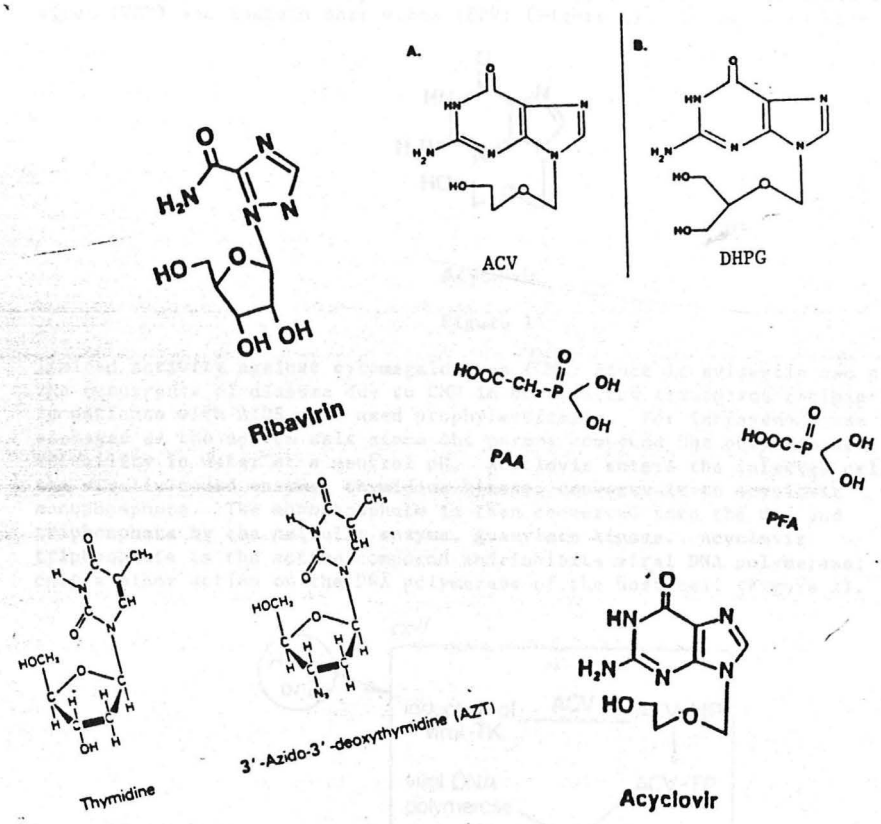
ANTIVIRAL CHEMOTHERAPY



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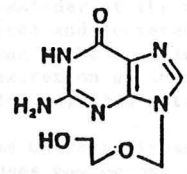
ACYCLOVIR

Acyclovir [ACV, acycloguanosine, 9-(2-hydroxyethoxymethyl) guanine] has activity against herpes simplex virus (HSV) types I and II, varicella zoster virus (VZV) and Epstein Barr virus (EBV) (Figure 1). It may also have



Acyclovir

Figure 1

limited activity against cytomegalovirus (CMV) since it evidently can prevent the occurrence of disease due to CMV in bone marrow transplant recipients and in patients with AIDS when used prophylactically. For intravenous use it is packaged as the sodium salt since the parent compound has only limited solubility in water at a neutral pH. Acyclovir enters the infected cell and the virally coded enzyme, thymidine kinase, converts it to acyclovir monophosphate. The monophosphate is then converted into the di- and triphosphate by the cellular enzyme, guanylate kinase. Acyclovir triphosphate is the active compound and inhibits viral DNA polymerase; it has only a minor action on the DNA polymerase of the host cell (Figure 2).

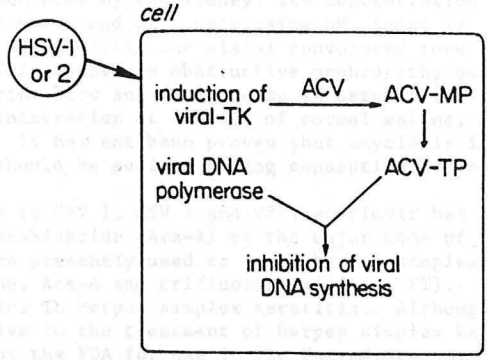


Figure 2: Dorsky, 1987

Acyclovir trisphosphate is also incorporated into the growing DNA chain of the virus and acts as a chain terminator since it lacks a 3'-hydroxy group. In EBV infected cells, the virus does not code for a thymidine kinase and the conversion of acyclovir to acyclovir triphosphate is accomplished by cellular kinases. EBV, however, is very susceptible to the activity of ACV-TP and this accounts for the inhibition of EBV replication. CMV also does not code

for thymidine kinase but it is less susceptible to ACV-TP. The order of activity of ACV against the various DNA viruses is HSV 1 > HSV 2 > VZV = EBV >> CMV. ACV is metabolized in the body to 9-(carboxymethoxymethyl) guanine: 8-14% of administered acyclovir is converted into this latter compound resulting from the oxidation of the terminal CH_2OH group of the side chain to a COOH group. The remainder of the compound is excreted into the urine intact; it is both filtered and secreted by the proximal convoluted tubule. A dosage adjustment has to be made in patients with renal failure. With impairment of the renal excretion of acyclovir, there is a slight increase in the formation of its oxidized metabolite.

There are three mechanisms wherein viruses can become resistant to the action of acyclovir. The viruses may become thymidine kinase deficient (TK^-), thymidine kinase defective (TK^d) or the DNA polymerase of the virus no longer is inhibited by acyclovir trisphosphate. TK^- mutants are most common. It was originally thought that these mutants were pathogenetically less virulent and might be spread less easily than wild type virus because the virus would have to use cellular enzymes to phosphorylate thymidine so that it could be incorporated into viral DNA. However, in patients with AIDS and other severely immunosuppressed persons it has become apparent that acyclovir resistant mutants can be pathogenetically virulent and cause extensive tissue destruction. In an abstract being prepared for the Fifth International AIDS Conference in Montreal in June, 1989, 30 patients will be described who have had severe disease due to acyclovir resistant mutants and who were treated with some efficacy with sodium phosphonoformate (foscarnet).

Acyclovir's major toxicity is obstructive nephropathy. During intravenous administration, when reconstituted the pH of the sodium salt of acyclovir is 11. At this pH the drug is quite soluble. Since acyclovir is both filtered and secreted by the kidney, its concentration increases along the course of the nephron and with decreasing pH, there is a tendency for crystallization to occur within the distal convoluted tubule and the collecting duct. This causes an obstructive nephropathy usually manifested by a decrease in urine flow and an increase in serum creatinine. This can be managed by the administration of a bolus of normal saline, mannitol or the use of a diuretic. It has not been proven that acyclovir is not a teratogen and hence its use should be avoided during conception or pregnancy.

