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Ninth International Symposium on Radiopharmacology

The University of Michigan Medical Center • Ann Arbor, Michigan
June 7-10, 1995

Symposium Sponsors

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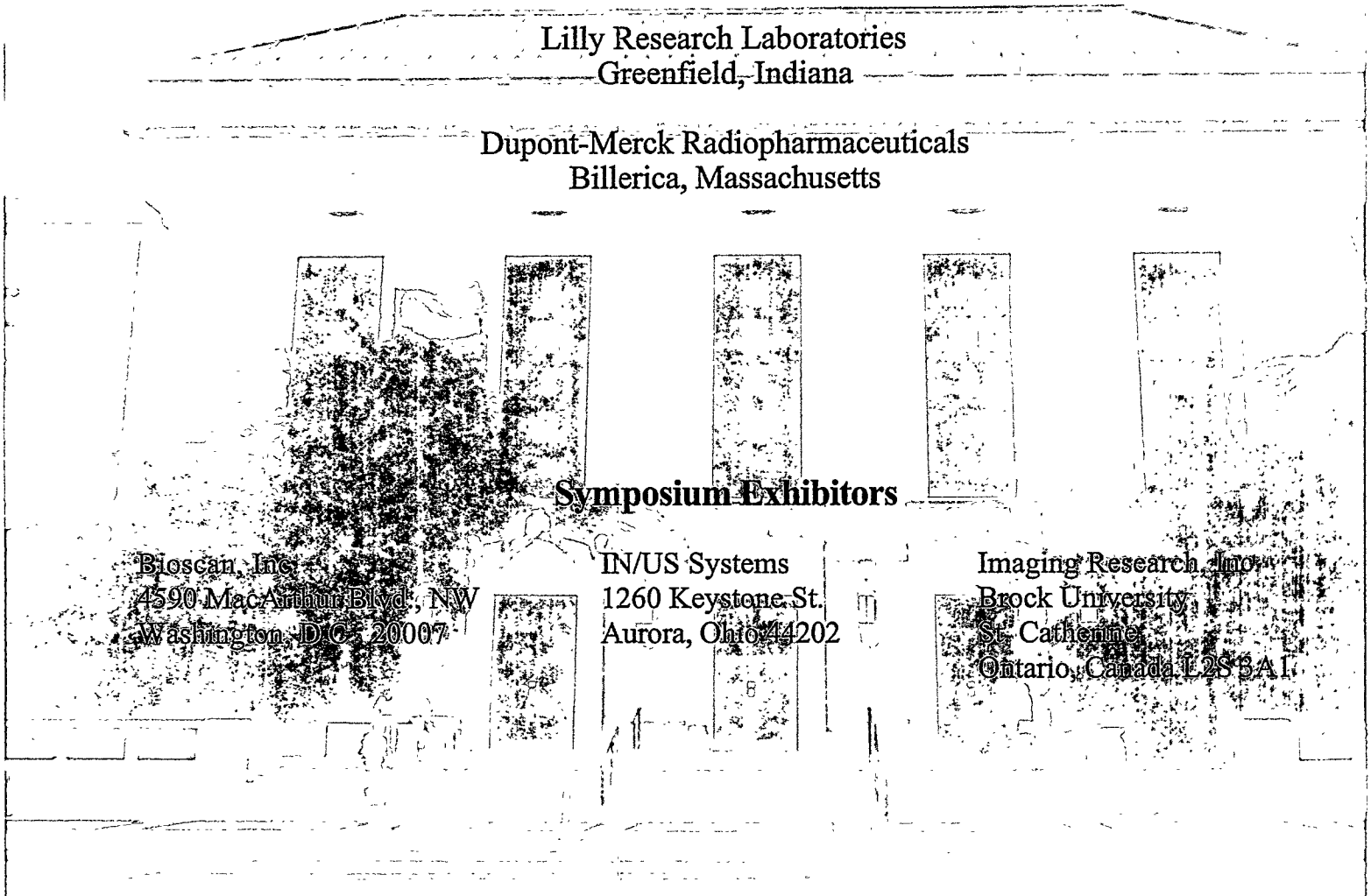

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Ninth International Symposium on Radiopharmacology

The University of Michigan Medical School • Ann Arbor, Michigan

June 7 -10, 1995

Symposium Objectives:

The goal of this Symposium will be to provide a forum for those international scientists involved in applying the principles of pharmacology and radiation biology to the development of agents for the diagnosis and treatment of disease. The program will highlight state-of-the-art progress in the development of those agents used in conjunction with some form of radiation such as radiopharmaceuticals, radiopaques, photo- and radiosensitizing drugs, and neutron capture agents. An underlying pharmacokinetic parameter associated with all these agents is the need for site-specific delivery to an organ or tumor. Therefore, a major goal of the symposium will be to address those pharmacologic principles for targeting molecules to specific tissue sites. Accordingly, session themes will include receptor-mediated processes, membrane transporters, antibody interactions, metabolic trapping, and oligonucleotide-antisense mechanisms.

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Program Schedule

Tuesday, June 6

7:00-9:00 pm Registration and Evening Reception Rackham Building Lobby

Wednesday, June 7

8:00 Registration/Coffee and Rolls

8:30 Chair's Welcome

8:35 Dean's Welcome

8:40 **Keynote Address - Dr. David Kuhl**
"Dissecting the Elements of Degenerative Brain Disease Using PET/SPECT"

9:30-10:00 Coffee Break - Exhibitors

10:00 **Neurotransmitter/Neuroreceptor**
Dr. Bill Eckelman, Chair

10:00 **Plenary Lecture - Dr. Kirk Frey**
"Quantitative Neurochemistry from In Vivo Radiotracer Distributions: Physiologic Considerations and Caveats"

10:50 Dr. K. Mardon, presenter
"In Vitro and Metabolic Evaluation of [^{123}I]-N-Methyl-4-Iododexetimide: A SPECT Radiotracer for Studying Myocardial Muscarinic Receptors"

11:15 Dr. T. R. DeGrado, presenter
"Uptake and Retention Mechanisms of para-[^{18}F] Fluorobenzylguanidine (PFBG) in Rat Heart"

