Clini News

August / September 2003 Drug Information Center Al Jazeira

Top five questions:

Q1: Can Plavix ® Clopidogrel be given via naso-gastric tube?

Answer: there is no particular study to evaluate this route of administration, however there is no restriction if clinical practice necessitate the use of this route, knowing that the bioavailability of Clopidogrel is unaffected by food or antacid. It is recommended that the tablet be crushed just before administration.

Q2: Does Evista ® Raloxifen need dose adjustment in case of renal insufficiency?

Answer: Raloxifene is a selective Estrogen modulator (agonist / antagonist properties); the main indication of which is the prevention and treatment of postmenopausal osteoporosis. The liver extensively metabolizes the drug; only 0.2% is excreted unchanged and less than 6% as glucuronide via the kidney. In the osteoporosis treatment and prevention trials, Raloxifene and metabolite concentrations in women with estimated creatinine clearance as low as 21 ml / min. is similar to women with normal creatinine clearance. Therefore no dose adjustment is needed in case of renal impairment.

Q3: If a Patient with Dyslipidemia had reached the maximum dose of Statin, yet the LDL cholesterol is still extensively high, which Antihyperlipidimic agent can be added with proved efficacy and safety in combination?

Answer: Combination therapy is the next logical step for patients who do not achieve lipid goals with monotherapy. The addition of **Cholestyramine (Questran)** is both effective and no evidence of interactions with Statins, the gastrointestinal adverse effects of cholestyramine are dose related so it is best to prescribe the lowest effective dosages to increase tolerability**. Fibrate**- Statin has the biggest concern for safety, as this combination was associated with 9% of statin induced rhabdomyolysis cases which had been reported to the FDA from 1997-2000.
However Statin- **Niacin** combination still has the potential for drug –drug interaction, Niacin potentiate statin induced myopathy and rhabdomyolysis, but to lesser extent than Fibrates, There are 4 reports out of 871 rhabdomyolysis cases were attributed to this combination. Another possibly safe combination is with **Ezetimibe**, the first of a new class of lipid lowering agents, it works by inhibiting cholesterol absorption from the intestine and was found to be more effective than placebo in “Add-On” study, a multi-center, placebo controlled study, when it was added to ongoing Statin mono-therapy.

Q4: For how long can Intravenous Acetylcysteine be used in the management of Acetaminophen (Paracetamol) toxicity?

Answer: There is controversy for the optimal dose, duration, and timing of Acetylcysteine administration for the management of Paracetamol toxicity.
There are two regimens had been developed based on 2 multicenter open label trials for the intravenous administration:

- 20- hour regimen, which delivers 300mg/kg (150mg/kg infused over 15 minutes, followed by 50mg / kg infused over 4 hours, then 100mg /kg infused over the next 16 hours).
- 48- hour regimen, which delivers 980 mg/kg (140mg/kg as loading dose, followed by 70 mg /kg every 4 hours for a total of 12 doses).

These 2 regimens differ in the time and laboratory criteria, when to start treatment with Acetylcysteine, the absence of a comparative trial for these 2 regimens makes it difficult to determine which one is preferable. However it was found in both trials that starting treatment within 10 hours of Paracetamol ingestion decreases significantly the risk of hepatotoxicity, while the risk increased if the treatment was started 10-24 hours after ingestion.
The treatment after 24 hours after paracetamol ingestion is proposed to improve the outcome in patients with fulminant hepatic failure, although this data was studied on 50 patients only. Waiting for larger controlled studies, delayed Acetylcysteine is recommended and should be continued until there is recovery from paracetamol induced fulminant hepatic failure or the patient's death.

Q5: In case of pregnant women, do we need to reduce the dose and the frequency of dosing of antibiotics in an attempt to reduce the teratogenic effects?

Answer: All antibiotics diffuse across the placenta to some extent and most of them will reach a concentration similar to that of the mother plasma.
There are many antibiotics that are contraindicated or relatively contraindicated during pregnancy e.g. Tetracycline, Fluoroquinolones, Co-Trimoxazole and Metronidazole.
Our discussion will include only those, which are safe or relatively safe to be used during pregnancy.
Pregnancy causes a lot of pharmacokinetic changes that are more pronounced in the third trimester, plasma volume increases by 40-50% thus increasing the volume of distribution for both lipid and water soluble drugs, concentration of plasma Albumin decreases, however the total plasma protein remain relatively unchanged. The total plasma concentration of albumin – bound drugs decrease due to hemodilution and the clearance may be increased due to increased cardiac output, and an increase in renal and liver blood flow. These all may necessitate higher loading, maintenance doses and frequency of dosing for some antibiotics like Cephalosporins and Penicillins in cases of life threatening infections to prevent failure of treatment and hazards of infection.

