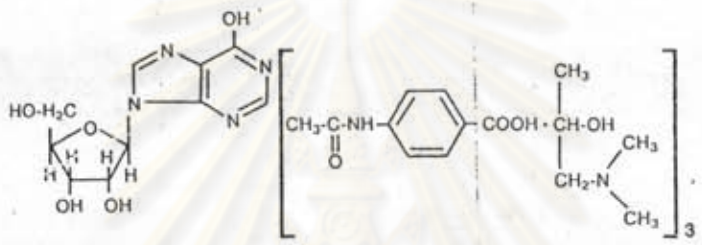
Chapter III

Inosine pranobex

Inosine pranobex (Inosiplex, Methisoprinol or Isoprinosine R) is a synthetic compound of N-N-dimethylamino-2-propanol p-acetamidobenzoate and inosine in a 3:1 molar ratio.



3.1 Pharmacodynamic Studies

Inosine pranobex was first introduced as an antiviral agent but it also exerted antitumoral activities in vivo which are thought to be secondary to an immunomodulating effect (Campoli-Richards, Sorkin and Heel, 1986).

In tissue cultures Inosine pranobex has been reported to inhibit the replication of several RNA and DNA viruses including herpes simplex, CMV, LAV, HTLV-III, adenovirus, vaccinia, polio virus, Influenza types A & B, rhinovirus, echovirus, rabies, encephalomyocarditis and eastern equine encephalitis viruses (Campoli-Richards et al, 1986).

Apart from its direct antiviral effects, Inosine pranobex also exerts many in vitro effects on immune cells. When co-incubated with PHA and lymphocytes, it stimulates, RNA synthesis (Ginsberg, and Glasky, 1977), lymphoblast transformation and lymphotoxin production (Bradshaw and Sumner, 1977) induced by PHA. Its effects as an antiviral and T-lymphocyte stimulating agent is similar to thymic hormones (Caspritz and Hadden, 1987). Monocytes, natural killer cells, polymorphonuclear cells and complement functions have also been reported to be enhanced by Inosine pranobex (Campoli-Richards, 1986).

In animal studies, when administered together with ALS, cortisone (Ginsberg and Glasky, 1977) or 6-MP (Mishell and Dutton, 1967) Inosine pranobex provides a protective effect against these immunosuppressants.

As the term immunomodulation implies, Inosine Pranobex does not only enhance immunologic functions. In cases with overfunctioning of the immune system such as SLE, it provides normalization of the immune function. IgG synthesis in patients with SlE is decreased when Inosine pranobex is administered, while there is no such suppression in normal subjects (Nakamura et al., 1983). It was also demonstrated that Inosine pranobex showed a selective enhancement of T-suppressor cell proliferation in SLE, a disease known to exhibit deficient suppressor cell activity (Nakamura et al., 1983).

3.2 Pharmacokinetics

Following a single oral dose of Inosine pranobex, peak plasma concentrations of Inosine pranobex occurs after one hour. However, 2 hours after administration, plasma concentrations decrease to undetectable amounts. Inosine pranobex has a very short plasma half life of about fifty minutes following an oral dose. The major excretory product of the inosine moiety is uric acid, while the p-acetamidobenzoate and N-N-dimethylamino-2-propanol components are excreted in the urine as glucuronidated and oxidized products, respectively, as well as being excreted unchanged (Campoli-Richards, 1986).

3.3 Therapeutic trials

Inosine pranobex has been tried in several viral infections such as SSPE, rhinovirus and influenza virus infections with variable but mostly beneficial results (Campoli-Richards, 1986). Leukemic patients under chemotherapy were shown to suffer less from infections under Inosine pranobex therapy (Caspritz and Hadden, 1987).

In several clinical trials with herpes simplex infection, Inosine pranobex was shown to be of benefit in primary herpes progenitalis in terms of healing time. In recurrent herpes progenitalis and labialis it also provided some improvement in symptomatology but the healing time was unchanged (Campoli-Richards, 1986).