In disease due to HSV 1, HSV 2 and VZV, acyclovir has essentially succeeded adenine arabinsoide (Ara-A) as the major mode of therapy. The three drugs that are presently used to treat herpes simplex keratitis in the U.S. are idoxuridine, Ara-A and trifluorothymidine (TFT). Trifluorothymidine is the drug of choice in herpes simplex keratitis. Although acyclovir ointment is effective in the treatment of herpes simplex keratitis, it has not been approved by the FDA for use in the United States. In a double-blind controlled trial of acyclovir versus Ara-A in biopsy proven herpes simplex encephalitis, the mortality in the Ara-A recipients was 54% as compared with 28% in the acyclovir recipients ($p=0.008$) (Figure 3). In this study, mortality was affected by receiving acyclovir, the duration of disease before entry into the study, age, and the Glasgow coma score on entrance into the study. In the treatment of herpetic encephalitis, acyclovir is given as 10mg/kg q 8 h for a 10 day period. When given in a prophylactic manner, acyclovir prevents the occurrence of orolabial herpes. When given

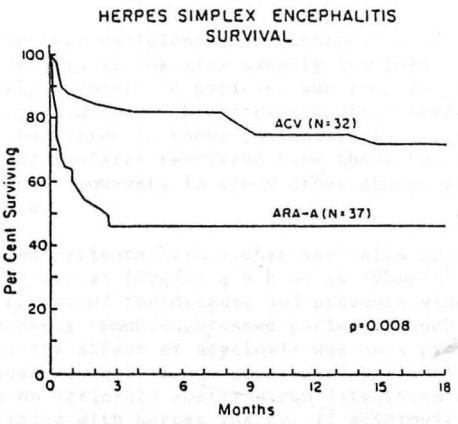


Figure 3: Whitley, 1986

therapeutically, either topically or orally, acyclovir has no clinically significant benefit in the management of orolabial herpes. Double-blind controlled studies of primary herpetic gingivostomatitis have not been reported but the oral form of the drug should be effective considering the morbidity and duration of this disease process. In immunosuppressed patients, acyclovir given orally or intravenously prevents the occurrence of orolabial herpes and can also be used to treat this disease effectively. In these patients, the dose of acyclovir when given for therapy intravenously is 5mg/kg q 8 h or 250mg/m^2 q 8 h. Orally, it can be given as 400mg 5x/d for 7-10 days. In prophylaxis, dosages of 200mg 5x/day are usually utilized.

In diseases caused by HSV 2, acyclovir and adenine arabinoside have been shown to be equivalent in the treatment of neonatal herpes. In immunocompetent patients with first episode, true primary genital herpes, acyclovir given intravenously or orally proved to be effective. The oral dose is 200mg 5x/day for 10 days. ACV was less effective in patients who had neutralizing antibody against HSV 1 and/or HSV 2 at the time of entry into the study and who were considered to be examples of first episode, non-primary patients. In patients with recurrent genital herpes, when given in a patient-initiated manner, acyclovir reduced the average time to complete healing by 1.5 days. There was no effect on symptom scores between patients receiving acyclovir versus placebo. Topical acyclovir as a 5% suspension in polyethylene glycol has an effect on herpes simplex lesions in immunosuppressed patients. It has a minor clinical effect on first episode, true primary genital herpes and no clinical effect in recurrent genital herpes. When given to prevent recurrences, in from one tablet a day up to 5 tablets a day, acyclovir is an effective prophylactic agent in genital herpes. In patients who have frequent episodes of recurrent disease, acyclovir prevents recurrences in 85% of those receiving the drug whereas all control patients had episodes of genital herpes within a 6 month study period. When the drug is stopped, however, episodes begin again and the first episode is oftentimes severe. Some patients have been on prophylactic acyclovir longer than 4 years and to date no toxic manifestations of the drug

have been noted in long term recipients. Prelesional prodromes, that is, a sensation of itching or pain in the area usually involved by recurrent herpes, occur relatively commonly in patients who receive prophylactic acyclovir and there are episodes of breakthrough viral shedding without evidence of vesicular formation in these patients. In one study, approximately 50% of the isolates recovered from those receiving acyclovir were acyclovir-resistant. However, in every other study, all the isolates were acyclovir sensitive.

In immunosuppressed patients with either varicella or herpes zoster, intravenous acyclovir given as 10mg/kg q 8 h or as 500mg/m^2 q 8 h for 7-10 days ameliorates the course of the disease and prevents visceral dissemination. In severely immunosuppressed patients, such as bone marrow transplant recipients, the effect of acyclovir was more pronounced than that of Ara-A. In other less severely immunosuppressed patients, the effect of intravenous acyclovir on varicella zoster virus infections equals that of Ara-A. In normal patients with herpes zoster, if acyclovir is given at 800mg 5x/day for 7 days within 48 hours of the onset of the rash, there was a significant difference in rash progression when compared with placebo controls. There was, however, no effect in ophthalmic zoster in one study. Anecdotal reports attest to the efficacy of acyclovir when given to patients with the Ramsay-Hunt syndrome. In chicken pox in normal young adults, any clinical effect of acyclovir upon the course of infection is minimal. In varicella pneumonia, however, although controlled trials have not been performed, acyclovir does appear effective in ameliorating the disease process.

Acyclovir has been utilized in two trials of infectious mononucleosis. There was an effect on virus shedding in pharyngeal secretions while the drug was being given and the overall symptom score was less for acyclovir recipients than in placebo controls but the clinical effect was minor. Acyclovir has been given to immunosuppressed patients with B cell lymphoproliferative syndromes due to EBV but only transiently influences the course of this disease. In a case control study of the chronic fatigue syndrome, patients were assigned to receive either placebo or acyclovir, intravenously at 500mg/m^2 q 8 h for one week and then orally at 800mg 5x/day for an additional 3 weeks. There was no difference in outcome between placebo controls and those patients given acyclovir. When given intravenously to bone marrow transplant recipients from 5 days before to 30 days after allogeneic marrow transplantation, acyclovir at 500mg/m^2 q 8 h reduced the risk of both cytomegalovirus infection and disease in seropositive patients; it was also associated with significantly increased survival in these patients.

