South African Pharmacology Society



39th Congress 2005

Vineyard Hotel, Cape Town

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South African Pharmacology Society

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*Abstract not available at time of print

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South African Pharmacology Society

WELCOME

It is with great pleasure that I welcome all delegates, honorable guests, and members of the pharmaceutical industry and scientific community, on behalf of the South African Pharmacology Society, to this 39th Annual Congress of our Society in the most exciting city of Cape Town!

The theme of this year's congress, Pharmacology in the Developing World, could not have been chosen better in view of the urgent health care needs of the developing world and we look forward to your participation.

Our previous visit to Cape Town and University of Cape Town hosting our annual meeting in the early 1990s was indeed memorable and we have been looking forward to this 2005 opportunity. This meeting promises to further foster the critical interaction between basic and clinical pharmacology as initiated by IUPHAR and our members and other delegates are invited to actively participate to strengthen this initiative.

International and other guests play a most important role during our congress and you are most welcome. Thank you for sharing your knowledge and expertise with us, and I believe you will also be enriched by our participation. For some of you it is your first visit to South Africa, a world in one country and Cape Town, a city where old and new converges with immense beauty. Cape Town is uniquely dominated by its table-shaped mountain set on a peninsula of rocky heights, lush valleys and oceans. Thus we look with great anticipation towards Cape Town - 2005.

Our colleagues of the University of Cape Town have brought together an excellent basic and clinical programme with exciting social opportunities, and we congratulate them in advance. Enjoy a wonderful and stimulating congress in the Mother City of Cape Town!

Pharmacology Greetings

Douglas W. Oliver
President

South African Pharmacology Society

WELCOME

Dear Colleagues

It gives me great pleasure to welcome you to Cape Town for the 39th annual SAPS congress. It has been a while since UCT last hosted the congress.

Our congress theme is Pharmacology in the Developing World. A large proportion of the programme is devoted to the "big three" infectious diseases in the developing world: HIV, tuberculosis and malaria. The other prominent theme is the importance of traditional medicines and the prospect of discovering new drugs from plants used in traditional medicines. We have invited an exciting array of local and international guest speakers covering a broad range of basic, clinical and policy issues relevant to pharmacology.

Many people have helped put together the congress. I would particularly like to thank Karen Barnes, Marc Blockman and Peter Smith from the congress organizing committee. I have also received a lot of advice and support from the SAPS EXCO, particularly Tiaan Brink.

We hope you'll be able to spend some time exploring the scenic beauty and many activities available in and around Cape Town. Enjoy yourselves!

Gary Maartens
Chair: Congress Organizing Committee

South African Pharmacology Society

CONGRESS PROGRAMME

	Tuesday 13 September		
16h30 - 17h30	SAPS Executive Committee meeting		
18h00 - 18h30	Cocktail - Welcoming *(Gary Maartens - convenor)*		
18h30 - 19h30	**Plenary** – ***David Back:*** PK considerations for antiretroviral therapy		

	Wednesday 14 September	Thursday 15 September	Friday 16 September
08h30 - 09h15	***Chair: Gary Maartens*** **Plenary** – ***David Back:*** Interindividual variability in antiretroviral therapy: a role for TDM?	***Chair: Wim du Plooy*** **Plenary** – ***Kelly Chibale:*** Medicinal chemistry in developing countries	***Chair: Douglas Oliver*** **Plenary** – ***Collet Dandara:*** African Pharmacogenetics
09h15 - 09h45	***Mairin Ryan:*** The role of pharmacoeconomic evaluation in expanding access to HIV/AIDS interventions	***Marc Blockman:*** Ethical issues in designing clinical trials for complementary & traditional medicines	***Ivan Havlik:*** Curdlan sulphate in falciparum malaria
09h45 - 10h30	***Chair: Karen Barnes*** **Free papers** ***Susan Cleary:*** Cost-effectiveness of antiretrovirals in the public sector ***Norah Katende-Kyenda:*** Fluconazole in the management of AIDS-related fungal infections: a 1 year exploratory study of patterns of drug prescription and patient profiles at Nelson Mandela Academic Hospital ***Jean Nachega:*** Adherence to antiretroviral therapy and survival	***Chair: Pieter van der Bijl*** **Free papers** ***Yusuf M Wael:*** Clinical investigation of Silybum marianum seed extract (silymarin) treatment in type II diabetic patients ***Ortrun Meissner:*** Traditional healers are not just diviners or herbalists ***Wim du Plooy:*** Corticosteroid randomisation after significant head injury: CRASH trial – ethics in action	***Chair: Tiaan Brink*** **Free papers** ***Viren Rambiritch:*** Pharmacokinetics-Pharmacodynamic modeling of Glibenclamide in type 2 diabetic subjects ***Douglas Oliver:*** *In vitro* and *in vivo* pharmacology of a novel guanidine ME10092 ***Brian Harvey:*** Increased hippocampal NO synthase activity and stress responsiveness after imipramine discontinuation: Role of $5HT_{2A/C}$-receptors ***Pieter Van der Bijl:*** Permeation of the peptides MDY-19 and MEA-5 through human vaginal mucosa
10h30 - 11h00	**Tea**		
11h00 - 11h45	***Chair: Jacques Snyman*** 11h00-11h25 – ***Karen Cohen:*** Non-nucleoside reverse transcriptase inhibitors & rifampicin 11h25-11h45 – ***Tiaan Brink:*** Introduction to SAPS – current strategies and exciting future	***Chair: Peter Smith*** **Plenary** – ***Quinton Johnson:*** Indigenous Medicine: Respice Prospice	***Chair: Gary Maartens*** **Plenary** – ***Helen McIlleron:*** Pharmacokinetics of antituberculous drugs
11h45 – 12h30	**Plenary** – ***Karen Barnes:*** Combination anti-malarial therapy in action	**Plenary** – ***Cailean Clarkson:*** Use of LC-MS-NMR in drug discovery	**Plenary** – ***Mairin Ryan:*** International trends in the use of pharmacoeconomic evaluation to influence reimbursement
12h30 - 14h00	**Lunch and posters**		
14h00 - 14h30	***Chair: Peter Smith*** **SAPS Young Scientist Award papers** ***Eliya Madikane:*** Novel antimycobacterial compounds from *Warburgia salutaris* ***Jacolene Myburgh:*** The relationship between GABA levels and anxiety as determined by an animal model of post-traumatic stress disorder	***Chair: Brian Harvey*** ***Brian Rayner:*** New insights into hypertension in black Africans	**CLOSE**
14h30 - 15h00	***Izelle Grobler:*** The modulating effects of myo-inositol and prototypical antidepressants on markers of cellular resilience in cultured human neuroblastoma cells ***Anita Pretorius:*** The effect of ozone exposure on the viability and function of cultured human cell lines	***Ushma Mehta:*** Practical strategies for pharmacovigilance in developing countries	
15h00 - 15h30	**Tea**		
15h30 - 16h30	***Chair: Peter Smith*** **SAPS Young Scientist Award papers** ***(…continued)*** ***Tracy Seaman:*** Antimycobacterial activity of plants traditionally used to treat respiratory ailments and the isolation of anacardic acids from Ozoroa paniculosa ***Erina Basson:*** Effect of ultrasound on transdermal permeation of diclofenac and the temperature effects on human skin ***Ianda Viljoen:*** Surfactant as a permeation enhancer of peptide drugs through porcine lung tissue	***Chair: Ronel Kahler-Venter*** **Free papers** ***Ane Korff:*** The effects of stress on components of cellular resilience in an animal model of post-traumatic stress disorder ***Schaun Korff:*** The effects of pharmacological treatment on stereotypic behaviour and key parameters in a putative animal model of OCD ***Van Eyk AD:*** Porcine vaginal mucosa as an *in vitro* permeability model for human vaginal mucosa ***Gerry Swan:*** Toxicity of diclofenac sodium to African White-Backed Vultures (*Gyps africanus*)	
16h30 - 17h30	**SAPS Annual General Meeting**		
17h30 for 18h00	Cocktails & snacks followed by the **Servier Satellite Symposium – *Lionel Opie***		
18h30 for 19h00		**Congress Gala Dinner** with **Award Ceremonies**	

South African Pharmacology Society

Invited Speakers

South African Pharmacology Society

INVITED SPEAKER

David John Back

RESUMÉ

David Back is Professor of Pharmacology at the University of Liverpool and established the Liverpool HIV Pharmacology Group in 1987. The Liverpool Group have numerous ongoing pharmacokinetic (TDM, IQ, drug-drug interactions, pharmacological mechanisms of resistance) and pharmacogenomic (phenotype-genotype) studies. They also run the highly successful web site www.hiv-druginteractions.org and have recently joined with colleagues in Vanderbilt and Lausanne to launch www.hiv-pharmacogenomics.org.

PRESENTATION

TITLE

Interindividual variability in antiretroviral therapy: a role for TDM

AUTHOR

David Back
Pharmacology Research Laboratories, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF. UK

ABSTRACT

As access to highly active antiretroviral therapy widens, and the number of licensed antiretrovirals increases, it is important to elucidate how best to optimise therapy. Although there may be only a single licensed dosage of a drug, in reality decision making regarding dosing can be complex when faced with the range of possible drug combinations to be used in patients of varying weight, hepatic and renal status, baseline genotype, race and sex. In this context we must keep in mind the concept of individualised patient care. Drug-drug interactions, drug-food interactions, drug-herbal interactions, concomitant diseases and individual genetic predisposition are responsible for considerable variability in the pharmacokinetics (PK) of antiretrovirals (ARVs). Pharmacological variability can affect both anti-HIV response and impact toxicity. Understanding variability (ie the role of drug metabolising enzymes, drug transporters etc) and strategies to optimise therapy in the face of such variability (ie TDM and/or IQ) is important.

South African Pharmacology Society

INVITED SPEAKER

Karen I. Barnes

RESUMÉ

Karen Barnes is an Associate Professor in Clinical Pharmacology at the University of Cape Town. She moved into the field of Clinical Pharmacology ten years ago after gaining broad clinical experience in internal medicine, paediatrics, obstetrics and gynaecology, oncology and cardiothoracic surgery. Her main research interest is in ensuring optimal evidence based malaria treatment policies through conducting large scale research programmes exploring the public health impact of changes in malaria treatment policy, particularly artemisinin-based combination therapy policies. She is a member of a number of national, regional and international malaria advisory bodies. Karen is responsible for convening the undergraduate pharmacology training programme at UCT, to focus on the knowledge and skills clinicians require to ensure rational drug use. She has convened three "African Courses in Problem-based Pharmacotherapy Teaching" on behalf of the World Health Organisation, and has been a guest facilitator of similar courses in the Netherlands, South Korea and Japan.

PRESENTATION

TITLE

Combination anti-malarial therapy in action

AUTHOR

Karen I Barnes, Division of Clinical Pharmacology, University of Cape Town

ABSTRACT

Early effective malaria treatment remains the key intervention aimed at limiting malaria morbidity and mortality, which are currently increasing primarily as a result of increasing drug resistance. Artemisinin-based combinations are widely being recommended to improve cure rates, decrease malaria transmission and delay antimalarial resistance. Despite the large public health burden of malaria and widespread use of SP (as monotherapy and increasingly in combination with artesunate), there is very limited data available on SP kinetics and the relationship between SP pharmacokinetics and its therapeutic efficacy against the asexual and gametocyte stages of falciparum malaria. A better understanding of this PK-PD interaction would facilitate optimising the useful therapeutic life of the artesunate-SP combination, the least expensive and simplest ACT regimen currently available.

