Abstracts of the Conference

Discoveries in Pharmacy and Pharmaceutical Sciences by The University of Toledo College of Pharmacy Toledo, OH

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The University of Toledo, College of Pharmacy is comprehensive, with BS, MS and PhD degree programs in the pharmaceutical sciences, a Doctor of Pharmacy Program, residency programs and post doctoral learning opportunities. The objective of this presentation is to describe some active research programs and core laboratories and to initiate discussions that will lead to collaboration. The college has active research programs in organic synthesis, drug design and development, infectious disease, biosensors, neuroprotective potential of cacao flavanol in cerebral ischemia, Alzheimer's disease, environmental toxicology, and diabetes. Summary data will be preselected for several research areas. The functions of core research laboratories will be described.

The college also has a continuum of learning opportunities from the summer pharmacy camp for rising high school seniors to preparation of MS (industrial pharmacy, pharmacology and toxicology, and pharmacy administration) and PhD students in medicinal chemistry. The Center for Drug Design and Development hosts post doctoral students and sabbatical visitors as well as undergraduate and high school students who are interested in experiencing actual drug research by shadowing professionals.

The Pharmaceutical Care and Outcomes Research Laboratory assists health care providers by providing research capabilities to evaluate pharmacy practice outcomes and demonstrating the impact and cost savings generated from clinical services. The laboratory is staffed with faculty and graduate students trained in outcomes research and pharmacoeconomics.

The college has an impressive record in regard to innovation. The research awards for the college during the fiscal years 2005 through 2008 totaled $6.3 million. To help place this information in perspective, the national average for invention disclosures per $10 million in research is 4.3. The average across the University for the same four-year period was 6.9 disclosures per $10 million in research. The college's average was 15.9 invention disclosures per $10 million in research, which shows an innovation enterprise that rates more than three times the national average and double UT's average.

Research Based Pharmaceutical Programs: ***Experience of Leslie Dan Faculty of Pharmacy, University of Toronto***

Rob Macgregor
Leslie Dan Faculty of Pharmacy University of Toronto, Canada

The Leslie Dan Faculty of Pharmacy is the largest in Canada. The Faculty has education programs that relevant to several areas of Pharmacy and the Pharmaceutical Sciences. This talk will provide an overview of research based programs in the Faculty. It will also show how the Faculty programs fit into the larger context of the University of Toronto.

Overview of Non-Clinical Safety Assessment in Drug Development

Dr. Hanan Ghantous
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Drug development is a term used to define the entire process of bringing a new drug or device to the market. It is an integrated, multidisciplinary endeavor which includes drug discovery, chemistry, pharmacology, nonclinical safety testing, manufacturing, clinical trials, and regulatory submissions. In drug development, it is important to know and understand the legislation and other documents establishing the regulatory authority of the different agencies as well as the specific enabling documents that have been published (21 CFR, ICH Guidance, Agencies specific Guidance, etc.) and the supporting guidelines. However, it is also of practical importance to understand the scientific approach which ultimately drives decision making in the drug review divisions that constitute the real world of pharmaceutical development.

This presentation will give an overview of the contributions of each area, with a focus on non-clinical safety assessment, and some of the challenges that can arise. It will also cover specific non-clinical guidance as M3(R2) – Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Title: Screening of Natural Products for Drug Development in Reference to Anticancer Therapy

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No one denies that the pharmaceutical industry is facing an unprecedented challenge and there are big crises in the new drug development processes. Since 1995, the number of new drugs launched into the market has declined by 50%, despite the doubled investments and rapid technical progress. Thus, to enhance the efficiency of drug discovery, we need not only investments and newer techniques, but also newer concepts. In spite of huge developments of pharmaceutical and medical technologies, novel therapeutic modalities are still necessary for some major diseases, such as cancer, AIDS, cardiovascular diseases and diseases due to aging. Medicinal plants represent a primary source for pharmaceutical industry. However, the source seems to be endangered by sharp climatic changes due to global warming in the world. Large quantities are used in the preparation of infusions and decoctions both in countries where traditional medicine is still of social, economic and therapeutic importance and in the so-called industrialized countries, where an over-growing proportion of the population is using medicinal plants for self-medication. An even greater amount of medicinal plants is used by industry in the preparation of a wide spectrum of derivatives ranging from total extract to extracts with a high content of active constituents to chemically pure products, the latter being used directly as medicaments or as starting materials for the synthesis of other products. This paper outlines biological screening of medicinal plants, focusing on anticancer activity. In conclusion, the most proper strategies for the utilization of medicinal plants through biological screening in the developing countries are discussed taking into account that environmental changes due to the global warming will have a deep impact on natural resources of developing countries.

Title: Cytochromes P450 as Targets for Drug Development

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Background: The drug metabolizing enzymes are a diverse group of proteins that are responsible for metabolizing a vast array of xenobiotic compounds including cancer drugs. The cytochromes P450 (CYPs) are a superfamily of mixed function oxidases that are unique in their ability to oxidize xenobiotics, but under hypoxic conditions also can reduce certain chemical functionalities. There is now growing evidence that CYP1A1, 1B1, 2J2, 2S1 and 2W1 are expressed and in some instances over-expressed in many human tumor types. The presence of certain CYPs may reflect a resistance mechanism by diminishing the pharmacological activity of anticancer drugs whilst specific CYPs can also modulate cell proliferation by the formation or conversion of endogenous signaling molecules. The potential for CYP-selective metabolism of xenobiotics coupled to their broad substrate specificity provides a unique opportunity to design drugs whose activity is dependent on a critical functional group that can be unmasked or restored by CYP metabolism selectively in tumor tissue.

Results: We have identified the aryl-based chloromethylindolines as a novel class of agent, which lend themselves to being great candidates for use in prodrug strategies. The electronic distribution and lipophilicity of the chloromethylindoline subunits are important determinants in regioselective oxidation by specific CYP isoforms. We have synthesized and biologically evaluated several libraries of chloromethylindolines and have shown them to be activated in several CYP1A1 expressing cell lines. In vivo, we have used the CHO cell line as proof-of concept since it does not naturally express significant levels of drug metabolizing CYPs whilst accommodating stably transfected CYP1A1 as an enriched variant. Significantly, we have shown one agent, ICT2700, to possess tumor-selective activity.

Drug penetration into solid tumours; novel opportunities for therapeutic intervention

Dr Roger Phillips
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Impaired drug delivery to solid tumours is a significant factor that limits the response of tumours to chemotherapy. The factors which determine drug delivery to tumours are complex but the extent of the vascular supply, the pharmacokinetic properties of the drug and its ability to leave the blood vessel and penetrate through avascular regions of tumours are critically important factors. An additional barrier to drug delivery is elevated interstitial fluid pressure in tumours which hinders the normal process of convective fluid flow from capillaries into tissues. Whilst impaired drug delivery is recognised as a major contributing factor to drug resistance, understanding the underlying mechanisms will paradoxically provide novel opportunities for therapeutic strategies designed to increase drug delivery, thereby enhancing efficacy. During this presentation, preclinical in vitro models for assessing drug transport across multicell layers will be described in the context of providing new experimental ‘tools’ for novel therapeutic approaches.

Volumetric Properties of the Human Telomeric Sequence

Rob Macgregor
Leslie Dan Faculty of Pharmacy University of Toronto, Canada

Purpose: We are interested in elucidating the role of water in the stabilization of the compact, folded structure adopted by 22-base oligodeoxyribonucleotide (ODN), 5'-A$(GGGTTA)_3$GGG. This ODN contains four repeats of the human telomeric DNA sequence, GGGTTA. The folded structure in mono-molecular and is stabilized by guanine tetrads. The conformation adopted by this and similar molecules is extremely sensitive to environmental parameters such as the nature and concentration of the counterions present in solution.

Methods: We have used pressure-perturbation calorimetry, , vibrating tube densitometry, circular dichroism spectroscopy, high pressure spectroscopy, and molecular dynamics simulations to measure the change in the volumetric and other thermodynamic parameters accompanying the denaturation of the folded form of the ODN.

Results: All of the techniques we used gave similar results. The volume change upon denaturing the folded structure of 5'-A$(GGGTTA)_3$GGG in Na^+-containing solution is approximately -50 cm^3 mol^{-1} depending on the Na^+ concentration. The expansivity change of the transition $(d\ V/\ T)_P$ is approximately four times greater than the change arising from the helix-coil transition of double stranded nucleic acids.

Conclusions: The volume change and the expansivity change are consistent with the increased solvent interaction of the denatured, coil state. Volumes calculated from simulations of the transition using molecular dynamics further corroborate the results. With some assumptions, we have calculated that the denatured state interacts with approximately 110 additional water molecules than the folded form. We wish also to point out that this is the first time that these methods have been used on the same sample prepared in the same lab. It verifies that the methods are reporting the same molecular events.

Pharmaceutical Drug Products Quality Requirements by JFDA

Ph. Hakimah Hoseh/ Head of registration unit / Registration Department JFDA
Ph. Soumah Al Qutob /Head of manufacturing factories unit/Inspection Department JFDA

Jordan Food and Drug Administration (JFDA) set regulations and guidelines to control the quality of the pharmaceutical products. These regulations and guidelines are being implemented by the pharmaceutical industry to assure the safety and efficacy of the drug products.
In Jan 2004, the JFDA issued article 6 of drug product registration requirements. This article states that for the drug product to be granted the marketing authorization, it must meet the three critical criteria; safety, efficacy, and quality.