ADENINE ARABINOSIDE (Ara-A)

Adenine arabinoside acts by inhibiting viral DNA polymerase after having been converted to Ara-A triphosphate. Ara-ADP and Ara-TP also interfere with the action of viral ribonucleotide reductase, thus interfering with the formation of deoxyadenine triphosphate (dATP) (Figure 4). Ara-A is sparingly soluble in water so that only 0.5 mg of the drug can be dissolved in 1 ml of vehicle. It is generally given as 10-15mg/kg/day over a 12 hour infusion

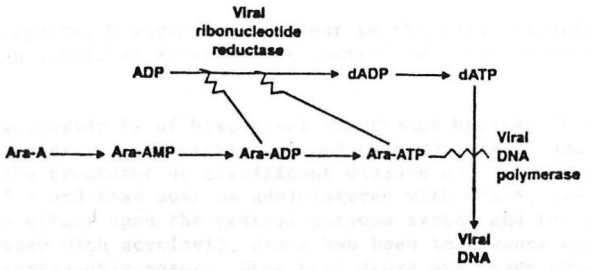


Figure 4: Verheyden, 1988

interval with the 10mg/kg course being given for complicated varicella zoster virus infections and the 15/mg/kg/day dose being given in herpes simplex encephalitis and neonatal herpes. If a 70 kg person were to receive 15mg/kg/day, that would necessitate the administration of approximately 2000cc of vehicle either as D5W, half-normal saline or normal saline. This consitutes a large volume of fluid administration particularly in the patient with herpes simplex encephalitis where there is a component of inflammatory cerebral edema. Ara-A is metabolized in the body to hypoxanthine arabinoside and this metabolite has approximately 10% of the antiviral activity of adenine arabinoside. The conversion of adenine arabinoside to hypoxanthine arabinoside is accomplished by the enzyme adenosine deaminase. The toxic effects of Ara-A involve the bone marrow with leukopenia and thrombocytopenia resulting in some patients given the drug for prolonged periods of time. Central nervous system toxicity can be seen, particularly in patients with combined renal and hepatic disease, and perhaps is the single most feared complication of therapy. Patients with central nervous system disease due to adenine arabinoside have the occurrence of insomnia, tremulousness, auditory and visual hallucinations and hyperactivity. Although this complication may disappear as the drug is withdrawn, in certain patients it has been noted to persist for a protracted period after the drug has been stopped. In some instances death has resulted. Ara-A has not been shown not to be a teratogen and therefore should not be given to pregnant women.

Ara-A has an effect mainly against herpes simplex viruses, types 1 and 2 and varicella zoster virus. It has been superceded in its role in herpes simplex encephalitis by acyclovir. In neontal herpes infection it is equivalent to acyclovir. When given intravenously to immunosuppressed patients with extending mucocutaneous herpes simplex infections, the drug had a result but not comparable to that of acyclovir. In complicated varicella zoster virus infections in immunosuppressed patients, Ara-A stopped the progression of the rash more quickly than placebo and visceral dissemination was prevented. In herpes zoster in highly immunosuppressed patients, namely, bone marrow transplant recipients, the effect of acyclovir was more beneficial than Ara-A. Ara-A has been utilized to treat encephalitis occurring in the course of herpes zoster without effect. Since the drug does penetrate the CNS and has an antiviral effect against varicella zoster virus, the lack of effect has been thought to be related to the fact that zoster encephalitis occurs primarily as an immunopathological process. There are

some anecdotal reports, however, that attest to the rapid clearing of zoster encephalitis when acyclovir is given but controlled trials have not been performed.

Adenine arabinoside is of historical importance because it was the first systemically administered antiviral compound that was tested and proven to be efficacious in the treatment of significant disease due to viruses. Because of the amount of fluid that must be administered with Ara-A, its bone marrow toxicity and its effect upon the central nervous system and the generally better results seen with acyclovir, Ara-A has been in essence superceded by that drug as a therapeutic agent. When both drugs are given together to animals with experimental HSV encephalitis, a synergistic effect was seen. Future studies are planned using the two drugs together in human encephalitis due to HSV.

SODIUM PHOSPHONOFORMATE (FOSCARNET)

Sodium phosphonoformate, foscarnet, has been developed by the Swedish pharmaceutical industry. It is closely related chemically to phosphonoacetic acid which, although it has anti-DNA viral properties, was never developed because it accumulated in bone (Figure 5). Foscarnet has an effect against

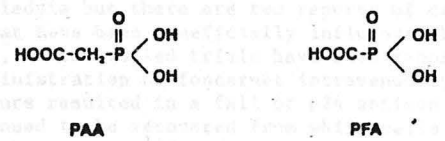


Figure 5

herpes simplex virus, types 1 and 2, varicella zoster virus, Epstein Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), and probably hepatitis B virus. Foscarnet inhibits viral replication by blocking the pyrophosphate receptor site of viral DNA polymerase or reverse transcriptase (Figure 6). Foscarnet is excreted into the urine intact without hepatic

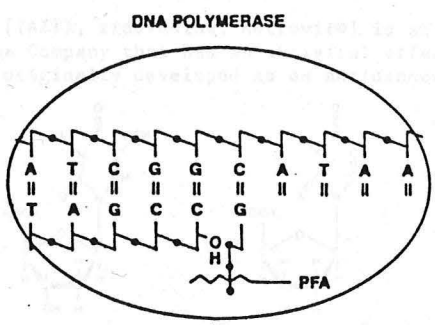


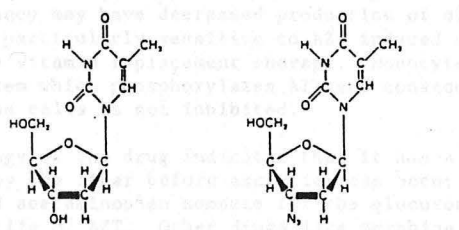
Figure 6: Verheyden, 1988

metabolism. Its side effects include thrombophlebitis, anemia, edema and renal dysfunction. A significant effect on white blood cells has not been seen. The mechanism of renal injury is not clear. In experimental situations, it inhibits the tubular reabsorption of phosphate by the proximal convoluted tubule. It can induce hypercalcemia, but the effect on serum phosphate has been variable with hypophosphotemia, hyperphosphotemia and no change in serum phosphate levels being noted. In 4 patients renal dysfunction occurred in the setting of volume depletion. Consequently, adequate volume repletion and maintenance are necessary when the drug is given.

