Abstracts of the Conference

Memorial Lecture

SPEAKER: Dr Adnan Badwan

The Jordanian Association of Pharmaceutical Manufacturers

InNoVaTiOn

New era of Jordan Pharmaceutical Industry

The necessity of innovation in the new era of Jordanian Pharmaceutical Industry

Abstract

Innovation is the driving force for drug research and development in the new era of Jordanian Pharmaceutical Industry

Plenary Lecture

SPEAKER: Dr. Seetaraju Gembali

Senior Vice President – R&D, Hikma Pharmaceuticals, Amman – Jordan

Product Development and ANDA Strategy

Pharmaceutical product development forms the backbone of health care industry for developing a safe, efficacious, bioavailable, bioequivalent and stable product. This technology combined with the regulatory requirements of developed markets is a challenge to the drug industry.

Timely development of a product and submission to regulatory agencies and obtaining the regulatory approvals needs strategy plan and flow of events.

Setting up timelines at macro level then to micro level and involving different departments at different stages is very much essential as it is a team effort.

ANDA's (Abbreviated New Drug Application) is more challenging activity for Generic drug industry especially in case of para –IV certification and / or "First to file strategy" this can be achieved with strategic planning.

Artificial Lipoprotein for Drug and Gene Delivery

Mohannad Shawer, Robert Lu

Specialized Pharma (S.T.D) Amman-Jordan, and School of Pharmacy, Temple University, PA, USA

Several anticancer compounds that have shown excellent efficacy are known to have high incidence of toxicity. The main reason of such toxicity can be due to lack of targeting ability of the drug in the body where in doesn't discriminate between normal and cancer cells. The main focus of this research is to create a new-targeted drug/gene delivery system.

Low-density lipoprotein, LDL is known to carry cholesterol in the body and deliver it to cells via receptor-mediated endocytosis. Elevated LDL-receptor activity was reported in several cancer cells. Consequently, LDL has been identified as a potential drug carrier system for anticancer drug targeting to benefit from preferential delivery into cancer cells.

Due to the practical problems associated with loading drugs into LDL, we investigated the possibility of creating a surrogate system that resembles the native lipoproteins in its chemical and physical properties. We incorporated a cholesterol-based compound, BCH, in lipoprotein-resembling submicron emulsion and studied the physical properties of the formulation as well the drug uptake into cancer cells (9 L rat glioma, and SF-767 human glioblastoma multiforme).

The second component of the artificial lipoprotein system is a hydrophobized protein/polymer that will associate at the surface of the submicron emulsion. We investigated the ability of hydrophobized polylysine to associate with the emulsion particles and the ability of this polymer/lipid system to carry DNA.

Different targeting molecules can be associated with these emulsion particles to target different tissues depending on the hydrophobized protein/polymer used. We described a detailed method to carry protein hydrophobization with minimal denaturation of the protein.

In conclusion were we able to formulate a lipoprotein-resembling submicron emulsion. We've shown the ability of this system to solubilize water insoluble compound and to deliver the drug to cancer cells. We've also shown the potential application of the artificial lipoprotein system in gene delivery.

Nanoparticles Surface Engineering for Designing a Long-Circulating Specific Targeting system.

Abdul Kahlik Dardas, Tariq Al-Qadi, Othman Al-Hanbali*

**** Al-Zaytoonah Private University of Jordan***

This study constructed an adsorption isotherm for poloxamine-908 onto the surface of model polystyrene nanoparticles of 232 nm. The isotherm was bimodal. After an initial sharp increase, the isotherm breaks at 40 mg/m2, then begins to rise again and finally levels off around 250 mg/m2. All features of the isotherm have been confirmed by repeated experiments, the thickness of the coating layer was measured by photon correlation spectroscopy and further confirmed the presence of the two plateau's. The presence of the two plateau's suggest confirmation changes of PEO segment of copolymer on nanoparticles surface. This was further confirmed by measuring the apparent and complex viscosities of each polymer coated system. The SEM images taken for the nanoparticles at various points on adsorption isotherm showed different arrangements and staking effects, again depending on the concentration of poloxamine-908 added and hence, polymer conformation on nanoparticle surface. These studies collectively demonstrated that in the first plateau, ethylene oxide chains assume a flat conformation, whereas at the top plateau ethylene oxide chains are in a brush-like conformation. An intermediate flat-brush conformation was observable at polymer concentrations between the two plateau's.

On the basis of these findings it is possible to design and surface engineering of biodegradable nanoparticles for site-specific drug delivery.

The Effect of Colloidal Silicon Dioxide on the Rate of Dissolution of Some Drugs

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For solid formulations, drugs to be absorbed from gastrointestinal tract (GIT), should be first dissolved in the GIT fluids. When dissolution of drug is the slowest step, so it may consider as an absorption controlling step. Many additives are used to increase the dissolution rate of drugs in their preparations, e.g., PEG6000 as a solid dispersion, casein hydralsate, Calcium sulphate dihydrate and Lactose.

Colloidal Silicon Dioxide is a common substance when added to tablets it works as a hardener, glidant, disintegrator, partial separator and adsorbent, especially for liquid active substances. It is a light, fine, white, amorphous powder and has a particle size of about 15 nm. Practically insoluble in water and mineral acids except hydrofluoric acid but . Aerosol200 can adsorb several substances including water, gases, e.g, NO, solution, and solid materials like ovalbumin.

studying The effect of Colloidal Silicon Dioxide (Aerosil200) on the release of four more common used drug substances, two of them solids (Diazepam and hydrochlorothia-zide) and the other two liquids (Vitamin A and vitamin E) were investigated using fixed quantity of drug substance with 0.5 and 1.0 g of Colloidal Silicon Dioxide Gel.

After 60 minutes dissolution showed no effect on hydrochlorothiazide, increasing 4 fold for diazepam, and for Vitamins A and E from zero to about 34.8 and 41.4% respectively.

it is possible to use Aerosil200 to improve dissolution of some drugs while it has no significant effects on others, therefore, each single substance should be studied separately.

Intranasal Drug Delivery Systems: Nasal Absorption of Insulin in Rabbits using Pluronic F127 as a carrier.

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Specialized Pharma (STD) and Faculty of Pharmacy, University of Jordan, Amman, JORDAN.

Peptide and protein drugs are usually administered as injections which are associated with patient complains. To avoid such problems and improve patient compliance, non-invasive intranasal administration routes are considered as DDS for such drugs because of the relatively high permeability of the nasal epithelial membrane and avoidance of first-pass metabolism.

This study was carried out to examine Pluronic F 127, a triblock uncharged copolymers and a thermogelling non ionic surfactant as a carrier for intranasal insulin delivery that promotes its absorption. Eight rabbits were used as the in-vivo animal model . Insulin was administered to the nasal cavity through the nostrils in a dose of 1IU/Kg in Pluronic F127. Glucose blood level determined by a validated method was used for indirect evaluation of insulin absorption. Subcutaneous injection and intranasal insulin solution of the same dose were used as references. Control groups were designed along with test groups. Blood samples were withdrawn up to 5 hours. One week wash out period was applied . Intranasal insulin in 10% of Pluronic F127 solution was evaluated. Administration of Intranasal insulin in 3% HPMC was used to study the effect of viscosity. All the results were analyzed using MS-Excel software and ANOVA, NCSS for statistical analysis. For calculating the area under the curve (AUC), WinNonlin has been used.

When a highly viscous gel of 3% HPMC containing insulin was applied intranasaly, no significant response was observed. The HPMC polymer did not enhance insulin permeation; on the contrary it decreased its absorption due to its high viscosity. However, formulation containing Pluronic F127 promoted and enhanced insulin absorption. The absorption from 10% Pluronic F 127 formulation, depending on AUC values, was found to be significantly higher than from insulin solution and insulin in 3% HPMC formulation and significantly lower than insulin S.C ($P<0.05$). Subsequently 10% Pluronic F127 formulation was further investigated in the presence of different enhancers. Propylene glycol monolaurate 5%, Tea tree oil 1% and Oleic acid 3% were tested as enhancers for intranasal insulin absorption. The three enhancers were added separately, and their effect on the intranasal absorption of insulin was evaluated. Although Fatty acids and their esters are well known for their action as absorption enhancers, the results in this study showed that they did not enhance insulin absorption from nasal delivery system containing 10% P127, except oleic acid. Tea tree oil behaved differently and increased blood glucose level.

In conclusion Pluronic F 127 it self showed a good enhancing effect for insulin absorption from intranasal delivery which rendered it a candidate for further investigation and optimization.

A Novel Superdisintegrant Based on Chitosan as a Natural Polymer

Iyad Rashid, Mayyas Al-Remawi, Adnan Badwan

The Jordanian Pharmaceutical Manufacturing Company ***(JPM).***

Chitosan silica represents a challenging superdisintegrant in many pharmaceutical applications. The 'intimate' association between chitosan and silica, without no chemical reaction, creates an insoluble, hydrophilic, highly absorbent material. Consequently, resulting in superiority in water uptake, water saturation for gelling formation, and compactibility amongst other superdisintegrants. The new superdisintegrant has an outstanding functionality that does not depend on water wicking and swelling properties, in fact it translates it into superior disintegration characteristics that allows it to function as a pharmaceutical filler. Studies have shown that chitosan silica delivers superior performance in wet granulation formulations, and is the only distintegrant that is effective at all concentrations in tablet formulation.

Effect of Cyclodextrins on the solubility of Acidic Drugs

Dr. Ahmad Abdo

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Cyclodextrins (CD) including α-, β-, HP-β- and γ-CD enhances the solubility and bioavailability of acidic drugs including diclofenac, etodolac, ketorolac, meloxicam, piroxicam, and tenoxicam. The enhancement of solubility depends on several factors including: pH, ionic strength and cyclodextrin.

Results and discussion: complex formation constant reflects the strength of interaction between the drug and CD. The solubility of acidic drugs increased with CD concentration. Interaction of the drug and CD depends on several factors including: shape of the drug, dimensions of the drug, solubility of the drug, CD cavity size and pH. Increasing the pH decrease the interaction between the investigated drugs and the CDs due to the fact that neutral drugs interact strongly with the CD cavity while ionized drugs interact less. α-CD has the least complex formation constant(s) compared with other CD investigated because of its small cavity size. β-, HP-β- and γ-CD exchange roll in enhancing the solubility of the investigated drugs.

Complex formation constant does not necessary reflect the enhancement of solubility of the drug. Phase solubility has different shapes including A_L, A_P and B_S. In case of B_S, solubility decreases after certain concentration of CD. In formulation, attention should be considered for the shape of the phase solubility isotherm to make it at a concentration before descending.

Phase solubility isotherm shape may change by changing the pH of the solution, since the change of pH produce different species of drug thus a new way of interaction is obtained.

CDs increases the solubility of acidic drugs, while increasing the pH reduces the effect of CD on the enhancement of solubility. Increasing the ionic strength of the solution may enhance the overall solubility of the drug in the presence of CD.

Trouble Shootin in Pharmaceutical Film Coating

Dr. Derar Omari
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Film coating is a process that involves the deposition of a membrane, consisting of film former (polymer), plasticizer, colorant and other additives, onto the surface of a pharmaceutical dosage form, typically a tablet or a granule. The film coat is relatively thin (10-100µm). The process is not new since it is used in both paints and adhesive industries and technologies involved are getting more and more advanced. However, defects do occur in film coat and thus affect the release of drug from the dosage form and its therapeutic effect. In this presentation the most important defects commonly found in film coated tablets will be discussed with particular reference to their identification and possible solutions.

Film defects can generally be divided into 3 groups depending in the complexity of the solution:

GROUP 1: consists of defects that can be easily corrected by changing one or more of the process parameters eg. Temp., spray rate,..etc. This includes blistering, chipping, picking and pitting.

GROUP 2: consists of defects which can only be remedied by changing a combination of process conditions and film-coating formulations. Includes color variation, infilling, mottling and orange peel.

GROUP 3: consists of defects that require a more fundamental approach include changing the core formulation in addition to changes in the film formulation and process conditions. This group includes bridging, cracking/splitting and peeling.

Most of these defects are due to the internal stresses of the coated dosage form which are given in the following equation;

$$P = \frac{E}{3(1-\neg)}\left[\frac{\Phi s - \Phi r}{1-\Phi r} + \Delta \sim (cubic)\Delta T\right]$$

Where P is the overall internal stress in the film coat applied to tablet substrate, E is

$$\frac{\pm}{E} \leq \frac{1}{3(1-\neg)}\left[\frac{\Phi s - \Phi r}{1-\Phi r} + \Delta \sim (cubic)\Delta T\right]$$

Young's modulus of the film, ν is its Poisson's ratio which measures the relative ability of a material to deform in a direction at right angles to the tensile stress, Φs is the volume fraction of the solvent at the point where the liquid coating formulation first behaves like a solid, Φr is the volume fraction of solvent remaining in the dry film at ambient conditions, Δα is difference between the thermal expansion (volumetric or cubic) coefficient of the tablet and the coat, ΔT is the difference between the glass transition temperature of the coat and the ambient temperature. It was proposed that cracking in coated tablets will occur if P is greater than or equal to tensile strength (σ) of the film i.e., $P \geq \sigma$. By this, the equation can be rearranged to obtain the following relationship:

Thus σ/E serves as a measure of the level of internal stress in a film if the right hand of equation is assumed to be constant. The larger its value, the higher the crack resistance of a film.

Process Analytical Technologies

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Process Analytical Technologies (PAT) are techniques which are used in many industries including pharmaceutical industry and apply a broad range of systems. PAT is defined as "systems for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process" (Hussain, FDA 2002). This requires a coordination of multiple systems including process analytical chemistry tools, information management tools, feedback process control strategies, and strategies for product/process design and optimization.

PAT will become an important part of the pharmaceutical industry because PAT can improve efficiency and capability of pharmaceutical processes while verifying and improving product quality. The advantages that

the pharmaceutical industry gains by implementing PAT include reduced risk of scrap and recalls, improved process understanding with quality "by design", improved capacity utilization and reduced cycle times, and eventual reduction in product development time. The current methods to verify product quality, final product testing at the end of manufacturing and some process operation ranges, cause low manufacturing efficiency and require a very high level of regulatory scrutiny (Hussain, FDA 2002). For example, PAT allows for quick identification of out of the ordinary situations when the critical product properties are defined up front. Therefore, the time to respond to problems is greatly reduced and much time and cost can be saved. This presentation deals with a variety of process analytical techniques that could be used to monitor pharmaceutical processes to ensure the quality of the final dosage form.