Applications submitted for marketing authorization, should be evidenced by all necessary documents to prove their acceptability. These documents vary according to application type, originator new drug, generic, toll manufacturing, technology transfer, under licensing, nature of the product (chemical or biological), and type of dosage form.
Manufacturing sites approval and compliance with GMP requirement is a requirement for granting marketing authorization of any pharmaceutical product.

Effective Jan 2010, JFDA implemented the requirement of registration file to be submitted in CTD format which includes the fife modules. Module three, the Quality Module, is totally required, with exception of the complete pharmaceutical development, and process validation, (process validation protocol and complete method validation is a must) However batch records and retrospective process validation are inspected to prove acceptable scale-up during regular inspections.
Follow up of quality continues through regular periodic inspection, requirements of post approval changes, pharmaco-vigillance, re-registration requirements and JFDA quality lab analysis for marketed batches.

I will discuss in details our requirements, with comparison of international requirements, the need for amendments and suggested recommendations.

Pharmaceutical Quality by Design: The Road Ahead
Are We Ready?

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The US FDA Modernization Act of 1997 initiated a change in policy and thinking that culminated in the release in 2002 of a concept paper "*Pharmaceutical cGMP for the 21st century – A Risk Based Approach*".
This paper expresses the Authority Desire State that the industry to achieve a level of process understanding consistent with controlling process variability and assuring product quality in "real-time" while the batch is being manufactured. This concept became known as Quality by Design (QbD).

According to the ICH Q8 (R2) guidance, the pharmaceutical QbD is a science-based development approach that begins with predefined objectives and emphasizes product and process understanding and control based on sound Science and Quality Risk Management. In pharmaceutical QbD approach, the Critical to Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs) at each stage throughout the product and manufacturing process development need to be identified and their impacts on the finished product quality must be understood and controlled.

The relationship between CQAs, CMAs, and CPPs is a multidimensional combination and interaction of input variables. It is known as a Design Space, wherein material attributes and process parameters can vary without having an impact on the product quality. Quality by Design does not end as a product is commercialized. Manufacturing experience should continuously be integrated with existing knowledge to enhance the product and process understanding.

A successful Quality by Design implementation is based on two key elements mentioned in ICH Q8: determination of a Design Space and application of Process Analytical Technologies (PAT) to enhance baseline knowledge of product and processes.

This presentation is intended to introduce the concept of new Pharmaceutical Quality – A Risk Based Approach by applying the Quality by Design principles.

Process Analytical Technology

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Process analytical technology (PAT) has been defined by the United States Food and Drug Administration (FDA) as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA).

The concept actually aims at understanding the processes by defining their CPP's, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing while at the same time reducing over-processing, enhancing consistency and minimizing rejects.

This presentation will discuss some spectroscopic tools (UV-Vis, FTIR, NIR, Raman, headspace mass spectroscopy) that can be used to gain better insight into processes as well as some key aspects of PAT implementation in industry for assuring product quality during the manufacturing process.

Bringing Risk Mitigation Strategy to the Risk-Averse Pharmaceutical Industry: Better Late than Never

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Since the introduction of the ICH Q8, 9 and 10 guidelines in 2004, 2005 and 2007, a new "language" was introduced between the pharmaceutical product developers and the regulatory bodies in the US, Europe and Japan. This language includes vocabulary like quality target product profile, critical quality attributes, critical process parameters, risk assessment, design space, PAT etc. While the vocabulary might sound new, the underlying concepts they carry had existing foundations in the minds of formulation and process development scientists in the pharmaceutical industry. What the new guidelines and language brings is a systematic approach to develop pharmaceutical product that is based on better scientific understanding and takes into account risk as an inherent and critical component of the development process. In other words, the new approach aims to enhance the scientific side of product development at the expense of (but not replacing) the artistic side.

According to ICH Q9, 2005, risk assessment is not commonly used in designing formulations and manufacturing processes. The guideline describes several risk management tools and their potential applications within all aspects of the pharmaceutical industry (quality, regulatory, development, production, facilities, equipment, utilities, materials, laboratory and packaging). This presentation aims to illustrate how a risk management tool, Failure Mode, Effects and Criticality Analysis (FMECA), can be applied in the area of manufacturing process design and development. The product selected for the presentation is a taste masked intermediate intended for incorporation into orally disintegrating tablets for pediatric administration.

New Advances in Drug Allergy Research

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The majority of immune-mediated drug allergic reactions *appear* to be primarily T cell-mediated. Drug-specific human CD4 or CD8 T cells have been isolated from blood and/or skin mononuclear cells from patients with adverse reactions to a variety of drugs. Interestingly, some drug specific T cell clones are stimulated by the parent drug, indirectly challenging the hapten hypothesis of drug allergy. The working assumption concerning drug allergic reactions is that either the parent compound, or more likely a reactive metabolite, covalently binds to proteins *in situ*, forming "neoantigens" that provoke an adverse immune response. This model is probably very simplistic and even misleading. Almost certainly there are genetic susceptibility factors in drug allergy. Identified susceptibility factors include HLA haplotypes, some of which code for MHC antigens that have been shown to bind parent drug and produce markers such as cytokines associated with allergic reactions. However, it is becoming increasingly apparent that a second "danger" signal is needed to provoke drug allergy. Thus, drug metabolism may produce a reactive intermediate that is both a danger signal as well as a potential hapten. Other sources of "danger signal" include concurrent infections (possibly accounting for the increased prevalence of allergies to antibiotics), concomitant exposure to more than one drug, or exposure to endogenous signals, such as those generated by irritation. A complete pattern of possible factors is beginning to emerge concerning causation of drug allergy: genetic susceptibility, concurrent generation or exposure to danger signal(s), and induction of drug-specific immunity. Immunogenicity (either inherent as with biologic drugs or due to hapten formation) and presence of anti-drug antibodies are not likely sufficient to produce adverse drug reactions: this lesson has emerged from development of therapeutic proteins. Even IgE-mediated reactions, though well-understood at the effector level, involve complex genetic factors at a minimum. Finally, the various types of pathology thought to be immune-mediated have expanded and the possible mechanisms appear more diverse. For example, recent investigations suggest that different cascades of cytokines may contribute to the heterogeneity of clinical presentations in a fashion more complicated than implied by the now classic Th1/Th2 paradigm.

Biopharmaceuticals
The manufacturing Process

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Objective: The objective of this plenary lecture is to explore the process of manufacturing biopharmaceutical products on a large scale and to give insight on some of main issues related to it.
Main topics: definitions, large scale production, regulatory requirements, evaluation of products.

Discussion:
The terms such as ‘biologic’, ‘biopharmaceutical’ and ‘products of pharmaceutical biotechnology’ or ‘biotechnology medicines’ have now become an accepted part of the pharmaceutical literature. However, these terms are sometimes used interchangeably and can mean different things to different people.

The manufacture of pharmaceutical substances is one of the most highly regulated and rigorously controlled manufacturing processes known.

This Presentation aims to overview the manufacturing process of the biopharmaceutical products. It will cover in brief four major themes: (a) a description of the infrastructure of a typical manufacturing facility, and some relevant operational issues for the biological and nonbiological based products. (b) Sources of biopharmaceuticals; (c) upstream and downstream processing of biopharmaceutical products; and (d) analysis of the final biopharmaceutical product.

Docking-Based Comparative Intermolecular Contacts Analysis as New 3D QSAR Concept for Validating Docking Studies and *In Silico* screening: NMT Inhibitors as Case Study

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The significant role played by docking algorithms in drug discovery combined with their serious pitfalls prompted us to envisage a novel concept for validating docking solutions, namely, docking-based Comparative Intermolecular Contacts Analysis (dbCICA). This novel approach is based on the number and quality of contacts between docked ligands and amino acid residues within the binding pocket. It assesses a particular docking configuration based on its ability to align a set of ligands within a corresponding binding pocket in such a way that potent ligands come into contact with binding site spots distinct from those approached by low-affinity ligands and *vice versa*. In other words, dbCICA evaluates the consistency of docking by assessing the correlation between ligands' affinities and their contacts with binding site spots. Optimal dbCICA models can be translated into valid pharmacophore models that can be used as 3D search queries to mine structural databases for new bioactive compounds. dbCICA was implemented to search for new inhibitors for candida N-myristoyl transferase inhibitors as potential antifungal agents. The process culminated in 5 selective antifungal agents with micromolar minimal inhibitory concentrations against *Candida albicans*.

Effect of Microgravity on the Pharmacokinetics of Ibuprofen in Humans

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Pharmacokinetics of ibuprofen was studied under microgravity (μG) conditions and compared to those at normal gravity (1G) in humans. 6 healthy human volunteers were given 600 mg oral dose ibuprofen during 1-day simulated μG anti-orthostatic bed rest position (ABR), then at normal position (1G) in sequential design with 7 days washout time. Saliva and plasma samples were obtained up to 8 hours after dosing. Ibuprofen was not detected in all saliva samples. Pharmacokinetic parameters in plasma were calculated by either non compartmental analysis or one compartment model using Kinetica program. Absorption kinetic parameters were then predicted by ADAM and PE modules using Simcyp program. Results have showed increased rate of ibuprofen dissolution and absorption; and hence faster onset of action under uG conditions. However, rate of drug elimination and bioavailability was not affected by uG, suggesting no need for dose adjustment.