The following box includes some important points to be considered before prescribing to pregnant women:

General principles of prescribing during pregnancy:

- Prescribe drugs only when necessary.
- Use the lowest effective dose for the shortest possible time but remember that under treatment poses risk for both the mother and the fetus.
- Use minimum number of drugs, as some teratogenic drugs have been shown to act synergistically.
- Prescribe older, more established drugs instead of newer drugs.
- Teratogenic risk should be considered when prescribing for any woman who becomes pregnant.

Psychotropic drugs induced Hyponatremia

Psychotropic medication-induced hyponatremia is an important clinical problem if not recognized and treated early. US food and drug administration had received a lot of reported cases of Hyponatremia / SIADH associated with psychotropic medication from 1966 to 1999, Most of which were associated with SSRIs (811 reports), and Fluoxetine (Prozac®) represented more than 50% of these case reports (436 reports).
ADRAC (Australian Drug Reaction Advisory Committee) had received a total of (311 reports) of Hyponatremia with the SSRIs and Venlafaxine, in more than two- thirds of the 311 reports, the SSRI was the only suspected drug.

Hyponatremia:

Initially patients may be asymptomatic or may experience nausea, malaise or confusion. As the serum concentration continue to drop, further symptoms include headache, muscle cramps, lethargy and agitation.
Stupor, seizures and coma usually occur when the sodium concentration is below 120 meq / L or when the drop is very rapid.
The risk of SSRIs induced Hyponatremia found to be increased with

- Advanced age
- Female gender
- Concurrent medication that can cause hyponatremia i.e. Diuretics
- Medical co morbidity (edema, liver disease,etc)

From the above it seems that elderly female who is already on diuretic treatment will be at high risk of developing hyponatremia when one of the SSRIs to be added to her treatment. The risk was found to be higher during the first 2 weeks of treatment, and the mechanism of Hyponatremia appears to be via induction of SIADH.

Drug safety update:

Topiramate (Topamax®) may decrease sweating and consequently elevates body temperature.

Information about this safety updates has been sent to doctors and pharmacists working in Canada to ensure that they are aware of the new safety information.
There have been rare reports of decreased sweating and increased body temperature in patients taking Topamax®.

Decreased sweating and increased body temperature may have potentially serious health consequences, (two reports of hospitalization). Reports have primarily involved children and most cases have occurred in association with exposure to warm weather and/ or energetic activity.
Parents should ensure sufficient water intake by their children who are taking Topamax® prior or during exercise or exposure to warm weather, and they should contact health care professional if they noticed symptoms of decreased sweating and increased body temperature.

New Formulation:

Influenza Virus Vaccine live, Intranasal

Influenza is a highly infectious respiratory viral infection that causes recurrent epidemics of acute diseases in persons of all ages.
Type A and B influenza viruses are the principle causes of influenza in human.
Each year the vaccine should be changed due to continuous mutation of the viral genome, the currently available form is the injectable form, which is suitable to be used starting from 6th month of age. Recently 17th June 2003 the FDA had approved an intranasal, trivalent, cold-adapted, live, attenuated influenza vaccine for use in healthy persons aged 5–49 years to prevent influenza A and B. The newly approved vaccine provides an important new option for vaccinating healthy persons who are 5-49 years of age, and either wishes to avoid influenza or are in close contact with persons at high risk for developing serious complications from influenza infection.

The new product is named FluMist®, which is a single dose (0.5 ml) has to be divided (0.25ml) and placed in each nostril as vaccination for adults, children who had already received vaccination the previous year will receive the same adult dose, however children who are vaccinated for the first time need to receive 2 separated doses (60 days apart) each of which is (0.5ml).

Adverse reactions:

Nasal congestion, rhinitis, and sinusitis were reported more significantly more often by FluMist users during the clinical trial compared to Placebo.

Cautions and contraindications:

- Children or adolescent who are receiving Aspirin should not receive FluMist
- Patients who are receiving immunosuppressive treatment should never receive life vaccines
- Patients who are receiving antiviral treatment should not receive FluMist until 48 hours after the cessation of antiviral therapy, and antiviral therapy should not be administered until 2 weeks after administration of FluMist unless medically indicated.

Pregnancy:

It is category C; it should not be administered to pregnant women

Lactation:

Caution, as it is not known whether it is excreted in breast milk, and possibility of shedding vaccine virus due to the close proximity of a nursing infant and mother.

All references are available upon request at "Drug Information Center", Al- Jazeira Hospital, Abu Dhabi. Ext.518.