On the proper choice of the internal standard for LC/MS/MS analysis

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LC/MS/MS technique has been employed within the last decade as the method of super sensitivity and selectivity for the determination of drugs in biological fluids. Although this appeared to be true in many cases, care should be taken in optimizing the operating conditions so that reliable results could be obtained. Based on our experience we report on cases of drug analysis in biological fluids (simvastatin) where it was necessary to use isotopically labeled internal standard in order to obtain reliable results that satisfy the FDA guidelines.

For simvastatin the method was based on liquid-liquid extraction followed by separation on a C18 analytical column. Simvastatin was monitored at m/z = 419.2 and daughter at m/z =199.2, while the simvastatin-d6 was monitored at m/z = 425.3 and daughter at m/z =199.3.

Satisfactory method performance (in accordance with the FDA guidelines) was obtained. Such performance was shown not achievable without the use of the labeled internal standards. This report further emphasizes the need for labeled internal standards in this kind of analysis.

Floating Drug delivery systems using Metronidazole as a model drug

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Gastric retentive dosage forms are highly useful for the delivery of many kinds of drugs. They would provide the best results for drugs that act locally in the stomach or those absorbed primarily from the stomach . The use of floating dosage forms (FDF) is one of the methods used to achieve prolonged gastric resident time . Formulation of Metronidazole (MDZ) as FDF provides an opportunity for both local and systemic drug action for eradication of H. Pylori which is a Gram-negative bacterium that is associated with gastric inflammation , peptic ulcer and gastric cancer . This study was undertaken in order to formulate effervescent single-unit and non-effervescent multiple-unit floating drug delivery system (FDDS) for Metronidazole . Multiple-unit systems FDF are thought to overcome the gastric emptying nature of the ordinary single-unit systems.

Floating property was accomplished by two distinctly different technologies; effervescent &

noneffervescent methods . In the effervescent method, a cardon dioxide generating agent; e.g. sodium bicarbonate, was incorporated in hydrophilic polymers matrix together with Metronidazole . Double ring-mesh modified apparatus II device was used in the dissolution study of the polymer matrix.

In the noneffervescent method, ionotropic gelation of sodium alginate in calcium chloride solution was utilized for the formulation of multiple-unit FDF of Metronidazole. Buoyancy was attributed to the use of olive oil held in the alginate gel beads matrix.

Different formulation parameters were studied in both methods and their effects on the floatation and in vitro drug release profiles were investigated.

Studying Factors Affecting Transformation of two polymorphic forms of Fluconazole

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The active ingredient as well as the excipient in solid dosage forms can undergo a variety of physical transformations. Such changes can be induced during pharmaceutical processing and storage and can affect pharmaceutically important properties such as solubility, stability, powder flow, tabletting behavior and dissolution rate which ultimately can cause variations in the performance of the product. In order to assure product uniformity; it became necessary to control the physical forms of the solid materials in the product.

The purposes of the present study were to study various factors that may affect polymorphic forms of fluconazole polymorph I and polymorph II. These factors include trituration, compression, relative humidity, seed effect, and solvent of crystallization.

Effect of mechanical force on transformation of fluconazole polymorph II was studied. Full transformation was obtained for polymorph II by manual trituration, and significant transformation occurred for the same polymorph during tabletting. On the other hand, polymorph I proved to be stable during compression.

Humidity effect on both polymorphs I and II was studied. Both polymorphs (I and II) transforms to monohydrate. But polymorph I proved to be more stable, and less susceptible to changes, as it required more time to transform than polymorph II.

Seed effect was studied. It was proved statistically that it has no effects on transformation kinetics.

Solvent of crystallization effect was studied. Statistically, there is a significant difference between samples kept in silica gel desiccator and samples kept in dichloromethane desiccator. The mechanism of transformation was expected to change from PT model to solvent mediated transformation.

Determination of the mechanism of uptake of organic vapors by chitoasn

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It was of interest to investigate the possible interactions that might occur between chitosan and various compounds of different polarities using solvent vapor sorption and Fourier Transform Infrared Spectroscopy (FTIR). The sorption system was composed of a gas inlet, a 2 meter gas cell and a gas outlet. The experimental setup allowed quantification of the free vapor and therefore the amount of the sorbed vapor by chitosan powder. The BET equation was applied to the experimental data to obtain the apparent monolayer sorption capacity (Sm) and the parameter C, which is related to the heat of interaction.

Results demonstrated that the surface areas obtained for chitosan from the BET analyses for heptane, 1,4-dioxane and methanol were 421, 379 and 58 m2/g respectively. These values were extremely higher than the value obtained from nitrogen vapor adsorption isotherm (4.56 m2/g). The difference is attributed to the partitioning of these compounds into the chitosan particles. The large difference in the Sm values between the nonpolar (heptane and 1,4-dioxane) and the semipolar compounds (methanol) also suggested that the polarity of the solvent might have a significant effect on the partitioning of the these compounds into the chitosan particles. The results obtained from this study also confirmed what was previously described regarding the ability of chitosan to act as a “fat magnet” or a “fat sponge”.

Enhancing effect of oleic acid on lidocaine hydrochloride permeability across buccal mucosa

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The aim of this study was to evaluate the effect of oleic acid as a penetration enhancer on mucoadhesive buccal lidocaine hydrochloride patches permeability across porcine buccal mucosa.

Various multilayered medicated buccal patches were developed using carbopol 971P as a mucoadhesive polymer, ethylene vinyl acetate (EVA) as a backing layer, oleic acid as a penetration enhancer and lidocaine hydrochloride as a model drug. In vitro permeation studies were conducted at 37 ± 1 oC using the Franz cells. Saline phosphate buffer of pH 7 was used as a receptor medium. Drug permeated was analysed using HPLC. The cumulative amount of drug permeating (Q) through a unit surface area of mucosal tissue (g/cm2) was plotted versus time, and the flux (J) was calculated from the slope of the linear (steady state) part of the line obtained. The slope was calculated using linear regression analysis of the data. Lag time was obtained by extrapolating the steady state lines to the time axis.

The same permeation profile was obtained for all types of patches, with a progressive decrease in the lag time, which was the least when 1% w/v oleic acid was used. The lag times before the appearance of lidocaine hydrochloride in the receptor cell for the tested patches were < 2 hours.

All prepared patches significantly prolonged the permeation of lidocaine hydrochloride through porcine buccal tissue as compared with a control solution. The steady state fluxes for the patches containing oleic acid as penetration enhancer were significantly ($P<0.05$) higher than those patches prepared without penetration enhancer (standard patch).

Results showed that oleic acid was found to exert a marked permeability effect across porcine buccal mucosa for lidocaine hydrochloride.

Plenary Lecture

SPEAKER: Pharm. Lara M. Abbasi

Pharmacy 1 International

Modern trends in Retail Pharmacy

The traditional image of a pharmacist is changing rapidly, it is shifting from the traditional image as someone who only dispenses medications in a community setting to a more dynamic, patient oriented professionals committed to fulfilling the health care needs of their patients.

The public appreciates the value of medications, but they do not understand the role of the community pharmacist in helping to maximize the safe and effective benefits of their medications.

Although pharmacists do not have the most visible job in health care they can play a critical element to the delivery of quality patient care.

No matter what is the size of the pharmacy, the location or sales volume the new trends will prove to be useful.

The days of "product dispensing" are over. Pharmaceutical care enhances the professionalism of the pharmacy practice as well as improves the patients' overall health care.

Plenary Lecture

SPEAKER: Dr. Seetaraju Gembali

Senior Vice President – R&D, Hikma Pharmaceuticals, Amman – Jordan

Bioequivalence and Dissolution Requirements for Generic Market

The success of any generic product is based on its equivalence with the available branded product / originator product. Especially the solid dosage forms are more critical as far as bioequivalence is concerned due to its complexcity of formulation and different stages / steps of process involved.

Designing a suitable discriminative dissolution testing method is an art of scientist. The level of confidence in success of Bioequivalence is based on in-vitro dissolution data. Thus dissolution testing is a boon to Generic industry as BE study is most expensive component in the Generic product development.

Dissolution testing not only helping in increasing confidence levels for success of in-vivo performance but also helps the regulatory authorities to grant the bio-waiver based on in-vitro dissolution data in different media.

OTC Presentation

Pharm. Sohila Batarseh,

JFDA.

*** Definitions:**

- Self - Care

-Self - Medication

*** Role of the physician:**

Why physicians must be familiar with OTC medications ?

***Role of pharmacist:**

Advising patients on self treatment (Community Pharmacist)

*Factors that influence individual attitudes , values and practices relative to self care .

-Attitudes / Beliefs

-Demographics

-Economics

-Education /Knowledge

*Misuse & Abuse of OTC medicines.

*Labeling & Packaging Issues .

*Decision of free pricing .

*Risks & Benefits of free pricing of OTC medicines .

Jordan commitment and application of patent law and data protection law

Ph . Hakimah Hoseh

Head of registration unit, registration department, JFDA

My talk will give an idea about the implementation of the patent law and data protection law in the field of registration drugs by the Jordanian food and drug administration JFDA.

Jordan is a WTO (World Trade Organization) member since 1999, and as a result several laws and regulations have been issued as:

-the Patent law no 32 issued in 1999,

And Data protection and Trade secrets no 15 issued in 2000.

Jordan also has singed several agreements as FTA (Free Trade Agreement)and PCT(Patent Cooperation Treaty) agreements and as a result more commitments are implemented regarding drugs as given three years data protection for the second use of a medicine .

As a result JFDA worked to issue several laws regarding drug registration which include articles regarding data protection and patency.

Still more regulations are updated and more criteria's are under updationg .

A NEW ERA IN PHARMACY ACCESS

Pharm. Nidaa Bawaresh

Jordan Pharmacovigilance Center -Head of /Jordan Pharmacovigilance Center (JPC)

No medicine is 100 percent safe for all people in all circumstances

Pharmacovigilance Is the science & activities relating to the detection , assessment , understanding & prevention of adverse effects or any other drug related problems. Why do we need pharmacovigilance in Jordan?

- Patients
- New molecular entities drugs
- Studies
- Internet access
- Fast registration system
- Established :2001 (training & software)
- Promotional campaign : June 2001
- Membership: 2002 (Spontaneous Reports) JPC committee: 2003
- ADRs guideline Primary draft : 2003
- Widespread internal responsibilities: 2005
- Membership in WHO Vigibase- online system: 2005

Pharmac-ovigilance
and The Role of The Pharmacists

Pharmacist Nancy Ghabboun

Head of Administrative Quality Department in the Quality Directorate in the Ministry of Health

- Definition of Pharmacovigilance(PV, PhV).
- Why do we need PV?
- History of PV.
- Development of PV Internationally and locally.
- Pharmacovigilance In Jordan:
  - Pharmacovigilance Regulations
  - Pharmacovigilance Center
- Primary Method in PV.
  - Spontaneous Reporting System
  - -Signal
- Main Stakeholder in SRS
- Who are Health Professionals Responsible for Reporting ADRs?
- Hallmarks for an effective spontaneous reporting system (SRS):
- What are you supposed to report to JPC?
- Spontaneous Report Form
  - -How to fill it?
- Processing of the SRs in the JPC.
- Role of the pharmacist in SRS internationally and locally.
- Importance of the pharmacist's role in SRS.
- Practical requirements enabling pharmacist's ADR reporting
- International and local PV Cases.
- Example for Drug safety issues.

The Clinical Trial Unit (CTU)

Wafa Al-Khateeb, M.Sc.

Jordan Food & Drug Administration (FDA) , Clinical Pharmacy, Head of CTU-JFDA

The Hashemite kingdom of Jordan is considered one of the pioneers in the field of clinical trials as it is the only country in the region that has a law for the clinical trials which is Law of Clinical Studies, Provisional Law No. (67) For the year 2001

As the safety and wellbeing of the participants in the clinical studies being held in Jordan are the two major considerations of the Jordan Food and Drug Administration, the Clinical Trials Unit was established within the JDFA in August 2004.

A committee is formed at the administration called (clinical studies committee) and chaired by the Director General and the membership of specialists from the JFDA, the Director of pharmacy at the Royal Medical Services and five persons representing universities and private sector who are specialized in the field of kinetic, analytical pharmacy, biostatistics, clinical pharmacy, pharmacology.

Clinical studies are in general divided into:

a) Therapeutic clinical studies: Any clinical study performed on sick or healthy volunteers.

b) Non-Therapeutic clinical studies: Any study performed on healthy volunteers in terms of effectiveness, kinetics, bioavailability and bioequivalence. Clinical studies shall not be performed on human beings unless by his written approval (signed consent form) and after undergoing the medical tests necessary for his/her safety.

Clinical studies shall not be conducted unless the conducting authority has obtained an authorization from the Minister upon a recommendation from the Clinical Studies Committee. They include public and private hospitals, which possess technical potential to provide the required emergency and intensive care in addition to laboratory that caries out clinical tests. University academic institutions, specialized scientific research institutions and pharmaceutical manufacturing companies, which have the required technical potentials, are also included.

Another committee is formed within the conducting authority called (The Institutional Review Board Committee) consisting of at least five members from both sexes with enough experience and quite competent provided that one of them should be legal advisor in addition to a representative from local community.

Both the Clinical Studies Committee and Unit in the JFDA assume certain responsibilities and powers.

Role_of_Dispenser_in_Promoting_Rational_Drug_Use

Pharm. Adi Nuseirat

JFDA.

Medically inappropriate, ineffective, and economically inefficient use of drugs is commonly observed in the health care system throughout the world. The need for promoting appropriate use of drugs in the health care system is not only because of the financial reasons with which policy makers and managers are usually most concerned, it is also one essential element in achieving quality of health and medical care for patients and the community. Obviously, this should also become the concern of practitioners. Actions or intervention programs to promote the appropriate use of drugs should, therefore, be continuously implemented and systematically incorporated as an integral part of the health care system. There are many different factors which affect the irrational use of drugs. In addition, different cultures view drugs in different ways, and this can affect the way drugs are used. The major forces can be categorized as those deriving from patients, prescribers, dispensers, the workplace, the supply system including industry influences, regulation, drug information and misinformation, and combinations of these factors. The impact of this irrational use of drugs can be seen in many ways: Reduction in the quality of drug therapy leading to increased morbidity and mortality, Waste of resources leading to reduced availability of other vital drugs and increased costs, Increased risk of unwanted affects such as adverse drug reactions and the emergence of drug resistance. Pharmacists (Dispensers) are the final link between the medication and the patient and they must aware the importance of implementing rational drug use.

Pharmaceutical and medical Information management

Pharm. Amnah Samara

The Jordanian Pharmaceutical Manufacturing Company (JPM).

Research programs require and produce huge volume of data and information.

Information is regarded as a reserve. More specifically it is the fourth source that maybe possessed by organization beside material, human & financial, this is why Information is knowledge-based industry. The flow of information and management of knowledge are critical at all areas and levels from the initial drug discovery through drug development and product launch and finally to post marketing support.