Identification and Functional Characterization of Novel Antimicrobial Peptides from the Venom of the Scorpion *Androctonus amoreuxi*

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Scorpion venoms are rich sources of biologically-active peptides. Most of the peptides identified from scorpion venoms are disulfide-bridged and function as ion channel modulators. Until recently, little interest has been shown in the non disulfide-bridged peptides yet more than 10 antimicrobial peptides lacking this modification have been identified from scorpion venoms. Here we report the identification, structural characterization and precursor cDNA cloning of four novel antimicrobial peptides from the venom of the scorpion, Androctonus amoreuxi. These peptides were found to be structural homologs of a known antimicrobial peptide named BmKb1 originally identified in the venom of the scorpion, Buthus martensi Karsch.

Synthetic replicates of two of the four sequences identified displayed inhibitory activity against Staphylococcus aureus, Escherichia coli and Candida albicans, and they also displayed haemolytic activity against horse erythrocytes. The two synthetic replicates of the natural peptides differed by only two amino acid residues but they exhibited significant differences in activity by a factor of two against S.aureus. Secondary structure prediction analysis indicated that this was probably due to conformational changes in the secondary structure of these peptides. At the high concentrations which were required to inhibit both E.coli and C.albicans, no significant differences in potency was observed between the two peptides, however, their haemolytic activity was dramatically increased at higher concentrations. These data indicate the importance of identifying the major structure/activity determinants within these peptides as a prerequisite for optimisation as potential therapeutics.

Abinitio Quantum Mechanic Calculations of New Models of 6- Methoxy Substituted Naphthalene Derivatives

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The 6- methoxy -2-alkyl naphthalene derivatives Naproxen , Nabumetone are analgesic and non steroidal anti-inflammatory drugs of the arylalkanoic acids family . It is they are used to relieve pain or inflammation caused by arthritis.

In an effort to increase affinity and selectivity at receptor side . Nitric oxide (NO) is an important biological messenger involved in a variety of physiological processes .New series of 6- methoxy -2-naphthyl derivatives were synthesized and identified their structures using FTIR spectrophotometer and ^{1}H NMR and ^{13}C NMR techniques .A new chemical entity with analgesic activity will introduced exhibiting (COX inhibiting nitric oxide donors , CINODs) may increase analgesic activity . Molecular modeling calculations (MM)showed the compound with lowest strain energy (S.E) is the more stable form , as well as application of Lipinski s rule for calculated drugs , and expected acts as nitric oxide donors.

Population Pharmacokinetics of Loratadine after 10 mg Single Oral Dose to Healthy Volunteers

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Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H1 receptor antagonistic activity. Loratadine is rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult subjects with times to maximum concentration (Tmax) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. The purpose of this study is to determine the population pharmacokinetics of loratadine after oral administration. 72 healthy male subjects gave written informed consent to participate in such studies before screening. Studies were approved by the Institutional Review Board. The studies were performed in accordance with the declaration of Helsinki (Washington, USA, 2002) and current GCP guidelines. Subjects, age 23 ± 3.57 years, were within 15 % of their ideal body weight and were judged to be healthy based on medical history, physical examination, complete blood count and serum chemistry. Following a ten-hour overnight fast, a single oral dose of 10 mg loratadine tablets were administered orally followed by 240-ml water. Blood samples were collected in heparinized tubes at pre-dose, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 & 96 hours after dosing. Blood samples were harvested to plasma and stored at –20 0C until analyzed by a validated liquid chromatography- mass spectrometry (LCMSMS) technique. Mean & population plasma level profiles were examined Simultaneous data fitting of all individuals was done using Kinetica® program *version 4.1*. The results proved the validity of this specific and sensitive method for the intended use. The method was proved linear over the range of concentration 0.10-20.00 ng/ml (r>0.999). The lower limit of quantification was proved to be 0.1 ng/ml with 95% accuracy; while precision as CV was 7.44%. Intra-day accuracy ranged 91.9 - 97.2% at high and low QCs, respectively. Whereas inter-day accuracy ranged between 93.57 (CV 4.35%) and 98.78% (CV 5.78%). Population elimination and absorption rate constants and half life values were 0.19 hr-1, 3.65 hr, 1.31 hr-1 and 0.53 hr respectively. Moreover, Distribution and redistribution rate constants and lag time were 0.31 hr-1, 0.02 hr-1 and 0.32 hr respectively. The non-compartmental estimate of maximum drug concentration was 3.02 ng/ml and occurred after 1.30 hr. Population pharmacokinetic parameters for loratadine were essentially uncovered. The population elimination half-life value for loratadine was proved to be 3.65 hours**.**

Evolution of Clinical Pharmacy: Practice and Education
(The need for clinical pharmacy, responsibilities, barriers and future plan)

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One of the most dramatic changes affecting pharmaceutical education and the future of pharmaceutical practice is the emerging concept of clinical pharmacy. This concept has emerged since the late fifties or early sixties. Clinical pharmacists are uniquely trained in therapeutics and provide comprehensive drug management to patients and providers (includes physicians and additional members of the care team).

It is evident that clinical pharmacy activities influence the correct use of medicines, medication errors, drug-drug interaction, prescribers' attitudes , and drug-related policies. Despite these professional initiatives, recent studies suggest that the clinical pharmacy practice revolution still has significant hurdles to overcome .

The clinical pharmacy services are not fully implemented in our countries, the purpose of this presentation is to focus on some aspects that may pave the road to implement clinical pharmacy activities. These include:-

1) Clinical pharmacy services and the Patient care journey

2) Expanding Roles for Pharmacists

3) Clinical pharmacy activities: Common Practice Models

4) Outcomes: Impact of clinical pharmacy services assessed and its impact on our health care system

5) Challenges in Advancing the Profession of Pharmacy

6) Strategic for future developments in clinical pharmacy
   a) Clinical governance
   b) Developments with medicines: personalized medicines, Pharmacogenomics
   c) Changing public expectation
   d) The colleges of pharmacy: shift from teaching to learning
   e) continuing professional education and Development
   f) Role of the Ministry of Heath, and pharmaceutical industries

Over The Counter Drugs' Price Deregulation in Jordan: The Case Of Paracetamol

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Objectives: This research aimed to evaluate the implementation of over the counter drugs (OTC) prices' deregulation policy in Jordan.

Methods: Comprehensive two questionnaires were designed; one for pharmacists (retailers) and the other for patients (consumers); 311 pharmacies and 1545 patients were randomly included.

Results: The majority of pharmacists' sample (response rate=96.8%) confirmed that medicines' prices are crucial to Jordanians living in a lower middle income country who cannot afford prices increase, and paracetamol (the most commonly utilized OTC product in Jordan) price deregulation will lead to increase in its price. However, most pharmacists tend to cooperate rather than compete in setting up OTC prices if deregulated. Moreover, most of the patients' sample (response rate=96.6%) confirmed that paracetamol price deregulation will not decrease its price.

Conclusions: The study concludes that prices of paracetamol products are to increase if deregulated. Given current Jordanian economic situation, it is recommended that OTC drugs' prices kept controlled.

Gender Differences in Aminoglycoside Induced Nephrotoxicity. A Prospective, Hospital - Based Study.

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Aim: Impact of gender on aminoglycoside induced nephrotoxicity is still controversial and inconclusive. The objective of this study was to investigate the nephrotoxic potential of amikacin (AK) and gentamicin (GM) in male and female hospitalized patients.

Methodology: A one-year, non-interventional prospective study of patients administered either GM or AK. The study was carried out at the internal medicine department of Al-Watani governmental hospital. Nephrotoxicity was defined as a blood creatinine (Cr) increase of ≥ 0.5 mg/ dL from the basal (normal) Cr level. Data were entered and analyzed using SPSS 16.

Results: A total of 94 patients were identified (GM, n = 45 and AK, n = 49). Male and female patients on GM had comparable characteristics except that males had significantly higher number of co-existing chronic diseases. No gender differences were observed in gentamicin induced nephrotoxicity (37% in males versus 33.3% in females, $P = 0.8$). Male and female patients on AK were also comparable in demographic and clinical characteristics. However, significant differences in gender susceptibility were observed with AK induced nephrotoxicity (31.6% in females versus 6.7% in males, $P = 0.043$). Pattern of serum creatinine changes in patients on GM were comparable between males and females. However, in females on AK, s.cr levels were rising sharply after the fourth day compared with that in male patients on AK.

Conclusion: Gender differences in aminoglycoside induced nephrotoxicty were seen with AK where females were more vulnerable to nephrotoxicity. Such gender differences did not exist with GM.

Antimicrobial resistance among bacterial pathogens isolated from urinary tract infections in North Palestine

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Background: Antibiotics are frequently prescribed. However, they are often administered before the pathogen's culture and sensitivity results are known. As the distribution of causative organisms and bacterial resistance rates vary in time and place, recent local data are essential to guide clinicians to the best choice of treatment.

Objectives: To investigate culture-positive infections in patients visiting general practitioners to determine the frequency of the uropathogens and to determine the susceptibility of these isolates to commonly used and newer antimicrobial agents.