11:35 Dr. C. S. John, presenter
"High Affinity Sigma Receptor Radioligands: Radiochemical Synthesis of 2-[I-125]BP and 3-[I-125]BP, Biodistribution and In Vitro Binding to Breast and Melanoma Tumor Cells"

12:00-1:30 pm Lunch Break

1:30 **Transporter/Radiopharmacology**
Dr. Donald Wieland, Chair

1:30 **Plenary Lecture - Dr. Michael Kuhar**
"Imaging Dopamine Transporter: From Drugs to Disease"

DISCLAIMER

2:20 Dr. Mike Kilbourn, presenter
"In Vivo Imaging of Monoaminergic Nerve Terminal Losses Using Ligands for the Synaptic Vesicle Monoamine Transporter"

2:40 Dr. Carol Nelson, presenter
"Regional Upregulation of GlucoseTransport Proteins in Tumors and 2-Deoxyglucose Retention"

3:00-3:30 Coffee Break - Exhibitors

3:30 **Endocytosis**
Dr. Jamey Weichert, Chair

3:30 **Plenary Lecture - Dr. Martin K. Bijsterbosch**
"Selective Drug Delivery by Means of Receptor-mediated Endocytosis"

4:20 Dr. Kevin Rice, presenter
"Pharmacokinetics and Biodistribution Analysis of Carbohydrate Ligands for the Asialoglycoprotein Receptor"

4:40 Dr. Jamey Weichert, presenter
"Lipoprotein-like Microemulsion for Selective Hepatocyte Delivery of Lipophilic CT Imaging Agents"

5:00-6:00 pm Time with Exhibitors/Refreshments

Thursday, June 8

8:00 am **Metabolic Trapping**
Dr. Leonard Wiebe, Chair

8:00 **Plenary Lecture - Dr. Thomas Woolf**
"Tacrine-induced Elevations in Human Liver Marker Enzymes: Reactive Metabolite and Metabolic Trapping Studies"

8:50 Dr. L. I. Wiebe, presenter
"Radiolabelled Tyrosinase Inhibitors for the Detection and Imaging of Neural Crest Tumors and Malignant Melanomas: Radioiodinated 2-Iodo-N-acetyl-4-S- cysteaminyl Phenol (2-I-N-Ac-4-SCAP)"

9:10 Dr. Guiliano Mariani, presenter
"Biochemical Modulaton by 5-Fluorouracil and Folinic Acid of Tumor Uptake of 5- [^{123}I]Iodo-2'–deoxyuridine Infused Intra-arterially in *Patients with Liver Metastases from Colorectal Cancer"*

9:30 Dr. Raymond E. Counsell, presenter
"The Influence of Molecular Structure on the Tumor Retention of Phospholipid Ether Analogs"

10:00-10:30 Coffee Break - Exhibitors

10:30 **In Vitro/In Vivo Methodology**
Dr. Ray Pohland, Chair

10:30 **Plenary Lecture - Dr. John Caldwell**
"The Essential Roles of Radioisotopes in Pharmaceutical Research and Development"

11:20 Dr. Alain A. Schweitzer, presenter
"Contribution of Electronic Autoradiography to the Assessment of the Site-specific Delivery of Radiolabelled Agents"

11:45-1:30 pm Lunch Break

1:30 **Boron Capture Neutron Therapy**
Dr. Scott Wilbur, Chair

1:30 **Plenary Lecture - Dr. Albert Soloway**
"Boron Neutron Capture Therapy - A Binary System for the Chemoradiotherapy of Cancer"

2:20 Dr. George W. Kabalka, presenter
"In Vivo Biodistribution and Pharmacokinetics of BNCT Agents Using PET and MRI"

2:40 Dr. D. Scott Wilbur, presenter
"Comparison of In Vivo Distributions of Simple Radiodinated Borane and Carborane Cage Molecules"

3:00-3:30 Coffee Break - Exhibitors

3:30 **Photodynamic Therapy**
Dr. Johan van Lier, Chair

3:30 **Plenary Lecture - Dr. David Kessel**
"Principles of Photodynamic Therapy"

4:20 Dr. B. W. Henderson, presenter
"The Determinants for the Tissue Response to Photodynamic Therapy"

4:40 Dr. Johan van Lier, presenter
"Radiolabeled Photosensitizers for Tumor Imaging and Therapy"

5:00-6:00 Poster Session/Refreshments

7:00 pm Banquet, Michigan Union

Friday, June 9

8:00 am **Radiosensitizers**
Dr. Kenneth Krohn, Chair

8:00 **Plenary Lecture - Dr. Ted Lawrence**
"Radiosensitizers"

8:40 **Plenary Lecture - Dr. Andrew M. Rauth**
"Tumor Hypoxia and Nitroimidazoles"

9:20 Dr. Richard F. Schneider, presenter
"Nuclear Medicine Markers of Tumor Hypoxia and Radioresistance"

9:40 Dr. J. S. Sebolt-Leopold, presenter
"Bioreductive Drugs: A New Generation of Hypoxic Cell Radiosensitizers"

10:00-10:30 Coffee Break

10:30 **Immunology**
Dr. Alan Fritzberg, Chair

10:30 **Plenary Lecture - Dr. Harold Dvorak**
"Selective Tumor Targeting: Difficulties and Some Possible Solutions"

11:20 Dr. S. A. McQuarrie, presenter
"Pharmacokinetics and Radiation Dosimetry of ^{99m}Tc Labelled Monoclonal Antibody 170H.82 in Breast Cancer Patients with No Circulating Antigen"

11:40 Dr. P. L. Beaumier, presenter
"The Pharmacology of Pretargeting Components: Optimizing Therapeutic Targeting"

12:00-1:30 pm Lunch Break

1:30 **Peptide/Steroid Receptors**
Dr. Brahm Shapiro, Chair

1:30 **Plenary Lecture - Dr. Thomas O'Dorisio**
"Peptide Radiopharmaceuticals"

2:20 Dr. R. V. Hay, presenter
"Scintigraphy of Acute Inflammatory Lesions with the Radiolabeled Human Cytokines Interleukin-8 and Neutrophil-Activating Peptide 2"

2:40 Dr. R. N. Hanson, presenter
"Synthesis of 11-Substituted-17α-Iodovinyl Estrogens and In Vitro Studies of Their Binding to the Estrogen Receptor"

3:00-3:30 Coffee Break

3:30 **Oligonucleotide**
Dr. Don Hnatowich, Chair

3:30 **Plenary Lecture - Dr. David Piwnica-Worms**
"Challenges of Imaging Gene Translation with Radiolabeled Oligonucleotides"

4:20 Dr. J. L. Urbain, presenter
"Scintigraphic Imaging of Oncogenes with Antisense Probes: Does It Make Sense?"