Clinically, it has been utilized as a topical drug in orolabial herpes and in genital herpes. Although an antiviral effect in genital herpes was shown, a Canadian multi-institutional study found that foscarnet applied topically had no clinical effect upon genital disease. This was in contrast to prior Swedish trials. It has been used to treat disease due to acyclovir-resistant mutants of herpes simplex virus, predominantly in AIDS patients and the effects of the drug in this situation have been impressive. It has also been used to treat cytomegalovirus infection in transplant recipients and in patients with AIDS. It has been given to patients with CMV retinopathy in AIDS with amelioration of the disease; however, maintenance therapy continues to be necessary. It has an effect against Epstein Barr virus and hepatitis B virus. There was only a clinically minor effect in infectious mononucleosis but there are two reports of cases of hepatitis B viral infection that have been beneficially influenced by the use of foscarnet; however, no controlled trials have been reported. In HIV infection, the administration of foscarnet intravenously at a dosage of 50mg/kg every 8 hours resulted in a fall of p24 antigen levels. However, viable virus continued to be recovered from white cells in patients given this drug. There also was an effect on CD4 cell count. Foscarnet can cross the blood brain barrier and should be able to inhibit HIV replication within macrophages since it does not have to be activated in order for it to have an antiviral effect. In HIV infections, forcarnet must be continued in order to have an antiviral effect and this necessitates intravenous infusions.

AZIDOTHYMIDINE (AZT)

Azidothymidine [(AZT), zidovudine, Retrovir®] is an agent manufactured by Burroughs-Wellcome Company that has an antiviral effect against HIV (Figure 7). It was originally developed as an anticancer chemotherapeutic



Thymidine 3'-Azido-3'-deoxythymidine (AZT)

Figure 7

agent but did not prove to be usable in this regard. Azidothymidine is structually similar to thymidine except that it has an azide (N≡N) group at the 3' position of the deoxyribose ring. AZT has excellent penetration across the blood brain barrier. In order for activity to occur, AZT must be triphosphorylated to AZT-TP which is then incorporated into the growning DNA chain where it acts to terminate the chain because it is not possible with the presence of the azide group to form 5', 3' phosphodiester linkages (Figure 8). AZT-TP also inhibits the activity of reverse transcriptase.

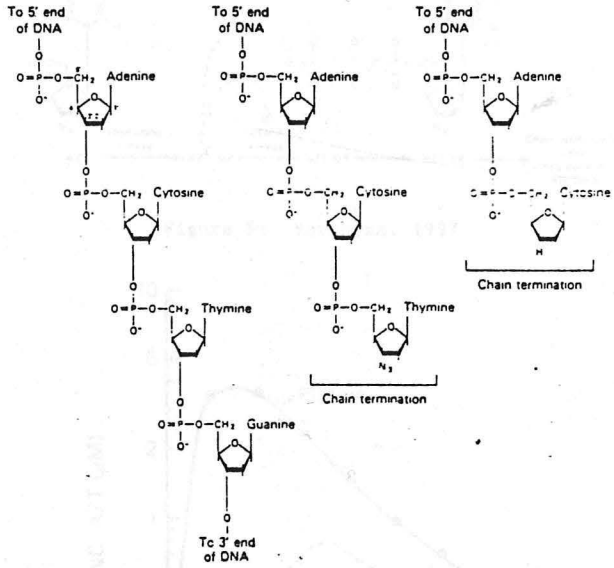


Figure 8: Yarchoan, 1987

AZT-MP also interferes with the activity of the enzyme deoxythymidine monophosphate kinase (Figure 9). This enzyme converts dTMP to dTDP which is finally converted into dTTP. As a consequence, deoxythymidine monophosphate accumulates in cells treated by AZT and these cells have decreased levels of dTTP. This contributes to the toxicity of the drug. Patients with folate or vitamin B12 deficiency may have decreased production of dTMP by the cell and may, therefore, be particularly sensitive to AZT induced dTTP depletion unless they receive vitamin replacement therapy. Monocytes are known not to have an active system which phosphorylates AZT and consequently HIV replication in these cells is not inhibited.

The pharmacology of the drug indicates that it has a short half life and is glucuronidated by the liver before excretion can occur (Figure 10). Drugs like probenicid and acetaminophen compete for the glucuronidation pathway and increase the half life of AZT. Other drugs like morphine and a sulfonomide could have a similar effect but these have not been documented. Although the original U.S. trial in HIV infections was with 250mg of AZT given orally

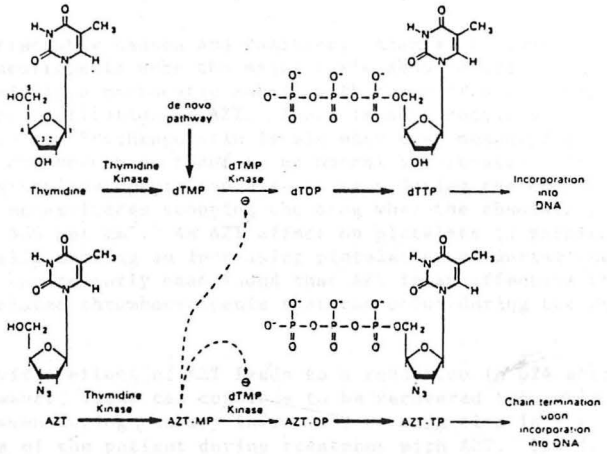


Figure 9: Yarchoan, 1987

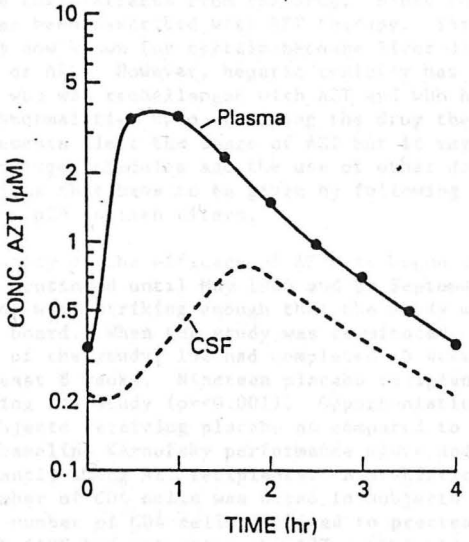


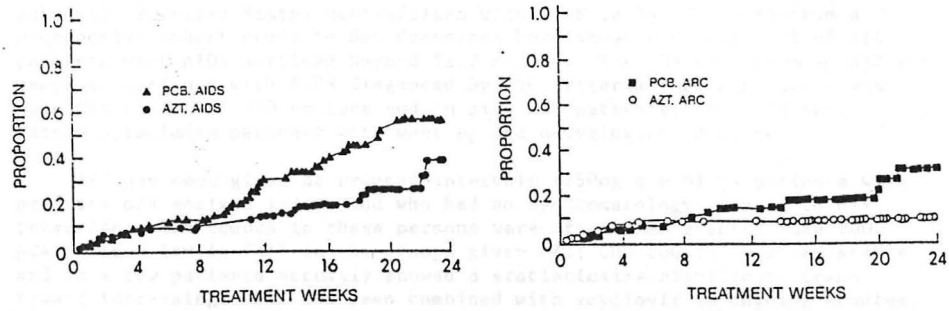
Figure 10: Yarchoan, 1987

q 4 h, the present dosage regimen is 200mg q 4 h. Levels of AZT in the blood are known to be affected by renal and hepatic disease and by body size. Since AZT is a toxic moiety it may be possible to reduce this toxicity by paying closer attention to serum levels of AZT. Toxic effects of AZT seen more commonly in AZT recipients than in placebo controls included nausea, myalgias and insomnia. Some AZT recipients had to have the drug stopped