Pharmacokinetic parameters we derived from intensive sampling of over 400 patients with uncomplicated malaria treated with SP or SP plus artesunate, and the association of these pharmacokinetics with patients' baseline characteristics and treatment outcome will be presented. Preliminary results show that an adequate clinical and parasitological response was associated with the artesunate-SP treatment group, and sulfadoxine pharmacokinetics (AUC and day 7 concentrations) as well as mutations in pfdhfr and pfdhps enzymes and baseline parasite density. The less significant role of pyrimethamine pharmacokinetics is explained partly by the high frequency of pfdhfr mutations in our southern African population but remains even after adjusting for these mutations. The addition of artesunate was associated with an increase in sulfadoxine clearance, increasing the importance of adequate SP dosing and quality when used as an ACT. The collection and analysis of intensive sampling PK in as adequate number of malaria patients to adequately explore the complex PK-PD relationship is achievable using filter paper blood spots in remote public healthcare facilities in southern Mozambique and South Africa.

South African Pharmacology Society

INVITED SPEAKER

Marc Blockman

RESUMÉ

Dr Marc Blockman was born in Cape Town, South Africa on June 18th 1964. He graduated BPharm(UCT) with distinction, MBChB(UCT) and then became the first graduate in Clinical pharmacology with an MMed degree from the University of Cape Town, and recently obtained the post graduate diploma in international research ethics. He is a specialist clinical pharmacologist at Groote Schuur Hospital and the University of Cape Town, as well as senior lecturer.

1. He has been involved in the science of pharmacology and its application to clinical medicine for 23 years.
2. He is recognised as an expert on National and Provincial Drug Policy, serving on the Medicines Control Council Committee of South Africa, becoming Chairman of the Essential Drugs Programme and being appointed an Executive member of the PAWC Pharmaceutical Advisory Committee.
3. He exemplifies a strong culture of evidence based medical practice.
4. He is a member of the Western Cape Clinical Guideline Advisory Committee, to assess Service Packages within the Province.
5. He serves on many formulary development teams and was consultant to the Medical Advisor for the Council for Medical Schemes for the PMB algorithms.
6. He serves as an International Consultant for the WHO, assessing drug policy and drug regulation in many countries and advises on the implementation of remedial systems where appropriate.
7. He is currently Deputy Chairman of the Health Sciences Faculty Research and Ethics Committee in which a significant portion of the work deals with clinical trials of new medicines.
8. He is an enthusiastic and dynamic teacher of clinical pharmacology and is a Distinguished Teacher at UCT. He serves on the new curriculum development committee of the Health Sciences Faculty, and has been appointed coordinator of the 4th year MBChB course.
9. He has been appointed as a staff mentor for the Health Sciences Faculty student mentor programme as well as member of the Faculty's Medical Board.

PRESENTATION

TITLE

Ethical issues in designing clinical trials for complementary and traditional medicines

AUTHOR

Marc Blockman

ABSTRACT

The popularity of complementary and alternative medicines (CAMs) is considerable: the one year prevalence of CAM usage is 42% in the United States and 20% in the United Kingdom. Generally speaking CAMs has not been subjected to the orthodox gold standard of controlled clinical trials, though a few have. In 1992, the Office of Alternative Medicine at NIH was established precisely for the purpose of funding clinical evaluations of the efficacy of complementary therapies.There are very few differences between the ethics of conventional medicine and those of CAM. In fact, many of the ethical rules applicable to conventional medicine such as requirements of informed consent, practice boundaries, and duties involving confidentiality and privacy translate across to the arena of CAM. In addition, much of the regulatory framework governing conventional medicine, which incorporates many ethical obligations, also translates to CAM practice. The focus of this talk will be the ethical aspects of clinical trials with CAM.

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INVITED SPEAKER

Kelly Chibale

RESUMÉ

Highest Degree obtained: Ph.D
Institution Where Obtained: University of Cambridge (UK) Year of Graduation: 1993
Research Interests: Medicinal chemistry of anti-infective (anti-malarial, anti-HIV/AIDS and anti-tuberculosis) and anti-cancer agents
Current position and institutional affiliation: Associate Professor, University of Cape Town, South Africa

Appointments:

1987-1989	Technical Officer, Development Chemist, Kafironda Explosives, Zambia
1989-1992	Cambridge-Livingstone Trust Scholar and Graduate Student, Department of Chemistry, University of Cambridge, England (UK), with S. G. Warren
1992-1994	Sir William Ramsay British Postdoctoral Fellow, Department of Chemistry, University of Liverpool, England (UK), with N. Geeves
1994-1996	Wellcome Trust International Prize Travelling Research Fellow, Department of Chemistry and the Skaggs Institute of Chemica Biology, The Scripps Research Institute, La Jolla, California, USA, with K. C. Nicolaou
1996-2000	Lecturer, Department of Chemistry, University of Cape Town, South Africa
1998	Wellcome Trust Visiting Fellow, University of Cambridge, UK, with S. G. Warren
1999-2000	Wellcome Trust Visiting Fellow, University of Dundee, UK, with A. H. Fairlamb
2001-2003	Senior Lecturer, Department of Chemistry, University of Cape Town, South Africa
2002	Invited Professor, Université des Sciences et Technologies de Lille, (France), June/July, 2002, with J. S. Brocard
2002	Sandler Sabbatical Fellow, University of California San Francisco (USA), Sept- December 2002, with J. H. McKerrow
2004-	Associate Professor, Department of Chemistry, University of Cape Town

PRESENTATION

TITLE

Medicinal Chemistry In Developing Countries

AUTHOR

Kelly Chibale
Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa
E-mail: chibale@science.uct.ac.za

ABSTRACT

One of the challenges inherent in drug discovery in developing countries such as those in Africa in part revolves around making a rational decision about a good starting point. While African scientists do not have the luxury of access to large synthetic chemical libraries, they have a powerful resource in natural products that are uniquely endemic to the continent. However, for natural products to be useful drug leads they must lend themselves to optimization through medicinal chemistry. Interestingly, recent examples in drug discovery have demonstrated that screening of derivatives of natural products is even more effective than screening of the natural products alone. This underscores the importance of integrating the areas of natural product isolation, structure elucidation and biological evaluation into medicinal chemistry programs. This lecture will focus on highlighting selected examples of good starting points for medicinal chemistry programmes in general and specifically in the author's research.

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INVITED SPEAKER

Cailean Clarkson

RESUMÉ

Cailean Clarkson is an Assistant Professor at the Danish University of Pharmaceutical Sciences. She received her B.Sc. in Microbiology and Biochemistry (1997) followed by a B.Sc (MED) (HONS) and Phd from the Department of Pharmacology at the University of Cape Town. Her work is centered on the development of hyphenated techniques such as HPLC-DAD-SPE-NMR for the rapid dereplication of natural product mixtures. Other research interests include the identification of drug metabolites using hyphenated techniques and the bioactivity of medicinal plants.

PRESENTATION

TITLE

Use of LC-DAD-SPE-NMR in drug discovery

AUTHOR

Cailean Clarkson
Natural Products Research Group, Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, 2100, Copenhagen, Denmark

ABSTRACT

The hyphenation of high-performance liquid chromatography (HPLC) with NMR/MS spectroscopy is now a well established analytical tool in pharmaceutical and natural product research. The most recent advance in HPLC-NMR/MS is the addition of an automated sold-phase extraction (SPE) unit. The main advantages of introducing a SPE interface between the chromatography and NMR, are i) concentration of diluted analytes from the HPLC eluent into a small volume NMR flow-probe, and ii) possibility of multiple analyte trapping on the same SPE cartridge. The HPLC-SPE-NMR technique is capable of providing 1D and 2D NMR data for full or partial characterization of a range of analytes, following analytical scale separation of sub-milligram quantities of complex mixtures. This eliminates the need for preparative isolation of milligram quantities of compounds for the sake of structure elucidation. Applications include drug discovery, metabolomics/ metabonomics, quality control of herbal drugs, food science, and many more.

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INVITED SPEAKER

Susan Cleary

RESUMÉ

Susan Cleary is a researcher in the Health Economics Unit, School of Public Health, UCT. Over the past five years, she has specialised in economic issues relating to Antiretroviral Treatment (ART) including the cost-effectiveness of ART, costs and barriers to scaling-up ART, and the political-economy of AIDS policy-making.

PRESENTATION

TITLE

The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa

AUTHORS

Susan Cleary and Andrew Boulle

ABSTRACT

Background:
Given the size of the HIV pandemic in South Africa, scaling up antiretroviral treatment (ART) represents a key public health challenge. Priority setting and budgeting could be assisted by economic data on the cost-effectiveness of ART.

Objectives:
To estimate HIV healthcare utilisation and costs, human resource requirements and the cost-effectiveness of ART.

Methods:
Cost-effectiveness with Markov modelling was used to consider the cost per Life Year (LY) and Quality Adjusted Life Year (QALY) of treating adults for opportunistic infections and HIV-related conditions and events either with ART, or without. Costs, outcomes and quality of life were assessed in the first public sector clinic-based ART project in South Africa.

Results:
Life-expectancy on ART was 12 years compared to 2 years in the absence of ART. Discounted QALYs were 5.5 and 1.2 for the two policy options respectively, and the incremental cost-effectiveness ratio for ART was US$977 per QALY gained.

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INVITED SPEAKER

Collet Dandara

RESUMÉ

Born: 22-09-72 in Zimbabwe.
Qualifications: BSc General Degree, Bachelor of Science Honours in Biochemistry, MPhil and Doctor of Philosophy (University of Zimbabwe).
Research interest: pharmacogenetics, pharmacogenomics and toxicogenomics. Postdoctoral fellow in the division of Medical Biochemistry (UCT).
Email: cdandara@curie.uct.ac.za, cdandara@yahoo.co.uk

PRESENTATION

TITLE

Pharmacogenetics and its relevance

AUTHORS

Collet Dandara

ABSTRACT

Pharmacogenetics seeks to understand the individual differences in the DNA sequence and their role in the variability to drug response. The role of pharmacogenetics is better defined by the presence of highly predictive genotype-phenotype associations. Although most drugs are used in the entire population, there are significant variations in safety and efficacy. Broadly, pharmacogenetics has a potential in the development of therapies that are patient, as defined according to their genotypes. Besides the potentially huge impact of pharmacogenetics in the way medicines will be prescribed, this discipline will also have profound consequences on people's understanding of race and ethnicity. This presentation will review the polymorphisms in drug metabolising enzymes, transporters and receptors on their role in influencing the dose response relationships between individuals and the importance of specific. The importance of pharmacogenetics in the treatment of diseases such as HIV/AIDs, malaria and tuberculosis will be highlighted.