4:40 Dr. Mrinal Dewanjee, presenter
"Tumor Cell Killing by Y-90 Labeled Bc12 Antisense Oligodeoxynucleotide Probes"

5:00-6:00pm **Radiopharmacology Business Meeting**

Saturday, June 10

8:00 am **Animal Models of Disease**
Dr. Michael Kilbourn, Chair

8:00 **Plenary Lecture - Dr. Daniel Weinberger**
"Animal Modeling of Schizophrenia"

9:00 Dr. D. M. Raffel, presenter
"Application of the Isolated Perfused Rat Heart Model to Cardiac Radiotracer Development"

9:20 Dr. Mrinal Dewanjee, presenter
"Quantitation of Neutrophil Dynamics and Retention in Internal and External Flow Oxygenator During Cardiopulmonary Bypass Operation in Yorkshire Pig Model"

9:40 Dr. M. R. Kilbourn, presenter
"Unilateral Intra-Cerebral Neurotoxin Injections; Animal Models of Disease and Applications in Radiotracer Evaluations"

10:00-10:30 Coffee Break

10:30 Dr. P. Som, presenter
"Autoradiographic Microimaging InRadiopharmaceutical Research"

10:50 Dr. Donald H. Hnatowich, presenter
"A Method for the Facil Preparation of MAG3 Conjugated DNA Used as an Alternative ^{99m}Tc-Labeling Method to Avoid Nonspecific Protein Binding"

11:10 Dr. Edward Domino, presenter
"PET/Brain Topographic EEG Correlation Study with Nicotine and Tobacco Smoking"

11:30 am Closing Remarks

The University of Michigan Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing education for physicians.

The University of Michigan Medical School designates this continuing medical education activity for 23.25 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

KEYNOTE SPEAKER: PROFESSOR DAVID EDMUND KUHL

Professor Kuhl is one of the founding fathers of computed tomographic medical imaging, functional brain imaging, and nuclear medicine in general.

His involvement with nuclear medicine dates back to his days as a medical student where his construction of the photoscanner earned him the Borden Undergraduate Research Award. After graduating in 1955 from The University of Pennsylvania School of Medicine, he served in the U.S. Navy and returned to The University of Pennsylvania for a radiology residency. It was during this time that he developed the first tomographic nuclear medicine scanning device (an example of single photon emission computed tomography or SPECT). This report in 1964 preceded the development of x-ray transmission computed axial tomography (CAT) by 8 years. The image reconstruction algorithms for both SPECT and CAT are essentially similar and thus Kuhl may be considered the founder of modern crossectional medical imaging. These principles were subsequently brought to bear on the imaging of positron-emitting radionuclides with the application of positron-emission tomography (PET) to the quantitative evolution of regional brain physiology using ^{18}F-fluorodeoxygluose (18-FDG). This technique depicted regional levels of brain glucose metabolism and the coupling of metabolism to functional activity in various physiological and pathological states. Amongst the disorders of great interest have been the dementias including Alzheimer's disease. Coupled with these studies, Professor Kuhl has been amongst the leaders in the development of new and innovative radiopharmaceutical tracers to probe cerebral function in health and disease.

Professor Kuhl rose rapidly through the ranks at The University of Pennsylvania to become Professor of Radiology, Professor of Bioengineering, Chief of Nuclear Medicine and Vice Chairman of Radiology. He subsequently joined UCLA as Professor of Radiological Sciences and Chief of Nuclear medicine. It was during this time, in large measure to his efforts, that brain PET developed into a widely used diagnostic modality. Since 1986, Professor Kuhl has been Professor of Internal Medicine and Radiology and Chief of Nuclear Medicine at The University of Michigan.

Professor Kuhl's awards and honors are legion and include: The Ernst Jung Prize for Medicine from the German Jung Foundation, The EH Grubbe Gold Medal Award of the Chicago Medical Society and Chicago Radiological Society, The Louise and Lionel Berman Foundation Award for Peaceful Uses of Atomic Energy, The SC Beening Award in Medicine from Indiana University, The Distinguished Graduate Award of The University of Pennsylvania School of Medicine, The Javites Neuroscience Investigator Award of the NIH, The William C. Menninger Memorial Award for Distinguished Contributions in Psychiatry and a Doctor of Humane Letters honors course from Loyola University. He is AOA, a founding member of the American Board of Nuclear Medicine, a member of the Institute of Medicine of the National Academy of Science and 26 other learned societies and boards.

Plenary Lecturers:

Martin K. Bijsterbosch, Ph.D.
Dr. Bijsterbosch is Assistant Professor of Biopharmaceutics, University of Leiden and the Leiden/Amsterdam Center for Drug Research. He is best known for his research dealing with the site-specific delivery of drugs to tissues by receptor-mediated endocytosis.

John Caldwell, Ph.D.
Professor of Pharmacology and Toxicology, St. Mary's Hospital Medical School. Professor Caldwell is an internationally recognized authority on drug disposition and factors affecting drug metabolism. He is the author of over 350 publications and nine edited books.

Harold F. Dvorak, M.D.
Chief, Department of Pathology, Beth Israel Hospital, Boston, and Mallinckrodt Professor of Pathology, Harvard Medical School. Dr. Dvorak's recent publications address antibody targeting of tumors, effect of tumor microenvironment, antigen density and antibody dosage factors, and the effects of vascular peptides on antibody targeting.

Kirk Frey, M.D., Ph.D.
Associate Professor of Internal Medicine and Neurology at The University of Michigan Medical School. Dr. Frey is noted for his research on new radiotracer ligands for neuroreceptors and their use in the diagonsis of various movement disorders such as Parkinsons Disease.

