Bisphosphonates at 50. Bones and Beyond
La Hulpe 10th March 2017

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and

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Sir Edward Mellanby
Can We Teach Old Dogs New Tricks?!
Bisphosphonates. A 40+ year Journey From Water Softeners to Blockbuster Drugs

Towards a molecular explanation of actions of bisphosphonates

>R2

R1

>25,000 publications in PubMed

Davos

Risedronate in Farnesyl Pyrophosphate Synthase

Russell RG. *Bisphosphonates: The first 40 years.* Bone. 2011 Jul;49(1):2-19
The Beginning.....1960s
Polyphosphates are water softeners.

Bill Neuman
Herb Fleisch

Pyrophosphate is the body’s natural water softener

1965 Paper

“Alkaline phosphatase regulates mineralisation by hydrolysing PPi”


EXCRETION OF INORGANIC PYROPHOSPHATE IN HYPOPHOSPHATASIA

R. G. G. RUSSELL
B.A. Cantab.
RESEARCH ASSISTANT,
MEDICAL RESEARCH COUNCIL MINERAL METABOLISM RESEARCH UNIT,
THE GENERAL INFIRMARY AT LEEDS*

HYPOPHOSPHATASIA is an inborn error of metabolism characterised by three main features (Rathbun 1948, Fraser 1957): (1) defective mineralisation of bone; (2) diminished alkaline phosphatase activity in plasma and tissues; (3) increased urinary excretion of phosphoryl-ethanolamine.

This paper reports an additional biochemical abnormality in this disease—namely, an increased renal excretion of inorganic pyrophosphate (PPi).

Prof Charles Dent kindly provided access to the children with hypophosphatasia, but gracefully declined to be a co-author!

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Enzyme Replacement with Alkaline Phosphatase in the Bone Disease, Hypophosphatasia, becomes a Reality

Pyrophosphate (PPI) is the body's natural water softener and regulated by alkaline phosphatase

Michael Whyte

Baseline

Week 24

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Chemical Relationships.
Phosphates, Pyrophosphate and Bisphosphonates

Inorganic Phosphate (Pi)

Inorganic Pyrophosphate (PPI)
Chemically and Enzymatically Labile

Inorganic Polyphosphate as acid,
where \( n = 1 \) to \( 100+ \)
(eg Graham salt)

Bisphosphonate (BP) as acid
Chemically Stable
Early Studies With Bisphosphonates

- Inhibit mineralisation
  - Vitamin D-induced AORTIC CALCIFICATION
    - Francis, Russell & Fleisch,
      - Science 165, 1264-6, 1969

- Inhibit bone resorption
  - PTE-induced resorption in mouse calvaria
    - Fleisch, Russell & Francis,
      - Science 165, 1262-4, 1969

Modelling of Metaphysial Bone
- Schenk, Merz, Muhlbauer, Russell & Fleisch.
  - Calcified Tissue Research 11, 196-214, 1973
When we were young........

Graham Russell & Herb Fleisch

Dave Francis
The birth of bisphosphonates
Science Vol 165, 1969

Diphosphonates Inhibit Hydroxyapatite Dissolution in vitro
and Bone Resorption in Tissue Culture and in vivo

Abstract. Two diphosphonates containing the P–C–P bond, \( \text{Cl}_2\text{C(PO}_3\text{HNa)}_2 \) and \( \text{H}_2\text{C(PO}_3\text{HNa)}_2 \) retard the rate of dissolution of apatite crystals in vitro. They inhibit bone resorption induced by parathyroid extract in mouse calvaria in tissue culture and in thyroparathyroidectomized rats in vivo.