Inosine pranobex was administered in a randomized controlled fashion to children with cancers who developed herpes zoster. Progression of new dermatome lesions, extent of skin dissemination and the maximum percentage of dermatome involvement were not improved by Inosine pranobex. Cellular immunity, as determined by lymphocyte responsiveness to varicella zoster antigen and PHA, was not enhanced by drug treatment (Feldman et al., 1978).

Seven out of nine atopic patients with several mollusca contagiosa showed improvement within 3-4 weeks of inosine pranobex administration (Gross, Jogerst and Schoepf, 1986).

In genital warts, the combined use of oral Inosine pranobex plus podophyllin or cryotherapy greatly increased the cure rate (94%) over that obtained with the conventional treatment alone (41%) (Mohanty and Scott, 1986).

Of current interest is the finding that Inosine pranobex, given to HIV-infected patients yielded beneficial results in both clinical and laboratory parameters which reached statistical significance in PGL patients. Circulating natural killer and T-helper cells were increased in numbers and the patients' sense of well-being was improved (Wallace & Bekesi, 1986).

3.4 Side Effects

Inosine pranobex is an extremely safe drug. Continuous ingestion over 13 years has not revealed any toxicity or immunosuppressive actions as seen with other antiviral agents (Caspritz and Hadden, 1987). The only side effects associated with Inosine pranobex to date have been transient increases in serum and urinary uric acid concentrations and occasional transient nausea associated with the large number of tablets ingested (Campoli-Richard, 1986).

3.5 Dosage and Administration

The recommended adult oral dosage of Inosine pranobex is 1 gram (2 tablets) 3-4 times daily. In children the usual oral dosage is 50 mg/kg/day, given in divided doses throughout the normal waking hours. Dosages up to a maximum of 100 mg/kg daily administered in 4 to 6 equally divided doses may be administered.

Caution should be observed in treating patients with gout, urolithiasis or kidney dysfunction because of the slight, transient increases in serum uric acid concentration that the drug may produce. Monitoring of serum uric acid concentrations is recommended in these patients (Campoli Richards, 1986).

3.6 Mechanisms of Action

The in vivo antiviral and possible antitumor activity of Inosine pranobex is believed to result from an enhancement of host immune responses due to the drug. The drug does not by itself stimulate resting lymphocytes, but augments immunological processes by lymphocytes once they have been triggered by mitogens or viral antigens (Campoli-Richards, 1986). The lack of effect of Inosine pranobex on the proliferation of lymphocytes not stimulated by an antigen indicated that Inosine pranobex is not itself a mitogen nor an inducer of mitogenic factors (Hadden, Hadden and Coffey, 1976).

Other immunomodulating agents such as lipopolysaccharides, levamisole and polyadenylic acid polyuridylic acid augment mitogen-induced lymphocyte proliferation in vitro and have been linked to cyclic nucleotides in their actions. The action of Inosine pranobex is different from these immunopotentiating agents (Hadden et al., 1976) and involves RNA synthesis (Ohnishi et al., 1982). A theory which has been advanced for the effect of Inosine pranobex on host and viral RNA synthesis is that one component of the drug or the drug complex links itself to the ribosomes of the infected cells, provoking a sterical modification which renders an advantage to cellular RNA over viral RNA in the competition for the linkage

with the ribosomal combining sites. The consequence would be a non-reading or incorrect reading of viral RNA, with incorrect transcription of the viral genetic codes (Campoli-Richards, 1986).

Inosine pranobex causes further increases in total RNA and mRNA syntheses in PHA-treated lymphocytes. This finding is in good agreement with the finding that Inosine pranobex does not show mitogenic action by itself but promotes proliferation of lymphocytes which have already been triggered by T-cell mitogens such as PHA and Con-A (Ohnishi et al., 1982). Thus Inosine pranobex suppresses viral growth and potentiates host defenses by suppressing viral RNA synthesis and promoting host RNA synthesis.

A second theory for the immunostimulatory action of Inosine pranobex is that the drug stimulates the production of lymphokines which triggers the molecular events that lead to the altered expression of immune functions. This theory is supported by reports that mononuclear cells from peripheral blood of healthy subjects, the aged and patients with rheumatoid arthritis or SLE or AIDS respond to Inosine pranobex in vitro by increased elaboration of lymphokines (IL-1 and IL-2) (Campoli-Richards, 1986).