David A. Kessel, Ph.D.
Professor of Pharmacology and Medicine, Wayne State University School of Medicine. Well known for his research on the mode of action of anticancer drugs and photosensitizing agents.

Michael J. Kuhar, Ph.D.
Professor of Neuroscience, Pharmacology and Psychiatry, Johns Hopkins School of Medicine and Chief of Neurosurgery Branch, National Institutes of Drug Abuse and Addiction Research Center. Internationally known expert on the interactions of drugs and radiopharmaceuticals with central nervous system neurotransmitter receptors and transporters.

Theodore S. Lawrence, Ph.D.
Associate Professor of Radiation Oncology and Director of the Division of Cancer Biology, The University of Michigan Medical School. Dr. Lawrence has published extensively on the subject of utilizing various halogenated nucleosides to enhance the sensitivity of various cancers to radiation therapy.

Plenary Lecturers:

Thomas M. O'Dorisio, M.D.
Professor of Medicine, Physiology, Pathology and Human Nutrition and Director of the Division of Endocrinology and Metabolism, Ohio State University School of Medicine. Expert on peptide receptor agonists and antagonists especially in the area of somatostatin-like drugs.

David Piwnica-Worms, M.D., Ph.D.
Associate Professor of Radiology, Malinckrodt Institute of Radiology, Division of Radiation Sciences, Washington University Medical School. Dr. Piwnica-Worms is noted for his research involving the multidrug resistance P-glycoprotein for targeting radioligands to specific tissues and for his views on radiolabeled oligonucleotides.

Andrew Michael Rauth, Ph.D.
Physicist at the Ontario Cancer Institute and Professor of Biophysics at the University of Toronto. Dr. Rauth's research interests include radiation biology, mechanisms of drug action and the radiobiology of solid tumors.

Albert H. Soloway, Ph.D.
Professor of Medicinal Chemistry, College of Pharmacy, Ohio State University. Dr. Soloway is noted for his research on drugs for the treatment of cancer and especially boron compounds for neutron capture therapy.

Daniel Weinberger, M.D., Ph.D.
Chief, Clinical Brain Disorder Branch, National Institute of Mental Health, Neuroscience Center, St. Elizabeths, Washington, D.C. Dr. Weinberger is the recipient of numerous awards for his studies on brain disorder research.

Thomas Woolf, Ph.D.
Section Head of the Drug Metabolism Group in the Pharmacokinetics and Drug Metabolism Department at Parke-Davis Pharmaceutical Research located in Ann Arbor, Michigan. Dr. Woolf started his career at Parke-Davis approximately 10 years ago and has played a key role in developing and applying *in vitro* metabolism and bioanalytical approaches to drug discovery and development.

Poster Session

1. Pharmacokinetics of N-[C-11] Labeled b-Substituted and Unsubstituted Phentermine in the Rhesus Monkey Brain Metabolism Resistant Probes for Monoamine Uptake Sites

   Hanson, R.N., et al.
   Dept. of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts, USA

2. *In Vitro* and *In Vivo* Evaluation of an Iodine-123 Labeled Derivative of the Dopamine D1 Receptor Antagonist A-69024

   Mardon, K., et al.
   Biomedicine and Health Program, ANSTO Sydney, Australia

3. Synthesis and Preliminary Evaluation of No-carrier-added (n.c.a.) 4-Fluoro-3-[^{131}I]iodobenzylguanidine([^{131}I]FIBG)

   Vaidyanathan, G., et al.
   Duke University Medical Center, Durham, North Carolina, USA

4. Approaches to Attain Higher Specific Activity Radioiodinated MIBG Up to a No-carrier-added Product

   Franceschini, R., et al.
   Sorin Biomedica S.p.A., Saluggia, Vercelli, Italy

5. Synthesis and Biological Evaluation of E- and Z- [^{125}I]-N-(Iodoallyl)-2b-Carbomethoxy-3b-(4-Fluorophenyl)Tropane(IACFT): A Selective SPECT Agent for Imaging DA Transport Sites

   Hanson, R.N., et al.
   Dept. of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts, USA

6. Effect of Polar Head Groups on the Tumor Retention of Phospholipid Ether Analogs

   Rampy, M.A., et al.
   Department of Pharmacology, The University of Michigan, Ann Arbor, Michigan, USA

7. Evaluation of [I-125]-12-[*m*-iodophenyl]-dodecylphosphocholine for Breast Tumor Imaging: Biodistribution, Imaging, and Autoradiographic Analyses.

   Rampy, M.A., et al.
   Department of Pharmacology, The University of Michigan, Ann Arbor, Michigan, USA

8. The Evaluation of Stereochemical Factors in the Tumor Retention of Phospholipid Ether Analogs

   Pinchuk, A.N., et al.
   Department of Pharmacology, The University of Michigan, Ann Arbor, Michigan (USA)

9. Radioiodinated Steroidal Aromatase Inhibitors for Mechanistic and Metabolic Studies

   Darby, M.V., et al.
   College of Pharmacy and OSU Comprehensive Cancer Center, Ohio State University, Columbus, Ohio, USA

10. Differential pattern of Tumor Uptake of 5-[^{125}I]Iodo-2'-deoxyuridine Instilled Intravesically and of Mitotic Activity in Patients with Bladder Cancer

    Mariani, G. et al.
    Nuclear Medicine Service DIMI, University Genoa, Italy

11. Pharmacokinetic Evaluation of Biodistribution and Radiation Dosimetery of ^{99m}Tc-D-Glucaric Acid in Humans

    Mariani, G. et al.
    Nuclear Medicine Service DIMI, University Genoa, Italy

12. Correlation Between Lipophilicity and Cardiolipin Binding of ^{99m}Tc Oxo and ^{99m}Tc Nitrido Complexes of Biguanides

    Neves, M.
    Instituto Tecnológico e Nuclear-Departamento de Radioisótopos, Estrada Nacional, Portugal

13. ^{99m}Tc-PAO-Azomycin Glucuronide (^{99m}Tc-PAO-AZG): Synthesis and biological evaluation as a marker of hypoxic tissues.