Methods: A prospective study was conducted on bacteria isolated from the urine of patients with UTI who visited community medical centers in the city of Nablus, Palestine between November 2007 and April 2008.

Results: A total of 375 uropathogens were collected from 306 females (81.6%) and 69 males (18.4%). More than 90% of isolated bacteria were Gram-negative bacilli and Escherichia coli (64.8%) were the most common pathogen. Approximately 10% of the isolates were Gram-positive with Staphylococcus saprophyticus (5.6%) as the most common species. High resistance rates were recorded for E. coli against first line orally administered agents, such as trimethoprim/Sulfamethoxazole (37%), Nitrofurantoin (29%), Ampicillin (65%), and Naladixic Acid (37%). E. coli remained highly susceptible to Amoxicillin/Clavulinic acid, Ciprofloxacin, Cefataxime and Ceftriaxone with sensitivities of 87.8, 82.8, 88.9, and 88.9% respectively.

Conclusion: The isolated bacteria from the urine of patients with UTI showed limited susceptibility to first-line antimicrobial agents. Our results highlight the need for developing specific guidelines in North Palestine where elevated resistance to antimicrobials should influence prescribing decisions.

The use of unlicensed and off-label medicines in pediatrics; review and recommendations.

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Due to lack of sufficient data, and to a lesser extent the lack of appropriate formulations, approximately 80% of all commercially available medications are not licensed for use in children.[1] Pediatric treatment is usually more complex than treatment for adults e.g. poor availability of pediatric formulations, difficulty in measuring and administering medicines and the uncertainty about doses for use in children.[2]

Due to the relative lack of licensed products for the treatment of children, many of the prescriptions for hospitalised children, and a lesser proportion of prescriptions in primary care, involve use of medicines without a license for use in children (e.g. reformulated adult medicines) or outside of the license recommendations (off-label).[1] If a medicine does not have a licensed indication for use in children, the Patient Information Leaflet (PIL) will contain no details regarding its use in this population. [1] Since such use of medications is necessary in pediatric practice, to offer the best treatment for sick children, healthcare professionals are forced to 'guestimate' the doses to be administered, often based on body weight or estimated body surface area.[3] This situation has been alleviated somewhat in recent years with the publication of the compendium 'Medicines for Children', and earlier this year through the publication of the BNF for Children.[4]

Parents may often be unaware of unlicensed and off-label drug use in their children. It is the role of the prescriber to convey this information to parents without causing any confusion or distress. Unfortunately, such circumstances can put parents and doctors in an awkward situation, which may lead to lack of trust and affect the treatment negatively. There is a distinct lack of research on parental knowledge and views of the general public about the use of unlicensed and off-label medicines in children.[5]

A number of high profile cases of dosing errors, some of which have caused fatalities, have been reported regarding the use of unlicensed and off-label medicines in children. Medication errors in children have three times the potential to cause harm when compared with similar errors in adults.[1] Nonetheless such prescribing is essential if children are not to be denied therapeutic advances. [3] Most clinicians believe that children should not be denied the benefit of such medicine use simply because pharmaceutical companies have not preformed the necessary research to extend their product license to include children. Furthermore, in most of the cases the benefits of using unlicensed and off-label medications outweigh the risk of not using them. [1] In general, however, it is important to note that the prescription of unlicensed or off-label medicines is expected to be the exception, rather than the rule, although physicians will generally use them so long as they produce beneficial results.[4]

Assessment of antibiotic's use among children during hospitalization

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Objectives: To assess the use of antibiotics in children during hospitalization according to indication, patient's age and weight, and drug's route of administration.

Methods: A review of all antibiotics prescribed for children were admitted to medical ward in university of Jordan hospital over two months. All surgical and trauma cases were excluded. The study was conducted in March and April 2008. Data involved indication, patient's age and weight, and drug's route of administration. The collected data were tabulated and kept in special registry file maintained by the authors.

Results: 189 cases were admitted to medical ward over two months. Cases were classified into five major groups: acute febrile illnesses 20(10.6%), 93(49.2%) of cases given the diagnosis URTIs, LRTIs, and gastroenteritis, UTIs 47(24.9%), seizures 14(7.4%), and neonatal diseases 15(7.9%).
A total of 285 antibiotics were prescribed for all cases and 73(38.6%) of them were prescribed one or more antibiotics. Patient's age range was four months to 12 years and patient's weight range was 2.5 kg to 36 kg.
122 (42.8%) of antibiotics were prescribed by incorrectly doses according to indication, patient's age and weight and drug's route of administration.

Conclusions: Greater attention and caution is highly needed and recommended when antibiotics prescribed for children especially according to indication and dose calculations. There is a definite antibiotics abuse and antibiotics policy and guidelines is recommended.

Partial Protection of Verapamil against Gentamicin Nephrotoxicity in Rats

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A number of male rats (40) were used to test the protective efficacy of verapamil a calcium channel blocker (CCB)against gentamicin nephrotoxicity .
They were divided into four groups: group-1 control , giving only water , group – 2, they were administered gentamicin IP 80 Mg/Kg, group-3, administered verapamil orally 10 mg/Kg and group -4 administered gentamicin and verapamil at the same time . the period of study was 10 days .

Nephrotoxicity was induced by using gentamicin for 7 days ; this was evidenced by marked elevation in blood urea nitrogen (BUN) and plasma .
Creatinine (Pcr) when compared with control . BUN increased from 20 $\pm$ 1.4 to 205 $\pm$ 7 and pcr from 0.75 $\pm$ 0.08 to 4.2 $\pm$ 0.3 mg/100 ml).
Coadministration of verapamil with gentamicin decreased the rise in BUN and pcr , their values reached to 90 $\pm$ 13 and 1.5 $\pm$ 0.9 mg /100 ml respectively .

Our data suggest that supplementation of verapamil decreased the severity of acute renal failure (ARF) in rats, this supplementation of verapamil decreased the severity of acute renal failure (ARF)in rats , this supports previous studies in which CCBS Offer renoprotection in ARF,the exact mechanism of this protection need further study .

Key words: Acute renal failure, plasma creatinine, blood urea nitrogen, calcium channel blockers, Endothelium derived relaxing factor.

Anti-bacterial Properties of Melatonin against *Mycobacterium tuberculosis in Vitro*

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*** National Reference Laboratory

57 isolates of *Mycobacterium tuberculosis* and *bovis* were identified; they were isolated from different clinical sources which included sputum, bronchial wash, abscess, pleural fluid, gastric fluid, eye fluid, and CSF, also urine and ear swab. This investigation was carried out on 198 patient attended National Reference Laboratory for T.B during September 2009. Also the study declared that the ratio of separation of this bacterium from male was (67.6%) and it's higher than the ratio of separation this bacterium from females which was (32.3%). The susceptibility of *Mycobacterium tuberculosis* to melatonin was evaluated. Many concentrations of melatonin were prepared to investigate it as antibacterial drug against multidrug resistant *Mycobacterium tuberculosis* and *Mycobacterium bovis*. Suspension bacteria (10^{-1}, 10^{-3} and 10^{-5}) were cultured on Lowenstein-Jensen media (LJ) contains melatonin, while control media without this drug. Six isolates were chosen according to their susceptibility patterns; they were resisting to Rifampicin, Streptomycin, Isonicotinic –hydrazide and sensitive to Ethambutol. In conclusion, these *in vitro* studies clearly demonstrate anti-bacterial effects of melatonin. Among possible mechanisms, it is concluded that melatonin showed antibacterial effects against multidrug resistant T.B by reducing intracellular substrates. Identifying the mode of action could be of great help in developing and researching new anti-bacterial drugs.

The effect of hot and cold water extractions of tobacco leaves on the human serum (AChE) enzyme Activity

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The chemical constituents in Nicotina Tabacum were studied; the results revealed that the aqueous extract solution contain glycosides, alkaloids, resins and saponins groups. An alkaloid compound was isolated and identified as nicotine. The effects of mixture of alkaloids crude and purified nicotine on cholinesterase activity were studied.
The obtained results showed that both compounds have an inhibition effect on the enzyme activity, and the highest inhibition percentage was 45.16% which occurred at concentration of 0.1 g/ml of nicotine and 40.42% for the concentration of 0.1 g/ml of hot water extract, and 32.0% at concentration 0.1 g/ml for cold water extract.

The kinetic studies for nicotine as an inhibitor of the enzyme was done, and Linweaver-Burk plot was used to determine the type of inhibition, the result showed that nicotine caused a non-competitive inhibition of (AChE) enzyme.

Effects of Bay Leaves on Blood Glucose and Lipid Profiles on the Patients with Type 1 Diabetes

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Bay leaves have been shown to improve insulin function *in vitro* but the effects on people have not been determined. The objective of this study was to determine if bay leaves may be important in the prevention and/or alleviation of type 1 diabetes. *Methods*: Fifty five people with type 1 diabetes were divided into two groups, 45 given capsules containing 3 g of bay leaves per day for 30 days and 10 given a placebo capsules. *Results* All the patients consumed bay leaves shows reduced serum glucose with significant decreases 27% after 30 d. Total cholesterol decreased, 21 %, after 30 days with larger decreases in low density lipoprotein (LDL) 24%. High density lipoprotein (HDL) increased 20% and Triglycerides also decreased 26%. There were no significant changes in the placebo group. *Conclusion*, this study demonstrates that consumption of bay leaves, 3 g/d for 30 days, decreases risk factors for diabetes and cardiovascular diseases and suggests that bay leaves may be beneficial for people with type 1 diabetes.

