# PHARMACOLOGICAL DIGEST

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## Use of Clostridial Collagenase in Clinical Practice

Mammalian collagenases belong to the family of metalloproteinases. They specifically cleave collagen and thus play an important role in the metabolism of collagen in mammalian tissues. The localisation of the enzyme in burn wounds - within cells as well as within the wound site - suggests that the enzyme directly takes part in the healing mechanisms. In healthy subjects, where wounds normally heal by primary intention, the amount and activity of endogenous collagenases are sufficient for the removal of dead tissue from the wound. In patients presenting with chronic nonhealing wounds such as pressure sores, venous leg ulcers and diabetic ulcers etc. may cause an impairment of endogenous collagenase production and activity, and thus lead to insufficient removal of dead tissue. Although the mechanism of action of collagenases during the wound-healing process is not yet fully understood, pharmacological and clinical data show the beneficial effect that can be achieved by the supplementation of clostridial collagenase to necrotising wounds.For this reason it seems appropriate to consider the application of clostridial collagenase to such wounds in order to reinforce the body's own cleaning and healing mechanisms.

*[Journal of Clinical Drug Investigation 1998; 15(3): 245-252.]*

## Use of Famotidine in Infants and Children : Despite the Lack of FDA Approval

The histamine type-2 receptor antagonists (H2RAs) have made a significant impact on the prevention and management of gastroesophageal reflux and ulcers. The University of Virginia Pharmacy and Therapeutics Committee has recently approved a therapeutic interchange program for this class, with famotidine as the agent of choice. It offers the advantages of having relatively few adverse effects and no significant drug interactions. Famotidine is currently approved by the Food and Drug Administration for both treatment and maintenance therapy of duodenal ulcers, gastric ulcers, pathological hyper-secretory conditions, and gastro-esophageal reflux disease in adults, but not for use in children. Despite the lack of FDA approval, the H2RAs have been widely used in the pediatric population. There are nearly a dozen publications describing famotidine use in infants and children. The majority of these studies have focused on the use of famotidine in the prevention of stress erosions. The ideal dosing regimen is still debated. However, additional clinical trials, particularly in infants and young children, are needed to better establish the safety and efficacy of current dosing strategies.

*[Pediatric Pharmacotherapy 1998; 4(2)]*

## Is Enalapril Safer Than Nisoldipine in Hypertensive Diabetics?

Cardiovascular disease is the leading cause of death in people with non-insulin-dependent diabetes mellitus (NIDDM). One means of reducing cardiovascular risk in this group is to treat hypertension. ACE inhibitors, such as enalapril, and calcium-channel blockers, such as nisoldipine, are commonly used antihypertensives. As part of the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, this study compared the incidence of fatal and nonfatal myocardial infarction (MI) over a 5-year period between 235 NIDDM patients receiving nisoldipine and 235 NIDDM patients receiving enalapril. The results appear to indicate that "an ACE inhibitor is the preferred antihypertensive agent, rather than a dihydropyridine calcium-channel blocker, for the prevention of cardiovascular complications, specifically myocardial infarction, in patients with NIDDM."

*[The New England Journal of Medicine. 1998; 338: 645-652.]*

## New Research on Cancer Genes

The human gene most frequently linked to oncogenesis -- p53 -- was the subject of much research. The p53 gene, in normal cells, suppresses tumor activity. Mutations in the gene allow unrestricted cellular growth and tumor formation. The Schering-Plough Gene Therapy Study Group used an adenovirus to deliver the normal p53 gene into tumors in patients with various types of tumors. Phase I trials showed that the gene was successfully delivered into various solid tumors: colon cancer metastatic to the liver, ovarian cancer, melanoma, head and neck cancer, and nonsmall-cell lung cancer. In a study of children with neuroblastoma, researchers found abnormal levels of the unmutated p53 protein in tumor cells in cytoplasm, which suggest that, in neuroblastoma, the p53 is not mutated but is somehow inactivated. E1A is another suppression gene, one that has suppressed metastasis, induced apoptosis (programmed cell death), and countered the overexpression of the breast cancer gene HER-2/neu. In a 12-patient study, researchers were able to transfer E1A into tumor cells using liposomes, and E1A expression led to HER-2/neu suppression in breast and ovarian cancer cells. Several studies looked at p73, a gene thought to be produce a p53-like protein. Discovery and cloning of p51, another possible p53 family member, was reported at the annual meeting of the American Association for Cancer Research (AACR) by Japanese researchers.

*[Pharmacotherapy News Network : Apr. 1, 1998: Cancer Update: News from the annual meeting of the American Association for Cancer Research.]*

## Memantine: An Investigational Drug for the Alleviation of Neuropathic Pain

Memantine is an orally available N-methyl-D-aspartate (NMDA) antagonist, which has been shown to inhibit prophylactically or therapeutically enhanced feelings of pain caused by nerve damage. It currently is undergoing clinical trials in patients with neuropathic pain. In a recent phase II clinical trial, memantine subjects with painful diabetic neuropathy experienced significant reductions in pain compared with placebo-treated subjects. In contrast, it was not effective in controlling pain in subjects with postherpetic neuralgia.