South African Pharmacology Society

INVITED SPEAKER

Ivan Havlik

RESUMÉ

Graduated in 1969 with MSc degree from College of Chemical Technology, Prague, Czechoslovakia and obtained PhD degree in Pharmacology in 1974 from Czechoslovak Academy of Science Institute of Pharmacology Prague, Czechoslovakia. Currently he is head of Division of Pharmacology, Department of Pharmacy and Pharmacology, University of the Witwatersrand.

Prof I Havlik's research interests include:
- Prophylaxis, treatment and basic research in Malaria
- Malaria transmission blocking drugs
- Clinical Pharmacokinetic
- Immunopharmacology, Rheumatoid arthritis

He is a member of different professional societes and member of editorial board of the the International Journal of Immunopharmacology. Published over 50 research papers and delivered over 150 conference presentations.

PRESENTATION

TITLE

Curdlan sulfate in plasmodium falciparum malaria

AUTHORS

Havlik I, Thuma P*, Looareesuwan S**, Kaneko Y***
Dept of Pharmacy & Pharmacology, University of Witwatersrand, South Africa. *Macha Malaria Research institute, Choma, Zambia. **Faculty of Tropical Medicine, Mahidol University, Thailand. *** Ajinomoto Co., Inc., Tokyo, Japan.

ABSTRACT

Curdlan Sulfate a sulfated 1,3,--D-glucan (CRDS) has been shown in pre-clinical studies to address the pathology of severe/cerebral malaria. Thus CRDS is a potential candidate as an adjuct medication for treatment of severe/cerebral malaria.

CRDS was tested in four clinical phases to address safety, efficacy and potential interaction in vivo of CRDS with classical antimalarials.

CRDS seems to augment disease process along the line of the results obtained from laboratory based research.

South African Pharmacology Society

INVITED SPEAKER

Quinton Johnson

RESUMÉ

Quinton Johnson completed his undergraduate training at UCT, graduating with a PhD from UWC in the Medical Sciences. He was a Postdoctoral Fellow at Oregon Health Sciences University and Visiting Scholar at the Harvard Schools of Public Health and Medicine. He graduated from the Executive Education Senior Leadership and Management Programme at the Harvard Business School, with a speciality in Strategy and Competition. He became founding Chairperson of the Medical Biosciences Department at UWC and founding Director of the SA Herbal Science and Medicine Institute. Furthermore, he is the SA Director of The International Centre for Indigenous Phytotherapy Studies, and has supervised over 50 research graduates.

PRESENTATION

TITLE

Indigenous Medicines: Respice Prospice

AUTHORS

Quinton Johnson
South African Herbal Science and Medicine Institute, University of the Western Cape

ABSTRACT

The process of discovering new drugs is extremely complex, prohibitively costly and highly unpredictable. In fact, the current cost of discovering and developing a medicine may be as high as $1.9 billion, over a period of about 20 years. Consequently, drugs that reach the marketplace are priced to provide appropriate returns on large-scale investment. Often times, these life-saving medicines are well beyond the reach of millions of people who simply cannot afford them. Indeed, 80% of people living in the developing world rely on indigenous herbal medicines based on ancient knowledge systems. To that end, the World Health Organization and the World Bank have increasingly moved toward recognizing the potential of these indigenous herbal medicines as safe, effective and affordable therapeutics. Our major challenge will be to create a world-class platform through partnership, with a mission to scientifically and clinically validate indigenous herbal medicines for better human health.

South African Pharmacology Society

INVITED SPEAKER

Helen McIlleron

RESUMÉ

Helen McIlleron is a senior medical researcher in the Division of Clinical Pharmacology at the University of Cape Town. The pharmacokinetics of antituberculosis drugs in patients formed the basis of her PhD thesis which was completed in 2004.

PRESENTATION

TITLE

Pharmacokinetics of antituberculous drugs

AUTHOR

Hellen McIlleron

ABSTRACT

Target therapeutic antituberculosis drug concentrations based on large studies with pharmacokinetic data and outcomes have not been defined. Although favourable treatment outcomes are achievable in approximately 95% of patients with pulmonary tuberculosis who receive 6-month rifampicin-based regimens under study conditions, low or high drug levels may be critical where there is incomplete drug delivery, variable drug quality, different disease presentations (with pathogens in various sites and metabolic states), HIV-co-infection, severe illness, co-morbid disease and malnutrition. Moreover, the possibility should be entertained that drug products of sub-optimal quality may be less well absorbed in patients with more severe disease or malnutrition. It is therefore important to identify (and where possible, to limit) factors associated with pharmacokinetic variability in tuberculosis patients. The pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol were explored in 142 hospitalized patients, and several important determinants of drug concentration variation were identified.

South African Pharmacology Society

INVITED SPEAKER

Ushma Mehta

RESUMÉ

Ushma Mehta is a senior researcher at the University of Cape Town's Division of Pharmacology. She directs a WHO global training centre on vaccine safety and is involved in research and policy work related to pharmacovigilance in public health programmes.

PRESENTATION

TITLE

Practical strategies for pharmacovigilance in developing countries

AUTHOR

Ushma Mehta

ABSTRACT

There is growing appreciation for the need to incorporate pharmacovigilance into public health programmes where new medicines/combinations are widely introduced in communities with a poor health care infrastructure. Examples include new vaccines, artemisinin-based combination therapy (ACTs) and highly active antiretroviral therapy (HAART). Often, the safety profile of these new medicines are poorly understood in local settings. Concerns about the safety of these medicines can devastate public health programmes. Monitoring the safety of medicines in such situations is extremely challenging.

This presentation describes practical, targeted pharmacovigilance strategies currently being tested in rural and urban settings in South Africa and elsewhere. Examples of such strategies include:

- Confidential enquiries into sentinel events (e.g. deaths)
- Targeted adverse event surveillance programmes
- Intensive hospital-based studies
- Community-based studies
- Qualitative research

Illustrative examples from such studies will be described as well as challenges and recommendations for developing a pharmacovigilance plan in developing countries.

South African Pharmacology Society

INVITED SPEAKER

Brian Rayner

PRESENTATION

TITLE

New insights into hypertension in black Africans

AUTHOR

Brian Rayner, Division of Hypertension, University of Cape Town

ABSTRACT

Hypertension is more prevalent and severe in urban black populations compared to whites, and is associated with a greater degree of target organ damage for any given blood pressure level. In general blacks respond well to diuretics and calcium channel blockers, and less well to β-blockers and ACE inhibitors compared to whites. The exact mechanisms that contribute toward differences in blood pressure between blacks and whites are still not fully understood, given the multifactorial aetiology of essential hypertension. Various lines of evidence strongly suggest black patients are more salt sensitive than whites, which is due to a tendency to retain sodium in the kidney. Inherent differences in ionic transport mechanisms, the renal epithelial sodium channel; the renin-angiotensin-aldosterone system and vasoactive substances may be a partial explanation, but analysis is compounded by disparate socioeconomic conditions between blacks and whites. At present, there is no complete explanation for these differences, and further research is required.

South African Pharmacology Society

INVITED SPEAKER

Máirín Ryan

RESUMÉ

Dr Máirín Ryan is a clinical pharmacist and a health economist who has worked in HIV care since 1995. She is currently the Chief Pharmacist at the National Centre for Pharmacoeconomics in Ireland and Lecturer in Pharmacoeconomics in the Department of Pharmacology & Therapeutics, Trinity College, Dublin.

PRESENTATION

TITLE

The role of pharmacoeconomic evaluation in expanding access to antiretroviral therapy

AUTHOR

Máirín Ryan

ABSTRACT

The advent of combination antiretroviral therapy has coincided with massive reductions in HIV-related morbidity and mortality. However treatment of HIV/AIDS imposes a significant financial burden and therefore expenditure on drug therapy has been the subject of detailed analysis. Cost of care information is required to assess the economic impact of treatment, to compare the cost effectiveness of alternative treatment strategies, to determine the affordability of interventions and to facilitate healthcare resource planning. Economic analysis in high income countries has demonstrated that ART is cost effective. Much work is needed to further clarify how limited resources for HIV/AIDS interventions in developing countries can be best utilised to maximise health outcomes. Collecting high quality local cost data alongside the expansion of ARV treatment programs is of paramount importance to identify the most cost effective approaches and thereby save the greatest number of lives for the fixed budget available.

TITLE

International trends in the use of pharmacoeconomic evaluation to influence reimbursement

AUTHOR

Máirín Ryan

ABSTRACT

All EU Member States have introduced various pricing and reimbursement policies in an attempt to contain pharmaceutical expenditure and influence prescribing towards a more cost-effective use of therapies. The strategies include price controls, restriction of publicly reimbursed drugs by positive or negative lists, promotion of generic markets, prescribing budgets, patient co-payments and economic evaluation of medicines. Overall, the success of these cost containment measures is varied and pharmaceutical expenditure continues to rise in Europe. The use of economic evaluation in decision making has increased over the past few years. Several countries have encouraged economic evaluation of new medicines to ensure that only medicines proven to be both clinically and cost-effective are reimbursed or made available on formularies. This approach is often referred to as “the fourth hurdle” and is seen as a barrier to market entry in addition to the requirements to demonstrate efficacy, safety and quality.

South African Pharmacology Society

Free Papers

South African Pharmacology Society

FREE PAPER

TITLE

Effect of ultrasound on transdermal permeation of diclofenac through human skin

AUTHOR

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ABSTRACT

Objectives:
In the present study the effects of therapeutic levels of ultrasound on the permeation of diclofenac through human skin, as well as ultrasonic-induced heating and temperature-flux relationships, were investigated. A further objective was to develop an in vitro human skin diffusion model and assess its in vivo predictive value.

Methods:
The permeation of diclofenac through frozen/thawed human skin using a continuous flow-through perfusion system and the temperature increases following sonication using a calibrated thermistor, were determined in vitro following the application of therapeutic ultrasound (10 min, 2 W/cm^2, 3 MHz, continuous). Non-sonicated controls were included in the study. Flux rates for sonicated and control groups of specimens were compared using a F-test for entire curves. Flux rates of $^3H^2O$ across human skin at various temperatures were also determined.

Results:
Mean flux values of diclofenac across sonicated skin were statistically significantly higher ($p<0.05$) than those observed for non-sonicated skin controls, over the entire course (24 h) of the experiment. Temperature increases of approximately 10^{o}C occurred following sonication. Flux rate changes of $^3H^2O$ across skin between 37^{o}C and 42^{o}C were shown to be reversible.

Conclusion:
Ultrasound increased the transdermal permeation of diclofenac across human skin, but the results of the present study did not support the sonication-heating theory. The results obtained concurred with those of two published in vivo studies.

South African Pharmacology Society

FREE PAPER

TITLE

Non-nucleoside reverse transcriptase inhibitors and rifampicin

AUTHOR

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ABSTRACT

First-line antiretroviral therapy (ART) in the public sector in South Africa comprises two nucleoside reverse transcriptase inhibitors, and either efavirenz or nevirapine. The high disease burden of both HIV and tuberculosis (TB) means that many HIV infected patients will require concurrent treatment with rifampicin-based TB treatment and ART including nevirapine or efavirenz.

This presentation outlines 2 local studies; the 1st exploring the pharmacokinetic interaction between rifampicin and nevirapine, and the 2nd describing clinical outcomes of patients treated concurrently with NNRTI-based ART and tuberculosis treatment including rifampicin, in a cohort of patients on ART in Khayelitsha, Cape Town.