because of intractable nausea and vomiting. Anemia and leukopenia, particularly neutropenia were the major toxic abnormalities attributable to AZT. The anemia is a macrocytic anemia with the macrocytosis being seen 1-2 weeks after the institution of AZT. There is an associated reticulocytopenia. Erythropoietin levels have been measured in patients receiving AZT and have been found to be normal or elevated. Leukopenia, particularly granulocytopenia can also be seen during the course of AZT treatment and necessitates stopping the drug when the absolute granulocyte count reaches 500 per mm^3. An AZT effect on platelets is marginal with some patients actually showing an increasing platelet count during therapy with the drug. It has recently been found that AZT is an effective therapy for the immune mediated thrombocytopenia that can occur during the course of HIV infection.

The antiviral effect of AZT leads to a reduction in p24 antigen levels in serum. However, virus can continue to be recovered from white cells, plasma, and semen during therapy indicating no reduction in the infectiousness of the patient during treatment with AZT. CD4 levels rise transiently after therapy is started but soon tend toward baseline. Patients with more advanced disease, a longer history of AIDS, greater debility, AIDS rather than ARC, low CD4 counts at entry, or reduced hemoglobin levels were more likely to have toxic effects from the drug. Since the original report, hepatic toxicity has been described with AZT therapy. The extent of this hepatic toxicity is now known for certain because liver disease is common in patients with AIDS or ARC. However, hepatic toxicity has been convincingly shown in a patient who was rechallenged with AZT and who had an increase in liver functional abnormalities upon receiving the drug the second time. Transfusion requirements limit the usage of AZT but it may be possible in the future with other dosage schedules and the use of other drugs to minimize the number of transfusions that have to be given by following serum drug levels and monitoring serum p24 antigen titers.

The original study of the efficacy of AZT was begun in February 1986. Patient enrollment continued until May 1986 and by September of that year the results of the study were striking enough that the study was terminated by an independent review board. When the study was terminated, 27 subjects had completed 24 weeks of the study, 152 had completed 16 weeks and the remainder had completed at least 8 weeks. Nineteen placebo recipients and one AZT recipient died during the study ($p=<0.001$). Opportunistic infections developed in 45 subjects receiving placebo as compared to 24 receiving AZT (Figure 11). The baseline Karnofsky performance score and body weight increased significantly among AZT recipients. A statistically significant increase in the number of CD4 cells was noted in subjects receiving AZT. After 12 weeks the number of CD4 cells declined to pretreatment values among AZT recipients with AIDS but not among the AZT recipients with ARC. Skin test anergy was partially reversed in 29% of subjects receiving AZT as compared with 9% of those receiving placebo. In the European and Australian counterpart of the U.S. study on AZT, Cooper and associates found a decrease in opportunistic infections after 6 weeks of therapy and this continued through the remainder of the study. Paradoxically, in this latter study during the first 6 weeks of therapy, AZT recipients had an increased number of opportunistic infections.



Proportion of Patients in Whom Opportunistic Infections Developed during the Study (Kaplan–Meier Product–Limit Method). The left panel shows infection among patients with AIDS who were receiving AZT or placebo (PCB), and the right panel shows infection among those with AIDS-related complex (ARC).

Figure 11: Fischl, 1987

After the U.S. study had ended, a compassionate plea program was instituted in which 4,805 patients with the acquired immunodeficiency syndrome who had experienced PCP previously received azidothymidine. Overall survival of these patients at 44 weeks after initiation of therapy was 73%. Hemoglobin level, functional ability as measured by Karnofsky score and stage of disease as measured by time since diagnosis of PCP affected outcome. The 44 week survival was 88% in patients with baseline hemoglobin levels of 12gm/dl or greater, Karnofsky scores of 90 or greater and a PCP diagnosis within 90 days of receiving AZT (Figure 12). Comparison was available from

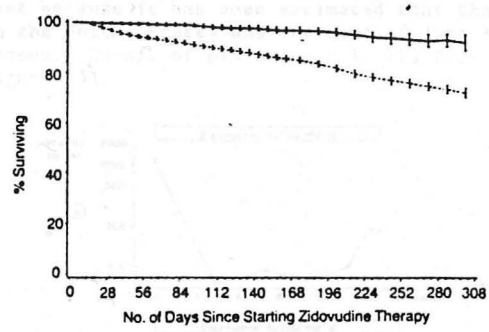


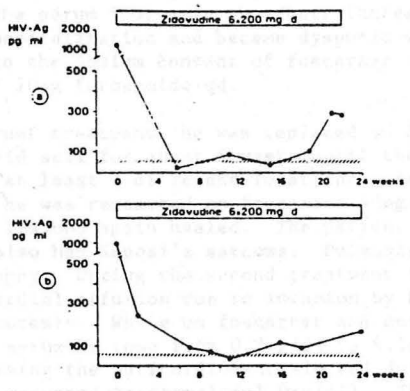
Fig 6.—Survival experience of patients with acquired immunodeficiency syndrome undergoing zidovudine therapy (with confidence limits) comparing those with all three positive prognostic indicators (solid line) (n = 681), ie, baseline Karnofsky score greater than or equal to 90, baseline hemoglobin level greater than or equal to 120 g/L, and confirmed *Pneumocystis carinii* pneumonia within 90 days, with all other patients (broken line) (n = 4124).

Figure 12: Creagh-Kirk, 1988

natural history data and suggests that AZT therapy is associated with increased 44 week survival of post PCP patients with AIDS. In New York City, between mid 1981 and December 1985, in patients diagnosed with AIDS based on PCP, the median survival was determined to be 10.5 months. Reported one year

survival of United States hemophiliacs with AIDS is 34.6%. Data from a prospective cohort study in San Francisco have shown that only 50% of all patients with AIDS survived beyond 11.2 months. The FDA has approved AZT for usage in patients with AIDS diagnosed by CDC criteria and in patients who have CD4 counts of 200 or less and in sick ARC patients. This latter category includes patients with wasting and neurological disease.