Published reports indicate that memantine also may be effective in the treatment of Parkinson's disease and acquired pendular nystagmus in patients with multiple sclerosis.
*[From issue No. 246 (March, 1998) of Medical Sciences Bulletin]*

## First Oral Drug for Erectile Dysfunction Approved

Sildenafil citrate, the first pill to treat erectile dysfunction was approved last month by the Food and Drug Administration. It acts by enhancing the by enhancing the smooth-muscle relaxant effects of nitric oxide, a chemical normally released in response to sexual stimulation. This smooth muscle relaxation allows increased blood flow into certain areas of the penis, leading to an erection. The pill, taken about an hour before sexual intercourse, is effective in about 70% of patients. The most common side effects include headache and indigestion. Some patients on sildenafil citrate (about 3%) also reported changes in vision, principally altered color perception.The drug should not be used with organic nitrates such as nitroglycerin patches or sublingual tablets because the combination may lower blood pressure. Because new drug has not been studied in combination with other treatments for impotence, the FDA does not recommend the use of such combinations.
*[Medical Tribune: Family Physician Edition 1998: 39(8)]*

## Treatment of LRTIs: Two Antimicrobials Compared

Lower respiratory tract infections (LRTIs) commonly require antimicrobial therapy. Historically, ampicillin has been used as a primary empiric agent. However, antimicrobial resistance among these organisms continues to increase. This has led to combining ampicillin with a beta-lactamase inhibitor, such as sulbactam, which protects ampicillin from enzymatic degradation. The efficacy and safety of intravenous ampicillin/sulbactam and cefoxitin, a second-generation cephalosporin, were compared in 75 inpatients with bacterial infections of the lower respiratory tract. Results demonstrated that ampicillin/sulbactam and cefoxitin have similar efficacy and safety profiles in the treatment of lower respiratory tract infections. Ampicillin/sulbactam is a cost-effective alternative in the treatment of these infections.
*[Infect Med 1998: 15(4):256,259-263]*

## Montelukast Approved for Asthma in Adults and Children

Montelukast was recently approved by the FDA for the prevention and chronic treatment of asthma in adults and children aged 6 years and older. It is the third antileukotriene agent (the first two being zafirlukast and zileuton) to be approved for treatment of asthma and the only antileukotriene approved for use in children. Montelukast is a potent and specific antagonist of the cysteinyl leukotriene receptor, known as the CysLT1 receptor, and thus inhibits the physiologic action of leukotriene D4 at this receptor. After oral administration, montelukast is rapidly absorbed, with mean oral bioavailability of 64%. Maximum plasma concentrations are reached 3 to 4 hours after administration of a 10-mg film-coated tablet and 2 to 2.5 hours after administration of a 5-mg chewable tablet. It is eliminated predominantly by metabolism followed by biliary excretion. The mean plasma half-life in young adults ranges from 2.7 to

to 5.5 hours. Clinical trial results suggest that it can be administered as controller therapy for patients with mild, persistent asthma whose symptoms are not controlled with as-needed beta agonist.
*[issue No. 246 of Medical Sciences Bulletin 1998]*

## Endocannabinoids: A New Class of Vasoactive Substance

Endogenous cannabinoids (endocannabinoids) have recently been identified in the CNS and attention has now turned to their cardiovascular actions. The prototypic endocannabinoid, anandamide, dirived from arachidonic acid, has been shown to be a vsorelaxant, particularly in the resistance vasculature. This vasorelaxation has been shown to be both endothelium-independent and -dependent, depending on the vascular bed. It has been proposed that an endocannabinoid may mediate the nitric oxide - and prostanoid-independent component of endothelium-dependent relaxations, as these responses are sensitive to a cannabinoid receptor antagonist and show similarities to anandamide-induced relaxations. In addition, it has recently been shown that anandamide is produced by endothelial cells. Clearly, much work is required to adequately define the physiological significance of endocannabinoids in the cardiovascular system.
*[TiPs 1998; 19: 55-58]*

## Nerve Growth Factor May Heal Corneal Ulcers

Neurotrophic corneal ulcers occur when the sensory innervation of the cornea is disrupted. Such ulcers lead to progressive corneal scarring and visual loss. There has been no effective known treatment for such ulcers, and management has consisted of protecting the remaining cornea to prevent extension of scarring and superimposed infection by surgically closing the eye or by the patient wearing a patch or protective contact lenses.A preliminary report by Italian researchers, Alessandro Lambiase and colleagues, showa that Topical application of eye drops containing nerve growth factor can heal corneal ulcers and restore damaged vision. It is the first to show a promising medical treatment for the disorder. If the treatment proves beneficial in the long term it may obviate the need for many corneal transplants.
*[BMJ 1998;316:1333]*