A preliminary analysis of 10 subjects taking nevirapine based ART who were intensively sampled in the continuation phase of TB treatment and again on completion of TB therapy shows a significant reduction in median Cmax, Cmin and AUC in the presence of rifampicin.

There was no significant difference in clinical outcome, as measured by virological suppression at 3 and 6 months, between patients on NNRTI based ART with concurrent TB treatment, and patients without concurrent TB treatment in the Khayelitsha cohort. However, when stratified by NNRTI there was a trend to decreased efficacy in the group taking nevirapine concurrently with TB treatment.

South African Pharmacology Society

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TITLE

Corticosteroid randomisation after significant head injury: CRASH trial ethics in action

AUTHOR

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ABSTRACT

The CRASH Trial was submitted for review in 2002. It was a large multi-centre, randomized, placebo-controlled trial. The trial was approved in the UK, Europe, North America, South America, Africa, Asia and Australasia. Approval to conduct the study was never granted for either MEDUNSA or the Polokwane Health Complex. The ethical considerations are discussed. The purpose of the study was to assess the effect of corticocosteroids on "death" and neurological disability. Mortality (before 1997) due to head injury showed that from 1061 patients treated with a corticosteroid 396 died (37%) 1 death prevented for every 50 patients treated. Of the 1087 patients, who served as controls 422 died (39%) no real benefit and even a small hazard. Only a large trial with 10 000 - 20 000 patients would be able to show any advantage. According to the protocol adult patients (>16) with head injury with some impaired consciousness (Glasgow Coma Score = 14) were admitted into the trial. Such patients would either receive a high dose of methylprednisolone infused over 48 hours or a placebo within 8 hours of injury. Only patients of whom the clinician was "substantially uncertain" (clinical equipoise) as to the appropriateness of a steroid were included. Patients in whom corticosteroids were contra-indicated and those who "certainly" should be treated with corticosteroids were excluded.

Can somebody with an impaired consciousness give consent? Was there real clinical equipoise? What was the risk-benefit ratio? A patient with an impaired consciousness cannot give consent, however the consent can be waived if it is the opinion of the clinician that a procedure or treatment might save the life of a patient. Real clinical equipoise only exists in the case where 2 established treatments are considered, not a treatment and a placebo. No actual benefit or harm can be expected. Completed in October 2004 the results (N=10008) showed that death from all causes within 2 weeks was higher in the methylprednisolone group (21.1%) than the placebo group (17.9%). The previous conclusion was "Neither moderate benefits nor moderate harmful effects of steroids can be excluded". New conclusion "High dose corticosteroids for acute traumatic brain injury significantly increase short-term mortality" and therefore "Steroids should no longer be routinely used in people with traumatic head injury". The decision of the Ethics Committee not to approve the protocol was justified by this finding. Reference: Clinical Pearls from the Cochrane Library, Corticosteroids for acute traumatic brain injury. Therapeutics Letter 55, Jan-March 2005

South African Pharmacology Society

FREE PAPER

TITLE

The modulating effects of myo-inositol and prototypical antidepressants on phospholipase-C-beta expression

AUTHOR

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ABSTRACT

Reduced myo-inositol (mIns) levels in the CNS have been reported in patients with depression, while several studies have demonstrated clinical efficacy of mIns oral supplementation in depression. Recent studies from our laboratory suggest that mIns pre-treatment modulates serotonin 5HT2A and muscarinic acetylcholine receptor function in cultured human neuroblastoma cells. The mechanism of action of mIns remains elusive. Also, several recent studies suggest that depression may be associated with neurodegeneration and that certain antidepressants display neuroprotective properties.

The aim of the current study was to determine whether mIns and prototypical antidepressants have a protective effect against glutamate-induced excititoxicity. Cultured human neuroblastoma (SK-N-BE) cells were pre-treated for 24 hours with different concentrations of either mIns, one of a series prototype antidepressant, or a combination of mIns and a prototype antidepressant, all with or without glutamate. Thereafter mitochondrial activity was determined utilising the MTT cell proliferation assay. mIns alone does not protect significantly against excitotoxicity. However, the current data suggest that it may protect against potential toxic effects of high concentrations of prototype antidepressants and that it may act synergistically in combination with lower concentrations of antidepressants. In conclusion, mIns treatment may be effective as augmentation therapy in depression.

South African Pharmacology Society

FREE PAPER

TITLE

Increased hippocampal NO synthase activity and stress responsiveness after imipramine discontinuation: Role of 5HT2A/C-receptors

AUTHOR

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ABSTRACT

The neurobiology and impact of antidepressant withdrawal is poorly understood, but is linked to long-term morbidity and possibly hippocampal shrinkage (MacQueen et al, 2003). Depression and antidepressant withdrawal have been associated with disturbances in excitotoxic glutamate-nitric oxide (NO) activity (Harvey et al, 2002; 2003). Interestingly, neuronal degeneration has been linked to excessive 5HT'ergic activity (Vaidya et al, 1999). We have studied 5HT2A/C receptor involvement, and effects on hippocampal NO synthase (NOS) and cyclic GMP accumulation, in imipramine (IMI) treatment and withdrawal.

Rats received either saline or IMI (15mg/kg/d ip) for 3 weeks, followed by withdrawal for 7 days. Animals received either saline or the 5HT2A/C receptor antagonist, ritanserin (RIT;4mg/kg/day ip), during withdrawal. Swim immobility and locomotor behavior together with determination of hippocampal NOS activity and cyclic GMP accumulation were determined. The actions of RIT alone were also studied.

IMI significantly decreased immobility time without effecting locomotor activity and significantly reduced NOS activity, as well as decreased cGMP, albeit not significantly. IMI withdrawal significantly increased swim immobility and profoundly increased NOS compared to chronic IMI and versus control. Cyclic GMP was also raised, but did not reach significance. RIT re-established the anti-immobility effects of IMI post withdrawal and reversed IMI withdrawal effects on NOS and cGMP without having pronounced anti-immobility effects of its own. RIT alone, however, activated hippocampal NOS and significantly elevated hippocampal cGMP.

Antidepressant discontinuation therefore increases stress responsiveness together with disinhibition of hippocampal NOS through a mechanism involving 5HT2A/C receptor activation. The resulting increased nitrergic activity may have significant implications for depressive illness and its treatment.

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Vaidya VA et al (1999). Neurosci Lett 262: 1-4.

South African Pharmacology Society

FREE PAPER

TITLE

Fluconazole in the management of AIDS-related fungal infections: A 1-year exploratory study of patterns of drug prescription and patient's profiles at Nelson Mandela Academic Hospital (NMAH)

AUTHOR

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ABSTRACT

Fluconazole is recommended to treat fungal infections: oesophageal candidiasis and cryptococcal meningitis, considered to be important causes of morbidity and mortality in AIDS patients. The aim of this study was to determine if fluconazole prescribing guidelines for clinical management are adhered to.

An exploratory study of routinely kept pharmacy records of fluconazole prescriptions for the period 1 April 2004 - 1 April 2005 was done. Analysis of patient's profiles included age, gender, diagnosis, dose and duration of treatment.

Fluconazole was administered to a total of 92 patients, of whom 61% were females and 39% males. The age range of patients varied from 5 months - 64 years with the highest proportion in the 30 - 40 year age - range. Oesophageal candidiasis accounted for 48% and cryptococcal meningitis (acute and secondary phases) for 47%. There were few repeat prescriptions for cryptococcal meningitis in secondary phase.

The results indicate that guidelines for prescribing fluconazole were not adhered to. The analysed prescriptions specifically for cryptococcal meningitis in secondary phase indicated few repeats, yet the patients should receive initial treatment, followed by lifelong therapy to suppress recurrences.

We recommend that, within the broader context of holistic HIV/AIDS management, prescription guidelines be made available to physicians and effective monitoring of patients be emphasized

South African Pharmacology Society

FREE PAPER

TITLE

The effects of stress on components of cellular resilience in an animal model of post-traumatic stress disorder

AUTHOR

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ABSTRACT

PTSD has no definitive treatment or cure and drugs currently used have limited efficacy and a delayed onset of action. The aim of this study was to identify components of neuronal signalling pathways affected by a time-dependent sensitisation (TDS) animal model of PTSD. Wistar rats were either left undisturbed (control; n=12) for 14 days, or subjected to our TDS model (TDS; n=12) which consists of a triple stressor (restraint, forced swim, halothane exposure) followed by a re-stress session (forced swim) 7 days later. Rats were sacrificed 7 days post-re-stress and their hippocampus and pre-frontal cortex dissected for neurochemical analysis. Statistical analysis showed no differences in hippocampal NOS activity or NOx levels between TDS and control groups, although NOx levels tended to be higher in the TDS group.

In support of this, hippocampal nNOS protein levels were significantly increased in the TDS group compared to control. In addition, hippocampal BDNF protein expression was significantly decreased in the TDS group versus control. Finally, there were no statistical differences between total hippocampal GSK-3? or ERK1/2 protein levels. In conclusion, exposure to our TDS model resulted in increased hippocampal nNOS and decreased BDNF protein levels, respectively. These and other components of neuronal signalling pathways could serve as targets for the development of new drug treatments for PTSD.

South African Pharmacology Society

FREE PAPER

TITLE

The effects of pharmacological treatment on stereotypic behaviour and key parameters in a putative animal model of OCD

AUTHOR

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ABSTRACT

The aim of this study was to determine whether fluoxetine had any effect on locomotor behaviour in a genetic animal model of spontaneous stereotypic behaviour (SB), Peromyscus maniculatus bairdii (deer mouse), and to relate these to effects on striatal versus cortical changes in cAMP. Mice were monitored for SB by computerized analysis using a Digiscan Activity Monitor and classified as either stereotypic or non-stereotypic. A further distinction was made between low stereotypic (i.e. not very active) and high (very active) stereotypic mice.

Stereotypic mice were injected intraperitoneally for 21 days with either (a) saline (n = 12) (b) a low fluoxetine dose (10 mg/kg, n = 20) or (c) a high fluoxetine dose (20 mg/kg, n = 20). 24 hours after the last injection stereotypic data was collected and mice were sacrificed for tissue collection. Cyclic AMP levels in both the striatum and prefrontal cortex were determined.

Fluoxetine at 20 mg/kg resulted in a significant decrease in SB in high, and a marginal decrease in low stereotypic mice. The drug furthermore slightly decreased behaviour when 10 mg/kg was used. A low dose fluoxetine significantly reduced cAMP levels in the cortex of both stereotypic groups, but not in the striatum of said groups. 20 mg/kg fluoxetine tended to decrease cAMP in the cortex and striatum of both SB groups, although this decrease did not reach significance.

In conclusion, fluoxetine modifies stereotypic behaviour in this genetic animal model and highlights the cAMP-cascade as an important neuro-molecular marker during stereotypy. This may have distinct value for further studies into the neurobiology and treatment of obsessive compulsive disorder (OCD).

South African Pharmacology Society

FREE PAPER

TITLE

Traditional healers are not just diviners or herbalists

AUTHOR

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ABSTRACT

The African traditional healer is usually thought of as being either a diviner or an herbalist. In reality, however, there exists a large number of different categories. The present study was undertaken to find out which other types of healers one may come across. Information was gathered through an extensive literature review on traditional practitioners in South Africa and neighbouring African countries on the one hand, and personal interviews with practising healers in the Eastern Cape region on the other.