One of the most important roles and activities of Information Departments in pharmaceutical companies, which is, providing information and the new advances and technologies in pharmaceutical information management science will be discussed.

In addition an overview of the Jordanian pharmaceutical industry sector will be introduced.

Bioequivalence Study of Two Formulations of Amlodipine Capsules in Healthy Volunteers

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The bioequivalence of a single dose of Lowrac Capsule containing 5 mg Amlodipine (JPM, Jordan) as a test product in comparison to Norvasc® 5 mg Capsule (PFIZER S.A., Belgium) as the reference product was studied. Both products were administered to Twenty eight (28) healthy male adult volunteers applying a fasting, single-dose, two-treatment, two-period, two-sequence, randomized crossover design with two week washout interval between the two periods. Twenty (20) blood samples were withdrawn from each volunteer over 144 hours period. A highly sensitive and specific LC/MS/MS method was developed and validated for the measurement of Amlodipine concentrations in plasma with a lower limit of quantitation of 0.1 ng/ml. From the plasma concentration-time data of each individual, the pharmacokinetic parameters; Cmax, Tmax, AUC0-t, AUC0-∞, Cmax/AUC0-∞ , λZ, T0.5, MRT, Cl/F and Vd/F; were calculated applying non-compartmental analysis. The pharmacokinetic parameters mentioned above were statistically analyzed by ANOVA test. Ln transformed values of the pharmacokinetic parameters; Cmax, AUC0-t and AUC0-∞ ; were also statistically analyzed by ANOVA, 90% Confidence Interval (CI) and Schuirmann's two one-sided t-tests. For the Tmax, the parametric point estimate of the difference between the mean values of the Lowrac and Norvasc Capsules was measured. Based on FDA criteria for bioequivalence the results of the above statistical tests demonstrated bioequivalence of the two products. The analytical method described in this study was found to be simple, rapid and robust and enables the determination of Amlodipine for pharmacokinetic and bioequivalence studies

Effect of intravenous administration of ondansetron hydrochloride plus dexamethasone in the prevention of cisplatin induced nausea and vomiting in patients with ovarian cancer

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Royal Medical Services (RMS), Jordan University of Science and Technology (JUST)

This study compares the efficacy and safety of three different I.V. dosage regimens of ondansetron (8 mg , 16 mg, and 24 mg) plus dexamethasone 20 mg in prevention of cisplatin-induced nausea and vomiting in patients with ovarian cancer.

A total of 45 patients were entered the study. Chemotherapy-naïve inpatients receiving high dose cisplatin (75 mg/m2) were randomized to receive ondansetron 8 mg plus dexamethasone 20 mg, ondansetron 16 mg plus dexamethasone 20 mg or ondansetron 24 mg plus dexamethasone 20 mg, given intravenously as a single dose 30 minutes before cisplatin administration. Cisplatin was given as a single infusion (≤ 3 hours). Patients were monitored for emetic episodes, adverse events, and laboratory safety parameters for 24 hours after cisplatin administration.

A total of 45 patients were entered the study. A single 16 mg dose of I.V. ondansetron hydrochloride plus dexamethasone 20 mg I.V. 30 minutes before chemotherapy was superior to the 8 mg single dose of I.V. ondansetron plus 20 mg I.V of dexamethasone, in preventing emesis (66.67% v 40%). Moreover, a single 16 mg dose of I.V. ondansetron hydrochloride plus dexamethasone 20 mg I.V. 30 minutes before chemotherapy is was superior to the 24 mg single dose of I.V. ondansetron plus 20 mg I.V of dexamethasone, in preventing emesis (66.67% v 46.67%). Ondansetron was well tolerated. The most common adverse event was headache.

Conclusion: A 16 mg single dose of ondansetron is more effective than a single 8 mg, 24 mg dose in the prevention of cisplatin induced acute emesis.

Effective Procurement Strategies to enhance efficient drug supply management, an international and Jordanian Prospective

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Drugs play a vital role in any health system, therefore, they have to be available at all times and be accessible to all the population. Drugs are also expensive and account for one third to two thirds of the total expenditures for health.Therefore demonstrating the effective procurement strategies hopefully will help in improving the currently practiced practices to make better use of the available resources and ensure that the necessary drugs are available at an affordable price at the right time and in the right place.

To describe and evaluate the drug management system and in particular the procurement strategies practiced in the ministry of health public sectors and perhaps to provide suggestions for its improvement.

To show that Jordan is in constant move towards achieving better health for all by improving the current health situations, improving the drug supply and by doing so insuring the availability, affordability, low cost but high quality drugs to the patients.

To learn lessons from a different system of pharmaceutical procurement used in a developed country as an example and so find out the weakness of the current procurement strategy in Jordan, and how to improve the availability and quality of drugs.

A comparative study was conducted between the procurement strategies practiced in some of Jordan's public health sectors and the procurement strategy practiced in the United Kingdom National health Services.

It can be said that currently practiced systems are not as efficient and effective as needed because they contain lengthy procedures with many committees involved and often have inadequate financing, which leads to delays in delivery and unnecessary complications.

The procurement step in the managing drug supply cycle of the mentioned organizations is conducted through tenders, including evaluation, classification of bids, and selection of the best bid based on specified criteria. The type of procurement method used greatly influence how much competition there is among potential suppliers and therefore affects the drug price and influence the total costs.

For the new joint procurement program in Jordan, it will be very early to predict its destiny since it is still a newborn project and only with time can we study and judge the outcome results of the new system.

Asthma Best Practice Selfmanagement Models in Australia

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The workshop aims to critically appraise different models of asthma care delivery in Australia. Four evidence-based asthma self-management (ASM) models involving collaboration between Asthma Educator's, General Practitioner's (GPs), and patients will be explored. The participants will be encouraged to contribute in identifying, analysing and discussing the major elements of the best practice models of self-management education for people with asthma and the feasibility of implementing best practice in developing countries

The workshop will start with short presentation of each of the models, followed by facilitated discussion: The projects are (1) Asthma Best Practice Model- An Asthma Educator run clinic at the Emergency Department (ED) or GP clinics providing ASM education to patients and providing recommendations of best practice to their nominated GP's. In collaboration with The Northern Hospital, Department of General Practice (DGP) - The University of Melbourne, Northern and North West Melbourne divisions of GP and Dianella Community Health Service; (2) Community Asthma Project - Asthma educators and community development staff visiting children with asthma and their families at their homes, engaging schools and community in ASM.

The project runs with Royal Children's Hospital in partnership with Dianella CHS, Doutta Galla CHC, Moonee Ponds PCP and Melbourne & NWM divisions of GP, (3) Western HARP Consortium Chronic Disease Management Program Asthma Project – A partnership of tertiary, primary and community health services in the western metropolitan regions of Melbourne have developed an innovative program to assist with the management of patients with paediatric asthma. This project targets frequent presenters at the emergency department of Sunshine Hospital through care planning and asthma education across the acute/community continuum; and (4) Whitehorse Division of GP's model of Asthma Educator run asthma clinics at general practices, with a project officer engaging GPs to identify patients eligible for "3+ Visit" Plans.

The results of each project will be presented and the practical significance will be highlighted for discussion.

Each of the above projects will be analysed to identify areas of strengths and weaknesses. This workshop will discuss the development of a best model of intervention as a result of this process of informed discussion and analysis of existing programs. The feasibility of a "best model" in different environments, including barriers and facilitators of the proposed model would be discussed.

Breath with ease: an interactive asthma CD for GPs and trainees

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The purpose of the project is to create an evidence-based, user-friendly and convenient CD-ROM for GPs, health professionals and trainees on asthma diagnosis and management in primary care setting. The CD integrates basic and clinical features of asthma. It incorporates learning loops with various levels of complexity, high levels of interactivity, self-assessment and clinical skills. The package provides learning opportunities to meet the variation in pace for the individual GP or trainee.

The tool was developed by a team of experts in educational technologies and asthma at the University of Melbourne and Monash University. The asthma CD starts with overview on asthma and its burden in Australia. The package is based on four case studies, demonstrating asthma in 4, 14, 22 and 67 year old patients with varying degrees of asthma severity. The latter case explains the overlap between asthma and chronic obstructive pulmonary disease (COPD). The case studies are enhanced by professional videos on asthma medication devices, techniques and asthma adherence; guidelines for asthma and COPD diagnosis and management; graphs demonstrating lung function tests; a glossary of asthma terms; and animations on clinical and patho-physiology of asthma. The animations can be used for patient education and engagement and health professionals' self-learning.

All the functionalities of the package will be demonstrated to the audience, including case studies, animations, lung function graphs and videos on medication devices, techniques and adherence.

Evaluation forms will be distributed to stimulate and engage the audience and to give feedback during and after the presentation.

Level of knowledge and health behavior of Jordanian diabetic patients in relation to gender differences

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Aiming to investigate the health behavior of diabetics in Jordan, a questionnaire was designed and distributed to a sample of the Jordanian population. The main points investigated were the habits implemented by the patients, their level of knowledge about the disease and the follow up the self-care procedures that should be used to reduce the complications of the disease or to monitor its progression, all in relation to their gender and level of education. A total number of 1525 diabetic patients (834 males and 691 females) participated in our study. Results indicated a poor level of knowledge of diabetic patients in Jordan in both genders and the highest awareness of more than 80% appeared in only three behaviors; keeping regular monitoring of blood sugar level, taking the diabetic medication as prescribed, and using home monitoring blood sugar device effectively.

Intranasal Desmopressin in the Treatment of Acute Renal Colic in Iraqi Patients

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There is a suggestion that an antidiuretic hormone-induced decrease in diuresis might contribute to the rapid relief of the acute pain in renal colic. This study was designed to evaluate the efficacy of desmopressin nasal spray compared with diclofenac given intramuscularly in patients with acute renal colic. The study included 75 patients randomized into three different groups; group A received desmopressin (40 μg, nasal spray), group B diclofenac (75 mg) intramuscularly and group C, both desmopressin and diclofenac. Pain was assessed using a visual analogue scale (a 10-cm horizontal scale ranging from `no pain' to `unbearable pain') at baseline, 10, 20 and 30 min after administering the treatments. On admission, the pain level was the same in all three groups. At 10 min the pain decreased in all groups to a level that was not significantly different. At 20 min groups B and C had similar mean pain levels (5.8), whereas in group A it was 5.7. At 30 min, groups B and C scored 3.0 and 2.5 respectively, and group A 6.1. All three treatments were equally effective at 10 and 20 min but at 30 min there was a stabilization/slight increase in pain level in group A. In conclusion, these results indicate that desmopressin may be used to treat renal colic either alone or combined, increasing the analgesic effect of other drugs like diclofenac

Non steroidal anti-inflammatory drugs

Pharm. Sawsan Khalid Jabateh

Jordanian Ministry of Health

(NSAIDs) are among the most commonly used pharmacological agent. When pain, fever, or inflammation is present NSAIDs and aspirin are often the drugs of choice, and their usefulness extends across a wide range of clinical conditions .

The NSAIDs exert their anti inflammatory effect by inhibition of the enzyme Cyclooxygenase (COX) , this mechanism is the basis for their therapeutic effect as well as their toxicity . Some of them are widely available both by prescription and over the counter , they are frequently used home remedy as pain killer for muscular aches , dysmenorrhea , and other related pain. As a result , people tend to underestimate their effectiveness . So this study is performed to assess the patient's knowledge of his illness, familiarity with non steroidal anti-inflammatory drugs (NSAID) and the common side effects of this group of drugs , as well as the frequency of the use of these drugs .

NSAIDs are probably safe in therapeutic doses as an analgesic and anti-pyretic, however , old adults have a high incidence of inflammatory -musculuskeletal disorder and NSAIDs are often prescribed. Long term use of the relatively high dose of NSAIDs , increase the risk of serious G.I. upset and bleeding . The objective of this study is to assess the patient's knowledge of his illness , his knowledge familiarity with NSAID medications and their side effects and thereupon , to evaluate the awareness, utilization , satisfaction and expectations associated with current available treatment . The second object of this study is to assess the prevalence use, and prescriptions size of this group of drugs among the patients and the physician respectively . The area of research , include patients and physicians in the hospitals belongs to Jordan M.O.H, VS patients and physicians in Jordan university hospital . The patients age group was ranged from (20 to 75) years old , the patients with complex co morbid diseases were excluded from the study .

A suggestion for the New Clinical applications for Taurine and Bromocriptine

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Our previous work has shown that high plasma taurine levels were found in hyperprolactinaemic patients; these levels returned to normal after bromocriptine (dopaminergic agonist, D2) treatment for three months. Furthermore we reported that bromocriptine decreased the myometrial PGI2 release in rats; whereas taurine increased the content of the myometrial PGI2 concomitant with the content of the mymetrum TXA2 in the rats as indicated in their metabolites. It was suggested that the activity of Na (+)-K (+)-ATPase could modulate the production of PGs in several tissues. Bromocriptine is shown to stimulate Na + /K + -ATPase in the liver of rats, meanwhile taurine inhibits sperm plasma membrane Na + /K+-ATPase. It is therefore, thought of interest to investigate the effect of bromocriptine, taurine or their combination on the isolated rabbit jejunum and on the rat uterus in vitro and their effect on the activety of Na (+)-K (+)-ATPase in the uterus was also examined in vivo. Methods, the effect of bromocriptine on the isolated tissues and after pretreatment of the tissue with sulpiride, haloperidol, cyproheptadine or taurine were studied in vitro. Rabbit jejunum and rat uterus (in estrus) were obtained by the usual methods and suspended at 37°C in oxygenated Tyrode's and DeJahlon's solutions respectively. Isotonic contractions were measured using Bioscience Isotonic Transducers. In Vivo treatment was also carried out to study the effects of bromocriptine mesylate 10mg/kg, taurine 200 mg/kg; or bromocriptine mesylate 10mg/kg + taurine 200 mg/kg, compared to a control group, in order to measure uterine Na+, K+-ATPase activity . The drugs were injected intraperitoneally daily for 14 days. Results, Bromocriptine 0.1 - 0.26 mM stimulated the isolated rabbit jejunum and the rat uterus. Sulpiride and haloperidol failed to antagonize the induced contractions. The latter were abolished by pretreating the tissues with cyproheptadine or taurine. Na+,K+-ATPase activity ATPase from rats uterus, pretreated with bromocriptine, showed significantly ($P < 0.01$) higher activity compared to controls. Taurine, on the other hand, caused a significant inhibition of the uterus Na + / K + -ATPase activity. Pretreatment with both taurine and bromocriptine abolished completely the effects of either bromocriptine or taurine alone on the uterus Na +/ K + -ATPase activity.