AZT has been given at reduced intervals (250mg q 6 h) to patients with positive p24 antigen levels and who had no symptomatology related to HIV infection. CD4 counts in these persons were oftentimes greater than 200. p24 antigen levels fell in the groups given AZT; CD4 counts remained stable and in a few patients actually showed a statistically significant trend toward increasing. AZT has been combined with acyclovir in ongoing studies. AZT was given at 250mg q 6 h and acyclovir was given at 800mg q 6 h. The effect on p24 antigen levels was similar to that seen with AZT alone; however, herpetic infections were diminished in the group receiving acyclovir. One study has suggested that this effect might extend to the prevention of CMV infection. Further studies on the combination of AZT and acyclovir are in progress and these drugs should not now be routinely given together until further data has been obtained. Studies are also in progress assessing the efficacy of AZT in preventing the development of AIDS in persons with CD4 counts between 200 and 500. When patients are placed on AZT for FDA approved indications, it has been found that they have better outcomes if concomitant prophylaxis for PCP is administered. The particular type of prophylaxis does not seem to matter as long as it is effective. In this regard inhaled pentamidine, the use of a double strength tablet of sulfatrimethoprim twice a day, dapsone with or without trimethoprim, and Fansidar have been found effective. The results of these studies will be watched for interest because it has been estimated that there are 1,000,000 infected people in the United States and the cost of just AZT approximates $540/mo for one person. Escape of p24 antigen levels from the AZT effect has been described (Figure 13).



Serum HIV antigen levels in two AIDS patients on zidovudine.

Figure 13: Reiss, 1988

Dideoxycytidine (ddC) has also been found to have a potent anti-HIV effect and lowers p24 antigen levels in patients being given the drug. This drug also penetrates the blood brain barrier but has been associated with severe painful peripheral neuropathy particularly in patients taking higher dosages of the drug. In some of these patients the peripheral neuropathy has not been reversible. Planned are studies alternating DDC with AZT since DDC has a different range of toxicities than does AZT. Other drugs undergoing development include ddA, d4T, ddAU, soluble CD4, and dextran sulfate.

In addition to the toxicities that have been mentioned with AZT already, there have been case reports suggesting that this drug can cause a polymyositis-like state with muscle wasting around the hips, buttocks and upper thighs. In several patients in England, an acute neurological process or the actual induction of subacute encephalitis has also been described in patients in whom AZT has been suddenly withdrawn. If the subacute encephalitis does occur after the rapid withdrawal of the drug, it must be an uncommon manifestation.

Case 1

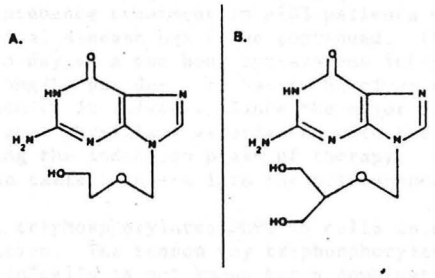
The patient was a 28 year old white man who had an extensive perirectal and perineal infection with HSV 2 and which continued to extend despite therapy with 1 gm of ACV five times per day. The virus was sent to Burroughs-Wellcome and was determined to be ACV resistant and TK^-. He was treated with adenine arabinoside intravenously at 15mg/kg per day for 10 days with no clinical or virological improvement. He was started on azidothymidine (AZT) 200mg q 4 h and the lesions improved until almost healed but later they recurred again and covered the perirectal area, both buttocks and the skin below the scrotum. The virus was determined to be susceptible to Foscarnet at a concentration of 16µgm/ml. The patient was treated with Foscarnet at 40mg/kg q 8 h for 16 days. He was also treated for bacterial suprainfection. At the end of the treatment period, the lesions were much improved and the virus could no longer be grown. The serum creatinine (Cr) remained stable but the serum inorganic phosphate increased. He gained about 20 lbs. during the hospitalization and became dyspneic with the weight gain. This was attributed to the sodium content of foscarnet and was readily managed by the use of 20mg furosemide qd.

After the foscarnet treatment, he was replaced on AZT, 200mg q 6 h, and ACV 800mg q 6 h and did well for about 6 weeks until the lesions recurred as crops of vesicles in at least 3 different locations. Because of increasing pain and discomfort, he was restarted on foscarnet 40mg/kg twice daily and given 15 doses. The lesions again healed. The patient had had prior episodes of PCP and also had Kaposi's sarcoma. Pulmonary involvement with KS was documented by biopsy. During the second treatment trial with foscarnet, he developed a pericardial effusion due to invasion by KS which subsequently required pericardiocentesis. While on foscarnet and during the accumulation of the effusion, the serum Cr rose from 0.9mg/dl to 4.1mg/dl. After stopping the foscarnet, performing the pericardiocentesis and during the next 2 weeks, the serum creatinine returned to normal (<1.0mg/dl). The patient subsequently died from KS and systemic MAI disease. His herpetic lesions were quiescent at the time of death.

Comment: Extensive disease due to an ACV TK^- resistant mutant of HSV 2. Improvement did not occur with Ara-A but did transiently with ACV alone. The ACV effect was short lived, however. He did respond twice to foscarnet therapy. Foscarnet induced renal disease occurred in the setting of impaired kidney perfusion. Although, theoretically, ACV sensitive virus should have remained predominant in the sacral root ganglion, after the first treatment course of foscarnet and while the patient was on high doses of ACV, the herpetic lesions recurred as clusters of vesicles in 3 separate anatomic sites.

GANCICLOVIR (DHPG)

Ganciclovir [DHPG, 9-(1,3-dihydroxy-2-propoxymethyl) guanine] is structurally similar to acyclovir only it has an hydroxymethyl group attached to the first carbon component of the ethoxy group in acyclovir (Figure 14).



It accumulates selectively in cells that are infected by cytomegalovirus. In order for it to be active, it must be triphosphorylated and the phosphorylation occurs at the 1-hydroxy position of the propoxy group attached to the methylguanine. When triphosphorylated, DHPG inhibits viral DNA polymerase. Triphosphorylated DHPG is also incorporated into the growing DNA chain of the virus where it acts to terminate chain elongation (Figure 15).