It was found that the categories most often described are diviners, herbalists, faith healers, traditional birth attendants, traditional surgeons, bonesetters and a variety of specialists. Although each category has its own distinctive features and functions, these may often overlap so that the boundaries become blurred. In addition, there are different grades in each category ranging from novices to consultants. Of interest was the fact that rural practitioners frequently display a marked specialization in one particular field, while urban healers tend to be 'general practitioners' who may describe themselves as diviners cum herbalists, who sometimes also possess the skills of a traditional midwife. The reason for this phenomenon is an economical one: in cities, few healers seem able to survive unless they both diagnose and treat their clients.

Whatever the present trend, it is important to trace the history of traditional healers and preserve the knowledge gained in order to protect a valuable African cultural heritage.

South African Pharmacology Society

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TITLE

The relationship between GABA levels and anxiety as determined by an animal model of post-traumatic stress disorder

AUTHOR

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ABSTRACT

Post-traumatic stress disorder (PTSD) develops after exposure to a traumatic event with the hippocampus and prefrontal cortex playing a crucial role in its pathophysiology. Lower than normal levels of GABA are implicated in PTSD as well as the possibility that pre-stress diminished GABA may be a predictive factor for PTSD. Diazepam, an anxiolytic benzodiazepine, increases GABA levels and is one of the established treatment options for PTSD. In this study GABA levels in both the hippocampus and prefrontal cortex of 12 rats were determined after exposure to acute, severe stress and a situational reminder 7 days later. GABA concentrations were measured by a high performance liquid chromatography (HPLC) method with electrochemical detection.

A second objective of the study was to establish a relationship between diazepam levels and anxiety. Following the establishment of a pharmacokinetic profile of diazepam in rat plasma, diazepam was administered at 5mg/kg to rats exposed to the stress-restress paradigm, whereafter aversive behaviour was measured in an elevated plus maze (EPM) at peak plasma levels, viz 1 hour. GABA levels were found to be increased in both the prefrontal cortex ($p<0.0001$) and the hippocampus ($p=0.1151$) following acute exposure to stress compared to levels found in the control animals. No statistically significant differences were found between the aversive behaviour of rats treated with diazepam when compared to the behaviour of stressed rats treated with vehicle only. These results indicate that acute severe stress causes an increase in GABA levels, a finding which is in agreement with previous findings. The lack of an anxiolytic effect of diazepam in the behavioural study however needs clarification.

South African Pharmacology Society

FREE PAPER

TITLE

Adherence to antiretroviral therapy assessed by pharmacy claims and survival in HIV-infected South Africans

AUTHOR

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ABSTRACT

Background:
Adherence to antiretroviral therapy (ART) improves survival after HIV infection. Our hypothesis is that pharmacy claims predict survival rates in HIV-infected South African adults.

Methods:
We studied 7,812 HIV-infected adult South Africans enrolled in a private sector HIV/AIDS disease management program and who began triple-drug ART combination between January 1999 and March 2003. ART adherence was calculated by dividing the number of months that patients has submitted claims by number of months since ART commencement. X^2 analysis and Cox proportional hazard models were used to identify variables associated with adherence and survival, respectively. Survival curves were compared between groups with the Log-rank test.

Results:
The mean age at ART initiation was 37±8 years; 4,605 patients (56%) were female and 7554 (96.7%) black Africans. The mean $CD4^+$ count and $\log_{10}$ HIV viral load at enrollment were 145±102 cells/mm^3 and 5.1±0.7 $\log_{10}$ copies/mL, respectively. ART adherence was >70% for 3,908 patients (50.0%), 4070% for 1,837 (23.5%) and, <40% for 2,067 (26.46%). Patients with >70% adherence were likely to be females than males (62% vs. 38%; $p<0.01$) but age <40 years and CD4+ count <200 cells/m^3 did not predict mean adherence ($p>0.4$). As of March 2003, a total of 718 patients died, yielding a crude mortality of 9.2%. In the multivariate Cox proportional hazard model, a threshold risk ratio at ART adherence equal to 80% was identified. The variables significantly associated with decreased survival were: low ART adherence (<80%) (RH 1.31; CI: 1.19-1.43), male gender (RH 1.34, 95% CI 1.15-1.56), age ≥40 years (RH 1.21, 1.04-1.41), baseline $CD4^+$ count <200 cells/mm^3 (RH 3.35, 2.62-4.26) and high baseline viral load (RH 1.75, 1.54-1.98 per $\log_{10}$ increase)

Conclusion:
Poor ART adherence as assessed by ART claim data is associated with decreased survival. Pharmacy claims may be a simple and effective tool for monitoring adherence as ART programs in sub-Saharan Africa are scaled up. Reasons for poor adherence in males need to be explored further.

South African Pharmacology Society

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TITLE

In vitro and in vivo pharmacology of a Novel Guanidine ME10092

AUTHOR

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ABSTRACT

Guanidine and its derivatives has drawn the attention as potential therapeutic agents some 30 years ago in view of the bioactivities in medicinal fields amongst others in cancer and virology. These medicinal properties have stimulated the design and synthesis of a wide variety of guanidine-like structures in order to explore their bioactivities [1,2]. We have recently investigated the medicinal chemistry of guanidine derivatives in the fields of HIV/AIDS, a2 adrenoreceptors, electron acceptors at the xanthine oxidase enzyme and ischaemic heart disease. We report here the in vitro and in vivo pharmacology of a novel guanidine (N-(3,4,-dimethoxy-2-chlorobenzylideneamino)-guanidine: ME10092). In vitro investigations of ME10092 included nitric oxide synthase (NOS), NAD(P)H oxidase, xanthine oxidase activities, alpha adrenoceptor binding affinities. In vivo studies with ME10092 were conducted for its cardiovascular effects on myocardial ischaemia and reperfusion in rats. Subsequently, studies were conducted with ME10092 on the Papio ursinus baboon investigation its effect on cerebral perfusion together with monitoring of the cardiovascular parameters.

These investigations indicate that ME10092 possesses a certain anti-oxidant activities by inhibiting xanthine oxidase enzyme, as well as NAD(P)H oxidase driven oxyradical formation. ME10092 also modulates the nitric oxide (NO) content in several tissues of the rat. In vivo data revealed cardio protective properties of ME10092 in the rodent. The non-human primate investigations indicated no significant cerebral perfusion effects using the split-dose single photon emission computed tomography (SPECT) at the dose and time-schedules applied in these studies. However, negative chronotropic effects and changes in blood pressure were induced by ME10092. These effects of ME10092 in the baboon strengthen the findings found in the rodent studies. In conclusion ME10092 exhibits various pharmacological activities of importance with potential therapeutic applications. 1. Doubell P.J.C. and Oliver D.W. (1992). Synthesis and Anti-HIV-1 activity of N Hydroxy-N1-Aminoguanidines Arzneimittel Forsch. 42, 65. 2. Oliver D.W. et al. Guanidines: From molecule to primate. 2nd International Symposium in Drug Discovery Research CTDDR-2004, 17-20 February 2004, Lucknow, INDIA, Medicinal Chemistry Research, 12(4) 180-181 (2003)

South African Pharmacology Society

FREE PAPER

TITLE

The effects of ozone exposure on the viability and function of cultured human cell lines

AUTHOR

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ABSTRACT

Exposure to ozone (O3) has been shown to have systemic effects, including dose-dependent oxidative stress. The latter is typically associated with an increased production of free radicals, resulting in membrane lipid peroxidation, protein oxidation, enzymatic inactivation, DNA destruction and apoptosis. The aim of the current study was to establish appropriate conditions and an experimental protocol for in vitro O3 exposure and preconditioning, utilising cultured human epithelial (HeLa) cells, and its effects on cell viability. Cultures HeLa cells were exposed to an O3 saturated physiological solution for various time periods whereafter cell viability was determined, utilising the standard Trypan blue and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) tests. To investigate the effect of O3 preconditioning on cellular plasticity, cells were also pre-conditioned by one or multiple short O3 exposures (0 or 5 min), incubated for eight hours in growth medium and re-exposed to O3 for 25 min. According to the Trypan blue test, acute O3 exposure compromised cell membrane integrity, with significant damage visible from 25 min, and a maximum at 60 min.

The MTT test, however, indicated only slight reduction in cell viability at mitochondrial level. Single pre-exposure of HeLa cells did not affect the response of the cells during re-exposure, while multiple pre-exposure was associated with a protective adaptation. In conclusion, the current data suggest that in vitro O3 exposure decreases HeLa cell viability by damaging cell membranes, with no significant effect on mitochondrial function. Importantly, multiple pre-exposure to O3 induces an adaptive response, whereby cell plasticity is upregulated.

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TITLE

Pharmacokinetics-Pharmacodynamic modeling of Glibenclamide in type 2 diabetic subjects

AUTHOR

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ABSTRACT

Anecdotal reports have suggested that glibenclamide, is being used at doses that exceed those likely to produce clinical control of elevated blood glucose.

A clinical study was therefore conducted to determine whether patients benefit from the use of these high doses of glibenclamide. Twenty two type 2 diabetics were recruited into a within-subject dose escalation study to evaluate the dose-response relationship of glibenclamide, blood glucose and blood insulin. After an initial washout period, a zero dose study was conducted followed by dose escalation through 2.5, 5, 10, 15 and 20mg daily doses at 14 day intervals. Dose escalation was guided by clinical examination, monitoring of blood glucose concentrations and checks for symptoms of hypoglycaemia. The relationship between dose and selected metrics of pharmacokinetic and pharmacodynamic (PKPD) response on glucose and insulin were investigated using conventional statistical methods and the mathematical modeling software package, NONMEM (non-linear mixed effects models).

Exploratory graphical analysis suggested that doses beyond 5 - 10 mg per day were unlikely to provide any additional reduction in blood glucose concentrations. PKPD modeling revealed that the maximum mean reduction in blood glucose concentrations (Emax) was only ~ 34% from a baseline of ~15 mMol/L. The dose producing 50% inhibition of glucose concentration (ED50) was estimated from the models to be in the region of 2.5 to 5mg per day. These analyses confirm that escalating doses of glibenclamide in these subjects was unlikely to produce any substantial clinical benefit.

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TITLE

Antimycobacterial activity of plants traditionally used to treat respiratory ailments and the isolation of anacardic acids from Ozoroa paniculosa

AUTHOR

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ABSTRACT

Nineteen species of plants traditionally used in South Africa to treat respiratory ailments were selected for antimicrobial screening. The focus of this study was tuberculosis and three strains of mycobacteria were screened with the broth micro-dilution and BACTEC 460 techniques. Plants with activity against M. smegmatis were Datura stramonium, Eriocephalus africanus, Helichrysum odoratissimum, Mentha longifolia, Tetradenia riparia and Xerophyta retinervis. Those with activity against M. aurum were Dioscorea sylvatica, Ozoroa paniculosa and Siphonochilus aethiopicus. The plants most active against M. tuberculosis were Tetradenia riparia, Xerophyta retinervis, Syzigium cordatum, Conyza scabrida, Datura stramonium, Ozoroa paniculosa, Helichrysum odoratissimum and Siphonochilus aethiopicus. The bark of the common resin tree, Ozoroa paniculosa, was further researched and anacardic acids were isolated by bio-assay guided fractionation. The activity of these compounds was evaluated against pathogens responsible for respiratory diseases, with IC50 values against Staphylococcus aureus being the most significant at 3.2 to 24μg/ml. Against M. tuberculosis the activities ranged from 32 to 125μg/ml. The compounds exhibited cytotoxcity to Chinese hamster ovarian cells at 45μg/ml to 64μg/ml.