In conclusion, Activation of serotonergic receptors may underlie the appearance of some side effects such as hallucinations observed in Parkinson's disease patients ingesting large doses of bromocriptine. Furthermore, on a wider basis, these results showed that bromocriptine and taurine were acting by clearly antagonistic mechanisms in the uterus in vivo and in vitro. The ability of taurine to inhibit uterine Na+, K+-ATPase activity, together with the role of taurine its role as an endogenous regulator of PGs, and with the suggestion of the activity of Na (+)-K(+)-ATPase modulates the production of PGs in several tissues, point to the functional correlations between taurine, PGs and K+-ATPase activity in the uterus. Thus, the result of the present study gives strong evidence for physiological and pharmacological roles of taurine in protection and implantation of embryo in different clinical fields. Therefore, on the base of these results of the present study, Bromocriptine could be used as postcoital contraceptive where taurine could be clinically used for protection and implantation the embryo especially in vitro fertilization.

Azathioprine induced pancreatitis

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Royal Medical Services (RMS)

Drug include acute pancreatitis is a rare but often lethal complication. Azathioprine is one of the incriminated agents out of multiple possible etiological factors .We present a case of 18 years old male patient. Known case of crescent glomerulonephritis and acute pancreatitis developed with azathioprine .

Oral Zinc Supplementation In pregnant women and its effect on birth weight

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A prospective, randomized study was carried out on pregnant women to evaluate the effects of oral zinc supplementation on the weight of newborns. No significant difference was found in the birth weights between the cases supplemented with 20 mg elemental zinc and controls receiving oral placebo ($p=0.57$).

Melatonin and Zinc in Improve Glycemic Control by Exogenous Insulin in Type 1 Diabetes Mellitus

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Many in vitro and experimental animal studies indicated that melatonin has an important role in regulation of blood glucose level through a modulating effect on insulin secretion and receptor interaction in peripheral tissues. No clinical data on the pharmacological use of this supplement in this respect were available to support its therapeutic role in diabetes mellitus.

This study was designed to evaluate the effect of adjuvant use of melatonin and zinc acetate to improve the glycemic control in type 1 diabetes mellitus patients poorly controlled with exogenous insulin.

This randomized, placebo controlled, double blinded clinical study was carried on 50 patients with type 1 diabetes mellitus with mild response to insulin treatment, they are allocated into three groups. Group A treated with a combination of 10mg melatonin and 50mg zinc acetate, group B treated with 50mg zinc acetate only and group C treated with placebo. All treatment formulas administered orally at bedtime for 90 days during which fasting serum glucose, glycated hemoglobin and C-peptide levels were evaluated before starting treatment and each 30 days during treatment.

Treatment of DM patients with melatonin and zinc improves glycemic control in the fasting and post-prandial state with significant reduction in HbA1c and elevation of insulin secretion.

Adjuvant use of a combination of melatonin and zinc improves the responsiveness of insulin-sensitive tissues to the exogenously administrated insulin doses in type 1 diabetic patients, an effect not related to the increase in residual β-cell functions.

Effects of Treatment with Zinc Sulphate on the Oxidative Stress State during Chronic Exposure to Lead in Humans

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Oxidative stress has been recently implicated in the pathogenesis of lead poisoning. Consequently, the potential protective effects of antioxidant agents had been raised. This study was designed to explore the potential protective effects of zinc against the oxidative stress due to chronic exposure to lead Lead-exposed workers were treated with 100mg zinc sulphate / day for 2 months, and the extent of oxidative stress was evaluated by measuring of erythrocytes and plasma content of GSH and MDA, in addition the Cu, Zn and Pb blood level were measured also. The results of this study showed that treatment with zinc sulphate significantly lowered MDA production and increased glutathione levels in plasma and erythrocytes. Blood lead levels, which were elevated significantly due to chronic exposure, showed a reproducible reduction after treatment with zinc sulphate, associated with improvement in copper and zinc levels in the plasma of lead workers. In conclusion, daily supplementation with zinc as antioxidant to lead exposed workers seems to be beneficial in the prevention of oxidative stress associated with chronic exposure.

Protective Effects of Benfotiamine in the Experimentally-induced Nephrotoxicity with Cisplatin in Rabbits

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Cell death is the component of many response patterns of living tissues to xenobiotics including cytotoxic drugs, and one of the possible ways to ameliorate this response is through interference with the process of apoptosis which can be fulfilled by many candidate substances like benfotiamine.

This study was designed to evaluate the possible cytoprotective effect of orally administered benfotiamine against cisplatin -induced nephrotoxicity in rabbits. Twenty adult rabbits are used in this study and allocated into 4 groups; treated as follow: Saline treated as controls, cisplatin (2.5mg/kg) treated group; benfotiamine (70mg/kg) seven days before and during cisplatin treatment and thiamine (70mg/kg) treated rabbits. At the end of treatment all animals are sacrificed, serum and kidney tissue homogenate are prepared for the assay of urea, creatinine, uric acid and thiamine in the serum; malondialdehyde (MDA), glutathione (GSH) and thiamine levels in kidney tissue homogenate. Kidney tissue sections are prepared for histological examination.

Benfotiamine treatment resulted in ameliorating the nephrotoxicity induced by cisplatin as evidenced by lowering serum urea and creatinine levels, while uric acid was not affected. Concerning the effect on oxidative stress parameters; MDA levels in tissue homogenate were significantly reduced while GSH levels not improved significantly. Histological evidences supported the biochemical parameters which indicate nephroprotective effect of Benfotiamine. The orally administered prodrug elevates thiamine levels in kidney tissue homogenate many fold greater than those produced by conventional thiamine. According to the results obtained in this study one can conclude that benfotiamine has the ability, through a mechanism not related to direct antioxidant property, to provide cytoprotective effects against drug-induced nephrotoxicity; and might be a good candidate to be tried experimentally and clinically in this respect.

High-throughput screening of natural products

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Despite competition from other drug discovery methods, natural products are still providing their fare share of new clinical candidates and drugs. Natural sources offer a wealth of chemically diverse compounds that have been evolutionary preselected to modulate biochemical pathways. Several industrial and academic groups are accessing this source using advanced technology platforms. Methods have been reported to generate large and diverse natural-product libraries optimised for high-throughput screening and for a fast discovery process. The use of hyphenated techniques such as LC/MS and LC/NMR quickly provides plenty of structural information, leading to an on-line structure determination of a variety of interesting compounds. Moreover, biological activity of natural compounds can be studied through the screening of biological target interactions involved in diseases such as cancer, inflammation, and viral infections.1,2

This high-throughput screening was performed using biological assay formats, such as the enzyme-linked immunoadsorbent assay (ELISA). Two proteins (VEGF3 and PlGF4) involved in the angiogenesis process were selected. Besides, the saturation-transfer NMR (STD-NMR) spectroscopy was used to characterize binding in tightly bound ligand-receptor complex.5 When a protein becomes saturated, ligands that are in exchange between a bound and the free form become saturated when bound to the protein. Subtracting a spectrum in which the protein is saturated from one without protein saturation produces a difference spectrum in which only the signals of the ligand (s) remain. Helix Bundle Protein involved in the HIV virus replication process was selected for this experiment.

A lot of compounds belonging to different classes of natural products (terpenes, phenolics, alkaloids) were tested. Only some phenolics, such as quercetin, apigenin, and isocorilagin showed to link to the VEGF and PlGF proteins. On the other hand, a class of sesterterpenes isolated from Salvia ssp., having a lactone residue, showed to link Helix Bundle Protein.

Antiandrogenic efficacy of *curcuma longa* (50% EtOH extract) with special emphasis on testicular cell population dynamics.

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The objective of this study the effect of *Curcuma longa* (50% EtOH) extract on fertility parameter on albino rats.

Plant extract was orally administered to the rats at dose 500mg /kg body weight/ day for 60 days.

Long-term ingestion of *Curcuma longa* (50% EtOH) for 60 days caused a great decrease in spermatogenesis in seminiferous tubules of the testes. Sperm motility and density were also significantly reduced in cauda epididymides and testes of the treated group. The weights of reproductive organs (testes, epididymides, ventral prostrate and seminal vesicle) were decreased considerably. The hormonal assay also showed significant decrease in testosterone levels. Testicular cell population dynamics also demonstrated a decrease in the number of both primary and secondary spermatocytes and spermatids in the treatment group. The number of female rats impregnated by male rats on long-term *Curcuma longa* (50% EtOH) diet had decreased. The number of implantations and the number of viable fetuses were also notably decreased in female rats impregnated by male rats ingested *Curcuma longa* (50% EtOH). Histometery of reproductive organs confirmed these results.

The aqueous extracts of *Curcuma longa* might have adverse effects on fertility parameter on albino rats.

A new method for isolation and purification of trigonelline from Trigonella-foenum graecum (fenugreek seeds)

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Fenugreek seeds (Trigonella-foenum graecum), F. Fabiaceae, contain some alkaloids such as trigonelline and choline, both are quaternary ammonium alkaloids. Using the classical methods for isolation of one of these alkaloids, the extract will contain both trigonelline and choline which have similar physicochemical properties such as a high polarity and high water solubility. Moreover, both alkaloids are sparingly soluble in non-polar organic solvents such as chloroform or acetone. In this study, trigonelline has been isolated with traces of choline and a new subsequent processes have been carried out for further purification before the use of preparative TLC.

Antibacterial activity of the Iraqi Rheum ribes root

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The antibacterial activity of the total ethanolic (TE), aqueous (AE) and organic (CE, CE2) extracts from the root of Rheum ribes was examined. Four anthraquinone aglycone components chrysopahnol, physcion, aloe emodin and emodin were isolated from the biologically active extract (CE2) and identified by spectroscopic analysis, the later compound is the first time recorded in this species. The bioactive MIC values of CE, CE2, emodin and aloe emodin were 500, 125, 500 and 125 5g/ml against Staphylococcus aureus, respectively. The extracts and compounds did not inhibit Pseudomonous aeruginosa and Escherichia coli at the highest concentration 4000 and 500 5g/ml, tested, respectively.

I. Hybridizing Pharmacophore and QSAR Modeling as a Method for Binding Site Flexibility Assessment: fXa as a Case Study.

II. Interesting Findings from In Silico Screening of A Catalyst-Based East-Mediterranean Natural Products 3D Database

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Part 1: The flexibility of activated factor X (fXa) binding site was assessed employing ligand-based pharmacophor modeling combined with genetic algorithm-based QSAR modeling. Four training subsets of wide structural diversity were selected from a total of 199 direct fXa inhibitors and were employed to generate different fXa pharmacophoric hypotheses using CATALYST over two subsequent stages. In the first stage, high quality binding models (hypotheses) were identified. However, in the second stage, the models were refined by applying variable feature weight analysis to assess the relative significance of their features in the ligand-target affinity. The binding models were validated according to their coverage as 3D database search queries and predictive potentials. Subsequently, genetic algorithm and multiple linear regression analysis were employed to construct different QSAR models from high quality pharmacophores and explore the statistical significance of combination models in explaining bioactivity variations across 199 fXa inhibitors. Three orthogonal pharmacophoric models emerged in the optimal QSAR equation suggesting they represent three binding modes accessible to ligands in the binding pocket within fXa.

Part 2: A 3D Catalyst-based structure database of components extracted from Middle-Eastern Natural herbs was constructed. The database offers basic molecular properties and multiconformer 3D structures of 26,034 natural compounds and their herbal origins, including basic herbal category (Latin name and family). The database was screened against farnesyl transferase, EGF tyrosine kinase and human protein tyrosine phosphatase (h PTP 1B). Results show that the database can be a rich source for searching for lead compounds, furthermore, it also shows that a single herb can produce a battery of compounds that can block certain bio-target, more interestingly, a particular herb might produce several compounds that block several bio-targets involved in a disease state.

The synthesis and microbiological evaluation of some novel derivatives of some natural and synthetic polymers

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Novel polymeric derivatives based on known pharmaceutical polysaccharides were synthesized and characterized. The new polymeric compounds were envisaged to have antimicrobial activities through two distinctive mechanisms: (i) chelation to essential divalent and trivalent metal ions required for microbial growth, and (ii) disrupting cell membrane integrity via forming stable polymeric ion-pair complexes with membrane constituents. However, a third class of targeted semisynthetic polymers was designed to act as antimicrobial agents via both mechanisms.

Various synthetic methodologies including carbodiimide coupling, halogen exchange, and nucleophilic substitution reactions were carried out.

Generally, the new polymers were characterized using infrared spectroscopy (IR), solubility studies, and ultraviolet spectroscopy (UV). However, some of them were characterized via argentometric assays due to their halogen contents.

Subsequently, the antimicrobial properties of the new polymers were evaluated utilizing diffusion and dilution methods. The most promising polymers were formulated in semisolid preparations, and challenged with four different microorganisms: E. coli, S. aureus, A. niger, and C. albicans. Some of the new polymers showed significant antimicrobial properties.

Furthermore, the capacity of two of the new polymers in inducing skin irritation was evaluated to assess the possibility of using such agents topically. It was found that the selected representatives were of minimal acute irritancy.

Structure activity relationships for Acetylenic amines as anticancer agents

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A major effort is now proceeding to develop anticancer agents through both empirical screening and rational designing of new compounds.

This study addresses the detailed screening structures activity relationships of anticancer agents in vitro for period 1981-2005.

ln our laboratories different series of acetylenic amines have been synthesized using different methods ,and tested against 60 different cancer cells in vitro.

Our results show that simple acetylenic molecular (N-propargyl amino acids, Amino acid propargyl ester, propargyl Coumarin ester) as a models give positive test against different cancer cells by the aid of NCI.The physical, chemical and spectroscopic determination will be discuss.

The aim of this paper the synthesis and study the SAR for acetylenic amines as anticancer cells in vitro.

.Aknowledgements : The author would like to thank National Cancer Institute (USA) for screening tests for all agents.

The Use of Bovine Immunoglobulin for Treatment of Infant Rotavirus diarrhea

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Department of Food Sciences, College of Agriculture, Baghdad University

Lyophilized anti-human rotavirus colustral immunoglobulin (Ig) was used to fortify infant formula, and then used for the treatment of infants suffering from rotavirus diarrhea.

Thirty infants were subjected to the trial, divided into 3 groups, 10 infants each. Infants in group 1 and group 2 received a volume of 800 ml milk of 0.1% (i.e. 0.8 g) and 0.125% (i.e. 1 g) Ig sequentially, daily within 48 hours of diarrheic symptoms. Infants in group 3 received non-fortified milk formula as control. Bowel motions were reduced from 6-9 and 6-10 to 2-3 and 1-2 in group 1 and group 2 sequentially. Virus titer was reduced from 1:32-1:256 to 1:16-1:2 in group 1, and from 1:32 to 1:2 in group 2 infants. Group 3 (control group) showed no changes. It is concluded that anti-human rotavirus colustral Ig- fortified milk is useful in the treatment of rotavirus diarrhea in infants.