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Inorganic pyrophosphate inhibits the precipitation (1, 2) and the dissolution (3) of hydroxyapatite crystals in vitro. Because pyrophosphate is present in plasma (4), tooth (5), and bone (6), we have suggested (7) that it might regulate both the formation and destruction of mineralized tissues in vivo. Although pyrophosphate and long-chain condensed phosphates can inhibit the deposition of calcium phosphate in chick embryo femurs in tissue culture (7) and in the aorta (8) and skin (9) of the rat, it has not yet been possible to demonstrate an effect on the resorption of living bone. This failure to influence bone resorption may be due to hydrolysis of the P–O–P bond locally in the bone by pyrophosphatase before it can reach its site of action.

Substances were therefore sought that would be related in structure to pyrophosphate but resistant to chemical and enzymatic hydrolysis. Various compounds containing the P–C–P bond have been synthesized and found to have an effect similar to that of condensed phosphates on the precipitation of hydroxyapatite in vitro and on calcification in vivo (10). In addition, they were also active when administered orally (10). We now describe the effect of two such compounds containing a P–C–P bond, namely, sodium dichloromethylenebisphosphonate \( \text{[Cl}_2\text{C(PO}_3\text{HNa)}_2] \) and sodium methylenebisphosphonate \( \text{[H}_2\text{C(PO}_3\text{HNa)}_2] \), on the dissolution of apatite crystals in vitro and on bone resorption induced by parathyroid extract in tissue culture and

To our knowledge the diphosphonates are still the only substances, apart from thyrocalcitonin (14), that can significantly inhibit bone resorption in vivo, although fluoride (15), orthophosphate (16) and estrogens (17) have been studied for their potential therapeutic effect in this respect. Since diphosphonates appear to be relatively nontoxic they might prove valuable in the treatment of osteoporosis and other human diseases that involve increased resorption of bone.

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Bisphosphonates Are Taken Up Avidly By Bone

- Bind to bone mineral
- Concentrate around and inside osteoclasts at sites of bone resorption
- Fluorescently-labelled bisphosphonate on bone surface and inside osteoclast
- Osteoclast membrane

The bisphosphonates have high tissue selectivity for bone
Bisphosphonates are Used to Treat Many Bone Resorption Disorders

Paget’s Disease

Myeloma

Bone metastases

Osteoporosis
Etidronate in Paget’s Disease

The Nuffield Orthopaedic Centre  Roger Smith

Smith Russell & Bishop, Lancet 1971

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Bisphosphonates (esp Zoledronate) Are Used to Prevent Skeletal Complications In Cancer (Hypercalcemia, Bone Loss And Fractures etc)

Note that alendronate and risedronate were never developed for treating cancer, despite being oral drugs.
Bisphosphonates are Used to Prevent Fractures In Osteoporosis

- **Wrist**
- **Spine**
- **Hip**

**Oral “blockbuster” BPs**

- **Alendronate**
  - ![Fosamax](image)
  - ![Atelvia](image)

- **Risedronate**
  - ![Actonel](image)

- **Ibandronate**
  - ![Boniva](image)

**Zoledronate is given once yearly iv**

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Drugs Used to Prevent Fractures

Non-Vertebral Fracture

- Calcium
- Vitamin D
- Calcium + vitamin D
- Alendronate
- Risedronate
- Ibandronate
- Zoledronate
- Raloxifene
- Strontium
- Denosumab
- Odanacatib
- Teriparatide
- PTH (1-84)

Favours treatment

- Favours control

Hip Fracture

- Favours treatment

- Favours control

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
3 years of IV Zoledronic acid (Annual) and Denosumab (2 x year) on Fractures

- Spine: 70% for Zoledronic acid Annual for 3 years*
- Hip: 40% for Zoledronic acid Annual for 3 years*
- Spine: 60% for Denosumab (3 years)*
- Hip: 20% for Denosumab (3 years)*

* Black, NEJM, 2007; *Cummings NEJM, 2009
Long-term Treatment of Osteoporosis

Phase III
- **ALN (n=596)**
  - n=439
  - n=350
  - n=247
  - Bone, NEJM 2004
- **PBO (n=397)**
  - n=288