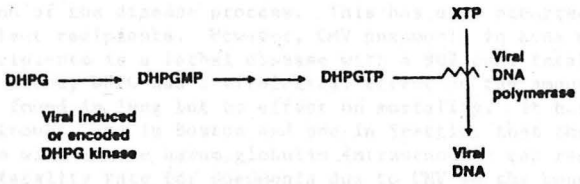


Figure 15: Verheyden, 1988

DHPG has a prolonged half life in infected cells in contrast to acyclovir and as a result of the selective phosphorylation and prolonged half life within cells there is an increased concentration of DHPG in the infected cell. Infected cells have 10 times the concentration of ganciclovir TP as opposed to uninfected cells. Ganciclovir TP is also incorporated into host cell DNA

acting as a chain terminator and can inhibit human DNA polymerase alpha. As a consequence of this enhanced activity against human DNA polymerase, toxicity can result, particularly in rapidly dividing tissues. Leukopenia is the major reason why ganciclovir has to be discontinued. Significant thrombocytopenia may also occur. Central nervous system effects can be seen with administration of the drug and hepatic disease has been reported. In animals, the drug also has an effect against gut mucosal cells and inhibits spermatogenesis. In rodents, tumors of the skin, liver, reproductive organs and stomach have been noted. There have been no such reports in humans but this potential must be considered before initiating therapy. Thus, ganciclovir has potential major toxicities and this should be considered when contemplating its use.

Most of the administered ganciclovir is recoverd intact in the urine and the dose has to be modified in patients with renal dysfunction. During the first part of therapy, usually termed induction therapy, the drug can be given as 2.5mg/kg intravenously q 8 h or 5mg/kg q 12 h for a 14 day period. After induction, maintenance treatment in AIDS patients with CMV retinopathy and CMV gastrointestinal disease has to be continued. The drug is usually given once or twice a day as a one hour intravenous infusion and the usual maintenance dose is 5mg/kg per day. It has to be given at least 5x a week and some patients require it 7x/week. Since the major toxic effect of the drug is leukopenia, most physicians experienced with the use of the drug discontinue AZT during the induction phase of therapy. AZT can be resumed with caution when the patient enters into the maintenance phase of therapy.

The enzyme that triphosphorylates DHPG in cells is a cellular enzyme induced by CMV infection. The reason why triphosphorylated DHPG has a prolonged half life in cells is not known but a combination of the phosphorylation and the prolonged half life leads to the accumulation of DHPG within infected cells. Ganciclovir is excreted by the kidneys and therefore the dose should be adjusted for patients with renal impairment. If a patient is undergoing hemodialysis, he/she should receive 1.25mg/kg once daily; the dose of the medication may be administered immediately after dialysis. Most clinical experience with ganciclovir has been in organ transplant recipients or in patients with AIDS. In renal, liver, heart and heart and lung transplants, the use of DHPG for a 10-14 day course has been associated with an amelioration of the disease process. This has also occurred in bone marrow transplant recipients. However, CMV pneumonia in bone marrow transplant recipients is a lethal disease with a 90% case fatality rate. When utilized alone, DHPG had a virological effect on the amount of virus that could be found in lung but no effect on mortality. It has now been found by two groups, one in Boston and one in Seattle, that the use of DHPG in combination with immune serum globulin intravenously can result in a lowered case fatality rate for pneumonia due to CMV in the bone marrow transplant recipient. Relapses can occur after this and they must be retreated with ganciclovir. The combination of ganciclovir with intravenously administered immune serum globulin represents the first time that CMV pneumonitis in the bone marrow transplant recipient has been successfully treated.

The other group in which DHPG is used most commonly is in patients with AIDS. The two most common indications for its use are retinopathy

progressing to blindness and CMV gastrointestinal tract disease, particularly colitis. CMV retinopathy is associated with retinal necrosis and it may result in both loss of visual field and decreased visual accuity. The retinitis is detected by ophthalmoscopy as either a perivascular yellow-white retinal lesion frequently associated with retinal hemorrhage or as a focal white granular infiltrate often without hemorrhage. Both lesions enlarge in a progressively expanding pattern and may involve macular vision. The administration of DHPG stops progression of the retinopathy in from 84 to 100% of patients. Nevertheless, even with an antiviral effect, retinal detachment can still occur resulting in blindness. If DHPG is not continued on a maintenance basis the retinopathy will recur and a course of induction therapy must be given again. In patients with gastrointestinal tract disease due to CMV good results have been found. Diarrhea can be reduced when colonic involvement is present. However, as with CMV retinopathy, the drug must be continued to be given or else relapse will occur. In patients who have CMV retinopathy and who are neutropenic, the intravitreous administration of DHPG has been found to be a successful therapeutic maneuver when performed by someone who has experience and skill in the procedure. Retinal detachment can occur as a complication of the application of drug in this manner. Patients have had breakthrough of disease due to CMV on the maintenance course of therapy. This has sometimes responded to reinduction therapy and DHPG resistant cytomegalovirus isolates have been found.

Case 2.

The patient was a 55 year old white woman who had endstage renal disease secondary to gold treatment of rheumatoid arthritis. She received her second renal allograft (cadaveric) on April 5, 1986. Cyclosporine A, azathioprine and prednisolone were administered. The kidney was found to have a weakly positive antiglobulin test. Because of poor kidney function and presumed rejection, she was given bolus solumedrol on 1, 2, 4 and 6 days after transplant. Plasmapheresis was performed for 5 days and antilymphocyte globulin was also given. On April 23rd the creatinine was 3.2 mg/dl and she was discharged from the hospital. She returned on May 5th with the new onset of fever. Three blood cultures for bacteria and fungi were negative. Cytomegalovirus complement fixation test titers rose from <1:8 on a serum specimen taken before surgery to 1:64 on the day of readmission into the hospital for fever. Buffy coat cultures were positive for cytomegalovirus. The illness of the second hospitalization was characterized by protracted fever. She complained of dysphagia but the barium swallow was negative. The platelet count decreased to 20,000 and upper gastrointestinal bleeding was demonstrated. An AST was 62 and the alkaline phosphatase rose from 70 to 278. Bile ducts by sonography were normal and the bilirubin at a peak was 1.8mg/dl with 0.8mg being direct. On May 31, 138 nucleated red blood cells were observed for every 100 white blood cells and the total white blood count was 4600. Gancyclovir at 5mg/kg q 12 h was begun on May 31 and continued for 10 days. One June 8 the patient became afebrile. On June 9 the nucleated red blood cell count was <1/100 white blood cells. The amylase peaked at 2076 on May 30. The amylase was 134 on June 4 at which time the platelet count had risen to 252,000. She developed candidemia secondary to line sepsis and was treated with 500mg amphotericin beginning on June 8. A bone marrow study done on May 26 revealed erythroid hyperplasia, megakaryocytes and a lymphoreticular infiltrate. Creatinine during this hospitalization

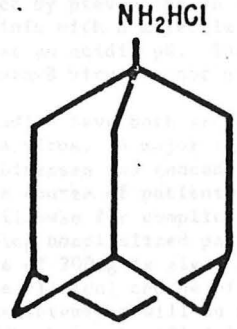
decreased from 3.4 to 1.1mg/dl. After the ganciclovir therapy, the patient noted pain on the left lateral chest area. A rib series was done to rule out a fracture. No fracture was found but the varicella zoster virus complement fixation test rose from 1:16 to 1:128.