    Kumar, P., et al.
    Division of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

14. Applications of Storage Phosphor Imaging Plates in Radiopharmacology

    Hopton, D. and Taylor, D.E.
    Bio-Imaging Group, Fuji Medical Systems, Stamford, Connecticut, USA

15. Disposition of ^{14}C-Olanzapine in Male and Pregnant Rats Determined by Quantitative Whole-body Autoradiography

    Chay, S.H., et al.
    Dept. of Biochemical Toxicology, Lilly Research Laboratories, Greenfield, Indiana, USA

16. Tissue Distribution of the Reverse Transcriptase Inhibitor [^{14}C]U-87201E in Rats by Quantitative Whole Body Autoradiography

Schuette, M.R. et al.
Drug Metabolism Research, The Upjohn Company, Kalamazoo, Michigan, USA

17. Alkyl Esters of Bisphosphonic Acids Do Not Bind to Calcified Tissues: Whole Body Autoradiography Studies of [^{14}C]U-91502 in Rats

Schuette, M.R. et al.
Drug Metabolism Research, The Upjohn Company, Kalamazoo, Michigan, USA

18. Electronic Autoradiography of ^{14}C in Whole Body Cryosections, Validation of the Method

Englert, D. and Schweitzer, A.
Packard Instrument Company, Meriden, Connecticut, USA and Drug Safety, Sandoz Pharma Ltd., Basel, Switzerland

19. Tissue Distribution of the Antiepileptic GABA Analog [^{14}C]-Isobutyl GABA in Rat and Monkey

McNally, W., et al.
Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan, USA

20. Highly Iodinated Boranes and Carboranes as X-ray Contrast Agents. *In Vitro* Evaluations of Blood Compatibility Based on Red Blood Cell Hemolysis and Protein Precipitation

Wilbur, D.S., et al.
Dept. of Radiation Oncology, University of Washington, Seattle, Washington, USA

21. Radiochemical and Biological Properties of ^{99m}Tc-Human Immunoglobulin Prepared via 2-Iminothiolane

Patricio, L., et al.
Instituto Tecnológico e Nuclear-Departamento de Radioisótopos, Estrada Nacional Portugal

22. Influence of the Labelling Method on Biological and Radiochemical Behaviour of IOR CEA 1-^{99m}Tc

Gano, L. et al.
Instituto Tecnológico e Nuclear-Departamento de Radioisótopos, Estrada Nacional Portugal

23. Antibody Labeling via DNA Hybridization

Hnatowich, D.J., et al.
Department of Nuclear Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts, USA

24. Comparative Pharmacokinetic Evaluation in Humans of Two Monoclonal Antibodies as Possible Immunoscintigraphy Agents for Pancreatic Cancer

Maraini, G., et al.
Nuclear Medicine Service DIMI, University of Genoa, Italy

25. Preliminary evaluation of a ^{67}Cu-Labelled Anti-Colon Carcinoma Monoclonal Antibody MAB35

Schubiger, P.A., et al.
Radiopharmacy Division, Paul Scherrer Institute, Switzerland

26. Molecular Modelling of the CE7 Monoclonal Antibody Variable Fragment

Hasler, P.H., et al.
Radiopharmacy Division, Paul Scherrer Institute, Switzerland

27. Effect of Lysosomal Inhibitors on the Fate of I-125-labeled Antibody in Athymic Mice Bearing Human Tumor Xenografts

Nakamura, K., et al.
Department of Radiology, Keio University School of Medicine, Tokyo, Japan

28. Evaluation of Some Direct Labeling Technologies of Tc-99m Monoclonal Antibody in Effiency and Targeting

Li, Y.J. et al.
Shanghai, Institute of Nuclear Research Academic Sinica

29. Pharmacokinetics and Radiation Dosimetry of ^{99m}Tc Labelled Monoclonal Antibody B43.13 in Ovarian Cancer Patients with Circulating CA 125 Antigen

McQuarrie, S.A., et al.
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

30. Tc-99m-labelled Aprotinin Used for Visualization of Renal Structure in Children with Nephrolithiasis Treated by Lithotripsy

Stembrowicz, Z., et al.
Central Clinical Hospital WAM, Warsaw, Poland

31. Radiolabeled 7a-Iodo-5a-Dihydrotestosterone. A New Radioligand for Androgen Receptor

Hoyte, R.M., et al.
Department of Chemistry, State University of New York, Old Westbury, New York USA

32. Tc-99m-P280: A Peptide Radiopharmaceutical for the Localization of Thrombosis and Embolism

Gregory, A., et al.
Department of Internal Medicine, The University of Michigan, Ann Arbor, Michigan, USA

33. Comparative Properties of 99m-Tc-Labeled Single-Stranded Natural DNA and A Phosphorothioate Derivative *In Vitro* and in Mice

Hnatowich, D.J., et al.
Department of Nuclear Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts, USA

34. Technetium-99m Labeled Single-Stranded DNA Probe for Imaging Thrombin in Viscera Formed During Cardiopulmonary Bypass

Dewanjee, M.K., et al.
Department of Radiology, University of Miami, School of Medicine, Miami, Florida, USA

Works in Progress

35. Metabolism and Pharmacokinetics of 2-Methyl-1-(2-methoxy-phenyl)-2-(3-pyridyl)-1-propanone: A Potential Radioligand for Functional Diagnosis of Adrenal Pathology

Zolle, I. et al.
Universitätsklinik für Nuklearmedizin, AKH, A-1090 Wien, Austria

36. Stannous Chloride Induces Breaks on Plasmid Deoxyribonucleic Acid

Bernardo-Filho, M. et al.
Biofisica e Biometria, I. Biologia, Universidade do Estado do Rio de Janeiro, Av. 28 de setembro, 87, 20551-030

37. Pharmacokinetic and Biodistribution of Radioiodine-125 in Rats: Preliminary Results

Mansouri, A. et al.
Laboratoire des Radiopharmaceutiques, Centre de Développement des Techniques Nucléaires. 2, Bd Frantz Fanon BP 1017 Alger-Gare, Algeria

A METHOD FOR THE FACILE PREPARATION OF MAG3 CONJUGATED DNA- USED AS AN ALTERNATIVE ^{99m}TC LABELING METHOD TO AVOID NONSPECIFIC PROTEIN BINDING

Winnard P. Jr. and Hnatowich D.J.
Department of Nuclear Medicine, University of Massachusetts Medical Center, Worcester, MA., USA