FIT + FLEX
- **ALN (n=3236)**
  - n=662
  - Black, JAMA 2006
- **PBO (n=3223)**

VERT-MN
- **RIS (n=815)**
  - n=81
  - Sorensen, Bone 2003
  - Mellstrom, Calc.Tis. Int. 2004
- **PBO (n=407)**
  - n=83

HORIZON
- **ZOL (n=3889)**
  - n=616
  - n=85
  - n=95
  - Black, JBMR 2012
  - Black, JBMR 2015
- **PBO (n=3876)**
  - n=617

FREEDOM
- **Dmab (n=3902)**
  - n=2343
  - Papapoulos, JBMR 2015
  - Bone, Lancet Diabet. Endocrin. (submitted)
- **PBO (n=3906)**
  - n=2207

No study was specifically designed to assess long-term antifracture efficacy.
Long-Term Effects of Anti-Resorptives on Total Hip BMD.

Denosumab Compared with Bisphosphonates

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Denosumab and Bisphosphonates Have Different Effects on Osteoclasts

Denosumab blocks RANKL

Denosumab blocks osteoclast differentiation and reduces osteoclast numbers

Graham Russell 2008

BPs bind to bone mineral, at sites of bone resorption

BPs cause loss of resorptive function (via inhibition of FPPS and prenylation of GTP-ases), but ‘disabled’ osteoclasts may persist
Clinically Utilised Bisphosphonates.
Different Mechanisms of Action

- **Early BPs:** non-nitrogen containing
  - Etidronate
  - Clodronate
  - Tiludronate
  
- **“Second” generation:** nitrogen-containing with short alkyl chains
  - Pamidronate
  - Neridronate
  - Alendronate (Fosamax)

- **“Third” generation:** (from medicinal chemistry optimisation): nitrogen-containing with branched or ring structure
  - Ibandronate
  - Zoledronate
  - Minodronate
  - Risedronate
  - Ox-14, a new BP

Incorporated into ATP analogues

N-BPs inhibit FPPS in mevalonate pathway

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Bisphosphonate Cellular and Molecular Mechanisms of Action

Statins inhibit here

HMG Co-A → Mevalonate → Farnesyl-PP → Squalene → Cholesterol

N-Bisphosphonates inhibit Farnesyl pyrophosphate synthase

Geranylgeranyl-PP reduced

Isoprenylation of GTP-binding proteins (Rab, Rho, Ras, Rac etc)

From Rogers, Reska, Russell 2002
Osteoclasts Are Inhibited in Different Ways by Denosumab, Cathepsin K inhibitors, and Bisphosphonates

**Bisphosphonates**

- Bisphosphonates (BPs) can also inhibit osteoclast differentiation.

- Bisphosphonates bind to bone mineral. Nitrogen-containing BPs inhibit the resorptive function of osteoclasts via inhibition of FPPS and prenylation of GTP-ases, but 'disabled' osteoclasts may persist.

**Denosumab**

- Denosumab binds to RANKL and blocks osteoclast differentiation and reduces osteoclast numbers to near zero.

- Denosumab blocks RANKL.

**Cathepsin K inhibitors**

- Cat K inhibitors do not directly affect osteoclast differentiation.

- Osteoclasts persist in the presence of Cat K inhibitors and may continue to produce 'clastokines' that stimulate osteoblasts.

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Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Mevalonate pathway. Multiple sites of inhibition by N-BPs

- HMG-CoA
- MEVALONATE
- phosphomevalonate
- mevalonate diphosphate
- IPP isomerase
- dimethylallyl diphosphate
- isopentenyl diphosphate
- FPP synthase (main site of action of N-BPs)
- squalene synthase
- CHOLESTEROL
- squalene
- farnesyl diphosphate
- GPP synthase
- Rab GGTase
- geranylgeranylated Rab proteins

Statins inhibit here

LIVER

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Mechanisms of Action of Bisphosphonates

Nitrogen-containing BPs

- mevalonate
- dimethylallyl diphosphate
- isopentenyl diphosphate (IPP)
- cholesterol
- farnesyl diphosphate (FPP)
- geranylgeranyl diphosphate (GGPP)
- farnesylated proteins
- geranylgeranylated proteins

N-BPs inhibit FPP synthase

Apppl

Non-N-BPs

- ATP-PCP metabolites

metabolites induce osteoclast apoptosis

From Russell et al, 2008

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
The Acute Phase response.