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TITLE

Toxicity of diclofenac sodium to African White-Backed Vultures (Gyps africanus)

AUTHOR

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ABSTRACT

Toxicity of diclofenac at 0.8 mg/kg was examined in 4 captive, non-releasable African White Backed Vultures (AWBV) in a randomised, two-arm, parallel study design under experimental housing conditions based on a fitted probit model for generating the dose-response2.

The first signs of acute toxicity occurred at 36 h and 39 h in the two diclofenac-treated vultures, respectively. Severe depression, closing of the eyes, drooping of the neck, abrupt recumbency and apparent coma, from which the vultures could initially be aroused, were observed. These signs persisted and appeared to increase with intensity until mortality a few hours later. A ten fold increased in plasma uric acid concentrations in comparison to the untreated controls were noted. Post-mortem lesions confirmed the presence of visceral gout with corresponding severe necrosis of the proximal convoluted tubules.

It was concluded that diclofenac at 0.8 mg/kg was as least or more toxic to the AWBV as the OWBV and that it could be used as a suitable surrogate model for further studies.

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South African Pharmacology Society

FREE PAPER

TITLE

Clinical investigation of Silybum Marianum seed extract (Silymarin) treatment in type-ii diabetic patients

AUTHOR

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ABSTRACT

Introduction:
The free radical production and consequently metabolic oxidative stress disorder is hallmark of chronic disease particularly in uncontrolled hyperinsulinemic type II diabetic patients. Inhibition of free radical production, its neutralization or correction of oxidative metabolic abnormality in diabetic patients following antioxidant therapy may influence the glycemic control.

Aim:
The present study was designed to investigate the efficacy of silymarin treatment with known antioxidant property on glycemic control in type II diabetic patients.

Methods:
A 12 month randomized double blind clinical trial was conducted in 80 non-insulin dependent diabetic patients in two well matched groups. One group (n=48) received 200mg silymarin tablet 3 times a day plus standard therapy, while the control group (n=32) received placebo plus standard therapy. The patients were visited every two month and glycosylated hemoglobin (HbA1c), fasting blood glucose, total cholesterol, LDL and HDL, triglyceride, SGOT and SGPT levels were determined at the beginning, after four month and at the end of the study.

Results:
There were significant decrease in HbA1c, fasting blood glucose, total cholesterol, LDL, SGOT and SGPT levels in silymarin treated patients as compared to placebo group.

Conclusion:
In present study the silymarin treatment to hyperglycemic type II diabetic patients for twelve months improved glycemic as well as lipid profile.

Key words:
Silymarin, Herbal medicine, Antioxidant, Type II diabetes.

South African Pharmacology Society

FREE PAPER

TITLE

Porcine vaginal mucosa as an in vitro permeability model for human vaginal mucosa

AUTHOR

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ABSTRACT

Objectives:
The availability of human tissue for experimental purposes is often problematical and use is thus made of animal tissue as models of the human tissue. In this study porcine vaginal mucosa was used as an in vitro permeability model for human vaginal mucosa using tritium-labelled permeants.

Methods:
Fresh porcine and human vaginal tissues were obtained from the Maitland abattoir and Louis Leipoldt Hospital, respectively, frozen in liquid nitrogen and stored at 85 degrees Celcius. In vitro permeability studies were performed using a flow-through diffusion apparatus. Tritium-labelled permeants (17β-estradiol, arecoline, vasopressin, oxytocin and water) were collected over 24 h (20 degrees Celcius, 2 h, 1.5 ml/h).

Results:
The mean and mean estimated steady state flux rates for water, arecoline and vasopressin were approximately 4%, 12% and 5% lower, respectively, through porcine vaginal mucosa as compared to human vaginal mucosa, while that for 17β-estradiol and oxytocin were approximately 17% and 53% higher, respectively. Using a F-test and comparing whole curves, statistically significant differences in the diffusion of 17β-estradiol, arecoline and oxytocin were indicated when comparing human and porcine vaginal mucosae.

Conclusions:
Porcine vaginal mucosa seems a good in vitro permeability model for human vaginal mucosa because the barrier lipid compositions in both are very similar, however, permeability towards all permeants tested do not always correspond closely. These differences must always be considered when using the animal model for in vitro experimental procedures.

South African Pharmacology Society

FREE PAPER

TITLE

Permeation of the peptides MDY-19 and MEA-5 through human vaginal mucosa

AUTHOR

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ABSTRACT

Objectives:
Peptides are emerging as a major class of therapeutic agents. Various transmembranal routes for their administration have been explored, in addition to parenteral delivery. Because of the interest in topical delivery of anti-HIV microbicides, it was the objective of the present study to investigate the in vitro permeation of a synthetic transport (MDY-19) and microbicidal (MEA-5) peptide through vaginal mucosa. Methods: The permeation kinetics of FITC-labelled MDY-19 (Mw = 2409.5 Da) and MEA-5 (Mw = 2911.4 Da) across human vaginal mucosa was studied by using a continuous flow-through diffusion system (20 degrees Celcius, 24h) and fluorospectrophotometry was used as a detection method.

The influence of a phospholipid surfactant on MDY-19 permeation and effects of de-epithelialization of the mucosa on MEA-5 flux rates were also investigated. ANOVA and Duncan's multiple range test were used to establish steady state diffusion kinetics. Results: Both peptides readily permeated through vaginal mucosa. A higher flux rate was observed for MDY-19 than for MEA-5, these rates being a function of the molecular weights of the peptides. The phospholipid surfactant enhanced the flux rate of MDY-19 approximately 1.5x. De-epithelialization of mucosal specimens significantly increased the average flux rate (2-3x) for MEA-5 compared with controls.

Conclusions:
The peptides MDY-19 and MEA-5 have good diffusion characteristics across vaginal mucosa and may be therapeutically useful. Removal of epithelium significantly increased the flux rates of MEA-5 across the mucosa.

South African Pharmacology Society

FREE PAPER

TITLE

Surfactant as a permeation enhancer of peptide drugs through porcine lung tissue

AUTHOR

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ABSTRACT

Introduction:
Extensive research efforts are directed towards exploiting the pulmonary route as a portal for non-invasive systemic delivery of therapeutic agents, such as peptides and poorly absorbed molecules. Because molecular weight and size influence the diffusion of drugs through the epithelial layer in the lungs, the use of a penetration enhancer may be of critical importance.

Objective:
This study investigates the role of a synthetic pulmonary surfactant in the diffusion of the therapeutic peptides vasopressin and oxytocin through porcine lung tissue.

Methods:
Synthetic surfactant was prepared by ultrasonic dispersion of phospholipids in saline. In the presence of surfactant, the flux rates of [3H]-labeled forms of vasopressin and oxytocin through porcine lung tissue were determined by using a continuous flow-through diffusion system. Mean steady state flux values were compared statistically using a t-test at a significance level of 5%.

Results:
In vitro, surfactant causes a statistically significant increase in flux rate of vasopressin and a decrease in that of oxytocin across porcine lung tissue.

Conclusion:
Molecular weight, electrostatic charge and partitioning of the peptides in surfactant play an important role in the diffusion differences found for vasopressin and oxytocin through lung tissue. The benefit of synthetic pulmonary surfactant as a permeation enhancer is supported by these studies.

South African Pharmacology Society

Posters

POSTER

TITLE

Treating AIDS-associated cerebral toxoplasmosis: tolerability of pyrimethamine-sulfadiazine compared with co-trimoxazole and outcome with adjunctive corticosteroids

AUTHOR

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Division of Clinical Pharmacology, University of Cape Town

ABSTRACT

Introduction:
Treatment of toxoplasmosis with co-trimoxazole became the standard of care in South Africa following the withdrawal of the supply of sulfadiazine. The limited experience with co-trimoxazole treatment of toxoplasmosis motivated this study aimed at comparing the two therapies in terms of adverse events and clinical outcome (including survival). The secondary aim was to determine whether concomitant corticosteroid therapy influences these outcomes.

Method:
Retrospective review of medical records of HIV-infected inpatients at Groote Schuur Hospital with a discharge diagnosis of cerebral toxoplasmosis confirmed by CT-scan between 1992 to 2000.

Results:
A total of 43 patients met inclusion criteria. The treatment groups (pyrimethamine-sulfadiazine vs. co-trimoxazole) were comparable with respect to age, sex, presenting neurological signs, CD4 count, TB comorbidity, concomitant steroid therapy. There was a trend for adverse events to occur less frequently in patients on co-trimoxazole (1/25 vs 4/18; $p=0.066$). Death occurred significantly more often in patients who had steroids co-administered ($p=0.018$), despite similar baseline neurological deficit in patients who did not receive steroids.

Conclusion:
Within this small retrospective study co-trimoxazole appears to be better tolerated than pyrimethamine-sulfadiazine. There was a significant association between the co-administration of steroids and increased risk of death.

South African Pharmacology Society

POSTER

TITLE

A retrospective review of theophylline toxicity

AUTHOR

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ABSTRACT

We aimed to describe the baseline characteristics and acute management of adults with theophylline toxicity in the Groote Schuur Hospital catchment area. All theophylline levels requested in the preceding 8 months were reviewed to identify patients with toxic levels (>110μmol/L), and an audit was conducted on the complete medical records of these patients. Of the 109 patients assayed, 61 with sub-therapeutic and 18 adults with toxic levels were identified; 10 were acute overdoses and theophylline had been prescribed in 11 cases. The nine cases with depression (all acute overdose) were significantly younger (p=0.004).

Clinical features consistent with theophylline toxicity were seen in all cases, although 89% of our patients had theophylline levels below that previously reported to be associated with symptoms of toxicity (430μmol/L). Potential drug interactions increasing theophylline levels were identified in 2 cases. Records suggest that acute management was generally adequate. However, only 2 of the 9 patients with a history of depression have a record of being referred for ongoing management. One patient died from COPD and another had a CVA. Although the low number of cases and generally adequate management of theophylline toxicity is reassuring, this small study suggests that emphasis should be placed on educating patients regarding the safe storage of their theophylline and avoiding dose and drug-interaction errors.

South African Pharmacology Society

POSTER

TITLE

The first steps in developing a useful African Herbal Pharmacopoeia

AUTHOR

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ABSTRACT

There is a constantly growing market for herbal medicines and many informed pharmacologists realize the potential value well-researched herbal products. Africa contains 25% of the world's species diversity, but African species contribute only a low percentage of plants commercialized and used as herbal medicines in Europe compared to species from China and India. This may be because insufficient information is available on the efficacy, safety and quality control of African medicinal plants. The ACP-European Union Centre for the Development of Enterprise funded a project to identify the 21 (and later another 29) African medicinal plant species with the highest potential of commercialization and to write trading standards/monographs for these species.