Effect of Melanocyte Stimulating Hormone on Plasma levels of Testosterone and Estradiol in Alloxan-Induced Diabetic Rats

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This study was designated to investigate the effect of Melanocyte Stimulating Hormone (MSH) on serum testosterone (T) and estradiol (E2) hormone concentrations in alloxan-induced diabetic rats. Eighty male and female Sprague Dawley rats, weighing 180-200 g, were divided into four groups of normal rats and four groups of alloxan-induced diabetic rats. The rats were injected intraperitonially (i.p.) a daily injection of 20 mg alloxan solution/ 100 g of body weight, for 10 days. Two groups of male rats (one normal and one diabetic)were injected with normal saline, the other two groups were injected with 2 ug of MSH/100 g of bogy weight, for 10 days. The same was applied to the female rats. Serum glucose concentrations were higher in diabetic rats than in the normal, whereas insulin, testosterone and estradiol levels were higher in moumal rats than the diabetic ones. The administration of MSH reduced serum glucose levels in diabetic rats to normal levels, and decreased estradiol levels in normal female rats, but increased testosterone levels in normal male rats. The present findings suggest that MSH plays an adaptive role during early stages of alloxaninduced diavetes mellitus.

Does Glucosamine Sulphate affect the Skin?

Maan M. Saleh Al-Sammarrie*
A. A. H. Al-Naimi**

Glucosamine is an amino monosaccharide derived from cellular glucose metabolis and it is a simple component or "building block" of more complex molecules. Glucosamine was considered to be an effective treatment for many joint diseases especially osteoarthritis. It is believed that glucosamine maintain healthy joint functions and rebuild damaged joint cartilage, tendons, ligaments and other connective tissue. It does this by stimulating the production of glycosaminoglycans (GAG's) which are the structural components of cartilage and connective tissue else where in the body.

Twenty male and twenty females adult mice (weighting between 23.3gm to 27.2gm), were divided into two equal subgroups (control and experimental); the drug was given at noon three hours after starvation it had been grinded and mixed with food and given as a single oral dose of 350mg/kg body weight per day for 35 successive days. Histological examination and statistical analysis of multiple sections of ventral and dorsal skin of male and female mice and of both subgroups were done by using hemotoxyline and eosin stain.

The results reveal that there was increment in the number of fibroblast which was more obviously seen in the ventral skin of the treated animals. This study confirms practically that glucosamine sulphate induces significant structural changes in the skin of mice.

Using glucosamine sulphate clinically for medical conditions rather than arthritic diseases is now the target of most recent researches, its ability to decrease wrinkles in the aged skin and promotion of wound healing with less scar tissue is consider to be a light for dermatologist and plastic doctors, plus its effect to rebuild any aged, injured and diseased tissue in the body.

The Effect of Methylcobalamin on the Adrenal Medulla

A.A.H. Dhiab Al-Naimi, Mohammed Al-Noaemi and Wafica Al-Naimi.

Faculty of Pharmacy. Al-Zaytoonah University, Jordan.

Methylcobalamin is one form of cobalamin that acts as a nerve growth factor. Since adrenal medulla is part of the nervous system, therefore, this study was designed to assess the effect of methylcobalamin on this gland in rats. Albino rats were injected with methylcobalamin for 14 days, adrenals were taken, fixed in Ortho's fixative, and embedded in paraffin. They were cut in thin sections and stained with H&E and Giemsa stain. They were studied under light microscope. The result showed that methylcobalamin has stimulated the adrenal medulla, which was expressed by dilated vessels and increase in the granularity and size of chromaffin norepinephrine containing cells. Sympathetic ganglionic cells have also increased in number and size. Cortical zona reticularis was hypervascular and hypertrophied.

This study suggests that, methylcobalamin might have acted directly through the sympathetic nerves on the adrenal medulla or indirectly on the medulla through the adrenal cortex resulting in an increase in number of norepinephrine containing cells and the ganglionic sympathetic cells.

The Effect of Anaerobic- Aerobic Efforts on Serum Iron and Hemoglobin

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** Faculty of Sport. Mosul University. Mosul. Iraq.*

*** Head of Pharmacy Department. Faculty of Pharmacy Al-Zaytoonah Private University of Jordan.*

This research deals with study of effect of anaerobic aerobic efforts upon hemoglobin and iron response in the blood serum and recognizing their mechanism.

Research Objectives:

1. Recognizing the differences in the response of hemoglobin and iron between pre-test and directly post-test of 400m running.
2. Recognizing the differences in the response of hemoglobin and iron between pre-test and recovery test of 400m running.
3. Recognizing the differences in the response of hemoglobin and iron between post-test and recovery test of 400m running.

Researchers Hypotheses:

1. There are significant differences in the response of hemoglobin and iron between pre-test and directly post-test of 400m running.
2. There are significant differences in the response of hemoglobin and iron between pre-test and recovery test of 400m running.
3. There are significant differences in the response of hemoglobin and iron between post-test and recovery test of 400m running.

Researchers Conclusions:

1. There is a significant increase in the level of TIBC in directly post-test comparing with the state of pre-test.
2. There is a significant increase in the level of TIBC after recovery test comparing with the directly post-test and the state of pre-test.
3. There is a significant increase in the level of Fe after recovery test comparing with the directly post-test and the state of pre-test.

Genotypic analysis of CYP2C19 in the Jordanian population and association of these polymorphisms with citalopram metabolism in vivo.

Reem Fawaz Abu Tayeh,

Faculty of Medicine, Jordan University

Objectives:

1) To validate and adopt a genotyping method for the CYP2C19, to be applied in Jordan in diverse Pharmacogenetic research studies including present and future clinical applications.

2) To identify and evaluate the frequency of the most common defective alleles of CYP2C19 in the Jordanian population, starting out with the most common defective alleles CYP2C19*2 and CYP2C19*3.

3) To correlate the CYP2C19 polymorphic genotype with the metabolic rate phenotypes of one of its substrate drugs; citalopram.

CYP2C19 alleles were identified by Polymerase Chain Reaction (PCR) - restriction fragment length polymorphism (RFLP). Method was adopted from literature with modification and proved its reproducibility in the Molecular Laboratory in Jordan University.

For metabolism of citalopram, a validated chromatographic method for quantitative determination of CIT and its metabolites was performed, which involved a liquid liquid extraction procedure followed by high performance liquid chromatography coupled to a fluorescence detection.

Of the one hundred Jordanian subjects, two were found homozygous PMs of *2/*2 genotype, and sixteen IM (*1/*2 genotype), while no CYP2C19*3 mutations were detected. Allele *2 is the predominant polymorphic allele in the Jordanian population, where the *1, *2, *3 alleles' frequencies are 0.9, 0.1, and 0 respectively.

As for the patients' group, only heterozygous extensive metabolizer (intermediate metabolizers [IM]) trait is detected in this study. This genotypic trait accounts for two out of the three patients (thirty three percent) of the low citalopram metabolic phenotypic trait.

The frequency and type of poor metabolizers of CYP2C19 among the Jordanian population resembles that of other non-Asian populations.

As for applying pharmacogenetics in clinical applications, there is the obvious need for more genotyping studies for other CYP2C19 isoenzymes.

Hepatitis C virus Abs, RNA and Genotype in patients with Hepatocellular Carcinoma

***Prof. Dr. WAQAR A., AL-KUBAISY, **Assis. Prof. Dr. AHMAD A. AL-AZAWI**

****Reportear of dep of community Medicine, Mrdical college , Al-Nahrain University***
*****Department of medicine/ oncology, Mrdical college , Al-Nahrain University***

Hepatitis C virus (HCV) was considered by several investigators to be a possible pathogenetic agent for hepatocellular carcinoma (HCC) in a number of countries.

To identify whether exposure to HCV, acts as a risk factor for HCC development. And the predominant HCV genotype among Iragi patients with HCC.

A case-control study was conducted consist of 65 patients with HCC compared to 82 patients having other malignant disease rather than HCC (control group). HCV Abs (anti-HCV) was tested for both groups, using subsequently third generation enzyme immunoassay (EIA-3) and immunoblot assay (Lia-Tek III) as screening and confirmation tested respectively. In addition, 26 positive anti-HCV Sera (both groups) were subjected to molecular analysis, using the most recently developed RT-PCR and DNA Enzyme immunoassay (DEIA) method (Sorin Biomedica Italy).

Anti-HCV seropositivity rate significantly was higher 17(26.1%) among HCC patient compared to 9(1.1%) control group. And HCV-RNA was confirmed positively in 12 and 2 sera of HCC and control group respectively with positive anti-HCV. Moreover, anti-HCV seropositivity was found significantly acts as a risk factor for HCC development (OR=2.37, 95%C.I=1.1-7). No significant association was detected between HCC and HCV genotypes. However, 7HCC patient were harboring HCV-1b (as a single or mixed pattern of infection). One HCC sera with positive HCV-RNA could not be type. While the remaining were infected by genotype 1a or 4.

Our study detected a significantly higher rate of anti-HCV seropositively in HCC patients. And HCV infection acts as a significant risk factor of HCC. Also HCC patient harboring HCV-1b in higher rate than their counter group.

In vivo expression of ganglionic long term potentiation in superior cervical ganglia from aged rats

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Sustained increase in central sympathetic outflow to ganglia may provide the repeated high frequency presynaptic activity required for induction of long-term potentiation (gLTP) in sympathetic ganglia, which was shown to be involved in the manifestation of neurogenic forms of hypertension namely stress-hypertension. Aging is often viewed as a progressive decline in physiological competence with a corresponding inability to adapt to stressful stimuli. Old animals have exaggerated sympathetic activity as well as increased morbidity and mortality during prolonged exposure to stressful stimuli. In the current work, the possibility of the endogenous *(in vivo*) expression of gLTP in ganglia of aged animals was investigated.

Blood pressure was measured using tail cuff method and compound action potentials (CAPs) were recorded from isolated superior cervical ganglia.

Electrophysiological evidence shows that mildly hypertensive aged rats have expressed gLTP *in vivo*. Firstly, a shift of input-output (I/O) curve of ganglia from aged rats to the left side of I/O curve of ganglia from adult rats. Secondly, failure of *in vitro* applied HFS to induce gLTP in ganglia isolated from aged rats, which indicates occlusion, due to saturation. Thirdly, *in vitro* inhibition of basal ganglionic transmission by blockers of gLTP (5-HT_3 antagonists) is observed in ganglia isolated from aged rats, but not in those from adult rats.

Our results demonstrate *in vivo* expression of gLTP in sympathetic ganglia of aged animals, which may contribute to the moderate hypertension often seen in aged subjects.

The effect of treatment with Nifedipine on malondialdehyde contents, and reduced glutathione levels in serum of pre-eclamptic women

Nawfal Am.Numan*, Nada N. Al-Shawi and Atyaf Mohammed

**** Al-Zaytoonah Private University of Jordan***.

Increased lipid peroxidation and reduced anti-oxidant activity may contribute to the development of complications in pregnancy. The objective of this study was to test the hypothesis that maternal serum lipid peroxidation products are increased and anti-oxidant decreased in women with mild and moderate pre-eclampsia; and study the effect of treatment with nifedipine on the above parameters.

Malondialdehyde (MDA), and reduced glutathione (GSH) were measured in maternal serum in the 3rd trimester of pregnancy, in normotensive pregnant women (n=15), mild pre-eclamptic untreated control (n=6), moderate pre-eclamptic untreated control (n=6), mild and moderate pre-eclamptic women treated with nifedipine (n=6), and (n=8), respectively.

Maternal serum levels of MDA and GSH were higher and lower, respectively in both cases of pre-eclampsia when compared to normotensive pregnant controls. Treatment with nifedipine shows a significant decrease and increase, respectively in MDA contents GSH levels in serum of both cases of pre-eclampsia when compared to normal pregnant.

Lipid peroxidation is involved in the pathogenesis of maternal pre-eclampsia, as evidenced by a significant increase in MDA contents and reduction of protective

anti-oxidant system manifested by GSH levels. Treatment with nifedipine effectively lowers blood pressure; reduce serum MDA contents and increases serum GSH levels in pre-eclamptic women.

A Comparative Study of the Effect of Nigella Sativa Fixed Oil, Eugenol Oil and Betamethasone on the Healing Rate of Recurrent Aphthous Ulceration

Dr Nasir A.Harchan

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This is a comparative study on the effect of Nigella sativa (black seed) oil, Eugenol oil and betamethasone on the cure rate of recurrent Aphthous ulceration.

Eighty patients suffering from recurrent oral ulceration were enrolled in this study; full investigations and clinical examination were done to prove that they are otherwise healthy.

Those 80 patients were divided into 4 groups. The 1st, 2nd and 3rd study groups were treated with Nigella sativa oil preparation, eugenol oil preparation and betamethasone 17- valerate respectively. The 4th group was treated with glycerin and considered as a control group.

Nigella sativa oil was diluted by glycerin in a ratio 1:10 to form a 10 % preparation. Eugenol oil was prepared in the same method.

Nigella sativa preparation, eugenol preparation and glycerin were instructed to be applied topically 3 times daily, while betamethasone twice daily.

Patients' assessment was done by using the (Oral clinical Manifestation Index "OCMI") before treatment, 4 days, and then 8 days after treatment.

Statistical analysis was done to the data obtained and the results showed that there was no significant difference between the effect of Nigella sativa fixed oil and corticosteroids but there was a significant difference between Eugenol and corticosteroids. Glycerin was of no effect on cure rate of recurrent aphthous ulcers.

Nigella sativa fixed oil is a new topical agent for promotion of healing of recurrent oral ulceration as compared with corticosteroids, however the latter has well known side effect.

Eugenol is recorded as another new topical treatment modality it has a narrow spectrum of use since it can not be recommended to patients with any previous hypersensitivity.

Comparative Study of the Effect of Silybinin and Pilocarpine on the Intraocular Pressure in Normotensive Rabbits

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Saad Abdul-Rehman Hussain

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Previous data indicates the effectiveness of silybinin hemisuccinate as a potential IOP-lowering agent. Although the exact site and mechanism of action have not yet been documented, silybinin might interfere with aqueous humor formation, a suggestion based on the observation that it delays IOP recovery rate after infusion of hypertonic NaCl solution and the ability to lower IOP in untreated eyes. The present study was designed to evaluate the interaction of silybinin hemisuccinate (0.75% solution) with pilocarpine (2% eye drops) and cyclopentolate (1% eye drops), for the aim of comparing the IOP-lowering effect of silybinin and pilocarpine in normotensive rabbits and to verify the possible site and mechanism of action of silybinin, using indentation tonometry.