Immunomodulatory Effects of Nitrogen-containing Bisphosphonates Through Effects on $\gamma,\delta$-T cells

Inhibition of FPPS by N-BPs leads to accumulation of IPP which stimulates $\gamma,\delta$-T cells

Uptake of N-BPs by PBMCs

$\gamma,\delta$-T cells involved in innate immunity, against tumors, parasites etc

 Release causes symptoms of the acute phase reaction

Thompson & Rogers 2004, J Bone Miner Res 19: 278-288
Range of Potencies of Bisphosphonates

Highly potent BPs used clinically are at this end of spectrum

Zoledronic Acid Has Long Lasting Effect On Reducing Bone Resorption (Serum B-Ctx) After Once Yearly Injection in Osteoporosis

Zoledronate has a remarkably long duration of action!

CTX is a biomarker of bone resorption

Osteopenic Women Given just 1 Infusion of Zoledronate 5mg

PINP is a biomarker of bone formation

Grey et al., Bone 50:1389, 2012
Distribution of $^{14}$C-labelled Zoledronic Acid in the Rat Skeleton After Intravenous Injection

From J Green 2002
Bisphosphonate Uptake and Detachment from Bone Surfaces. Effect of High Binding Affinity on Recirculation of BP on and off Bone Surfaces

High Affinity BPs eg Alendronate, Zoledronate

Avid uptake  Low desorption  High re-attachment

High Affinity BPs may diffuse less well in bone and remain nearer accessible surfaces

BPs can be detected in body fluids many months after injection

Nancollas et al Bone 2006
Do Biphosphonates act on Osteocytes?

Osteocytes

BPs may protect osteocytes from apoptosis and all may be equally effective if access occurs. Access may be better with BPs that have lower bone affinity.

Distribution of fluorescent BPs with different bone affinities
Red = lower; Green = higher

Osteoclasts in resorption cavity

At resorbing surfaces, the lower affinity compound diffuses further into the mineral.

Alan Boyde
The "Heineken" effect.
(Heineken beers reach parts other beers can’t reach!)

Lower affinity BPs should be able to gain access to more sites in bone than higher affinity BPs which will get ‘stuck’ at sites of first contact.

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Progress and Challenges

The Challenges
Have We Solved Osteoporosis?

No!

Fractures still occur

<50% of those at risk get treated (“The Treatment Gap”)

Poor compliance and adherence with oral therapies

Fear of side effects reduces use of BPs etc

- Osteonecrosis of the jaw (ONJ)
- Atypical femur fractures (AFFs)
Patient years of treatment in the EU

The number of patients treated has fallen in recent years

DDD/1000,000 population aged 50+ years

- Bisphosphonates
- Other

Ibandronate
Zoledronic acid

Teriparatide

Strontium ranelate

PTH(1-84)

Denosumab

Alendronate, etidronate, risedronate, raloxifene available before 2001


Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
The Media Likes Bad News Better Than Good…!!
Recent Controversies About Bisphosphonates (Esp. Long Term)

Safety:
- Osteonecrosis of the jaw (ONJ)
- Atypical femur fracture

The New York Times

Study Cautions Over Long Use Of Bone Drugs
F.D.A.’s Analysis May Change Regimes

FIGURE 1. Representative radiographs of f
Although each radiograph demonstrates f’s
Hypertrophied cortices outlined.
Don't throw the baby out with the bathwater!

Let's not throw the baby out with the bath water.

Benefit to Risk ratio strongly in favour of treatments (BPs and Denosumab)
Where Next?