Research Careers in the Pharmaceutical Industry

Dalia Johari and Mahmoud AlSwisi,
HIKMA PHARMA

Pharmaceutical Industry is growing very fast in Jordan, exporting to over 60 countries with 90% of the exports go to Arab countries.
Pharmaceutical Industry in Jordan is one of the first in MENA region that realizes the need to build strong R&D in order to compete with the global pharmaceutical industry for better life of patients.
In order to have a strong R&D, one of the main aspects is the human resources “our students” and the choices R&D of generic pharmaceuticals can offer to them. There are direct careers and other indirect careers.

Pharmaceutical Technologies

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•Purpose: Continuous processing is not a new concept. Outside of the pharmaceutical industry, in the petrochemical, chemical and food industries, for example, companies have been steadily switching their manufacturing operations to continuous processes, primarily for cost and quality purposes. The pharmaceutical industry has, however, been slower off the mark. Although there is a rising interest in the continuous processing concept, the industry, which is synonymous with batch manufacturing procedures, has been reluctant to take the leap.

•Methods: A short survey is given of some aspects of the application of thermoanalytical methods, especially differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetry (TG), in solid-dosage technology. The usefulness of these methods in the prediction of drug-excipient compatibility, studies of solid-dispersion systems, the analysis of enantiomers and racemates, measurement of the time of tablet disintegration, the analysis of drug formulations and studies of the processes of grinding and drying of drugs is discussed

•Results: Genentech has announced positive results from two Phase III studies of Lucentis, which showed significant improvement in vision for patients suffering from macular edema due to retinal vein occlusion (RVO).
During the trials, called Bravo and Cruise, patients given either of two doses of Lucentis showed a statistically significant improvement in vision as at six months compared patients given a placebo.
RVO occurs when blood flow through a retinal vein becomes blocked, causing swelling (macular edema) and hemorrhages in the retina, which may result in vision loss.
•Conclusions: We help employers, health plan administrators, and members recognize the value of their investment in pharmaceuticals. We utilize cost justification modeling, cost containment strategies, and healthcare reporting tools supported by scientific, clinical, and economical outcomes to provide our clients with an efficient and effective drug program.

TREATMENT OF PHARMACEUTICALS DURING WATER TREATMENT WITH OXIDATION PROCESSES

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The extensive incidence of different types of pharmaceutical compound in the aquatic environment threatens the purity of water. Reports indicate that surface water is the most affected by these pharmaceuticals. It was reported that pharmaceuticals pose a problem to drinking water utilities. Different treatment processes including chlorination, activated carbon, nanofiltration and reverse osmosis membranes were reported as efficient treatment option to remove different types of pharmaceuticals. Accordingly, most drinking water treatment plants include at least one of the above mentioned processes. Furthermore, pharmaceuticals were detected in ground waters. Sources for groundwater contamination were resulted from different man made activities such as, land application of sludge or manure contaminated with human or veterinary pharmaceuticals, river bank filtration of contaminated surface water into groundwater, and artificial groundwater recharge with contaminated water.

The aim of the present study was to assess the potential of Advanced oxidation processes, mainly ozone, UV and the combination of two (O_3+UV) to oxidize pharmaceuticals during water treatment. For this purpose, the concentration evolutions of selected environmentally relevant pharmaceuticals were determined in lab-scale experiments. In addition, rate constants of further pharmaceuticals were estimated based on their oxidation tendency. Both surface water and groundwater were used in the experiments. Finally, the rate constants were compared to rate constants available for chlorination process

Most of the studied pharmaceuticals showed an appreciable reactivity with Oxidation processes (in brackets apparent second-order rate constants at pH 7 and T 20 ºC): the sulfamethoxazole ($6.7x10^3$ $M^{-1}.s^{-1}$), roxithromycin ($2.2x10^2 M^{-1}.s^{-1}$), 17a-ethinylestradiol ($2x10^5 M^{-1}.s^{-1}$), and antiphlogistic diclofenac ($1.05\ X10^4\ M^{-1}.s^{-1}$). Experiments performed using natural water showed that oxidation with AOP's reacted fast with other sulfonamides and macrolides, the natural hormones estrone and 17b-estradiol as well as 3 pyrazolone derivatives (phenazone, propylphenazone, and dimethylaminophenazone). However, many compounds in the study were oxidation refractive. Experiments groundwater was partly performed at microgram/L to nanogram/L levels proved that the rate constants determined in pure water could be applied to predict the oxidation of pharmaceuticals in natural waters. Compared to ClO2, ozone reacted faster. Overall, the results indicate that AOP's will only be effective to oxidize certain compound classes such as the investigated classes of sulfonamide and macrolide antibiotics, and estrogens.

Ensuring Good dispensing practice among Community Pharmacists in Amman the Capital of Jordan"

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Objectives: To evaluate pharmacists and other dispensers' knowledge of Good Dispensing Practice (GDP) concept during their working time in order to provide rational drug prescribing to patients or their representatives to end up with minimizing any chance of dispensing error.

Methods: the study was performed in Amman, Jordan between March 2008 and May 2008. The participants (n=76) involved in the study were pharmacists (n=41, 54%) and pharmacist assistants (n=35, 46%).
The participants were asked to complete a provided questionnaire depending on their ambition, knowledge, and background without any external influence.

Results: The indications which were used in the study to evaluate the participants' understanding of Good Dispensing Practice concept showed that:-

- (67%, $P<0.005$) of the participants could not define the meaning of (GDP) as intended.
- (75%, $P<0.005$) of final check out of prepared medicines which are ready to be dispensed were made by the same person.
- (80%, $P<0.005$) of provided instructions to patient or his/her representative were repeated without feed back if the mentioned instructions had been understood properly.

Conclusion: pharmacists in general and other dispensers play a major role in the healthcare system to ensure rational drug prescribing. Great emphasize on proper education to assess their knowledge, continuous practical training, and supervision to ensure (GDP).

Managing Innovation in Drug Discovery: Challenges and Opportunities

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Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade. Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Developing products targeted for important public health needs (e.g., counterterrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging.

The drug discovery industry is unique in its unpredictability, but can innovation in drug discovery become manageable? The answer apparently is yes, according to many pharmaceutical executives, but the critical question remains: how can this mission be accomplished successfully? Because the research is performed by scientists, and their creativity and passion for science are the driving forces for innovation, one of the most important solutions to the challenge facing the industry seems to be finding ways to better lead and manage scientists.

Synthesis and Antibacterial Activity of New [1,2,3] triazolo[4,5-h]quinoline Derivatives as Potential Antimicrobial Agents

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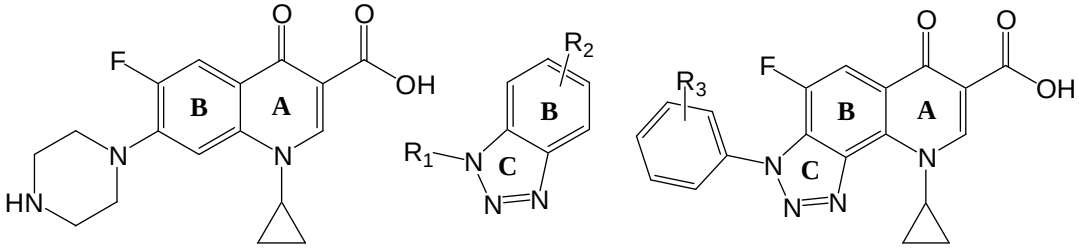
Objective: The objective of the present work is to synthesize and evaluate [1,2,3] triazolo[4,5-h] quinoline derivatives as potential antimicrobial agents.

Method: Fluoroquinolones are successful broad spectrum antibacterial agents e.g. Ciprofloxacin (**I**), with potential interest as anticancer, antidiabetic and antiviral. Recently a number of novel benzotriazole derivatives (**II**) have been reported to have many interesting biological activities like analgesic and anti-inflammatory and antitumor activities.



Ciprofloxacin (**I**) Benzotriazole (**II**) Triazoloquinolone **(III**)

Because of these potential biological effects of those heterocyclic compounds and their derivatives, the present work aimed at the preparation of tri- heterocyclic hybrid of [1,2,3] triazolo[4,5-h] quinoline (**III**) derivatives encompasing both systems and invistigate mainly their antibacterial properties.

Results: Direct interaction between 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and substituted aromatic amineproduced the 7-phenyl amino derivative.The latter was reduced with Na_2S_2O4 and followed by diazotization cyclization with $NaNO_2$ and HCl (below 5 ^oC) to produce target III. Synthetic compounds were characterized on the basis of spectral data and evaluated for their antibacterial activity against gram positive and gram negative microorganism.

Conclusion: Most intermediates and some of the targets have shown good antibacterial activity and were comparable to the reference ciprofloxacin, mainly against gram positive bacteria.

Effective patient interaction

Dr. Ahmad Al-Rusasi

Business development manager, drug information consultant and registration regularity affairs executive for both Al Noor drug Store and Union Drug Store in Amman/ Jordan.

