Clini News

October / November 2003 Drug Information Center - Al Jazeira hospital

Top five questions:

Q1: What is the pediatric dose of Tetracycline?

Answer: the package inserts for parentral and oral Tetracycline have warned against their use in children less than 8 years of age since 1972, this because of the potential for causing permanent discoloration of the teeth as well as enamel hypoplasia. Therefore Tetracycline should not be used in this age group unless other drugs are not likely to be effective. For children 8 years of age and older, the usual Oral daily dose is 25-50 mg / kg/ day divided in 2-4 equal doses, for Intramuscular route there are 2 doses according to the body weight:

-**Children over 40kg**: 250mg every 24 hours or 300mg in divided doses at 12 hrs.

-**Children less than 40 kg**: 15-25mg /kg /day up to a maximum of 250 mg in a single injection or in divided doses at 12 hrs interval.

Intravenous route is not encouraged.

Q2: which one of the following analgesics can be used for a woman who is breast-feeding, Diclofenac (Voltaren), Co-proxamol(Distalgesic) or Orphenadrine-paracetamol (Muscadol)?

Answer: both Diclofenac and Orphenadrine / Paracetamol are unknown whether being excreted in the milk or not, therefore better to Avoid. However Co-Proxamol is considered safe and compatible with breast-feeding by the American Academy of Pediatrics.

Q3: Does Metformin have any caution with Radio-study?

Answer: Yes, It is recommended that prior Radiology study Metformin should be stopped and should not be restarted for 48 hours after Iodinated contrast Media, the Kidney function should be assessed and should be in the normal range before beginning Metformin.

Mettformin should not be used in severe Renal Impairment, or in situations, which may induce acute renal failure.

Q4: Is there any link between the use of Cyclosporin and Gallstone?

Answer: Yes, In one study it was found that there is increased rate of incidence ~ 7% of Cholelithiasis out of 90 pediatric patients compared with incidence rate of 1% of the normal children (under 16 years) in the general population.

It was found also in several studies, that adult transplant patients (kidney and heart) patients had increased incidence of cholelithiasis when given Cyclosporin.

Q5: What is good alternative drug to penicillin for skin and skin structure infections for a patient who is documented to be allergic to Penicillin and Sulpha - containing drugs?

Answer: the Antibiotic of Choice is Azithromycin, the recommended dose is 500mg in the first day then followed by 250 mg daily for another 4 days.

This is FDA labeled Indication.

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 I

Both ACEIs and ARBs had already been confirmed to have clinical benefit in retarding the progression of chronic renal disease, favorable hemodynamic effects in heart failure, and a good control of blood pressure in patients with essential hypertension.

The fact that ACEIs and ARBs antagonize the Renin-Angiotensin System (RAS) at different levels suggests that these agents may have additive or even greater effect when used in combination, the rationale behind that is complete blockade of (RAS), Since ACEIs block the production of AngiotensinII by inhibiting the Angiotesin converting enzyme, but have no effect on non-specific chymase pathways that lead to the production of AngiotensinII. On the other hand ACEIs lead to accumulation of Bradykinin, which has the following potential benefits (potent vasodilator, increases endogenous tissue plasminogen activator, increases natruresis). Therefore combination therapy would lead to full blockade of the effect of AngiotensinII on the Angiotesin- type 1 receptor as well as preserving the accumulation of Bradykinin and its beneficial effects.

Evidence for Renal protective effect of the dual blockade:

- **Dual therapy and renal protection in non diabetics**

Although dual blockade therapy efficiently reduced the blood pressure and proteinuria in case of non-diabetic nephropathy*, large clinical trials still needed to be conducted, as the majority of dual blockade studies were small, add- on type with short follow up periods.

The only big randomized, controlled end point trial in hand is COOPERATE*, in which the investigators found a significant end point reduction with dual blockade therapy compared with monotherapy with Trandolapril or Losartan.

Over a 4 year period 256 non-diabetic patients with proteinuria where randomized to 3 treatment arms Dual blockade of(Trandolapril 3mg plus Losaratan 100mg), Trandolapril 3mg/day alone, or Losartan 100mg/day alone. There was a highly significant reduction in the primary end points (doubling of Serum craetinine and ESRD) during follow up compared with either monotherapy, independent of disease stage at inclusion.

The frequency of side effects with combination treatment was the same as with Trandolapril alone.