The result showed that 0.75% solution of silybinin was more potent than pilocarpine (2% eye drops) in lowering IOP in normotensive rabbits. Furthermore, the effect of their combination was higher and of longer duration than when silybinin administered 30 minutes after pilocarpine administration. In addition, elevation of IOP produced by cyclopentolate (1% eye drops) was decreased by silybinin, and pr-administration of cyclopentolate did not block its IOP-lowering effect. In conclusion, silybinin appears to be more potent than pilocarpine in lowering IOP in normotensive rabbits; and the pre- and post-instillation of pilocarpine and cyclopentolate provide experimental evidence that silybinin might interfere with aqueous humor formation as a possible mechanism of action.

Comparative study of the effects of enzyme inhibitors and inducers on serum and tissue availability of thiamine after single oral dose of the pro-drug Benfotiamine in rats

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Thiamine is known to have an important role in the protection of different types of cells and tissues against the damage produced by many drugs and toxins. The most important problem limiting the clinical applications of this approach is the poor absorption and bioavailability of thiamine from the sites of administration, a problem which can be solved by the use of the lipid soluble pro-drug for thiamine, benfotiamine. Accordingly, this project was designed to evaluate the serum and tissues availability of thiamine in rats after the administration of single oral dose of benfotiamine compared with that produced by the same oral dose of thiamine, in addition to study the effects of enzyme inducers and inhibitors in this respect utilizing HPLC technique. According to the results obtained in this study one can conclude that thiamine availability after administration of benfotiamine was more in serum, liver, kidney while in the brain more time may be required to reach maximum level.

Prevalence of Clinical strains staphylococcus Spp. With decreased sensitivity to mupirocin and investigating the responsible resistant mechanism

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Mupirocin, an inhibitor of bacterial isoleucyle - tRNA synthetase, has potent activity against Staphylococci including methicillin – resistant S. aureus (MRSA) strains. It is used to treat staphylococcal skin infections as well as to eliminate nasal carriage of MRSA. High-level resistance (MIC >512 mg/L) is due to the acquisition of the MupA gene that encodes a novel isoleucyl – tRNA synthetase that is not inhibited by mupirocin. Also, strains exhibiting low – level resistance (MIC 4 – 256 mg/L) due to point mutations in the native ileS gene have also been reported.

A total of 450 Staphylococci spp. isolates were included in this study. They were obtained from the collection of bacterial strains that is retained in the Microbiology Department, Medical School, University of Athens. ¶The strains had been isolated from various clinical materials in five Greek hospitals during the period 1999-2000. The sample included 258 S. aureus, 162 S. epidermidis and 30 isolates of other Staphylococcus species.

¶Minimum inhibitory concentration of mupirocin was determined by the agar dilution method. Susceptibility to other antibiotics was assessed by a disc diffusion method. Thirty-one (6.9%) of the isolates exhibited high-level resistance to mupirocin and Ten (2.2%) exhibited low-level resistance. All mupirocin-resistant isolates were also resistant to multiple antistaphylococcal antibiotics. There was a strong correlation between resistance to mupirocin and resistance to aminoglycosides and beta-lactams.

Detection of mupA was performed using a polymerase chain reaction (PCR) assay and mupA-specific primers. PCR confirmed carriage of the mupA gene by all isolates exhibiting high-level resistance to mupirocin. The gene was not found in any of the isolates with low-level resistance to the antibiotic.

Transfer of resistance to mupirocin by conjugation was performed by means of filter mating method. S. epidermidis isolate was able to transfer high-level mupirocin resistance, along with resistance to aminoglycosides, to a susceptible host. Plasmid DNA analysis indicated transfer of a 38 kb plasmid. Plasmids of similar sizes and restriction patterns were detected in all mupirocin-resistant clinical isolates. Hybridization experiments using a labelled mupA fragment as a probe documented the carriage of the mupA gene by the 38 kb plasmids. The mupirocin resistant isolates were typed by pulsed – field gel electrophoresis (PFGE) to determine their possible relatedness. Results of the PFGE typing showed the existence of various groups of isolates with distinct genomic patterns. These data indicated spread of mupA via related plasmids to epidemiologically distinct strains. Despite the limited use of mupirocin, staphylococci with mupA-carrying plasmids seem to be endemic in Greek hospitals. Thus it is likely that a more systematic use of the antibiotic could lead to the rapid spread of mupirocin-resistant strains.

P53 as An Indicator for the Prognosis of Oral Squamous Cell Carcinoma

Dr. Dunia AL- Fayad, B.D.S; M.Sc.(Oral Surgery); Ph.D.(Oral Pathology)

Faculty of Dentistry/ The Syrian International Private University for Science & Technology

P53 is a tumor suppressor gene, which plays a key role in cell cycle arrest, and induction of apoptosis in genetically damaged cell.

To detect the association between P53 positivity and progression of oral squamous cell carcinoma(O.S.C.C.)

Thirty sections of oral squamous cell carcinoma cases were collected during period from (2001-2004) from the archive of Department of Oral Pathology in the Faculty of Dentistry-University of Baghdad. Three negative control sections with normal oral epithelia were taken from the same archive, in addition three positive control sections of ductal breast carcinoma were chosen from the Teaching Laboratories of Baghdad Medical City.

Depending on the Cotran et.al.,(1999) that histopathological grading system is related to biological behavior of the tumor cells, our study detected that out of the total samples (30); 15, 5 and 10 cases were found as a well, moderately and poorly differentiated oral squamous cell carcinoma respectively.

Regarding the positivity of P53, our study found that only 6 (40%) cases of the well differentiated O.S.C.C. while 4(80%) cases of the moderately differentiated O.S.C.C.

Show P53 positivity. Surprisingly all the 10 (100%) cases of poorly differentiated O.S.C.C. show P53 positivity.on the contrary non of the normal oral squamous epithelia cases (control) show P53 positivity.

Our study detected a direct relationship between oral squamous cell carcinoma progression and P53 posistivity from 40% well differentiated to 100% poorly differentiated. Therefore We recommend the using P53 as an indicator for the presence and prognosis of the O.S.C.C.

Effect of a thienopyridinone on the growth and physiology of Escherichia coli

Dr Ziad Shraideh,

Jordan University (JU)-Amman-Jordan

A new synthetic thienopyridinone 2-cholro-7-cyclopropyl-4.7-dihydro-4-oxothieno-s{2.3-pyridine-5-carboxylic acid was tested for its antimicrobial activity. A concentration of 5 ug/ml completely inhibited the growth of Escherichia coli. Its , minimal inhibitory concentration was determined for different Gram-positive and Gram-negative bacteria. Bacillus subtilis, Klebsiella pneumoniae and pweudomonas aeruginosa were resistant to 100 ug-ml Staphylococcus aureus, E. coli, Salmonella typhi, shigissa marcescens and proteus Vugharis were semsitive to 5 ug/ml. this indicates possible uses for the compound in treating infections caused by the sensitive bacterial species .

WORKSHOPS

Workshop on Fundamentals of Clinical Pharmacy

Instructor: Dr. Abdulaziz Saddique Pharm.D., CPHQ, CSSMBB

Time Allocated: 2:30 Hours

Objectives

1. **To provide an overview of the various aspects of clinical pharmacy and the role of the clinical pharmacist in multidisciplinary healthcare teams.**
2. **To provide an overview of the information sources available for the assessment and monitoring of disease and drug treatment in individual patients.**
3. **To provide an understanding of how age, disease, genetic constitution and drug interactions can modify drug response.**
4. **To enable the student to understand how biochemical monitoring and therapeutic drug monitoring can assist in the management of drug therapy with certain drugs.**

Learning Outcomes

Upon completion of this workshop the participants should be able to:

1. **Give an account of the role of the clinical pharmacist as a member of the multidisciplinary healthcare team.**
2. **Describe the content of the information sources used in the interpretation and management of an individual patient's disease and drug therapy and assess their relevance in case study format.**
3. **Describe the effects of age, liver and kidney disease and genetic disposition on drug pharmacokinetics and assess their relevance in case study format.**
4. **List the clinically important features of therapeutic drug monitoring in individualizing therapy with drugs such as theophylline, gentamicin and other aminoglycosides, digoxin, phenytoin and other anticonvulsants, lithium, and apply these therapeutic principles to solving individual patient problems.**
5. **Demonstrate competence in pharmacokinetic calculations using elements such as creatinine clearance, steady state drug serum level, drug half-life and elimination rate constant.**

Workshop Plan

Presentation on the topics of the workshop, followed by examples and discussions. Case presentations and discussion, to be provided by participants following dividing them into groups. Each group will have 15 minutes for presentation.

Title of the Workshop: How to Establish TDM Services

Moderator: Dr. Sireen Shilbayeh, Associate Professor of clinical pharmacy

Of the many issues now confronting medical professionals none seems more important than the debate about the quality of care. Multidisciplinary quality improvement efforts are playing an increasing large role in medical care. Hospitals are increasingly trying to improve quality through developing multidisciplinary quality improvement projects.

Physician's active engagement in research, teaching and policy formulation concerning the quality of care will certainly advance these activities and elevate the overall performance of our health care system.

It has been shown that development of therapeutic drug monitoring services (TDM) can improve the quality of care.

Therapeutic drug monitoring is a relatively new clinical discipline that combines the determination of drug levels with the application of pharmacokinetic principles and pharmacodynamics to optimize dosage regimens in a patient. To date, in many countries worldwide it has been applied mainly to drugs with narrow therapeutic ranges such as aminoglycosides and vancomycin that may induce severe toxicity.

Several studies have documented the positive impact of TDM and clinical pharmacokinetic services on patient's outcome, reflected by a reduction on toxicity, a decrease on length of hospital stay and more important there was a trend toward lower mortality.

To start a TDM service we do require substantial effort to implement, a multidisciplinary team, and education effort to change behaviors and convince clinicians to change practice.

However, this type of service has not been well-established in Jordan. The aims of this workshop are:

1. To highlight the significance of TDM to patient care
2. To describe the process of organization of a TDM service
3. To bring attention to some important topics in dose adjustment such as serum level analysis and Bayesian curve fitting

Title of the Workshop: How to Establish TDM Services

Moderator: Dr. Sireen Shilbayeh, Associate Professor of clinical pharmacy

The workshop schedule will be as follows:

1. Procedures and organization of a Therapeutic Drug Monitoring (TDM) service (one hour)
2. serum level analysis vs. Bayesian Curve Fitting (30 mins)
3. TDM of vancomycin
4. Introduction to TDM software (15 mins)
5. working on simple patient cases at the computer (30 mins)

By the end of workshop the participants are expected to have had a better understanding of the feasibility of initiating TDM service lead by clinical pharmacists in hospitals. It is also hoped that they will also become more aware of their role in this type of service and its contribution to patient safety and cooperation between healthcare practitioners.

The target audiences are pharmacists working in hospitals and/ or interested in therapeutic drug monitoring. The workshop will be concluded by trying to formulate a stepwise plan to TDM service after identifying pitfalls of current practice through administration of a questionnaire to the participants.

The workshop schedule will be as follows:

Procedures and organization of a Therapeutic Drug Monitoring (TDM) service (40 mins)

serum level analysis vs. Bayesian Curve Fitting (30 mins)

TDM of vancomycin (30 mins)

Introduction to TDM software (10 mins)

Working on simple patient cases at the computer (30 mins)

Administration of a questionnaire to the participants and discussion (10 mins)

Anticoagulation workshop

Eman AlObary, Ms Pharm

Clinical Pharmacist, Hepatology, Anticoagulation Clinic
Department of Pharmacy Services
Riyadh Military Hospital, Saudi Arabia

Anticoagulation with warfarin requires careful management to avoid hemorrhage or thrombosis. The Anticoagulation Clinic (AC) has been suggested as a mechanism to reduce complications related to anticoagulation.

The AC offers a comprehensive range of patient-focused pharmacy services. The goal of the clinic is to optimize patients' anticoagulation therapy with warfarin and to bridge patients with a low molecular weight heparin /or unfractionated heparin while transitioning to warfarin. Patients are carefully monitored and followed using an established anticoagulation protocol including lab draws and follow-up visits.

Patients monitored by anticoagulation clinics (ACs) had better anticoagulation control, decreased complications, and decreased coasts compared to those followed by standard care management. An AC provides intensified care due to increased visits; this often prevents the need for admittance to the Emergency Department.

Recent trials have shown that clinical pharmacists can play a key role in disease management models for anticoagulation. Pharmacists managing ACs have successfully proven better continuity of care and improved patient outcomes. Therefore pharmacists should pursue roles in ACs as collaborative drug therapy managers.

The American College of Clinical Pharmacy (ACCP) advocates that in order to effectively manage an AC, the pharmacist should have the authority to order warfarin and adjust doses as necessary, conduct pertinent laboratory monitoring, and schedule patients to return to the clinic at the appropriate time intervals. The ACCP also advises that pharmacists should have the authority to conduct patient assessments, access health information, document interventions, and develop quality assurance programs on the interventions. By conducting ACs as a part of collaborative drug therapy management, pharmacists make decisions regarding anticoagulation and share the responsibility for patient outcomes with other members of the healthcare team.

The workshop will be conducted as follow:

1- Role of pharmacist in ACs
2- Guidelines/protocols for outpatient oral anticoagulation therapy management.
3- Cases

Drug information resources

Pharm.D Sayer Al-Azzam, Clinical Pharmacy, Pharmacy.

Pharmacist Belal Al-Husein , Clinical Pharmacy , Pharmacy.

Faculty of Pharmacy, Jordan University of Science and Technology (JUST)

Scientific Content:

1. Overview of drug information resources
2. Internet resources
3. Information resources in: General drug information, ADR, DI, Labs/Toxicology, Pregnancy/Lactation and OTC.

Objectives:

1. Analyze an information need to determine weather tertiary, secondary, primary or internet resources should be consulted and how to criticize them.
2. Recommend web sites that can be used to find high-quality disease state or medical condition information of various types and Asses their quality.
3. Be able to perform searches using databases to answer specific medical information questions.
4. Introduction and practical applications of pocket PC.

*** Visual Aids and other required facilities :**

Computers

POSTERS

Asthma best practice model in Northern Hospital, Melbourne

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Asthma, with its increasing prevalence and increasing severity in childhood, is the commonest reason for hospital admissions in children and a major cause of school absenteeism. The project aims to improve health outcomes for children and adults with asthma who present at ED of the Northern Hospital for asthma exacerbation, through the provision of best practice education and support model to enhance the uptake of written asthma management (action) plan in collaboration with GPs, nurse educator and patients.