The chelator benzoylmercaptoglycylglycyglycine (MAG3) has been used successfully to radiolabel proteins and other molecules with technetium-99m (^{99m}Tc) and radiorhenium (1-3). In the past, use of this chelator has been limited by its involved synthesis. In addition, the sulfur, which must be prevented from forming a disulfide, is protected in this chelator by a leaving group (benzoyl) which requires harsh conditions of extreme alkaline pH or boiling temperatures for deprotection. Accordingly, the chelator must be radiolabeled prior to conjugation (i.e. preconjugation labeling) to carriers such as proteins or peptides which cannot withstand harsh conditions. We have employed a simpler, two-step synthesis, of the N-hydroxysuccinimide derivative of MAG3 (NHS-MAG3) in aqueous solution and with commercially obtained reagents. Furthermore, because the protecting group (acetyl) is more easily removed (4), labeling with ^{99m}Tc of preconjugated MAG3-DNA may be accomplished rapidly at near-neutral pH and at room temperature.

MAG3 was synthesized by reacting triglycine with S-acetylthioglycolic acid for 15 min. at room temperature. Without purification, NHS-MAG3 was then prepared over several hours by DCC-mediated coupling to MAG3 of the in situ-generated N-hydroxysuccinimide. Again without purification, the NHS-MAG3 was coupled in 15 min. at room temperature to a 22-base single-stranded DNA through an amine on the 3' end. Radiolabeling was accomplished by transchelation from ^{99m}Tc-tricine with maximum yields obtained within 20 min. and at specific activities of up to 15 uCi/ug.

The ^{99m}Tc labeled DNA was evaluated for stability in comparison to the same DNA radiolabeled with ^{99m}Tc via the hydrazinonicotinamide chelator (SHNH). The radiolabel was found to be at least as stable to transchelation, both to serum proteins and to cysteine, and to pertechnetate oxidation. However, in contrast to SHNH-DNA, no evidence for protein binding of the labeled MAG3-DNA was observed. Since we have identified binding to proteins in serum and in tissues as a major disadvantage to the use of oligonucleotides and peptides labeled with ^{99m}Tc via SHNH (5), the MAG3 chelator may prove to be a more useful method of radiolabeling these reagents.

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2. Fritzberg AR., Kasina S., Eshima D., et al. Synthesis and biological evaluation of technetium-99m MAG3 as a hippuran replacement

3. Goldrosen MH., Biddle WC., Pancook S. et al. Biodistribution, pharmacokinetics, and imaging studies with ^{186}Re-labeled NR-LU-10 whole antibody in LS174T colonic tumor-bearing mice. Cancer Res. 50: 7973-7978; 1990.

4. Duncan RJS., Weston PD., Wrigglesworth R. A new reagent which may be used to introduce sulfhydryl groups into proteins, and its use in the preparation of conjugates for immunoassay. Anal Biochem 132: 68-73; 1983.

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PET/Brain Topographic EEG Correlation Study with Nicotine and Tobacco Smoking

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The aim of this study is to correlate regional cerebral blood flow (rCBF) with topographic electroencephalographic (EEG) changes in human volunteers. Nicotine in tobacco smoke was used as the variable to alter brain function after a 12 hr period of overnight abstinence in daily smokers. The subjects were all healthy young adults who smoked at least 15 cigarettes/day for 1 or more years. An $H_2{}^{15}O$ i.v. injection technique was used to measure rCBF. A high-resolution positron camera provided slices parallel to the anterior/posterior commissures (AC-PC) or orbitomeatal (OM) planes. The CBF measurement was repeated six times with intervals of 15 min in the following order. The first baseline (BLI), 5% carbon dioxide inhalation (CD1), cigarette smoking (CS1), the second baseline (BL2), 5% carbon dioxide inhalation (CD2), and cigarette smoking (CS2). During the measurement of CBF, the subjects were requested to keep their eyes closed. During BL1, BL2, CD1 and CD2, sham smoking was performed by using unlit filter tip cigarettes. Systemic blood pressure was monitored from the left leg at the beginning and end of the CBF measurement at each session. For the measurement of $PaCO_2$, arterial blood sampling was carried out at the beginning and end of PET scanning from the catheter inserted into the left radial artery. The latter was also used for the measurement of intraarterial radioactivity and arterial blood for assay of plasma concentrations of nicotine and cotinine. The mean values of $PaCO_2$ before and after the CBF measurements were used for the analysis. In order to measure nicotine and cotinine levels, arterial blood sampling was performed at the end of BL1, BL2, CD1 and CD2 and at the initiation and end of CS1 and CS2. The blood samples were subsequently analyzed for nicotine and cotinine by gas chromatography. Sixteen channels of spontaneous resting EEG were recorded with scalp electrodes using the 10-20 International System. The means of the digitized topographic EEG data were analyzed as a projection to a plane on top of the head. The EEG data were computed for each scalp lead for each frequency band: *delta*, 1.0-3.4 Hz; *theta*, 3.6-7.4 Hz; *alpha*, 7.6-10 Hz; *alpha*$_2$, 10.2-12.4 Hz, *beta*, 12.6-26 Hz. After smoking the first cigarette of the day (after 12 hrs of abstinence), there was a shift in the higher EEG frequencies toward the frontal areas of the brain. Similarly, rCBF increased primarily in the frontal and anterior temporal lobes as well as the cerebellum during smoking of the first cigarette of the day after a 12 hr abstinence. Although the plasma nicotine concentration increased in both smoking sessions, the increase in CBF was greater in the first than in the second smoking session. The dissociation between the two smoking sessions was regarded as evidence of acute tolerance to the second cigarette and a relative lack of tolerance to the first cigarette after a 12 hr period of abstention. Subjects who showed the best cerebral vascular response to hypercapnia also displayed the greatest increase in CBF during cigarette smoking. The present preliminary data indicate that there is a relationship between EEG and rCBF changes following tobacco smoking if plasma nicotine levels are sufficiently elevated. Current limitations involve different PET imaging planes and topographic EEG projections to a surface plane. These are solvable software differences that provide a unique opportunity to combine vastly different methodologies for a better understanding of brain function.

