# Tackling Autoimmune and Viral Illnesses With Inosine Pranobex

Inosine pranobex is a synthetic compound formed from the p-acetamidobenzoate salt of N-N dimethylamino-2-propanol and inosine in a 3 : 1 molar ratio. It exerts antiviral and antitumour activities *in vivo* which are secondary to an immunomodulating effect on both natural (nonspecific) and adaptive (specific) host defences.

### Inosine pranobex may act by restoring depressed T-lymphocyte function

The *in vivo* antiviral and antitumour effects of inosine pranobex are secondary to the immunomodulating activity of the drug. Although reports of poor *in vitro* antiviral activity of inosine pranobex are often in conflict with the reported *in vivo* antiviral activity of the drug, synergistic antitumour activity has been reported both *in vitro* and *in vivo* when the drug was used in combination with fluorouracil.

*In vitro* exposure of cells to inosine pranobex induces T-lymphocyte differentiation and potentiation of induced lymphoproliferative responses. The drug has been shown to modulate T-lymphocyte and natural killer cell cytotoxicity, suppressor and helper cell functions, as well as to increase the number of IgG and complement surface markers. Interleukin-1 and -2 production, and neutrophil, monocyte and macrophage chemotaxis and phagocytosis are also potentiated by inosine pranobex. The exact mechanism of action of inosine pranobex remains unknown. However, the drug may act to restore depressed T-lymphocyte function to normal by increasing lymphokine (interleukin-1 and -2) elaboration, or alternatively by increasing cell ribosomal RNA and protein synthesis while simultaneously inhibiting the use of cell ribosomal RNA for viral replication.

Some of the immunomodulating effects listed above have also been demonstrated in cells from patients administered the drug. In a double-blind comparison in patients with Herpes zoster, inosine pranobex produced a significantly greater restoration of E-rosette activity than placebo, and in 3 of 5 double-blind comparisons in patients with initial or recurrent Herpes simplex genitalis or labialis the drug significantly improved one or two of several immunological responses tested (phytohaemagglutinin response, lymphotoxin production, lymphocyte transformation response, skin test reactivity). Although open studies in patients with subacute sclerosing panencephalitis showed some immunological indices to vary during long term treatment with inosine pranobex, it is difficult to ascertain whether these were effects of the drug or manifestations of the disease process. Open studies in patients with Hodgkin's or non-Hodgkin's lymphoma and several studies in irradiated or post-surgery cancer patients (in which full details were not given) have reported that inosine pranobex may induce positive immunomodulating effects. However, further study is needed in this area. As compared with placebo, inosine pranobex has significantly increased the graft *versus* host response (an indicator of T-lymphocyte competence) in irradiated or chemotherapy-treated patients with cancer of the stomach, colon and/or rectum.

### Promise has been shown in some autoimmune diseases

In male patients with persistent generalised lymphadenopathy, who received inosine pranobex 3 or 4g daily for 28 days, several studies reported an improvement in natural killer cell number and function and some of them also reported a concomitant increase in total T-lymphocytes and helper T-lymphocytes; however, significant immunomodulation in patients with clinically apparent acquired immunodeficiency syndrome (AIDS) has not been reported. Two controlled studies have shown that long term treatment with inosine pranobex is associated with an increased rate of clearance of hepatitis B antigen from the serum of patients with acute hepatitis, and open studies in asymptomatic carriers and patients with chronic aggressive infection suggest a similar effect. In patients with autoimmune disease (alopecia totalis, universalis or areata, rheumatoid arthritis or aphthous stomatitis), small open studies intimate some positive inosine pranobex immunomodulating effects, but further study is needed.

### Kinetics are characterised by a short plasma half-life

Following a single oral dose of inosine pranobex, peak plasma concentrations of inosine occur after 1 hour. However, 2 hours after administration, plasma concentrations decrease to undetectable amounts. Inosine pranobex has a very short plasma half-life of 50 minutes following an oral dose. The major excretion product of the inosine moiety is uric acid, while the p-acetamido-benzoic acid and N-N-dimethyl-amino-2-propranol components are excreted in the urine as glucuronidated and oxidised products, respectively, as well as being excreted unchanged.

The recommended adult oral dosage of inosine pranobex is 1g 4 times daily. In children the usual dosage is 50 mg/kg per day given in divided doses throughout the waking hours.

### Inosine pranobex has produced encouraging results in a variety of viral illnesses

In therapeutic trials the usual daily oral dosage of inosine pranobex was 25 to 100 mg/kg or 3 to 6g divided into 4 to 6 doses.


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Double-blind placebo-controlled trials reported encouraging results in the clinical response and a decrease in the number of disease recurrences with the use of inosine pranobex in Herpes simplex labialis and Herpes simplex genitalis. However, conflicting results have also been reported in Herpes simplex genitalis. Similarly, while the drug appeared to be beneficial in the treatment of herpetic keratitis, zoster and varicella, further well-designed studies are needed.

Long term studies in subacute sclerosing panencephalitis, which compared inosine pranobex-treated patients to historical controls, determined that the drug both increased survival and decreased neurological deficiencies.

While inosine pranobex effected symptomatological benefits (*vs* placebo) in patients with experimentally induced influenza infection, several studies have reported that neither the incidence of illness nor seroconversion was significantly altered. Similarly, 2 double-blind placebo-controlled comparisons in experimentally induced rhinovirus infection reported conflicting results as to the benefits of inosine pranobex therapy.

Preliminary evidence suggests that inosine pranobex may improve some of the clinical symptoms associated with persistent generalised lymphadenopathy in immunodepressed males. However, these results must be interpreted with caution. The combined use of oral inosine pranobex plus conventional non-surgical treatment of genital warts resulted in greatly increased cure rates *versus* the rates for conventional treatment alone. Confirmation of these highly encouraging results in well-designed comparative studies will be awaited with interest.

A double-blind placebo-controlled study reported a statistically significant beneficial efect of inosine pranobex on liver function tests and some of the symptomatology in patients with acute type B viral hepatitis.

Double-blind placebo-controlled studies have also reported statistically significant therapeutic benefits with the use of inosine pranobex in tropical, but not ordinary, measles. Similarly, the infection frequency and duration (respiratory and/or urinary tract) in elderly institutionalised, seriously ill or surgical patients was significantly reduced after long term (3 months) therapy with the drug. Furthermore, open studies and case reports suggest possible therapeutic benefits with the use of inosine pranobex in other infectious diseases, and in alopecia, rheumatoid arthritis and other autoimmune disorders. Patients with amyotrophic lateral sclerosis given inosine pranobex for 3 to 6 months, and patients with progressive rubella panencephalitis, have not been reported to derive significant therapeutic benefit from the drug.

**The drug appears to be very well tolerated**

Inosine pranobex has not produced serious side effects. The only side effects associated with inosine pranobex therapy 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.

**Further controlled studies are required to determine ultimate indications**

While inosine pranobex may prove to be a valuable and innovative therapy for a number of diseases and infections for which currently no satisfactory therapies exist, the data available at present needs confirmation with additional well designed studies which have been subjected to the critical review of publication in full. The temptation can be strong to use a non-toxic drug of possible therapeutic benefit in a fatal and/or debilitating disease, such as SSPE or AIDS, or even in a merely painful, recurring and/or psychologically traumatic disease, such as herpes genitalis or labialis, against which the practitioner feels powerless. However, the interests of the patients would be better served by inclusion into well-designed and reported randomised studies which would resolve the doubts and firmly establish the place of the drug in therapy.

*Campoli-Richards DM, Sorkin EM, Heel RC. Drugs 32: 383-424, Nov 1986 [224 references]*