Clini News

December / January 2004 Drug Information Center Al Jazeira Hospital

## Top five questions:

*Q1: Can Minocycline exacerbate migraine attack?*

*Answer:* One of the most serious adverse effects of Minocycline is Pseudotumor cerebri (benign intracranial hypertension), which is characterized by the following symptoms; occipital pain, diplopia, blurred vision and nausea, which may be mistaken with Migraine headache.
However in the drug info leaflet of Minocin®, it is mentioned that cases of headache have been reported with its use.

*Q2: Is H. pylori eradication therapy (Amoyycillin, Clarithromycin, and omeprazole) compatible with breast-feeding?*

*Answer:* Amoxycillin is the only one of these 3 drugs that is considered to be safe and compatible with breast-feeding.
However Clarithromycin is unknown whether or not it is excreted in the human breast milk, the animal studies have shown that it is excreted in the breast milk in considerable amount, but no information whether or not the suckling animals had adverse effects. Due to lack of information, it is better to avoid its use during breast - feeding.
Omeprazole is unsafe as well as all PPIs based on animal studies. It is excreted in rodent's milk and the suckling pups have experienced various adverse effects including decreased ability of weight gain. However all the PPIs are associated with potential tumorigenicity in rodent studies.
In conclusion: PPIs, which is considered the cornerstone in most if not all protocols for eradication of H. Pylori should be avoided during breast feeding.

*Q3: Is Aescin (Reparil ®) safe to be used in case of renal impairment?*

*Answer:* Aescin is one of the active constituents of a medical herb named the Horse Chestnut; it has many medical uses, the most important of which is the treatment of chronic venous insufficiency.
According to many herbalists this herb and its constituents should be used cautiously in patients with hepatic and renal impairment. However some reports of acute renal failure in children who received high doses of Aescin (2-3 times higher than the

recommended dose), the course of the treatment was for an average of 4 days postoperatively.
Animal and in vitro studies suggest that high doses of Aescin may contribute to existing nephro-toxicity, especially if it was displaced from albumin.

*Q4: Is it safe for a psychotic patient who is on regular Risperidone and Valproic acid to use Sibutramine (Reductyl®) for weight control?*

*Answer:* Obesity is a common problem among patients with certain mental disorders like Schizophrenia, Bipolar disorder and binge eating disorder, this is either due to the course of the disorder itself, or due to the drugs that have been used for the treatment of such disorder i.e. antipsychotic – induced weight gain.
The use of centrally active compounds with weight loss properties (Dexfenfluramine and Sibutramine) to treat this problem for patient with schizophrenia is generally discouraged, since they recruit and engage monoamines implicated in the pathophysiology of mood and psychotic disorder, and there have been a number of reports of patients developing psychosis with manic and /or schizophrenic features while taking Dexfenfluramine, or Sibutramine. In addition there are lacking of large studies to address the safety of the use of this class of drugs in mentally ill patients with obesity.

*Q5: What is the dose of Itraconazole in the treatment of esophageal candidiasis in a patient who is ESRD and on hemo-dialysis?*

*Answer:* For the treatment of Oesophageal candidiasis the oral solution form is preferable than the capsule form, the recommended dose is 100mg, which is available in 10ml solution to be swished vigorously in the mouth for several seconds, then swallowed once daily for 21 days, the patient may use it for another 2 weeks after resolution of the infection, the dose may increase to 200mg if response is not satisfactory.
Dose adjustment does not seem required in case of renal failure or patients who are on hemo-dialysis.

## Evidence for the benefit of the clinical use of Angiotensin converting enzyme inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs) in Combination (Dual blockade) Part II

In the last issue the evidence for the beneficial use of dual blockade had been discussed for the prevention and treatment of nephropathy with or without diabetes mellitus, in this issue evidence for use in heart failure will be addressed.

Several trials have evaluated the result of combining ACEIs with ARBs in patients with heart failure.
In small-scale studies, dual blockade consistently showed superior results to ACEIs monotherapy with regard to exercise tolerance, hemodynamic effects and neurohormonal activation [1,2]
The **RESOLVD pilot study** [3] which involved 768 patients

who were randomized to receive 3 different doses of Candesartan (4,8 and 16mg) alone or Enalapril alone in a dose of (20mg/day), or in 2 combinations as follow (4mg Candesartan + 20mg/day Enalapril) and (8mg Candesartan + 20 mg/day Enalapril) to see the effect on exercise tolerance, ventricular function, neurohormonal parameters. The authors observed that although clinical outcomes data were not statistically significant for all treatment groups, there was trend toward better results in combination concerning prevention of left ventricular dilatation and improving ejection fraction. However dual blockade therapy was the only one to have decreased exercise tolerance at 18 and 43 weeks.
Unfortunately the study was prematurely stopped because there was higher numerical incidence of deaths in both the Candesartan and the Dual blockade groups compared with Enalapril alone. However this was not statistically significant and the study was not designed as a mortality / morbidity study.