The target population is patients attending the ED of the Northern Hospital for asthma exacerbations aged 4-64 years. Patients are identified from the ED database every few days, the Asthma Educator (AE) contact the patients by phone to invite them to participate and make appointment at a convenient time. The AE then assess patients at baseline and at 6 months using structured interview protocol and administer patient-centered self-management education program on asthma triggers; medication devices and adherence and written asthma action plan, supported by frequent reviews. Following each consultation, the AE send a copy of patient's summary by fax on gaps in knowledge, management and adherence and lung function test, to the patient's nominated general practitioner.

Current results: A third of the 425 eligible patients attended a consultation by the asthma educator, and 18% refused to participate. Of the 138 participants, 48% rated their asthma as moderate or severe, 40% thought their asthma was not well controlled and 57% were not satisfied with the level of control. When asked about smoking 38% of adolescent and 29% of adults were regular smokers, of those only 23% of adolescent and 47% of adults wanted assistance to quit. Although 80% of adults and 65% of children had seen their GP during the preceding three months, only 13% of adults and 32% of children have written asthma action plan. Feedback from patients with asthma and their parents and the hospital staff is positive.

Gap still exist in the management of asthma in the Northern region of Melbourne despite intensive programs targeting patients with asthma and their GPs. Therefore a patient-centered evidence-based self-management program such as this have great potential to improve patient care and reduce hospital demand, via identification of trigger factors, adherence to medication and uptake and use of written asthma plans. This should lead to improved quality of life for patients with asthma, reduced morbidity and mortality. Non of this is possible without the support of TNH staff.

Phytochemical study of *Salvia palaestina* Benth.

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The Lamiaceae family comprises about 200 genera and 3000 species. One of the largest genus of the family, *Salvia* L., is represented by over 900 species[1] and is widely distributed in various regions of the world. The main secondary metabolite constituents of *Salvia* species are terpenoids and flavonoids. The aerial parts of these plants contain flavonoids, triterpenoids, and monoterpenes, particularly in the flowers and leaves, while diterpenoids are found mostly in the roots. However, a literature survey indicates that some American *Salvia* species also contain diterpenoids in the aerial parts, and in few *Salvia* species, triterpenoids and flavones are present in the roots.

S. palaestina Benth. is widespread in southeastern Turkey where a preparation made from leaf extracts is commonly used in the folk medicine as a wound healer.[2,3] Previous phytochemical studies on the aerial parts of the plant reported the presence of modified abietane diterpenoids, ursolic acid, vergatic acid, lupane derivatives, and flavonoids.[2,4,5]

In this work we report the phytochemical study of the aerial part and root of *S. palaestina* acetone extracts. The dried plant materials were finely powdered and exhaustively extracted with acetone by maceration at room temperature. The purification of each extract was accomplished by different chromatographic techniques such as silica gel column, MPLC, and HPLC. The structural elucidation of pure compounds was achieved by extensive spectroscopic methods including 1D- (^{1}H, ^{13}C, ^{13}C DEPT, TOCSY, ROESY) and 2D-NMR experiments (DQF-COSY, HSQC, HMBC), as well as ESI-MS analysis.

Six abietane diterpenes were isolated from the roots, while three manoyl oxide derivatives, one labdane diterpene, one sesquiterpene, two triterpenes, two sesterterpenes, together with rosmarinic acid were purified from the aerial parts of the title plant. Among these constituents, sesterterpene derivatives were new natural products.

How Turkish and Arabic Speaking Community in Melbourne view diabetes?

Dr Nabil Sulaiman, Doris Young, John Furler, Helen Cobolt, Elainr Hadj, Deb O"connor

Australian residents born in the Middle East (ME) have the highest standardised ratios for self-reported diabetes mellites (DM) in 1995 and in 2001. One of these ME communilties is the Turkish and Arabic Speaking Community (TASC). Australian data on the prevalence and attitudes to prevention of T2D in TASC is lacking. This project aims to explore, knowledge, attitudes, and barriers to lifestyle changes to prevent T2D.

The study was based in a socioeconomically deprived area of Hume City, Melbourne and utilised 2 hours focus group (FG) techniques with professional TAS interpreter. TAS health workers in the area and families and friends of people with diabetes were engaged to recruit TAS men and women at risk of DM. Each FG was audio taped and transcribed verbatim in English. Thematic analysis was done by two staff independently.

41 females and 11 males participated in the five groups. The mean age of participants is 58.8 (41- 73 years). Participants were born in Turkey, Lebanon, Egypt, Iraq and Syria. The main themes were eating too much and frequently,stress and anxiety, no or little exercise, leaziness, obesity and wrong diet. Environmental factors included chemical addidtives and living in Australia not in the country of orgin. Specific barriers to exercise were identified such as fear of attacks in the streets, ageing, and no sense of fear from DM.

Stress and anxiety was predominant theme in all focus groups as well as diet and lack of motivation to exercise. New approach to diabetes prevention in TASC is urgently needed.

Current health education program is ineffective for TASC. Most effective are directive health education by doctors and large professional or peer-led group discussions.

Applications of Differential Scanning Calorimetry (DSC) in Pharmaceutical Research and Industry

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DSC is one of the thermoanalytical techniques which gained a wide applicaion in pharmacy. Various possibilities of using DSC are discussed.

Purpose: The present article aimed at application of DSC as a tool (1) to determine the melting point, enthalpy of fusion of temazepam, testosterone and its ester (NTA) (2) to investigate drug-excipient interactions of some benzodiazepines as well as praziquantel, (3) to study polymorphism of oxaminquine, (4) to construct the phase diagrams of estradiole/progesterone, (5) to evaluate the interaction of cyclodextrins with testosterone and monosialogangliosides (GM1), and (6) to study the kinetics of solid state degradation of glycine derivatives as models for peptide drugs.

DSC scanning was performed under the following conditions: sample weight 3-5 mg, scanning rate 10° C, N2 purge (30 ml/min.).

Temazepam, testosterone and NTA showed sharp melting endotherms (Tm of 160, 154.5, 110° C, respectively) with ΔHf values of 89, 12, 63 j/g, respectively). PEG and stearic acid were found to be incomapatibile with temazepam, medazepam and lorazepam. Unreported new polymorph of oxamniquine (Form III) was indicated. The reason behind the unexpected enhanced release of estradiole from combined contraceptives was owed to formation of a molecular complex with progesterone. Solid complex formation of testosterone (1-1 M) and GM1 (1-4 M) with cyclodextrins was confirmed. Finally, solid state parameters for the degradation of some peptide model drugs were determined.

DSC is a very useful analytical tool in many fields of pharmaceutical research, preformulation, drug evaluation and development.

Preparation of Solid Self-Micro-emulsified Lipid Systems (SMELS) for the Delivery of Hydrophobic Drugs

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The field of solid dispersion as an approach to improve the dissolution and hence the bioavailability of lipophilic compounds is known for very long yet, only few products exist on the market. The conversion of the drug from the amorphous metasatble state into the thermodynamically stable crystalline form on aging, and the low loading capacity to the drug have limited development in these systems. In this investigation, new systems identified as SMELS were developed using solid dispersion technology and self-emulsified lipid formulations. According to the type of solid carrier included and the class of lipid system, those new vehicles were classified into hydrophilic (h) and lipophilic (l) SMELS. Methods: Using the hot melting method, PEG 10000 was included in a hydrophilic lipid system to form h-SMELS, whereas carnauba wax was included in a lipophilic lipid formulation to produce l-SMELS. A model lipophilic drug was included in these complexes at increasing concentrations. Thermodynamic and XRD analysis were carried out and probed for 3 years. Results: Data obtained from XRD and DSC have shown that these new carrier systems form eutectic mixtures which have the potential advantage of high loading capacity of drugs in the high energy amorphous state. These systems were not affected by the aging processes as they maintained the drug in the amorphous form on storage. Conclusions: Solid self-emulsifying formulations which can replace the costly soft gelatin capsules were developed. These systems have shown less susceptibility to aging which can affect the dissolution of the active.

Synthesis and Pharmacological Activity of Selected Novel Indolinones as Cardioprotective Agents

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Activation of either tyrosine kinase (TK) or phosphoinositide-3-kinase (PI3K) has been shown to play a role in protecting the myocardium from ischaemia/reperfusion injury. The effect of both lavendustin A (non-receptor TK inhibitor) and wortmannin (PI3K inhibitor) on two novel indolinone carboxamides (C1) and (C2) were investigated. Administration of C1 and C2 to isolated perfused rat hearts subjected to 30 minutes regional myocardial ischaemia and 45 min of reperfusion significantly reduced infarct size (43.1±3.3% in control hearts versus 12.6±2.7 and 7.5±1.2% in C1 and 2 respectively, $p< 0.05$). The cardioprotection effect of C1 and C2 was not attenuated by Lav A or Wort (13.9±4.4, 15.6±2.5, 15.7±4.9 and 10.4±1.5% in Lav A+ C1, Lav A+C2, Wort+C1 and Wort+C2 respectively), indicating that neither C1 nor C2 exhibited their cardioprotection effect through activation of TK or PI3K.

In Vitro Anti-viral, Cytotoxic and Anti-Proliferative Evaluation of Some Selected Italian Plants

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The plant kingdom represents a prime source of potentially bioactive compounds. The number of natural compounds used to treat various ailments is constantly increasing, in evidence that nature embodies extraordinary potentiality to treat different diseases, sometimes even better than synthetic drugs. In the past decades, many bioactive compounds of pharmacological importance have been isolated from natural sources, including terrestrial plants, fungi, mushrooms, marine plants as well as animal species. The most interesting compounds have been synthesized with ingenious and sophisticated methods and in many cases natural compounds served as model for drug design in terms of enhancement of activity and decreasing toxicity.

In this study we have selected 14 wild plants growing in different sites in Italy, many of which are used in traditional medicine and they were tested in vitro for activity against a wide variety of viruses, fungi and bacteria. The plants were *Ailanthus altissima, Betula aetenensis, Bupleurum dianthifolium, Centaurea subciliata, Ceterach officinarum, Chenopodium botrys, Consolida regalis, Eryngium maritimum, Juniperus macrocarpa, Helichrysum litoreum, Nerium oleander, Selaginella denticulate, Tymus richardii subs. pnitidus.*

The most cytotoxic extracts were also evaluated for antiproliferative activity against a panel of human cell lines derived both from hematological and solid tumors including human acute T-lymphoblastic leukaemia, human splenic B-lymphoblastoid cells, human acute B-lymphoblastic leukemia, human skin melanoma, human breast adenocarcinoma, human lung squamous carcinoma, human hepatocellular carcinoma and human prostate carcinoma. The tests performed in this study were MTT assay, plaque reduction assays, anti-HBV assay, antibacterial assay and antimycotic assay.

The most active extracts for their anti-proliferative activity were those obtained from Nerium oleander, Centaurea subciliata and Ailanthus altissima.

Stability of Curcuminoids in Javanese Turmeric (*C. Xanthorrhiza*) Extract Formulated into O/W Emulsions

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Curcuma longa (turmeric) and C. xanthorrhiza (Javanese turmeric), are members of the Zingiberaceae family. Rhizomes are the most medically used parts of the plant. It mainly contains the following: curcuminoids, including curcumin; monodesmethoxycurcumin, didesmethoxycurcumin and methoxycurcumin, essential oil which contains turmerone and zingiberene, minerals (especially potassium) and vitamin C.

This plant has a variety of actions; anti-inflammatory, anti-oxidant, anti-arthritic, anti-oedemic, choleretic, hypotensive, antibacterial, antifungal, antiviral, anti-mutagenic, treatment of gastrointestinal disorders, anti-cancer, anti-hepatotoxic, abortifacient, possible androgenic effects, liver and gallbladder complaints, loss of appetite, insect repellent and insecticide. It is also used in the food industry as a colouring agent and in curry spices. Turmeric is well known for its traditional uses in folk medicine, e.g. treatment of epilepsy, asthma, skin disease, flatulence, liver problems, toothache, chest pain and colic. Furthermore, it is traditionally used in the treatment of diarrhoea, intermittent fever, bronchitis, colds, worms, leprosy, cystitis and kidney inflammation. It is externally used to treat bruises, leech and snakebites, eye infections, inflammation of oral mucosa, infected wounds and inflammatory skin conditions (Jayaprakasha et al. 2005, Maheshwari et al. 2006). This has brought attention to the beneficial activities of topical preparations formulated with the Javanese turmeric extract.

Chemical stability of the active constituents is well-recognized to be the most important quality determinant of any cosmeceutical product. Accelerated stability studies of curcuminoids in Javanese turmeric extracts were conducted under stress conditions for six months. Quantitation of the active constituents “curcuminoids” under stressed conditions has been evaluated by spectrophotometry of the pure and emulsified plant extract.

It has been shown that curcuminoids have degraded under certain conditions to vanillin, ferulic acid and feruroyl menthane which comply with the literature (Wang et al. 1997). Results have shown that they are more stable when formulated into O/W emulsions compared to their stability in dry or aqueous conditions. Therefore, the shelf life of the formulae can be estimated to be≈ 49 months at 25 ^{o}C, based on the Arrhenius extrapolations, and knowing that they were stable for three months at 40 ^{o}C.

Optimization and Validation of a New HPLC Method for the Analysis of Clopidogrel Bisulphate in a Pharmaceutical Formulation

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A reversed phase high-performance liquid chromatographic (HPLC) method was developed and validated for determination of Clopidogrel bisulphate in a pharmaceutical formulation.

The drug was chromatographed on reversed-phase C18 column, using mixtures of phosphate buffer/acetonitrile. The eluents were monitored at different wavelengths. The method was validated statistically for its linearity, accuracy, robustness and precision. Experimental design was used during validation to evaluate method robustness and for the determination of intermediate precision. Factors examined for statistical approaches include; laboratory, day, analyst, instrument, of organic modifier, wavelength and flow-rate. Due to its simplicity and accuracy, the method may be used for routine quality control analysis.

Studies on the Antihypertensive Effects of a Standardized Extract of *Solanum indicum* sp. Distichum.

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Solanum distichum fruits have been used in African folk medicine as an antihypertensive, but no studies have been reported to assess this effect. In the present study a standardized ethanolic extract of the fruits was tested for its blood pressure lowering effect in an L-NAME model of hypertension.