- New BPs
- BPs for delivering drugs to bone
- Non-skeletal effects
  - Life span extension
  - Cardioprotection
  - Tissue repair
Potency of Bisphosphonates Depends on the two Key Properties of Mineral Binding and Inhibition of Farnesyl Pyrophosphate Synthase (FPPS)

X-Ray crystal structure of FPPS enzyme

BP binding pocket within enzyme

Optimized “ring structure” within binding pocket


Bisphosphonates applied to hydroxyapatite (HAP) column

Bisphosphonates elute at different times related to their binding affinity for HAP

Is it Possible to Make “Designer” Bisphosphonates?
Eg Very potent but with lower mineral binding

OX-3

\[
\text{IC}_{50} = 15 \text{ nM (7.3 min)}
\]

OX-14

\[
\text{IC}_{50} = 2.6 \text{ nM (6.2 min)}
\]

OX-139

\[
\text{IC}_{50} = 6.3 \text{ nM (6.3 min)}
\]

Binding (retention time in minutes) to Hydroxyapatite Column

FPPS Inhibition

OX-14 (1-fluoro-2-(imidazo-[1,2-a]pyridin-3-yl)-ethyl-bisphosphonic acid) has the strongest inhibitory potency at the enzyme and has the lowest affinity for hydroxyapatite.
Explaining How Bisphosphonates Work 2017

Each BP has a distinct profile for mineral binding and inhibition of FPPS

Bone Mineral Binding

Biochemical Mechanism

Inhibition of FPPS

Mineral Affinity depends on N-H-OH angle

N-O Distance Differentiator

AIn=Pam>ZOL>Iban>
Min>Ris>NER>OX14

Ox14>ZOL>Min>Ris
>lban>Pam>AIn>NER

Graham Russell, University of Oxford, Mellanby Centre for Bone Research University of Sheffield, UK
Possible Uses of BPs in Parasitic Diseases

e.g. Malaria and Cryptosporidiosis

(Possible targets for BPs via FPPS and other mevalonate pathway enzymes?)

**Plasmodium**
- falciparum (human)
- vivax (human)
- knowlesi (primate)
- yoelii (rodent)
- berghei (rodent)

**Cryptosporidium parvum**

FPPS enzyme from Plasmodium
Novel Potential Effects of Bisphosphonates on Mortality & Longevity

- Reduce cancers eg colon
- Prevent heart attacks (MIs)
- Promote tissue repair
- Increase Live Span
Reduced Risk Of Colon Cancer Death In Patients Treated With Alendronate - Danish National Register Based Cohort Study.

Pazianas M, Abrahamsen B, Eiken PA, Eastell R, Russell RG

Osteoporosis Int 2012

39% reduction in deaths from colon cancer

- 33,011 osteoporosis patients, mean age 71.3 years, began alendronate 1996-2005
- 66,022 matched control subjects
- Mean follow-up 4.9 years
- 629 colon cancer deaths
  - 39% reduction in Aln users
- Overall mortality reduction 17%
Zoledronate Reduced Risk of All-cause Mortality by 28% Over Time in Hip Fracture Trial

Hazard ratio, 0.72 (95% CI, 0.56–0.93)

P=0.0117

Absolute risk reduction, 3.7%

28% reduction in deaths

Are Bisphosphonates New Geroprotectors?

- Several epidemiology studies suggest decreased mortality
- A reduction of 28% in death from any cause in osteoporotic women given zoledronate (Lyles et al. 2007)
- In combination with statins extension of lifespan in progeric mice and improvement in the ageing-like phenotype (Varela et al. 2008)

**Candidate Geroprotectors**
- Rapamycin
- Metformin
- Resveratrol
- Bisphosphonates?

28% reduction in deaths
Effect Of Statins And Bisphosphonates In A Model Of Human Premature Aging

*Life span in mice is doubled*

Inhibition of prenylation of progerin and preLamin A increases life span

Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging

Accelerated Ageing

Hutchinson-Gilford Progeria Syndrome (HGPS)

- Hutchinson-Gilford progeria syndrome is due to a mutation in prelamin A (progerin) that prevents its conversion to Lamin A. This results in accumulation of farnesylated prelamin A.
- This led to a trial of a farnesyl transferase inhibitor (FTI; lonafarnib) in 25 children with HGPS.
- A new trial using a combination of an FTI (lonafarnib), a bisphosphonate (zoledronic acid), and a statin (pravastatin) is underway in 45 children.