*To address the benefit of the dual blockade on mortality and morbidity, two big randomized controlled trials were done (**Val-HeFT & CHARM).***

**Val-HeFT [4]:**
This study involved 5010 patients with heart failure (NYHA class II, III, IV in addition they had LV dysfunction with EF <40%); all patients were on standard heart failure treatment, which of course include ACEIs (93%of the study population), Beta-blockers (35%), Digoxin, Diuretics and (Spironolactone ~38%).
Patients were randomized to receive Valsartan 160 mg twice daily or Placebo for mean of 23 months in addition to their existing therapy.
The 2 primary end points were

- Mortality
- Combined end point of mortality and morbidity
    - Incidence of cardiac arrest
    - Hospitalization for heart failure
    - Receiving IV Inotropic or vasodilator therapy for at least 4 hours without hospitalization.

The results showed no difference between the two treatment groups concerning mortality, but the combined morbidity and mortality end point was in favor of Valsartan group.
In subclasses analysis those who used ACE Is + Valsartan or placebo were 3034 patients and the results was in favor of the Dual blockade in the combined end point and to less extent in mortality alone.
*In a sub – group analysis of this study, it was shown that among the patients receiving ACEIs + Beta blockers at baseline, Valsartan had an adverse effect on mortality (p=0.009) and was associated with a trend towards an increase in the combined end point of mortality and morbidity.*

**These results had an Impact on the ESC guidelines 2001, in which this triple therapy (ACEIs+ ARBs + Beta blockers) is not recommended till further investigation to be done.**

**CHARM [5]**
One part of the Trion CHARM study is CHARM – Added trial, in which 2548 patients with CHF and LVEF < / = 40%, who had been taking an ACEI (Enalapril,

Lisinopril, Captopril, or Ramipril) in Optimum doses (96% of the patients) as part of conventional therapy, for at least 30 days prior to study entry, were randomized to receive either Placebo, or 4 or 8 mg candesartan once daily and the dose being doubled every two weeks, as tolerated up to the target dose 32 mg / day. The patients were followed for a median of 41 months.
17% of the patients were on Spironolactone.
**55% of the patients were on Beta-blockers at the beginning of the trial, and by the end the number had reached 64% in Candesartan group and 68% in the placebo group.**
The primary outcome were

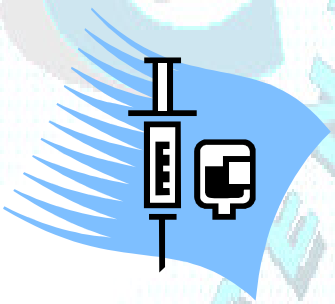
- CV death
- CHF hospitalization

The study showed that the addition of Candesartan to ACE inhibitors (and Beta blockers) gave clinical benefit, that was revealed in relative risk reduction of 15% of the primary end point CV death or hospital admission during the study duration (41 months).
In conclusion:
This study shows benefit of the addition of ARBs in patients on recommended doses of ACEIs, and also contradicts the Val-HeFT safety concerns about the addition of ARBs to background of ACEIs +Beta blockers.


(1) Hamroff et al **Circulation 1999** 99: 990 - 992
(2) Baruch et al **Circulation 1999** 99: 2658 – 64
(3) McKelvie etal **Circulation1999** 100: 1056 – 1064.
(4) Jay N.Cohn, And Gianni Tognoni **NEMJ** Dec 6, 2001 345, (23): 1667-75.
(5) **THE LANCET** 362. Sep. 6, 2003: 759-81


## New Labeling:

FDA approves revisions to Lovenox (Enoxaparin) labeling to address obese, Low weight and renally impaired patients



Aventis announced that the US FDA has approved a supplemental new drug application for its Lovenox® (Clexane ® in UAE) antithrombotic therapy to provide additional information on pharmacokinetics, precautions and dosing administration for obese and low – weight patients and those with renal impairment.
The revised labeling contains new data from pharmacokinetic studies required by the FDA and analysis of other safety data that pertain to specific patient populations, including;

- Obese patients
- Low – weight patients
- And those of severe renal impairment (Cl cr <30 ml / min).

The package insert provides a chart that may assist health – care providers in determining the proper dose for patients with **severe renal impairment**.

*All references are available upon request at*
*(Drug Information Center - Al Jazeira hospital) Tel.- 026214800 - Ext.- 518*