Metabolism and Pharmacokinetics of 2-Methyl-1-(2-methoxy-phenyl)-2-(3-pyridyl)-1-propanone: A Potential Radioligand for Functional Diagnosis of Adrenal Pathology

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The development of metyrapone derivatives as radioligands for functional diagnosis of adrenal disease has lead to the identification of 2-methoxyphenyl-metyrapone [2-MPMP, 2-Methyl-1-(2-methoxyphenyl)-2-(3-pyridyl)-1-propanone], and related 2-phenyl-substituted derivatives as potent inhibitors of adrenal 11β-hydroxylase, with high affinity for adrenal mitochondrial binding sites (1). Structure/activity studies indicated a 2-fold increase of the binding affinity of 2-substituted phenyl-metyrapones over metyrapone. 2-Bromophenyl-metyrapone (2-BrPMP) and 2-hydroxyphenyl-metyrapone (2-OHPMP) are suitable precursors for labelling with radioiodine and carbon-11, respectively (2,3).

Preliminary studies of the biodistribution of [^{11}C]2-MPMP in rats indicated a high lung- and renal accumulation of radioactivity with a fast elimination (3). HPLC analysis of plasma and urine samples using reference material of 7 potential metabolites verified the rapid metabolism of 2-MPMP, the major metabolites in urine were identified as glucuronide conjugates of 2-OHPMP (20%) and of the N-oxide of 2-OHPMP (50%). The majority of the drug/metabolites are excreted in 0-24 hours. The radioactivity measured in the lung is thus due to [^{11}C]CO_2 which is liberated by O-demethylation.

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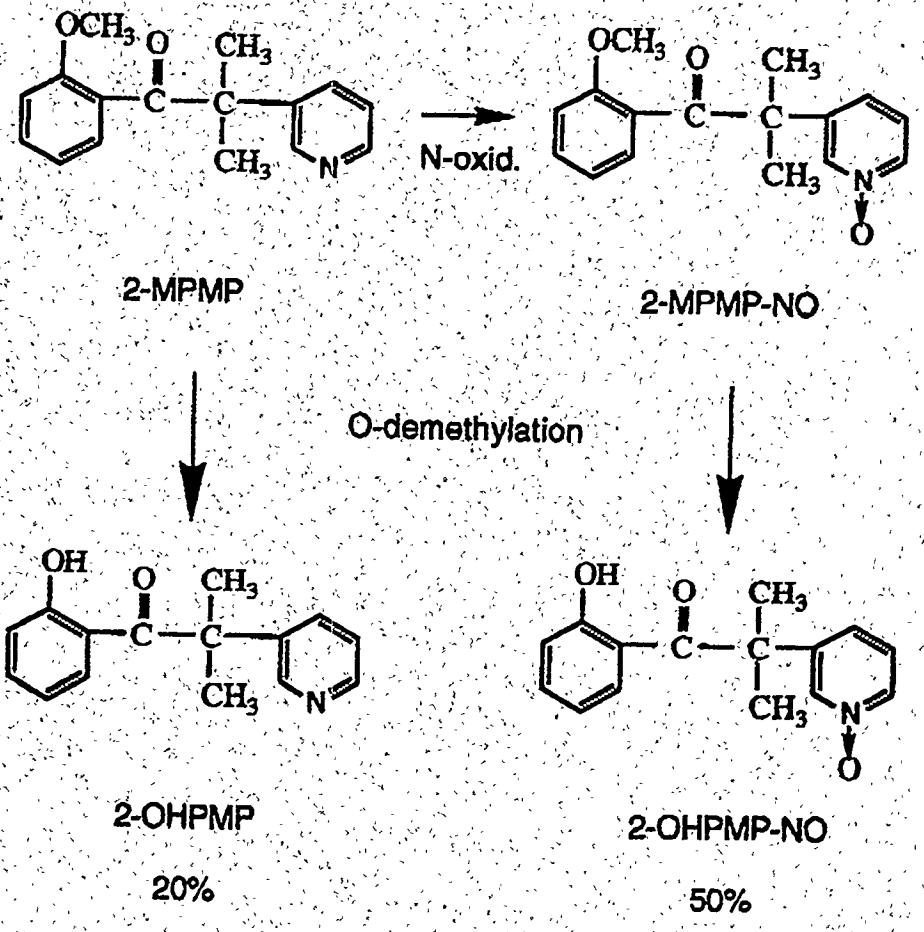
METABOLITES OF 2-METHOXYPHENYL-METYRAPONE
Identified as glucuronide conjugates in rat urine (0-24 h)



STANNOUS CHLORIDE INDUCES BREAKS ON PLASMID DEOXYRIBONUCLEIC ACID.

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Scientific obervations have been reported and suggest that stannous salts, as the $SnCl_2.2H_2O$, present low systemic toxicity in humans, but it may be highly irritant to skyn and mucous membranes (1). Olivier and Marzin (2), using an adapted SOS chromotest, reported positive results about the genotoxicity of $SnCl_2$. Tripathy et al. (3), described that stannous chloride is non-genotoxic to the wing primordial cells of *Drosophila melanogaster*. Ashby and Tennant (4), in a review of the carcinogenicity and mutagenicity of 301 chemical agents, stated that stannous chloride has carcinogenic activity in the thyroid gland. The relevance of these evaluations is due to the wide application of these metalic ions as a powerful reducing agent used in several situations as: (i) to pack can food, (ii) to prepare modern dental amalgams and (iii); to prepare ^{99m}Technetium-radiopharmaceuticals, besides other applications (1, 5, 6, 7).

The biological effect of stannous salts might depend on the physicochemical conditions and the route of its administration. In nuclear medicine, these salts can be directly administered to human beings by endovenous via and in these cases there are not doubt about their absorption into the body. The disparate and largely unexplained differences suggest that as a simple poisoning and/or a remarkable genotoxic agent stannous biological effect might be a fertile field for additional investigation.

In nuclear medicine procedures stannous salt is added to lyophilized kits to prepare ^{99m}Tc-radiopharmaceuticals. As the ^{99m}Tc-radiopharmaceuticals account for almost 80% or more, depending on the considered country, of the radiopharmaceuticals (7, 8, 9) used in nuclear medicine procedures, the knowledge and understanding of the biological effect of this reducing agent is highly significant.

