DRUG & THERAPEUTICS LETTER

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Contents

COX-2 Inhibitors and Thrombo-embolic Events

Cycloxygenase-2 (COX-2) inhibitors like celecoxib and rofecoxib are widely used for their higher gastro-intestinal tolerance as compared to nonselective NSAIDs. Analgesic and anti-inflammatory actions of COX-2 inhibitors are due to their effective inhibition of prostaglandin synthesis catalyzed by COX-2 iso-enzyme which is massively upregulated in inflammatory states such as rheumatoid arthritis.

Non-selective NSAIDs inhibit both COX-1 and COX-2 iso-enzymes. COX-1 is involved in synthesis of vasodilator and platelet aggregation inhibitor like prostacyclin, and platelet aggregator and vasoconstrictor like thromboxane A_2.

COX-2 iso-enzyme is responsible for production of large amount of prostacyclin from vascular endothelium but it is not responsible for production of thromboxane A_2 from platelets. In other words, selective COX-2 inhibitors do not inhibit the synthesis of thromboxane A_2 but inhibits the production of prostacyclin. This results in tilting of balance towards vasoconstriction and thrombosis. Hence it is suggested that low dose aspirin should not be stopped in patients with risk factors for thrombosis even if COX-2 inhibitors are concurrently prescribed.

Some prescribers are on false impression that COX-2 inhibitors would be safer as well as more

effective. There is no reason to expect that COX-2 selective inhibitors have greater efficacy because they are able just to inhibit the iso-enzymes responsible for inflammation.

It is established that maintenance of renal perfusion and function relies on renal prostaglandin synthesis. Conventional NSAIDs are known to impair renal function. The possibility that selective COX-2 inhibitors might not manifest this adverse effect has unfortunately turned out to be wrong.

Conclusion: COX-2 inhibitors became popular because of its lower risk of gastrointestinal bleeding and ulceration. However, the increased tolerance may come at the cost of an increased risk of thrombosis in patients with ischaemic heart disease.COX-2 inhibitors can also increase blood pressure, induce or worsen cardiac failure and impair kidney function like non-selective NSAIDs.

Sources:

- Day R and Graham GG. The vascular effects of COX-2 selective inhibitors. Australian Prescriber 2004: 27 (6): 142-5.
- Roberts LJ and Morrow JD. Analgesic-Antipyretic and Anti-inflammatory Agents. In Hardman JE and Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th edition. New York: McGraw-Hill. 2001: 687-732.

Brief Information

New WHO ORS-Formula

Numerous studies have been undertaken after recommendation of glucose-based ORS solution by WHO and UNICEF. The goal was a product that would be at least as safe and effective as standard ORS for prevention or treatment of dehydration from all types of diarrhoea but which, in addition, would reduce stool output or have other important clinical benefit. An approach has consisted in reducing the osmolarity of the ORS to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution's salt and glucose concentrations.

Studies to evaluate this approach were reviewed and recommendations were made to WHO and UNICEF on efficacy and safety of reduced osmolarity ORS in children with acute non-cholera diarrhoea and in adults and children with cholera. Because of the improved

effectiveness of reduced osmolarity ORS solution, WHO and UNICEF now recommend that countries use and manufacture the following formulation in place of previously recommended ORS solution:

Compositions	New formula	Old formula
Sodium chloride (In Gram)	2.6*	3.5
Trisodium citrate „	2.9	2.9
Potassium chloride „	1.5	1.5
Glucose, anhydrous „	13.5*	20.0
Osmolarity (mOsmol/l)	245*	311

* denotes the recent change in composition.

Patient Recovers from Rabies

Rabies virus causes acute encephalitis in humans. Once clinical signs appear, the disease is nearly always fatal, and treatment is only supportive. Only six cases of human survival from clinical rabies have been reported and each had received either pre- or post-exposure rabies prophylaxis. Recently, Centre for Disease Control, United States reported that a person had survived rabies without vaccination. The individual contracted the virus from an infected bat in September 2004 and did not seek medical care until symptoms appeared a month later. The patient was placed in drug-induced coma with ventilator support alongwith immunomodulating drugs and ribavirin, an antiviral agent. As reported in early January 2005, the patient was improving steadily and is expected to make a near-full recovery. This report provides a hope for finding a treatment for clinical rabies, especially for use in nations where fatality due to rabies is more common.

Drug Monitoring and Toxicology Laboratory

Therapeutic drug monitoring involves the measurement of serum drug concentrations, the results of which are utilized to optimize patient treatment. The Department of Clinical Pharmacology, TUTH is providing drug monitoring services since 1987. Presently it provides services for qualitative estimation of some drugs and quantitative estimation services are being provided for carbamazepine, phenytoin, phenobarbitone, paracetamol, salicylates and theophylline. In addition, estimation of serum cholinesterase activity is also being done for organophosphate poisonings. The summary of 265 samples received by the laboratory during Oct-Dec 2004 is as follows:

Drug/Enzyme	Reference range (normal limit)	Total samples (Oct – Dec 2004)	Results within normal limit	Results beyond normal limit
Carbamazepine	04 – 12 µg/ml	118	65	53
Phenytoin	10 – 20 µg/ml	78	19	59
Phenobarbitone	15 – 40 µg/ml	13	03	10
Paracetamol	10 – 20 µg/ml	14	05	09
Cholinesterase levels	3500-8500 U/l	42	13	29

The Drug & Therapeutics Letter, a publication from the Drug Information Unit (DIU), TUTH, is being restarted with the last issue. The format of the information has also been changed from the last issue. It includes a section on details about a drug or a group and other section includes brief information including findings from studies. It is published quarterly to highlight topics related to recent and relevant developments in Clinical Pharmacology & Therapeutics. Suggestions and comments are welcome. For more information please contact DIU.

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