Albino Wistar rats were rendered hypertensive by the intraperitoneal injection of L-NAME twice daily for 1 week, when the rats developed a high blood pressure (measured non-invasively) accompanied by bradycardia. Simultaneous treatment of animals with L-NAME and the extract (orally) prevented development of hypertension but did not significantly affect the bradycardia. Starting treatment with the extract in doses of 1-100 mg/kg orally for 1 week after the development of hypertension whilst continuing L-NAME administration, tended to normalize the systolic blood pressure in a dose dependent manner. However, oral administration of the extract to normal rats for 4 weeks in doses up to 300 mg/kg did not show any significant hypotensive effect. The present results show a definite blood pressure lowering effect of the extract in hypertensive but not in normotensive rats.

The Application of Percolation Theory on Binary Mixtures of Chitosan and Xanthan Gum

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The application of percolation theory on binary mixtures of Chitosan and Xanthan gum was examined through studying compressibility and compactibility of the individual components and their mixtures. The compressibility of the examined powders was studied according to Heckel equation, Gurnham equation and Leuenberger's theory of powder compression. These models indicated the more ductile character of Chitosan compared to Xanthan Gum.

Furthermore, the compatibility of the examined powders was analyzed, where the scaling law with a fracture exponent 2.7 was used. Percolation thresholds showed that higher pressures must be applied to form compacts with specific strength as the mass fraction of Xanthan Gum was increased. Moreover, relative bulk and tapped densities, tensile strength at compaction pressure 100 MPa, maximum tensile strength and the mean activation energy per unit volume indicated the percolation threshold of Chitosan, i.e. site percolation, occurred at equal mass fraction of the two polymers, where its particles form infinite cluster that span through the whole system.

Modulating Cytokines Production from Stimulated Whole Blood by Stress-Induced, Preovulatory and Pregnancy Hormonal Levels

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Estradiol, progesterone, prolactin and cortisol concentrations are substantially increased during pregnancy. Also, cortisol and prolactin levels are elevated during stress. In the present study, we sought to expose peripheral blood to estradiol, progesterone, prolactin and cortisol alone or in combination for 24 hours before stimulation with T-dependent (phytohemagglutinin: PHA) and independent activators (lipopolysaccharide: LPS) to study their immunomodulatory role on IL-12, TNF-α, IFN-γ, and IL-10 production in a whole blood model. This apparently would be similar to in vivo exposure conditions such as long term stress, preovulatory or pregnancy periods.

The present study showed that the stress-induced and preovulatory levels of prolactin and estradiol, respectively, increased the production of IFN- γ and IL-12 levels (and IL-10 in case of estradiol) in PHA+LPS stimulated whole blood, and inhibited hydrocortisone (100 nmol/L) suppressive effect on IFN-γ, IL-12 and IL-10 productions. In LPS-stimulated whole blood, however, prolactin enhanced only IL-10 production levels in a non-concentration dependent manner. Higher prolactin levels as in pregnancy did not modulate any of the cytokines but pregnancy estradiol concentrations, only induced higher IL-10 levels in PHA+LPS stimulated whole blood. All progesterone levels tested revealed no effect on any of the cytokines following whole blood stimulation.

Our results indicate that 1) long exposure time of prolactin and estradiol to whole blood modulates the production of cytokines in a concentration and stimulus dependent manner; 2) stress induced levels of prolactin and preovulatory estradiol concentrations can regulate cortisol-induced cytokine suppression and 3) eventhough the cytokine pattern is different, pregnancy estradiol and cortisol levels decreased IFN- γ/IL-10 ratio, thereby keeping the anti-inflammatory IL-10 levels favored during pregnancy which could be useful in regulating inflammatory-mediated autoimmune diseases

Measurement of Cytokines in Tissue Extracts: Application to Drug Modulation of Inflammatory Mediators

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Determination of protein cytokines in local tissues would help to evaluate their local role in health, sickness behavior, immune-mediated diseases as well as the effect of drugs on modulation of such cytokines.

Mouse tissues were collected following intraperitoneal administration of endotoxin-free PBS or lipopolysaccharide. A mild detergent, 0.1% Igepal, was added in a buffer to enhance cytokines extraction. The tissues were then disrupted, homogenized, centrifuged and the supernatants were collected and assayed using solid-phase immunoassays.

The presence of 0.1% Igepal extracted significantly more TNF-α from liver (322%: $p<0.01$), brain (358%: $p<0.05$), lungs (1600%: $p<0.01$), and more IL-10 from liver (220%: $p<0.001$), brain (4650%: $p<0.001$) than PBS alone. On the other hand, using 0.1% Igepal did not increase IFN-γ extraction from liver, spleen, brain, lungs, skin and kidneys more than PBS alone. Furthermore, i.p. administration of LPS induced a differential milieu of cytokines. LPS increased significantly the production of TNF-α, IFN-γ, and IL-10 from liver (521%, 123%, 72%: $p<0.01$, 0.04, 0.04), brain (470%, 122%, 280%: $p< 0.01$, 0.03, 0.01), peritoneal lavage ($p<0.001$) and blood ($p<0.001$). However, the pattern of increase was different for the above cytokines in spleen, skin, lungs and kidneys.

The extraction of protein cytokines from tissues was superior with addition of mild detergent. Furthermore, our results showed a differential cytokines response to LPS with respect to tissue and cytokine type. This method should provide an important tool for studying local protein cytokines in behavioral pattern, sickness behavior, and immune-mediated diseases as well as to determine local therapeutic efficacy of immunomodulatory drugs.

Involvement of the Pore-forming Protein DCCD-binding Site in Hexokinase Binding to the Outer Mitochondrial Membrane

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The proportion of hexokinase that is bound to the outer mitochondrial membrane is tissue specific and metabolically regulated. This study examined the role of the N,N-dicyclohexylcarbodiimide-binding domain of mitochondrial porin in binding to hexokinase I. Selective proteolytic cleavage of porin protein was performed and peptides were assayed for their, effect on hexokinase I binding to isolated mitochondria. Specificity of DCCD-reactive domain binding to hexokinase I was demonstrated by competition of the peptides for porin binding sites on hexokinase as well as by blockage hexokinase binding by N,N-dicyclohexylcarbodiimide. One of the peptides, designated as 5 kDa (the smallest of the porin peptides, which contains a DCCD-reactive site), totally blocked binding of the enzyme to the mitochondrial membrane, and significantly enhanced the release of the mitochondrially bound enzyme. These experiments demonstrate that there exists a direct and specific interaction between the DCCD-reactive domain of VDAC and hexokinase I. The peptides were further characterized with respect to their effects on certain functional properties of hexokinase I. None had any detectable effect on catalytic properties, including inhibition by glucose 6-phosphate. To evaluate further the outer mitochondrial membrane's role in the hexokinase binding, insertion of VDAC was examined using isolated rat mitochondria. Preincubation of mitochondria with purified porin strongly increases hexokinase I binding to rat liver mitochondria. Collectively, the results imply that the high hexokinase-binding capability of porin-enriched mitochondria was due to a quantitative difference in binding sites.

Study of the Effects on DNA of Two Isoxazolidinyl Nucleosides

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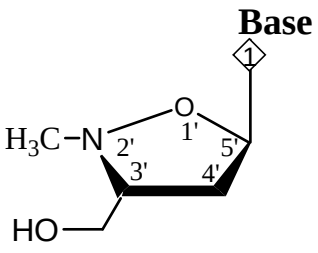
The pursuit of antiviral active compounds against different classes of viruses, in particular HIV, HBV and HTLV is an area of important and intense research.

In the present work, two novel Isoxazolidine nucleoside derivatives were successfully synthesized by replacement of the furanose ring by a N,O- heterocyclic ring as shown in figure. Both compounds were investigated for some biological activity, namely, mutagenic and antimutagenic properties. Using *Salmonella typhimurium* strains, TA97, TA100 and TA102, both compounds proved to be nonmutagenic which may be considered as encouraging results to further elucidate other biological activities. Antimutagenic testing of the synthesized compounds revealed that they are active against the base pair substitution mutagen, sodium azide. However, they did not show any indication as antimutagenic agents against hydrogen peroxide and mitomycin C (oxidative mutagens) or against nitrophenylenediamine(a frame shift mutagen) . The elucidation of the genotoxicity of these newly synthesized derivatives is of great importance to ensure their safety before proceeding towards any their practical use. Furthermore, testing their antimutagenicity could be an indication for their potential anticarcinogenic action.



Base
Thymine
Adenine

Bioequivalence Study of Two Formulations of Ketoconazole Tablet in Healthy Volunteers

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The objective of this study was to obtain the pharmacokinetic data of two marketed tablet formulations of ketoconazole and compare the relative bioavailability of the test formulation with reference formulation.

A single dose 12×2 double blind randomized crossover study of a generic formulation of ketoconazole tablet (2×200mg) and a commercial brand; Nizoral tablet (2×200mg, Janssen Pharmaceutica Beerse Belgica) was carried out. All the tablets met the United States Pharmacopoeia dissolution specifications. The plasma concentrations of ketoconazole were determined by using a modified rapid and selective reverse phase high-performance liquid chromatographic (HPLC) method. Plasma data was used to evaluate relative bioavailability and other pharmacokinetic parameters characterizing rate [peak plasma concentration (C_{max}) and time of peak concentration (T_{max})] and extent of absorption (AUC).

The mean peak plasma concentration (C_{max}) of ketoconazole of the two different formulations, A (reference) and B (test), were 7.08 ± 2.81 and 6.74 ± 2.20 mg/l at 1.70 ± 0.48 h and 1.73 ± 0.75 h respectively. The mean $AUC_{0-\infty}$ of the two products, A and B, were 39.07 ± 16.25 and 31.85 ± 14.64 respectively. Statistical analysis showed no significant differences between various pharmacokinetic parameters of the two different formulations. The 90% parametric confidence intervals for the mean of test/reference ratios of C_{max}, AUC_{0-12}, $AUC_{0-\infty}$ and $C_{max}/AUC_{0-\infty}$ were within the bioequivalence acceptable range (80-125%).

Results of this study showed that the extent and rate of absorption of ketoconazole tablets tested are comparable and the generic formulation is bioequivalent to the commercial product.

BMP2 Signaling Pathways Mediate *GNAS* Transcriptional Regulation in C2C12 Cells: Implications for Progressive Osseous Heteroplasia

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Progressive osseous heteroplasia (POH) is an autosomal dominant disorder characterized by ectopic bone formation within subcutaneous adipose tissue, followed by disabling and wide spread ossification within skeletal muscle and deep connective tissue. Previously we demonstrated that POH is caused by heterozygous inactivating mutations in the *GNAS* gene. *GNAS* contains multiple promoters and first exons and encodes several messenger RNAs: a stimulatory G protein alpha-subunit (Gsα), neuroendocrine-specific protein (NESP55), and extra large Gsα (XLsα), an isoform of Gsα, as well as some non-protein-coding RNAs. In the present study, we used the multipotent C2C12 mesenchymal mouse cell line to examine the effect of BMP2, a potent osteogenic morphogen, on the expression of *Gnas* gene products and osteoblast differentiation. BMP2 induced an increase in the expression of Runx2 and osteocalcin mRNA, markers of osteoblast differentiation, in a dose dependent manner. BMP2 also increased alkaline phosphatase activity. The stimulation of osteoblast differentiation by BMP2 was accompanied by enhanced Gsα protein expression. By contrast, BMP2 was an effective suppressor of XLsα and NESP55 mRNA expression. These data support a functional connection between *Gnas* gene products and osteoblast differentiation in C2C12 cells and a role for *Gnas* in mesenchymal cell differentiation to the osteoblast lineage.

Myoblasts Are Not the Likely Primary Target Cells of Gs 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.

Substetuted phenyl boronate esters of chloramphenicol as a potential latentiation form.

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Some novel compounds were synthesized as potential lamentation from. (table) these Compounds were heterocyclic derivatives of chloramphenicol some of which incorporative a boron atom. The boronate derivatives retained the antimicrobial activity of chloramphenicol.(invite) .

Table:- Minimun inhibitory comcentration range of substituted phenyl boronate esters of chlramphenicol measured against Staph. Aureus and E. coli in deionized water by a stan dard serial dilutions technique.

Compound Name	Minimum Inhibitory Concentration range (ug/cm)	
	Staph. Aureus	E.coli
Phenyl boronate ester	20-30	20-30
4-Bromopheny boronate ester.	5-10	5-10
3-Nitophenyl boronate Ester.	5-10	5-10
3.5- Trifluouomethy1 phenyl boronate ester	20-40	20-40
Chloramphenicol	5-10	2.5-5

Consideration of the results in table show that the substituted phenyl boronate esters are as or less active than the parent antibiotic, confirming the preliminary screening results obtained by the B.P??

It is of considerable interest that the substituted phenyl boron ate esters of chloramphenicol have any antimicrobial activity. It has been previously reputed that any reaction involving the C1 and C3 hydroxy, groups of chloramphenical leads to the formation of biologically inactive products, whin assissed in vitro. The boron ate esters are formed by reacting the hydroxyl groups on chloramphenicol.examination of molecular models of the substituted phenyl boronate esters of chloramphenicol, We suggested that models of the substituted phenyl boron ate esters of chloramphenicol, we suggested that the coordination of the boron aom with the amide nitrogen atom facli-lates retention of the active d-threo conformation. Suppot for this is provided by comparison with the biologically inactive analogues of the non boronate esters in which the boron atom is replaced by a Methane group. Such compounds do not retain the D-threo conformation due to the absence of the coordination bond fixing the conformation.

EFFECT OF AQUEOUS EXTRACT OF *S. NIGRUM* ON IMMOBILIZATION STRESS INDUCED ANTIOXIDANT DEFENSE CHANGES IN RAT PLASMA

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Solanum nigrum is commonly known as mako, is a medicinal plant found throughout India. The extract of this plant is found to cure various diseases probably through its antioxidant effect. In the present study the antioxidant potential of the leaves extract was evaluated on the modulation of restraint induced oxidative stress. Restraint stress induced pro-oxidant status of plasma was measured in terms of measurement of lipid peroxidation and free radical scavenging enzyme activities. Rats were treated with crude extract of *S. nigrum* alone, and both before and after 6 h of stress exposure. Pro-oxidant effect of rat plasma was evaluated by determining the activities of superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST) and lipid peroxidation (MDA). Six hours of restraint stress caused a significant decrease in the activities of SOD, CAT and GST, while increase in the levels of MDA. Both pre and post treatments of extract were found effective in restoring the stress induced altered free radical defense changes towards their control values, with a relative dominance by later. Six hours of restraint stress induced oxidative derangements in rats, by decreasing the levels of free radical scavenging enzymes, which is depicted by enhanced levels of (MDA). The post treatment of crude extract of *S. nigrum* was found more effective in restoring restraint stress induced changes in rat plasma than pre treatment. In order to reduce oxidative stress, observed in many pathological conditions, the *S. nigrum* leaves extract can be given both as a prophylactic and therapeutic supplement for scavenging free radicals.