Metal-Based Anti-Inflammatory Drugs: Superior Drugs to Cox-2 Inhibitors

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The Cox family of enzymes converts arachidonic acid to prostaglandins, which have a variety of important functions. However, the Cox-2 enzyme is induced at the site of inflammation and also contributes to inflammatory conditions, whereas Cox-1 regulates "house-keeping functions", e.g., platelet aggregation, gastric protection and renal function. Thus, it was believed that selective inhibition of the Cox-2 enzyme could be used to treat inflammation, without the side-effects of Cox-1 inhibition. As we now know, this is incorrect, with long-term gastrointestinal (GI) ulceration, renal toxicity and cardiovascular problems apparent to varying degrees with selective Cox-2 inhibitors, such as Vioxx and Celebrex. Thus there is a need for non-selective Cox inhibitors that also have reduced side-effects.

Indomethacin (IndoH) is a powerful non-selective Cox inhibitor, which is still used widely as a human pharmaceutical because its high efficacy enables it to be used to treat severe inflammatory conditions, despite approximately 30% of patients having to cease its use due to GI ulceration. Metal complexes of this NSAID, have far less GI side effects than IndoH, without any reduction in efficacy. Even animals that are very susceptible to GI ulceration, such as dogs, can safely be treated with CuIndo, whereas the parent drug can cause lethal ulceration of the GI tract. Because of the combination of high efficacy and low toxicity, CuIndo is sold as a veterinary NSAID for the treatment of horses, dogs and camels. In this talk, the reasons for the increased safety of the copper complex, as opposed to the parent drug, will be discussed, as will the results of animal studies that demonstrate that it has a much wider therapeutic window than the parent drug because of its high safety. The reasons for the greatly enhanced therapeutic value of the Cu drugs and their potential for human applications for treatment of arthritis and other forms of inflammation will be discussed.