Because of the general no agreement regarding its genotoxicity we decided to evaluate the potential genotoxicity of this reducing agent. This evaluation was done by measuring either the inactivation or the induction of SOS response in bacteria. The results reinforce the evidence that stannous chloride can exert a genotoxic effect by inducing and/or producing lesions in DNA (deoxyribonucleic acid) (10).

Asking for the molecular mechanism(s) involved in the production of $SnCl_2$-induced lesions in DNA, we decided to verify if its lethal effect could be mediated by the generation of reactive oxygen species (ROS) using catalase, ROS scavangers or ion metal chelator. We observed that in the presence of thiourea (100mM) the lethal effect was partly reduced. However, when we employed a more concentrated thiourea solution (1M), survival was totally restored. The same effect was observed using sodium benzoate (100mM), dipyridyl (10mM) or 2.400 units/ml of catalase (Table 1).

Table 1 - ROS scavengers and methal chelators protect *E. coli* cells to $SnCl_2$ inactivation

incubation time (min)	SnCl2 12.5 µg/ml	thiourea 1 M	sodium benzoate 100 mM	dipyridyl 10 mM	catalase 1.800 units/ml	catalase 2.400 units/ml
20	4.66×10^{-1}	9.41×10^{-1}	9.89×10^{-1}	1.2	9.86×10^{-1}	1
40	2.51×10^{-1}	9.95×10^{-1}	9.76×10^{-1}	1.01	7.14×10^{-1}	9.58×10^{-1}
60	2.50×10^{-1}	9.89×10^{-1}	9.89×10^{-1}	1.04	6.27×10^{-1}	9.24×10^{-1}

Values are means of 5 isolated experiments. Standard deviations did not exceed 15%. Cultures were incubated for various times, at 37°C, with shaking in the presence of $SnCl_2$ with different ROS scavengers and dypiridil at the mentioned concentrations. Aliquots of the suspensions were plated onto LB (10) medium for determination of survival fraction (N/No). At zero incubation time, N/No values for all the treatmens were 1.0.

The results have stimulated our group to investigate more deeply the interaction of $SnCl_2$ at molecular level. The methodology (11) employed (agarose gel electrophoresis) provides the observation of plasmid topology, and the supercoiled (form I) migrates to the open circle, relaxed (form II). The conformational changes could be due to the breaks occuring in the plasmid molecule. This technique enable us to analyse the reactivity of $SnCl_2$ or its counterparts (ROS) directly in the plasmid DNA.

Plasmid DNA was treated with increasing concentrations of $SnCl_2$, and the results suggest that in a dose-dependent, at pH 7.5, manner this reducing agent induces lesions at plasmid DNA (Figure 1).

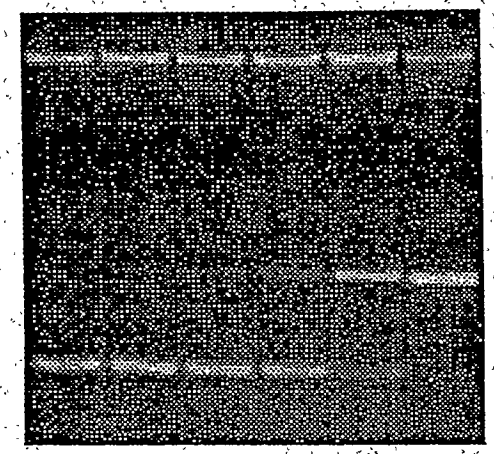

Figure 1 - pUC09 breaks induced by $SnCl_2$. Electrophoresis in 0.8% agarose gel of pUC09 plasmid after treatment with increasing concentrations of $SnCl_2$. Lanes: 1 - control; 2 - 12.5; 3 - 25; 4 - 50; 5 - 100; 6 - 200 µg/ml. I-supercoil form and II - relaxed form.

EDTA, that is a divalent ion chelator and sodium benzoate, that is a ROS acceptor when, incubated together with $SnCl_2$ protect the breaks at plasmid DNA level (data not shown). On other hand, when the pH is around 2.0, another property of $SnCl_2$ is observed. Instead of a completely degradation of the DNA induced by the acid, there is a protection caused by the presence of stannous ion in the solution. Interestingly, the conformational changes in the plasmid DNA induced, by $SnCl_2$, are maintained (data not shown). These results put together reinforce that stannous would be responsable for ROS producing by a Haber-Weiss/Fenton reaction and these ROS could be damaging DNA (12).

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PHARMACOKINETIC AND BIODISTRIBUTION OF RADIOIODINE-125 IN RATS
Preliminary Results

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Key Words : Radioiodine, Pharmacokinetics, Biodistribution, Radiopharmaceuticals

ABSTRACT :

The aim of this work is the determination of blood concentration time course of radioiodine-125, the calculation of some phamacokinetic parameters and the Biodistribution of radiodine-125 solution for iodination[1]. The results on the pharmacokinetics of 125 I-mIBG[2] are completed and compared with the results of the present work.

The radiochemical purity of radioiodine-125 solution was checked in two solvent systems

Male wistar rats are used for all experiments. The animals are sacrificed by decapitation after intravenous (IV) injection of radioiodine-125 solution at different time intervals.

The radioactivity of blood samples and tissues considered was performed by gamma counter.

The blood clearance results show a very high blood clearance during the first twenty four hours post-injection

The plasma binding of radioiodine-125 in percent dose of injected activity for different time intervals was assessed. Also, we observed a hight binding of radioiodine during the four first hours and an exponential decay after twenty four hours post-injection.

The tissue distribution results of radioiodine are presented in percent kilogram dose per gram.

The different results obtained in this study are statistically treated and discussed.

TableI. - Plasma binding of NaI-125 in % dose of injected activity for different time intervals.
(the values are given in normalized mean)

Time (h)	1	4	24	48	72	96	144
Blood	2.100	1.055	0.308	0.130	0.118	0.041	0.033
Supernatant	0.619	0.328	0.068	0.056	0.040	0.007	0.002
Precipitate	9.843	3.440	0.005	0.003	0.003	0.002	0.0008

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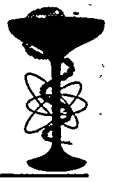

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