This is a pan African project involving a variety of role players in the medicinal plant industry. The criteria used for the selection of the species, the aspects to be covered in the profiles and the profile content have been validated by a workshop involving key role players from Africa and Europe. Safety of all products was evaluated in in vitro studies and identification criteria were developed to ensure adequate quality control. The results of this project will be made available on the Internet with open access before the end of 2005. This project should lead to a greater demand for African medicinal plants, to the production of these species in Africa thereby creating jobs and increasing the quality of life of Africans while delivering products that may be useful to inhabitants of Europe. This project would also identify areas requiring research and increase research co-operation within Africa. The database will be continually updated with latest information. An outcome of the workshop was the creation of the Association for African Medicinal Plant standards. This project may be a modest start to the eventual development of an African Herbal Pharmacopoeia.

South African Pharmacology Society

POSTER

TITLE

Antimicrobial activity of traditional herbal remedies used to treat wounds in Venda

AUTHOR

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ABSTRACT

The use of medicinal plants for the treatment of wounds has been based largely on historical/anecdotal evidence. Crude methanol and water extracts of 22 plants, used for the treatment of wounds in Venda, were screened for in vitro activity against two Gram-negative bacterial strains, Escherichia coli (ATCC 1175) and Pseudomonas aeruginosa (ATCC 9027) and two Gram-positive bacterial strains, Staphyloccocus aureus (ATCC 12600) and Staphylococcus albus (clinical isolate), as well as Candida albicans (ATCC 10231). In a radial-diffusion assay using the crude extracts, none of the extracts had activity against the Gram-negative organisms. Sixteen extracts inhibited the growth of the Gram-positive bacteria and 17 extracts inhibited the growth of C. albicans. The plant extracts with antimicrobial activity were further investigated using a modified test tube microdilution assay.

Of the 16 extracts, 11 were active at concentrations of ≥5 mg/ml against Gram-positive organisms and 10 extracts against C. albicans. Extracts of Combretum molle and Zanthoxylum davyi were the most active and inhibited the growth of S. albus, S. aureus and C. albicans at concentrations of 1 mg/ml and less. The active components of the crude extracts of the latter plants requires further investigation.

South African Pharmacology Society

POSTER

TITLE

Comparison of restricted versus extended blood testing intervals in determining bioavailability and bioequivalence assessment of fixed-dose drug combination(FDC) anti-tuberculosis drugs, isoniazid, rifampicin, pyrazinamide and ethambutol.

AUTHOR

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ABSTRACT

Setting:
The assessment of fixed-dose combination (FDC) formulation is widely accepted, however focus has been placed predominately on rifampicin within the FDC when assessing screening protocols. It would be advantageous for both the drug regulatory authorities and drug manufactures, for optimum minimum blood testing time intervals, that embraces all anti-tuberculosis active constituents within the FDC.

Objective:
To determine the restricted blood time intervals for testing novel fixed dose anti-tuberculosis drugs in 13 clinical trials conducted.

Design:
The blood level results of each of the active constituents of 13 different bioavailability and bioequivalence FDC clinical studies that were randomised, single dose, crossover design with appropriate reference formulations were analysed. The assessment conforms with the requirement as set out by the national drug regulatory authorities.

Results:
The pharmacokinetic parameters to determine bioavailability and Hauschke method to determine bioequivalence, revealed that a 6 points time protocol, namely 0, 1,2, 4, 6 and 8 hours, would be sufficient to determine quality assurance for FDC's already in the market, and a 11 point time protocol of 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours provide sufficient information, and is comparable to the conventional 15 time points for FDC's of up to four drugs.

Conclusion:
The findings would result in economic and convenience benefit for quality assurance testing of existing and novel FDC's

Key Words:
Tuberculosis, fixed-dose combinations, bioavailability, bioequivalence, testing

South African Pharmacology Society

POSTER

TITLE

Platinum pyridyl phosphines: synthesis and investigation of their behaviour in biological fluids.

AUTHOR

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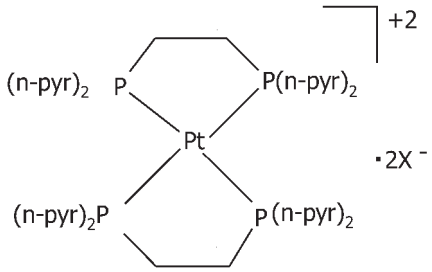
ABSTRACT

An important property of the platinum coordination compounds is the fact that the Pt-ligand bond has a thermodynamic strength of a typical coordination bond (say approximately 100 kJ/mol or belowless), which is much weaker than (covalent) C-C and C-N or C-O covalent single and double bonds, (which are between 250 and 500 kJ/mol).[1] The aim of this study was to synthesise complexes with stable Pt-ligand bonds in order to achieve a more practical compound in biological fluids. The synthesised products should have the typical ligand-exchange behaviour of Pt compounds, i.e. quite slow, which gives them high kinetic stability and results in ligand exchange reactions of minutes to days, rather than milliseconds to seconds observed for many other coordination compounds. These compounds can now be further explored in biological fluids.



I

n = 2, 3 or 4
X= halide
pyr = pyridyl

[1] Reedijk, J. (2003). New clues for platinum antitumor chemistry: Kinetically controlled metal binding to DNA PNAS, 100. 3611 3616. www.pnas.org

South African Pharmacology Society

POSTER

TITLE

The effect of serum on chemiluminescent measurements in isolated neutrophils

AUTHOR

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ABSTRACT

Whole blood chemiluminescence is a rapid and simple assay suitable for routine assessment of blood phagocyte reactive oxygen metabolite. In this study the influence of whole serum was investigated on isolated neutrophils to determine whether the inhibitory effect on neutrophils in whole blood was caused by an unidentified factor in serum or not.

Whole blood was diluted 1:9 with Hanks balanced salt solution (HBSS). Neutrophils were isolated using Percoll and resuspended in HBSS. Both were stimulated with phorbol myristate acetate (PMA). Through calculation, the amount of neutrophils were 105 cells whether they were isolated or in whole blood.

The superoxide production of isolated neutrophils with added serum was significantly lower compared to isolated neutrophils without serum. Neutrophils in whole blood also reacted significantly lower than isolated neutrophils without serum.

To conclude, it would be advisable to add serum to isolated neutrophils to achieve a more accurate representation of how neutrophils will react in whole blood. It can be assumed that serum do contain inhibiting factors that has an effect on neutrophil superoxide production after the cells were isolated when stimulated by PMA.

South African Pharmacology Society

POSTER

TITLE

Antituberculous drug-induced hepatotoxicity: clinical features and rechallenge in 82 cases.

AUTHOR

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ABSTRACT

Hepatotoxicity is the most common serious adverse event associated with TB treatment. The role of rechallenge remains controversial. We aimed to describe the baseline characteristics of patients with hepatotoxicity and possible predictors of successful rechallenge.

We conducted a retrospective record review of 82 adults with hepatotoxicity related to antituberculous therapy presenting to Groote Schuur and Brooklyn Chest hospitals. The median age was 44 years, 42 (53%) were female, 19 of 37 tested were confirmed HIV seropositive and 42 (53%) gave a history of alcohol abuse (more common in males (79%) than females (29%) $p<0.001$). The median duration of anti-tuberculous treatment prior to presentation was 3 weeks, and the median duration of symptoms was 2 days. Jaundice, the most frequent presenting feature, occured in 68 (86%) cases. Encephalopathy occurred in 15 (19%) cases. On presentation the median ALT and AST levels were 7x and 9x the upper limit of normal respectively, and the mean albumin level was 27.4 (25.6-29.2) g/L.

Rechallenge was successful in 47 (59%) of 76 patients in whom this was attempted. Risk factors associated with unsuccessful rechallenge in univariate analysis included older age ($p=0.003$), history of alcohol abuse ($p=0.034$), encephalopathy on presentation ($p=0.026$), baseline AST ($p=0.014$) and bilirubin ($p=0.008$). These factors should be considered before rechallenge is prescribed.

South African Pharmacology Society

POSTER

TITLE

Acute and chronic toxicity of luteolin-containing plant Artemisia afra in rodents

AUTHOR

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ABSTRACT

The aim of this study was to investigate the safety of Artemisia afra by determining the acute and chronic toxicity of its aqueous extract (AaAE) in mice and rats, respectively.

Mice were administered single oral or intra-peritoneal doses (1,5 to 24 g/kg) of AaAE, monitored for mortality and toxic symptoms over two weeks, and the LD50 values for each route calculated. Rats were given daily p.o. doses (0, 1 or 1g/kg) over three months, several haematological and biochemical parameters measured, and selected tissues inspected for histopathological changes after 90 days. Luteolin levels in AaAE and blood from the animals given the plant were determined by HPLC assay. The LD50 after acute i.p administration was 27% that after oral administration (i.e. 2450 mg/kg vs. 8960mg/kg). The rats in the chronic study survived the duration of the treatment, showed no significant changes in physical signs, haematological and biochemical parameters, except for transient decrease in AST activity. No significant difference was observed in organ weights, and the histopathological results showed normal architecture suggesting no morphological disturbances. The luteolin levels in the AaAE and rat plasma were 0,923± 0,015 μg/mg extract and 0, 133 ± 0, 032 μg/ml plasma, respectively. Collectively, the results indicate that A-afra aqueous extract via p.o and i.p routes is practically non-toxic and only slightly toxic in mice, and has low chronic toxicity potential and produces low plasma levels of luteolin in rats via p.o route.

South African Pharmacology Society

POSTER

TITLE

Ketamine and midazolam for conscious sedation - a study in healthy volunteers

AUTHOR

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ABSTRACT

Objective:
Dental phobia is a deterrent to good dental health. Traditional oral sedatives used to alleviate the anxiety gives unreliable results and as a result, many of these patients need general anaesthesia. This procedure is inherently more dangerous than general anaesthesia. Ketamine and midazolam used orally as conscious sedation is a more attractive alternative as it causes sedation, is anxiolytic and increases the pain threshold. It was decided to investigate the efficacy and safety of these two drugs in healthy volunteers.

Methods:
A study in ten healthy volunteers was conducted in which parenteral ketamine (2.5mg.kg-1) and midazolam (0.14mg.kg-1) were administered orally. Blood samples were drawn every 15 minutes. Patho-physiological parameters as well as effects on vital signs were monitored. The data was used to demonstrate certain pharmacokinetic parameters e.g. area-under-the-curve (AUC), bioavailability, elimination half-life for each drug respectively and in combination.

Results:
In terms of patho-physiological parameters, no untoward events were recorded. Liver enzymes, blood glucose and chemistry as well as blood gases remained stable. An increase in pain threshold as well as anterograde amnesia was demonstrated. The Glasgow Coma Scale showed that sedation and axiolysis had occurred. Both drugs in combination demonstrated good bioavailability and changes in blood levels of these drugs correlated with effects such as increase in pain threshold, amnesia and sedation.
No other untoward effects were noted and vital signs stayed intact.

Conclusion:
It can be concluded that the parenteral form of each drug in combination is effective and may be safely used when given orally.