Effective patient interaction has two major components — how the interaction is organized and how well the pharmacist uses communication skills. The effective use of communication skills is maximized by the use of an organized approach by the pharmacist. An efficient interaction with a patient enables the pharmacist to assess, triage, and if necessary, assist with product selection and provide counseling and follow-up. Use of verbal and nonverbal communication skills at each stage of the interaction ensures that a full description of the presenting complaint and associated symptoms, as well as other relevant information, is gathered from the patient.
There are three major components of an organized approach: assessment and triage, counseling, follow-up.
The "how" and "what" of communication are addressed for each component in this chapter. Most of the "how" of communication skills are covered in the Assessment and Triage section with skills specific to counseling and follow-up found in the next two sections. The "what" of the organized approach lists the types of questions to be asked or topics to be discussed at each stage.
Throughout the interaction, the participants (the pharmacist and the patient) alternate between the roles of "sender" and "receiver" of the message. As a sender, the pharmacist has the responsibility of ensuring that they are transmitting the message clearly, in language understood by the patient and in an environment that is conducive to clear transmission. As a receiver, the pharmacist has the responsibility of listening to what is being transmitted and providing feedback as to whether the message was understood.

POSTERS

Study of the Genotoxic Effect of Millard Reaction Products from Whey on Lymphocytes

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The cellular and genetic toxicity of maillard reaction products from whey with 1% concentration after boiling for (1, 3, and 5) hours and pH (11) were studied on lymphocytes which included the mitotic index (MI) and blast index (BI) in the presence of phytohaemagglutinin (PHA). It was shown that the effect of maillard reaction products on mitotic and blast indecies depends on the concentration used. The higher concentrations 2.5 and 5 mg/ml of whey maillard reaction products boiled for 1 hour showed highest inhibitory effects on the tested parameters. However, the concentration 1.25 mg/ml of whey maillard reaction product increased the cell efficiency in the MI and BI specially when boiled for 5 hours.

The Influence of Medical Sales Representatives' Work Engagement on Job Satisfaction and Self-perceived Performance: A Field Study at the Jordanian Pharmaceutical Companies

Abeer Ahmad Al-Rabayah

The purpose of this research was to identify the level of work engagement of medical sales representatives at the Jordanian pharmaceutical companies and to investigate its influence on their job satisfaction and self-perceived performance.

The population of the research consisted of all the medical sales representatives at the fifteen Jordanian pharmaceutical companies. The researcher used a questionnaire to collect the primary data from the whole population in order to achieve the research's objectives.

The results of the research showed that the level of work engagement among medical sales representatives at the Jordanian pharmaceutical companies is high. Furthermore, the results indicated that work engagement is related to job satisfaction and self-perceived performance; however its relationship with medical sales representatives' job satisfaction is stronger than its relationship with their self-perceived performance.

Even though the three dimensions of work engagement (vigor, dedication, absorption) are related to both job satisfaction and self-perceived performance, the results showed that dedication is the most influential work engagement dimension on medical sales representatives' job satisfaction while vigor is the most influential work engagement dimension on medical sales representatives' self-perceived performance.

The researcher recommended that sales managers and supervisors at the Jordanian pharmaceutical companies should develop a work engagement strategy to maintain a high work engagement level among the medical sales representative due to its positive influence on their job satisfaction and performance which will be eventually reflected on the organizational effectiveness. Furthermore, the level of work engagement among the medical sales representatives should be measured regularly in order to avoid the negative disengagement symptoms.

Vulnerability of Cough Syrups Marketed in Palestine to Microbial Challenge Test

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Background and Objectives: Microbial contamination of cough syrups can bring clinical hazards as well as physical changes in the product. The objective of the current investigation was to assess and compare the ability of imported and locally manufactured cough syrups to maintain minimum or no microbial growth after being challenged with different types of microbes.

Method: The growth of five microorganisms of known quanta of *S. aureus*, *E. coli*, *P. aeruginosa* and *C. albicans* was compared among five different cough products designated A through E. Two of the products (A and E) were locally manufactured while three (B, C and D) were imported products which contained different preservatives. Both A and E did not indicate the type of preservative used. Normal saline was used as a positive growth control. Growth of microorganisms into syrups was compared by counting the colony forming units (CFUs) from a subculture of inoculated syrups at zero, 3, 6, 24 and 48 hr intervals.

Results: 1) at time zero, growth of *S. aureus* was seen in all products except product B; 2) little or no growth of *C. albicans*, *P. aeroginosa* and *E. coli* was observed at time zero; 3) no growth of any of the tested microbes was seen when subcultures were done after 6 hours of inoculation; and 4) imported products showed lesser or no microbial growth compared to locally manufactured ones. Normal saline showed heavy growth of all tested microbes while unchallenged syrupsof the tested products showed no signs of microbial growth at all tested times.

Conclusion: despite the noticeable growth of *S. aureus* at time zero, all tested cough syrups passed the pharmacopeal guidelines regarding microbial challenge. Good manufacturing and packaging practices need to be implemented and maintained by local pharmaceutical companies. The Palestinian general public needs to be educated on the proper handling and storage of oral liquid pharmaceuticals to eliminate or reduce microbial contamination.

Bioequivalence of Atorvastatin and its active metabolites in healthy subjects applying a newly developed LC/MS/MS

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Objective: To assess bioequivalence between a single dose of generic product (Lipinorm tablets containing 40 mg atorvastatin produced by Medical Union Pharmaceuticals, Egypt) and the brand product Lipitor ® tablets containing 40 mg atorvastatin.

Material and methods: Forty eight (48) healthy male adult Arabic subjects were administered the generic and the brand products applying fasting, single-dose, two-treatment, two-period, two-sequence, randomized crossover design with two weeks washout period between dosing. Seventeen (17) blood samples were withdrawn from each subject over 60 hours period. Atorvastatin and its active metabolites ortho- & parahydroxylated atorvastatin concentrations were determined in plasma by a validated HPLC/MS/MS method applying FDA bioanalytical method validation guidance. D5-atorvastatin was used as Internal Standard (IS) for atorvastatin, while D5-ortho-hydroxy atorvastatin was used as IS for ortho-hydroxy atorvastatin and D5-para-hydroxy atorvastatin was used as IS for para-hydroxy atorvastatin. The linearity of the analytical method was established for concentrations range 0.3-50.0 ng/ml, 0.1-20.0 ng/ml and 0.1-5.0 ng/ml for atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin, respectively. The lower limit of quantitation was 0.3 ng/ml for atorvastatin and 0.1 ng/ml for both ortho-hydroxy atorvastatin and para-hydroxy atorvastatin. The pharmacokinetic parameters; C_{max}, T_{max}, $AUC_{0-t,}$ $AUC_{0-\infty}$, λ_Z and $T_{1/2}$; were calculated from the plasma concentration-time data of atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin of each individual applying non-compartmental analysis. These parameters were statistically analyzed by ANOVA test. According to FDA guidance on bioequivalence, the primary pharmacokinetic parameters used for bioequivalence evaluation; C_{max}, AUC_{0-t} and $AUC_{0-\infty}$; were statistically analyzed by ANOVA and 90% Confidence Interval (CI) tests using Ln transformed data of the parent drug atorvastatin.

Result: It was found that the 90% confidence intervals for the ratio T/R of the Ln transformed values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were well within the FDA bioequivalence acceptance range of 80-125%. Therefore, it is concluded from the present study that the two formulations of atorvastatin; Lipinorm and Lipitor ® tablets; are bioequivalent. Moreover, the newly developed analytical method applied in this study was sensitive, specific and reproducible for determination of atorvastatin and its primary active metabolites ortho-hydroxy atorvastatin and para-hydroxy atorvastatin in plasma. The method proved to be applicable for pharmacokinetics, bioavailability and bioequivalence studies of atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin.