Kieran et al Pediatrics 2007;120;834-841
Young et al Targeting Protein Prenylation in Progeria Sci Transl Med. 2013
Bisphosphonates Reduce the Risk of Myocardial Infarction in Patients with Rheumatoid Arthritis

ORIGINAL ARTICLE

Bisphosphonate Use Is Associated With Reduced Risk of Myocardial Infarction in Patients With Rheumatoid Arthritis

Frederick Wolfe,1 Marcy B Bolster,2 Christopher M O’Connor,3 Kaleb Michaud,4 Kenneth W Lyles,5,6 and Cathleen S Colón-Emeric3,5

28% reduction in heart attacks

• National Databank for Rheumatic Diseases, prospective study of RA patients, 2002-2011
• n=19,281. Number of patients ever on bisphosphonate: 5,891
• HR for MI among treated patients 0.72 (0.54-0.96) when on BP therapy compared to when on no therapy

Reduction of in-hospital mortality in patients who were treated with bisphosphonate prior to ICU admission

Preadmission bisphosphonate and mortality critically ill patients

Paul Lee1,5,7,8, Carmen Ng2, Anthony Slattery9, Priya Nair3,7, John A. Eisman1,5,7,8, Jacqueline R. Center1,6,7

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J Clin Endocrinol Metab. 2016 May;101(5):1945-53

59% reduction of in-hospital mortality in patients who were treated with bisphosphonate pre-ICU admission
Examples of Non-Skeletal Effects of Bisphosphonates

- Extension of life span and cardiovascular effects
- Enhanced DNA repair and tissue regeneration.
Zoledronate can protect human mesenchymal stem cells from radiation damage and cellular ageing
Where are we now? Bisphosphonates in 2017

BPs are well established in medicine with ~40yrs of use.

- Osteoporosis
- Bone oncology
- Paget’s disease etc

BPs are safe, and have well defined molecular and cellular actions

New indications possible for bone diseases and orthopaedics

Effects of BPs on the mevalonate pathway may lead to other non-skeletal applications, eg in immunology, parasitology, colon cancer, life span, DNA repair, radioprotection & tissue regeneration
Drug Discovery is not easy! Reflections on Then and Now For Bisphosphonates.

Modern drug discovery is based on identifying relevant targets (receptors, enzymes, cytokines etc).

Serendipity, luck and championship play a role

Challenges:
- Expense of R&D
- High failure rates
- Drug costs (generics are cheaper)
- Regulatory hurdles

- BPs are well established in medicine with >40yrs of use.
- Now in generic era and inexpensive
- Would they have succeeded if rediscovered in today’s environment?!
  - No ‘target’, or known mechanism of action
  - Low bioavailability (~1%)
  - Safety concerns
“New Tricks”, “Repurposing”
New Uses for Existing Drugs

Can we live to 120?!

- **Metformin**
  - From Type 2 diabetes to anti-ageing and Alzheimers

- **Rapamycin**
  - From immunosuppressant to anti-ageing

- **Bisphosphonates**
  - From bone diseases to anti-ageing and DNA repair
“New Tricks”, “Repurposing”
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**Bisphosphonates**
- From bone diseases to anti-ageing and DNA repair
Thank You!
Announcement

8th International Workshop on the Molecular Pharmacology and Therapeutics of Bone and other Musculoskeletal Diseases
Oxford, UK
30 June – 3 July 2018
www.molpharmworkshop.org