South African Pharmacology Society

POSTER

TITLE

In vivo and in vitro cardiovascular effects of the methanol extracts of Leonotis leonurus

AUTHOR

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ABSTRACT

Leonotis leonurus is used in traditional medicine for treatment of various ailments including high blood pressure1. An aqueous extract of the leaves and stems was found with a positive inotropic and a negative chronotropic effect on the isolated perfused rat heart and a dose dependent positive inotropic and negative chronotropic effect on anaesthetized normotensive rats[2]. The aim of this study was to determine the cardiovascular effects of fractions obtained by column chromatography of the methanol extract of L. leonurus on both the isolated perfused rat heart and anaesthetized, normotensive male wistar rats (250-350g). The hearts were rapidly excised from male wistar rats, cannulated and perfused retrogradely (langendorff) and antegradely (working heart) with Krebs-Henseleit buffer solution and solutions of fractions A C (L. leonurus). A side arm of the aortic cannula was connected to a Chart recorderV2 module via a BP cannula to record systolic pressure (SP), diastolic pressure (DP), mean arterial pressure (MAP), developed pressure (Du) and heart rate (HR). For in vivo experiment, rats were anaesthetized with sodium pentobarbitone (40mg/kg) IP route. After tracheotomy, the external jugular vein was cannulated for infusion of test substances.

The femoral artery was cannulated and connected via a pressure transducer to the PowerLab 4/20T for recording of SP, DP, MAP and HR. Methanol extracts of L. leonurus were dissolved in 1% dimethylsulfoxide in 0.9% NaCl, and control agents (adrenaline and atenolol) were dissolved in normal saline. Results were expressed as a difference between the base line preceding the administration of each tested substance and at steady state (± 3 minutes after the beginning of the IV infusion for in vivo; ± 5 minutes infusion for in vitro). They were analyzed using the Student's t-test. Differences between two related means were considered statistically significant for p values equal or less than 0.05. Extract C (0.01 to 0.05mg) significantly ($p < 0.05$) increased SP (5.06 ± 0.68 to 24.2 ± 1.87 mmHg), DP (3.74 ± 1.16 to 16.45 ± 1.74 mmHg), and increased HR (3.68 ± 0.64 to 21.61 ± 1.45 bpm) in anaesthetized normotensive rats. In isolated perfused hearts, fraction C (0.01mg/ml) increased SP, Du, Qe, Qa, CO and HR (10.96 ± 0.91; 28.27 ± 0.56; 4.36 ± 0.16; 13.45 ± 0.46; 15.44 ± 0.52 and 22.8 ± 0.95 respectively), decreased DP (9.42 ± 0.56). Atenolol (0.07mg/ml) significantly ($p < 0.05$) decreased the effect of fraction C on SP, Du, Qe, Qa, CO and HR. In conclusion, a fraction of the methanol extract of the leaves of L. leonurus has a dose dependent positive inotropic and positive chronotropic effect in the normotensive rat and on the isolated perfused rat heart. References 1. Hutchings, A. 1996. Zulu medicinal plants. Natal University Press, Pietermaritzburg. 2. Khan, F., Mugabo, P., Burger, A.P. 2001. Effects of Leonotis leonurus on the isolated perfused rats heart. Presented at the international immunopharmacology congress. September 2001. Sun City, South Africa.

South African Pharmacology Society

POSTER

TITLE

Evaluation of cisplatin and a novel platinum polymer conjugate for drug toxicity and drug distribution in mice.

AUTHOR

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ABSTRACT

The toxicity and distribution of cisplatin and 2 novel platinum polymer conjugates Pt-6 and Pt-7 were determined in serum and tissue of BALB/c mice at specific time points after intra-peritoneal administration of a drug bolus containing identical platinum (Pt) concentrations. Pt concentrations were determined in serum, liver and kidney at 5 and 15 minutes, respectively, after drug administration by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). It was found that the platinum polymer Pt-7 gave rise to a considerably lower Pt concentration in serum and considerably higher concentration in liver and kidney than cisplatin. LD25 measurements indicated that the Pt-7 polymer is considerably less toxic than cisplatin.

In vitro experiments and determination of IC50 values in a variety of human tumour cell lines, normal lymphocytes and fibroblasts confirmed that Pt-6 and Pt-7 polymers are 40500 times more toxic for tumour cells than for normal cells, perhaps reflecting preferential uptake. The toxicity of cisplatin was found to be only 1.6-40 times more effective in tumour cells. These interrelationships are supported by the observation that the tumour specific factor (TSF) for cisplatin is only in the region of 6 and much lower than for Pt-6 and Pt-7 where TSF's are in the region of 40 and 150, respectively. These results demonstrate that the platinum polymer conjugates exhibit a greater tumour specificity than cisplatin, killing tumour cells more effectively while being considerably less toxic for normal cells. It is concluded that the platinum polymer conjugates may be superior for cancer therapy and warrant further testing to assess their full clinical potential.

South African Pharmacology Society

POSTER

TITLE

A retrospective analysis and evaluation of the role of gastroscopy in patients who have approved Gastro-oesophageal reflux disease (GORD) from a private medical aid fund.

AUTHOR

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ABSTRACT

Gastroscopy is an important objective criterion in patients who have complications of GORD (oesophageal eg barretts, strictures or extra-oesophageal eg asthma, chronic cough) and in those in whom symptoms have not resolved after empirical therapy with a proton pump inhibitor. (NICE, BGS) . The unnecessary use of gastroscopy in patients without complication have caused costs to spiral out of control. A retrospective study(from a private medical aid) evaluated the role of gastroscopy in subjects approved for GORD therapy over a 2 year period.

The choice of the population was not based on the complication or the severity of the symptoms but on whether or not the attending doctor chose to have a gastroscopy done. All newly diagnosed GORD patients were on continuous drug therapy for the 2 years. Non-compliant patients who were treated for GORD previously and intermittently were excluded from the study.

Results:

	Patients without gastroscopy n(%)	Patients with 1 gastroscopy n(%)	Patients with > 1 gastroscopy n(%)
Patients with complications	15 (7%)	49 (21%)	48 (34%)
Patients without complications	196 (93%)	183 (79%)	95(66%)

Conclusions:
Patients with complications of GORD or in whom symptoms have not resolved, require objective criteria (gastroscopy) to diagnose GORD. Gastroscopy should not be unnecessarily used in patients without the complications, instead the patient should first be treated empirically.

South African Pharmacology Society

POSTER

TITLE

Providing medicines information to health professionals in South Africa: The role of the Medicines Information Centre

AUTHOR

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ABSTRACT

Profession	%
GP/Specialist	25.69
Pharmacist	58.5
Intern/Student	0.16
Nurse	0.87
Dentist	0.33
Medical Aid	1.26
Industry	1.4
Other Health Prof	0.97
Lay person	7.56
Wholesaler	3.23
Publisher	0.03

Region	%
Western Cape	70.12
Northern Cape	0.73
Eastern Cape	4.11
Gauteng	12.66
Mpumalanga	2.65
Limpopo	0.18
North West Province	0.60
Free State	0.57
Kwazulu Natal	7.56
Other (outside SA)	0.82

The large number of queries received by the MIC shows that there is a substantial need for accurate, unbiased and up-to-date medicines information. The MIC plays an important role in fulfilling this need by providing a free telephonic query answering service to all health professionals.

South African Pharmacology Society

POSTER

TITLE

Anti-Mycobacterium tuberculosis activity of 7-methyljuglone in combination with other antituberculous drugs

AUTHOR

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ABSTRACT

The recent increase in the incidence of tuberculosis with the emergence of multidrug-resistant (MDR) cases has lead to the search for new drugs that are effective against MDR strains of Mycobacterium tuberculosis and can augment the potential of existing drugs against tuberculosis. In the present study, we investigated the activities of a naphthoquinone, 7-methyljuglone, isolated from the roots of Euclea natalensis alone and in combination with other antituberculous drugs against extracellular and intracellular M. tuberculosis.

Combination of 7-methyljuglone with isoniazid or rifampicin showed synergistic activity against extracellular and intracellular M. tuberculosis. Combination of sub-MICs of 7-methyljuglone with isoniazid or rifampicin resulted in a four to six-fold reduction in the minimum inhibitory concentration of each compound. Fractional inhibitory concentration (FIC) indexes obtained were 0.2 and 0.5 respectively for rifampicin and isoniazid, suggesting a synergistic interaction between 7-methyljuglone and either isoniazid or rifampicin. The ability of 7-methyljuglone to enhance the activity of isoniazid and rifampicin against both extracellular and intracellular organisms indicate that 7-methyljuglone may serve as a promising lead compound for future drug development for treatment of tuberculosis.

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POSTER

TITLE

Effect of some calcium channels blockers in experimentally induced diabetic nephropathy in rats

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ABSTRACT

Introduction & Aim:
Diabetic nephropathy (DNP) is considered a CRD (Chronic Renal Disease); it is a major cause of illness and premature death in people with DM. Furthermore, it is considered the single most important cause of end stage renal disease in the western world and accounts for more than a quarter of all end stage renal diseases. The present study was designed to illustrate the role of CCBs (amlodipine and diltiazem) in prevention and treatment of DNP in rats.

Materials & Methods:
Eighty male albino rats weighing (130-180gm) were used in this study. These animals were subdivided into five equal groups. Insulinopenic diabetes was induced by STZ, two weeks later, 30 minutes of complete ischaemia was induced in the left kidney to induce diabetic nephropathy then treatment was started for 12 weeks. At the end of experiment urine samples and blood samples were taken for biochemical analysis and kidneys were taken after scarification for histopathological evaluation.

Results:
Combination of renal ischaemia with DM produced a significant increase in rat weight, rat kidney weight, BUN (Blood Urea Nitrogen) level, K/B (Kidney/Body weight) ratio, random blood glucose, 24 hrs urine proteins, and 24 hrs urine volumes and creatinine clearance. Treatment with diltiazem or amlodipine significantly lowered elevated SBP and elevated 24 hrs urine volumes. Furthermore, treatment with captopril produced a highly significant lowering of elevated SBP and elevated serum creatinine; and a significant reduction in elevated K/B ratio and proteinuria. Light microscopic examination of diabetic kidneys revealed glomerulopathy characterized by thickening of the glomerular basement membrane, mesangial matrix expansion, arteriolar hyalinosis and large proteinaceous deposits occluding some capillary loops and hyaline droplets within the glomeruli. Moreover, examination of kidneys of ischaemic animals by light microscope revealed focal tubular necrosis at multiple points along the nephron, interstitial edema and accumulation of leucocytes within dilated vasa recta.

Conclusion:
It can be concluded that, renal ischaemia hasten the progression of DNP, diltiazem and amlodipine have a tendency to reverse of changed parameters toward normal values except biochemical parameters, generally speaking, diltiazem is better than amlodipine in reversing biochemical and histopathological changes produced by DNP, and captopril reversed most of changed parameters except histopathological changes.

Recommendations:
Based on the obtained results from the present study, one can recommend that; 1) Diltiazem and amlodipine have a nephroprotective effect in DNP, therefore, they should be used in diabetic patients to protect and/or slow progression of DNP. 2) Captopril might be considered the first therapy for DNP. Moreover, combination of captopril with CCBs could be a more effective tool got protection and/or slow progression of DNP.

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