Novel Organic Derivatives of 5-methylenebarbituric Acid

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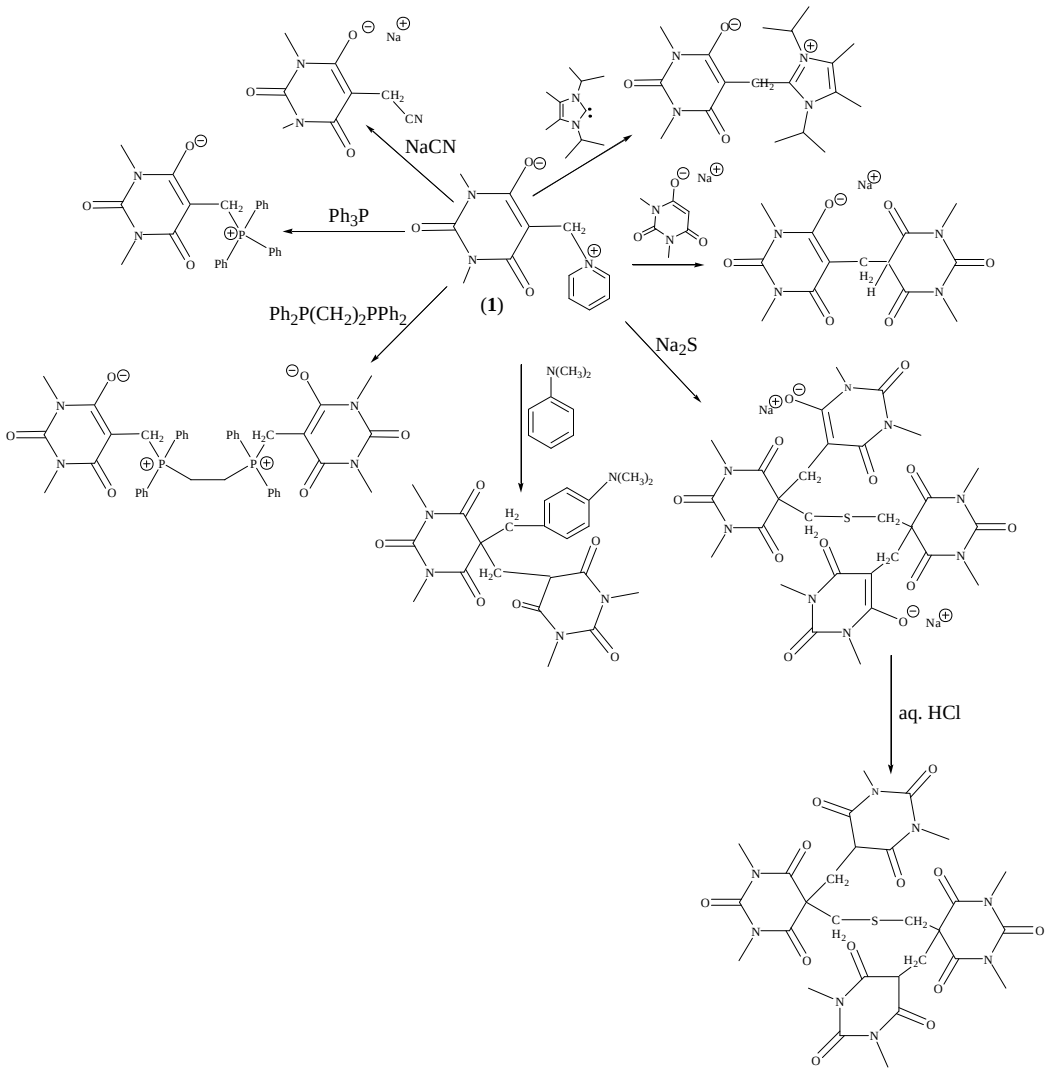
There has been much interest in barbituric acid derivatives in the past years owing to their potential application as drug. Condensation of 1,3-dimethylbarbituric acid with aqueous formaldehyde in the presence of pyridine produced zwitterionic pyridinium adduct (**1**); an important precursor in organic synthesis since the exocyclic methylene carbon atom exhibits electrophilic properties which enhances the substitution of a pyridinium fragment with various types of nucleophiles including cyanide, 1,3-dimethylbarbiturate and sulfide anions, imidazole carbene, triphenylphosphine, 1,2-bis (diphenylphosphino)ethane and N,N,-dimethylaniline. Spectroscopic techniques and x-ray diffraction analysis were used for structure determination.



Acute Poisoning in Children Admitted to El-Fateh Paediatric Hospital in Benghazi, Libya During (2008).

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Introduction and objective: Accidental poisoning among children is considered as a major problem in developing countries. The objective of the present study is to estimate the magnitude and causes of poisoning admission.

Method: A retrospective study of medical records of all children admitted with poisoning in El-Fateh Paediatric Hospital in Benghazi from January 2008 up to December. RESULTS: Number of children admitted was 144; the age ranged from less than one to 13 years old. Most of cases (59%) were admitted with mild symptom and the majority of them were boys (55.6%). Only few cases admitted to intensive care unit and there was no mortality recorded through the period of study. Most of cases were discharged within two days. Age group 1 to 3 years (48.6%) had the highest frequency of admission and the peak of admission was during summer. The most common cause of admission was due to ingestion of medication (56.9%) followed by food poisoning (27.15%) while 15.95% of admissions were due to house hold product exposure. Detergent was the leading cause of poisoning in the later group. In term of food poisoning, fast food was responsible for most cases which were among age group 6-13years. The most frequent medications taken by children were oral contraceptive pill, antihypertensive, and tricyclic antidepression drug.

Conclusion: Almost all admitted cases were accidental and medicines were the most consumed substances in addition, improper storage of toxic agents were the first risk factor of poisoning. Present results indicated that, children poisoning seems to be a common paediatric care problem which need to control and prevent.

Utilization of Anti-infective Agents in Surgical Departments in Two Governmental Hospitals in Palestine: a Comparative Study Using WHO ATC/ DDD methodology.

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Background: Excessive and inappropriate use of antibiotics is costly and contributes to the development of bacterial resistance. Information about anti-infective use in hospitals are lacking in Palestine. The parameter: Defined daily dose (DDD) per bed-days provides an estimate of consumption of drugs among hospital in-patients. This study was carried out to compare the consumption and cost of anti-invective agents in surgical department in two governmental hospitals in Palestine.

Methods: The study was carried out over a 1-month period (01.06.2010 to 30.06.2010) at Rafedia and Tulkarm governmental hospitals in north Palestine. Type, dose and duration of anti-infective agents utilized and number of days of hospitalization for each patient were obtained. Defined daily dose/100 bed-days and DU90% calculated and compared between the two hospitals for total and for each anti-infective agent. Anti-infective agents investigated were those intended for systemic use, i.e. group J of the Anatomical Therapeutic Chemical (ATC) classification and for classes of this group.

Results: During one month study period, 200 patients who had general surgery in both hospitals were investigated: 100 in Rafidia and 100 in Tulkaram hospital. Total DDD/ 100 bed-days were 166.22 for Rafidia hospital and 133.64 for Tulkaram hospital. The DU90% index for both hospitals 4. Despite differences in DDD, Metronidazole and Cefuroxime were the most commonly utilized anti-infective agents in Rafidia and Tulkaram surgical departments.

Conclusions: Differences in extent of utilization of anti-infective agents do exist even among similar departments of different governmental hospitals. A unified policy is required to be implemented by all governmental hospitals in the country. Comparison of the results obtained in this study with those published in other countries showed higher anti-infective utilization in Palestine compared with other countries.

Controlled Release Tablet Formulations of Isoxsuprine Hydrochloride 1: Using the Direct Compression Technique

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Purpose: Isoxsuprine hydrochloride (IH) is a direct myo-vascular relaxant drug, used in cerebral and peripheral vascular insufficiency. None of the conventional formulations is able to keep the plasma concentration of the drug in the therapeutic range for enough time duration owing to its short biological half life (1.5 hours). It is advisable to prepare the drug in sustained release dosage form to improve patient compliance and to achieve a steady state blood level with minimum side effects.

Methods: Different cellulosic polymers and methacrylate copolymers in addition to their combinations were used in different ratios to select the best level of the matrix forming material that provides the most sustaining effect utilizing direct compression technique. The effect of different types and concentrations of polymers on the release rate of the drug was investigated. The kinetic parameters for the in-vitro release of (IH) were determined and analyzed.

Results & Conclusions: The drug release decreased by increasing the concentration of the polymers in all the studied formulations. For cellulosic polymers, involvement of hydroxypropylmethylcellulose in 1:3 (drug: polymer weight ratio) gave more sustaining as the duration of release was about 7 hours. The retardation effect of Eudragit RSPM in 1:3 drug- polymer was found to be more than that of the other methacrylate copolymers with a duration of drug release of about 8 hours. The release rate from tablets prepared using polymer combinations is slower compared to that from matrices containing the single polymers. Tablets containing drug, Eudragit RSPM and Eudragit RLPO in weight ratio of 1:4:1 and that containing drug, hydroxypropylmethylcellulose and Eudragit RSPM in weight ratio of 1:1:4 gave the slowest drug release rate with a duration of about 12 hours. The release of (IH) from matrices prepared from single polymer followed Higuchi's diffusion model. However, zero- order release kinetics was elucidated for the release of (IH) from polymer mixtures.

Molecular Encapsulation of Biologically Active Glycolipids

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Glycolipids are a group of amphiphilic compounds frequently used in pharmaceutical field, food and cosmotics industries. Being amphiphilic in nature, glycolipids tend to form micelles in solution. This property might impair their bioavailability and permeability, create problems of biodespersibility and/or hinder their purification from natural contaminants. Therefore, it is essential to control or disrupt micelle formation. The interaction of three glycolipids with cyclodextrins (CDs) was found to be the best and interesting method tried to solve these problems. To prove the positive interaction of n-dodecyl-β-D-glycopyranoside (β-C_{12} G) and n-dodecyl-β-D-maltopyranoside (β-C_{12} M) amphiphiles, polarimetric and colourimetric methods were used. Hence, it was proved that both glycolipids form a 1:1 inclusion complex with α- and β-CD. Both glycolipids exhibited higher affinity to interact with α- than β- CD.
The interaction monosialoganglioside (GM1), one of the natural glycolipids available in the market, with α-CD was also investigated. For that purpose, conductometric measurements and ^{13}C-NMR dipolar-dephasing technique strongly support the interaction. It was found that the cmc of GM1 was shifted to higher values in presence of α-CD.

