roger Bellon → Rhône-Poulenc+Hoechst= Aventis+Sanofi-Synthélabo → SanofiAventis)
• US 1962

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POLYMIXIN B AND COLISTIN*
A Critical Comparison
NATHANIEL H. NOYES AND PAUL D. HOPKINSON,
M.D.
SALT LAKE CITY, UTAH

GRAM-negative bacilli, in particular pseudomonas species, are of increasing concern to the clinician as a cause of nosocomial and therapeutic problems. Among the antibiotics, polymyxin B has gained in importance as an aid in treatment of a wide variety of infections caused by pseudomonas species. All the pseudomonas species are considered Gram-negative bacilli.

In a collection of 1000 different strains of pseudomonas species, isolated from human beings and acute lethal toxicity in mice, all were found to be resistant to polymyxin B by intramuscularly, intravenously, or intraperitoneally administered antibiotics.

MATERIALS AND METHODS

In Vivo Susceptibility Testing
Fifty strains of pseudomonas species, isolated from clinical specimens submitted to the Clinical Microbiology Laboratory of the Salt Lake County General Hospital, were studied. Each isolate was stored until used at 6°C after overnight incubation in semisolid agar (commercially dried, potato) and was cultured in 0.01 sodium succinate. After overnight incubation at 6°C, the colonies were grown in a test tube containing 0.050 and 0.001 sodium per milliliter of saline. After incubation at 37°C, the largest colonies were examined. The results of the susceptibility testing were determined from the susceptibility of the bacteria to a minimum inhibitory concentration of sodium per milliliter of the antibiotic when grown in a test tube containing 0.050 and 0.001 sodium per milliliter.
(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 - Rifamocin

1972 - Minocycline
Minocycline approved.

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

1929 - Alexander
Alexander Fleming's discovery of penicillin.

1953 - Nitrofurantoin
Nitrofurantoin became available.

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

http://www.aida-project.eu
“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
“Re-developing” of old antibiotics: principles

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

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

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http://www.aida-project.eu
“Re-developing” of old antibiotics: colistin

Prior knowledge <2004

Non-clinical studies

2010

Randomised controlled clinical trial in critically ill patients

Production
Regulation
Nomenclature

Optimised usage

PK
outcome

microbiology

Current evolving knowledge

Number of Colistin publications

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“Re-developing” of old antibiotics: colistin

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

PK/PD

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

Microbiology:
- MIC, synergy, colonisation, res. mech.

Exposure:
- Efficacy, toxicity, resistance relationship

PK
- Sparse sampling

Superiority, safety, emergence of resistance

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

Prior knowledge

Gaps in knowledge

2010

Non-clinical studies

- MIC distributions
- kill dynamics
- exposure-res.
- PK/PK/PD

new UTI animal model

PK/PD modelling

PK/PD modelling

PK modelling

PK/PK/PD modelling

RCT

Nitrofurantoin vs fosfomycin-tromet.
IUTI due to MDR

PK
- volunteers
- patients

endpoints
- microbiol
- clinical
  - efficacy
  - safety
  - res

microbiology

Current knowledge

~ 1970s-1980s

Formulations
Regulation

PK

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“Re-developing” of old antibiotics: minocycline, rifampicin

Prior knowledge

2010

Non-clinical studies

PK/PD

combination testing

PK/PD modelling of combination

RCT

minocycline+rifampicin vs linezolid
MRSA SSTI, oral

PK
• sparse sampling

endpoints
• microbiol
• clinical
  ➢ efficacy
  ➢ safety
  ➢ res

microbiology

Gaps in knowledge

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

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
Issues and strategies for the future

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