* *Only abstracts are available*

- *Kinacid S. Nephrol Dial Transplant 2002.* ***17*** *(597-601)*
- *Ferrari P. et al J Hypertens 2002* ***20*** *(125-135)*
- *Keng-Thye Woo et al Kidney Int 2000 58 (2485-2491*
- *Luis M. Ruilope et al J Hypertens 1999 18 (89-95)*

**Only abstract is avialble*

- *Nayuki Nakao et al The Lancet Jan 2003 vol 361 issue 9352 (117-124).*

- **Dual therapy and renal protection in diabetic nephropathy**

The use of dual blockade of RAS in this indication also did not have solid evidence by large trials; only few studies have been published even though the indication seems obvious*.

Type I - DM

In one study * Benazepril 20mg once daily, 80mg of Valsartan once daily, and the combination of both were used in a randomized double blind crossover manner with placebo in **20 patients** with **diabetes mellitus Type I** and **diabetic nephritis** for 8 weeks. At the end of this period Albuminuria, 24 hour BP, and GFR were measured. All treatment groups significantly reduced albuminuria and BP compared with placebo, Benazepril and Valsartan were equally effective. Dual blockade induced an additional reduction in albuminuria of 43% compared with any type of monotherapy, and reduction in systolicBP by ~7 mm Hg, and diastolic BP by 7 mmHg compared with monotherapies.

The GFR was reversibly reduced on dual blockade compared with monotherapy and placebo.

The author concluded that dual blockade of RAS may offer additional renal and cardiovascular protection in Type I diabetic patients with diabetic nephropathy.

Type II- DM

The Candesartan and Lisinopril Microalbuminuria (CALM) study is the largest dual blockade trial concerning diabetic patients*.

This randomized double blind study was performed on 197 patients between 30 and 75 years of age who were previously diagnosed as Type II – DM, hypertensive with microalbuminuria.

The patients were treated with either 20 mg of **Lisinopril**, 16 mg of **Candesartan**, or both drugs in combination.

After 4 weeks of placebo treatment, patients were treated with Lisinopril or Candesartan for 12 weeks. Thereafter, patients continued with either monotherapy or the combination of Lisinopril and Candesartan for additional 12 weeks.

The entire three-treatment regimens significantly reduced BP from baseline to 24 weeks, **with dual blockade significantly being the most effective.** The trial also found greater reductions in the urine albumin – creatinine ratio with the combination treatment 50% compared with Lisnopril alone 39% and Candesartan alone 24%. However the difference were not significant after adjusting for Diastolic blood pressure, baseline value and weight.

Conclusion: Candesartan is as effective as Lisinopril in reducing both BP and microalbuminuria. However the combination is well tolerated and more effective in reducing the blood pressure, and also has greater but non-significant reduction in Albuminuria than monotherapy.

There are few other small studies* have been published on using dual blockade treatment to treat hypertension and nephropathy in patients with Diabetes millets, only sites are mentioned at footnote.

* *Jacobsen et al JASN 2003, 14 (4) 992*
* *Mogensen CE, Neldam S. et al BMJ 2000, 321: 1440-1444*
* *Hebert LA et al Am J Nephrol 1999,* ***19:*** *1 - 6*
* *Rossing K et al Diabetes care 2002* ***25:*** *95 -100*
* *Agarwal R et al kidney Int 2001* ***59:*** *2282 -2289*
* *Kuriyama S et al Hypertens Res 2002 Nov,* ***25 (6) : 849 -855***

This article will continue in the next issue of Clininews inshaaAallah

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Drug safety Updates:

Rifampicin plus pyrazinamide should not be used together in the treatment of Latent TB infection according to CDC:

The August 8, 2003 MMWR had an article on Adverse event Data and Revised American Thoracic Society / CDC recommendations against the use of Rifampicin and Pyrazinamide for treatment of latenet Tuberculosis infection.
This combination was approved to be used for the treatment of LTBI for 2 month regimen (Rifampicin 600mg OD + Pyrazinmide 15 – 20 mg / kg /d) in April 2000, since then increased reports of Rifampicin / Pyrazinamide associated severe liver injury 48 cases, 11 were fatal, including 2 known to be HIV- infected.
The CDC had collected data from cohorts of patients in the US who received Rifampicin / Pyrazinamide for the treatment of LTBI from 2000 to 2002. They found high rates of hospitalization and death from liver injury with this combination.
The response of CDC contain the following comment "*Although we are recommending against the use of Rifampicin / Pyrazinamide regimen, we continue to strongly support the treatment of LTBI as a key component of CDC's effort to eliminate TB. Fortunately, other regimens for the treatment of LTBI are safe and effective*"
It is important to note that the recommendation against the use of Rifampicin / Pyrazinamide combination for the treatment of LTBI does not apply to the appropriate use of Rifampicin and Pyrazinamide in multidrug regimens for the treatment of persons with active TB disease.

All references are available upon request at
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