Stability studies: A major concern about marketed Tablets

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Purpose: To evaluate *in-vitro* Bioequivalence along with physical as well as microbiological stability testing parameters for non-sterile products (tablets)

Methods: Various methodologies has been performed like appearances, hardness, friability, Weight uniformity, Content uniformity, Similarity Factor (F2), Disintegration, Microbiological testing for non sterile products and *In-vitro* drug release kinetics were studied using DRKS v.2010 software,

Results: After interpretation of data using indigenous software it was found that drug release were in tolerance limit as per USP having value 98.79 %, 87.84% and 90.92%. *In-vitro* bioequivalence studies (similarity factor) indicated that LNP B was bioequivalence with standard formulation LNP A having F2 = 54.74 but LNP C showed a different pattern of drug release (f2 = 47.13) as compared to LNP B, and mean dissolution time (MDT) was in the range of 0.0 to 0.8. Microbiological testing data revealed that open tablets may act as a source of microbial assisted communicable diseases during the treatment because lots of microbial colonies were observed in LNP B and LNP C this may be due to microbial contamination via excipient / personally/accidently. Physical stability studies suggest that there is a considerable effect of environmental conditions on tablets. Like hardness of the tablets was increased due to applied stress (higher temp) and same time friability decreased except in one brand showing 0.6%. Weight variation and content uniformity data was in the USP specified limits.

Conclusions stability studies are very necessary not only for the tablets but also for other formulations to predict the chemical, physical and microbial stability parameters on storage in different climatic zones as per ICH guidelines to deliver a safe and efficient therapeutic agent.

Storage, Utilization and Cost of Drug Products in Palestinian Households

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Background and Objective: Appropriate storage and use of medications in households may decrease drug wastage and unnecessary hazard. The objective of this study was to investigate storage, utilization habits, and cost of medications in households in Palestine.

Methodology: This is a cross sectional, anonymous, questionnaire-based study of 465 households in northern Palestine. The Drug product inventory in the surveyed households was investigated and family members were interviewed.

Results: A total of 465 households were assessed, 50 were excluded. The total number of drug products in the 415 households was 5505; the mean ± SD was 13.3 ± 7.8. Level of father's education, presence of chronic disease and insurance coverage were the variables that showed a significant relationship with the amount of drug products found in the households. Most of the drug products (43.4%) were stored in relatively unsafe places around the house within the reach of children. Approximately one third (32.5%) of the drug products were not in their original container. The percentages of unused drug products, expired, or those with no clear expiry date were 32.7%, 17.7% and 11% respectively. Estimated drug wastage in the 415 households and nationwide would be 16,100 and 19 million USD respectively. The most common drug categories encountered in households were alimentary, musculoskeletal and anti-infective agents. The most common individual drugs encountered were: paracetamol (8.5%), ibuprofen (4.9%) and diclofenac (3.7%).

Conclusion: Medications were stored in large quantities in Palestinian households, and a large percentage was being wasted. Drug-use assessments and a comprehensive evaluation of the current national drug policies are warranted to curtail this problem.

Isolation and structural elucidation of the secondary metabolites from the roots of Scorzonera judaica growing in Jordan

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The genus Scorzonera belongs to the Cichorieae tribe which comprises approximately 100 genera and 1500 species, many of these species are edible and are used as vegetables or salads. The genus Scorzonera is well known for its ability to synthesize numerous classes of bioactive natural products. In Jordan Scorzonera judaica Eig "Jordanian Viper's Grass" known by Bedouins as "Ga'foor" is an edible plant. In this work the powdered roots of Scorzonera judaica were defatted with n-hexane and successively extracted with $CHCl_3$, $CHCl_3$-MeOH (9 : 1), and MeOH, by exhaustive maceration. The plant synthesizes different classes of secondary metabolite including lignans, dihydroisocoumaris and phenolic derivatives were isolated. Sophisticated techniques were used for the structural elucidation including NMR, 1D-TOCSY, DQF-COSY, NOESY, HSQC, HMBC and ESI-MS.

The Hypolipidaemic Activity Of Novel Indole-2-Carboxamides In Triton Wr-1339-Induced Hyperlipidaemic Rats: A Comparison With Bezafibrate

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Abstract
Using Triton WR-1339-induced hyperlipidaemic rats as an experimental model, we investigated whether compound 1 [N-(3-benzoylphenyl)-1H-indole-2-carboxamide] and 2 [N-(4-benzoylphenyl)-1H-indole-2-carboxamide], A novel anti-hyperlipidaemic agents have any effect on plasma triglyceride (TG) ,total cholesterol (TC) and high-density lipoprotein cholesterol levels (HDL-C) levels. Hyperlipidemia was developed by intraperitoneal injection of Triton WR-1339 (200 mg/kg body weight). At a dose of 15 mg/kg body weight, compounds 1, 2 and BF significantly reduced the elevated plasma triglyceride levels after 7 and 24 h. Furthermore, high-density lipoprotein-cholesterol levels were remarkably increased in all treated groups after 7 and 24 h compared to the hyperlipidaemic control group. However, only compounds 1 and 2 treated groups obviously showed a significant reduction in plasma total cholesterol levels after 24 h. It is therefore reasonable to assume that compounds 1 and 2 may have a promising potential in the treatment of hyperlipidemia and coronary heart diseases.

Biogenetic Conversion Of Phytoalexines From Vicia Faba

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The biogenetic conversion between wyerone(I), wyerone acid(II) and their 11,12-, dihydrowyerone (IV) , dihydrowyerone acid (VI) has been investigated. Labeled wyerone and dihydrowyerone were obtained by feeding sodium (2- 14C) acetate to CuCl2- induced Vicia faba cotyledons, and separation by HPLC.

Some of the wyerone was used for semisynthesis of wyerone acid. The three titled compounds were then fed to induced bean cotyledons to establish any possible interconversion. Incorporation data indicated the highest, 13.5% conversion of wyerone to wyerone acid, accompanied by 7.01% incorporation of dihydrowyerone into dihydrowyerone acid. The data indicated 0.46% conversion of wyerone acid into dihydrowyerone acid with a small conversion, 0.27% of wyerone into dihydrowyerone acid. The results indicated that wyerone acid has been derived from wyerone, most probably by oxidation.

Emulsion Polymerization of Propene with Carbon Monoxide Using Water Soluble Palladium(II) Complexes

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Three types of water soluble palladium complexes 4a-h with hydroxyalkyl, phosphonate and amine substituents attached to the phosphorus donors were employed in the emulsion copolymerization of propene/CO. The effect of using of different substituents in the catalyst on (i) the regioregularity; (ii) the molecular weight, and (iii) the glass transition temperature and the melting point (Tg and Tm) was investigated. The catalysts employed together with cyclodextrin and undecenoic acid enables achievement of stable colloidal latices of propene/CO copolymers (emulsion products) with high solid content (17%) , high molecular weight (6 ×104) with Mw/Mn 2-4, typical particle size in the range 62- 127 nm, glass transition temperature in the range +17 to -2 °C, which is in the range desirable for latex application, and Catalyst productivities of up to 1 × 104 TO. Methyl β-cyclodextrine increases the productivity of catalysts and solid content by about%. Interestingly, the undecenoic acid was found to be incorporated in the chemical backbone of the propene/CO copolymer causing an increase stability of dispersions and decrease of glass transition temperature of polyketone.

The Alternative possibility for Myoblasts as A major Target Cells of Gsα Inactivating Mutations in Progressive Osseous Heteroplasia

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Progressive osseous heteroplasia (POH) is a human genetic disorder characterized by ectopic bone formation in skin and subcutaneous tissue during infancy, with progression to deep skeletal muscle later in childhood. POH is caused by heterozygous inactivating mutations in the human GNAS gene, which encodes Gs-alpha (Gsα), the alpha subunit of the G stimulatory protein of adenylyl cyclase. Gsα is ubiquitously expressed, but the target cell population of Gsα insufficiency that leads to ectopic ossification in skeletal muscle tissue is unknown.

We hypothesized that myoblasts may be a muscle tissue target cell of Gsα haploinsufficiency that mediates the disabling progressive heterotopic ossification in POH. As a model system we used the mouse myoblast C2C12 cell line to study the response of the Gsα signaling pathway to genetic and pharmacologic manipulation. C2C12 cells have the capacity to express an osteogenic phenotype under the pharmacologic influence of bone morphogentic protein (BMP) stimulation in vitro. We expected that Gsα insufficiency will promote osteoblastic differentiation with BMP stimulation.

In contrast to our prediction that decreased Gnas mRNA induces osteoblastic markers, we found that C2C12 cells transfected with Gnas siRNA showed a reduction in Runx2 and osteocalcin gene expression, while over-expression of Gsα enduced increased Runx2 and osteocalcin gene expression. Additionally, we found that BMP2, a potent osteogenic morphogen, which lead to terminal osteoblast differentiation induced the expression of Gsα mRNA and protein. Finally, we found that the up-regulation of Gsα by BMP2 was mediated by Smad1, since cultures transfected with Smad1 siRNA constructs exhibited reduced Gsα expression levels compared to transfected controls.

Collectively, these data show that decreased Gsα expression by genetic or pharmacologic manipulation inhibited rather than promoted osteoblast differentiation in C2C12 cells. These data suggest that myoblasts are not likely to be the direct cellular targets of GNAS inactivating mutations in POH. A more likely cellular target for Gsα haploinsufficiency in POH includes bipotential progenitor cells that have the capacity to differentiate into adipocytes or osteoblasts, or an even more primitive mesenchymal stem cell population. Definitive identification of the muscle tissue target cell that responds to GNAS haploinsufficiency by differentiation into an osteogenic phenotype will facilitate cell-mediated targeting of therapies for POH.