Comment:

This case represents a patient with severe symptomatic cytomegalovirus infection with positive buffy coat cultures who had fever, pancreatitis, hepatic dysfunction, upper gastrointestinal tract bleeding, thrombocytopenia and severe hemolytic anemia which reversed rapidly with the institution of gancyclovir therapy. She had a fungal suprainfection due to line contamination. This was treated with amphotericin B and she eventually made a uneventful recovery, leaving the hospital with a serum creatinine of 1.1-mg/dl. The chest pain she experienced most probably represented herpes zoster without an eruption. Since the patient mounted a good immune response to her infection, no maintenance therapy had to be given.

AMANTADINE AND RIMANTADINE

Amantadine and rimantadine are structurally similar analogs which have an effect against influenza A virus but not against influenza B virus. Both are weak bases with the amino group in amantadine sitting on top of a tricyclic cage structure (Figure 16). The amino group in rimantadine is



Amantadine hydrochloride

Figure 16

separated from the tricyclic cage structure by a methyl group. Amantadine is excreted into the urine unchanged. It is not metabolized whereas rimantadine is metabolized. The dosage for the two drugs is the same, namely, 100mg twice a day for the adult. Since rimantadine has a larger molecular weight, the same dose of drug results in fewer millimoles administered to the patient. It has been suggested that this difference in millimoles and its metabolism might account for some of the lesser neurotoxicity seen with

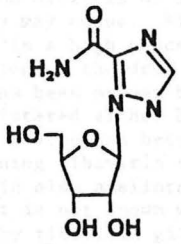
rimantadine. It was once throught that the dose of rimantadine would not have to be adjusted with renal failure since it was metabolized but recent evidence indicates that a slight modification of dose is necessary. The major side effects associated with amantadine have been related to the central nervous system and the drug has caused insomnia, tremulousness, jitteriness, and an inability to concentrate. In renal failure patients, who are given amantadine without a dosage modification convulsions may occur. Rimantadine at the dosages given has a lesser amount of central nervous system side effects and the dose only has to be modestly adjusted with renal dysfunction. It is expected that rimantadine will essentially take the place of amantadine over a period of time. In the Soviet Union, rimantadine has been given to many people since it was introduced; side effects are suggested by Russian investigators to be minimal.

The mechanism of action of amantadine and rimantadine are not known for certain although it is suggested that they interfere with penetration of the host cell by the virus or uncoating of the virus by the cell. In one hypothesis, influenza A virus is taken up by the cell and assumes a position within an endosome. The viral membrane then fuses with the membrane of the endosome and the RNA of the virus enters the cell cytosol. The fusion of the viral and endosomal envelopes is pH dependent and is interfered with by the weak bases, amantadine and rimantadine. In a series of experiments, it has been found that amantadine resistant isolates can have that resistance mapped to the gene (Gene 7) coding for matrix protein and M2 protein. A single amino acid substitution in the transmembrane domain of the M2 molecule (amino acid 30 or 31) results in amantadine resistance. This finding may infer that amantadine exerts its effect by preventing an interaction of the fusion component of the hamagglutinin with a molecule (M2) which spans the viral envelope and which occurs at an acidic pH. The lack of effect of either of these drugs against influenza B virus is not understood.

Amantadine and rimantadine have both prophylactic and therapeutic effects against influenza A virus. A major study by the National Institutes of Allergy and Infectious Diseases has concentrated on the problem of whether rimantadine can benefit the course of patients admitted into the hospital within 5 days of onset of illness for complicated influenza. This study is ongoing and involves studying hospitalized patients with influenza A. An initial dose of rimantadine of 200mg is given followed by 100mg twice a day for a total of 7 days. The clinical course of the infection as well as quantitative virological measurements will be made during the study to ascertain whether rimantadine has a beneficial effect in these patients. It is to be expected that among the patients admitted to the study will be patients with primary influenza A pneumonia. It has not been ascertained whether amantadine or rimantadine has an affect against influenza A virus pneumonia. In influenza A virus pneumonia, the case fatality rate approaches 75% and this figure has not been modified by improvements in antibiotics and ventilator assistance. Physicians need to know when influenza A virus is active in the community so that they can administer amantadine or rimantadine either as prophylaxis or as a therapeutic modality. Amantadine also can be given under selected circumstances to personnel in the hospital where it has been found that its administration can abort influenza A virus transmission on hospital wards.

RIBAVIRIN

Ribavirin is a nucleoside analog that was synthesized in 1972 (Figure 17). In the cell it is phosphorylated to ribavirin triphosphate (RTP) (Figure 18).



Ribavirin

Figure 17

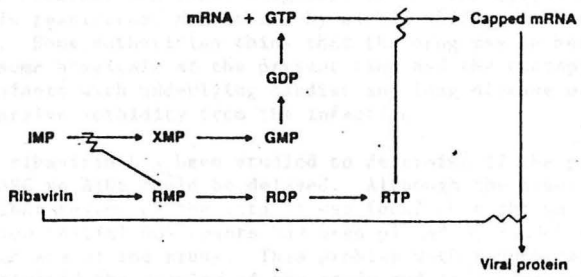


Figure 18: Verheyden, 1988

Ribavirin monophosphate interferes with the conversion of inosine monophosphate to xanthine monophosphate and this prevents an accumulation of guanosine triphosphate and deoxyguanosine trisphosphate, which are essential for RNA and DNA production. Ribavirin triphosphate also interferes with the methyl capping of guanosine triphosphate. In influenza A virus replication, viral messenger RNA is transported to the nucleus where a methylated guanosine cap is placed on the message so it can be recognized and translated by host cell polyribosomes. Another site of action of ribavirin occurs at the level of translation of viral messenger RNAs into proteins. As a result of having multiple sites of action, it has been difficult to select for ribavirin resistant isolates.

Ribavirin has an effect against both RNA and DNA viruses. It is known clinically at the present time predominantly for its ability to inhibit respiratory syncytial virus (RSV) and influenza A virus. Clinically, it also has an effect against Lassa fever virus (an arenavirus) infections in humans and Korean hemorrhagic fever (caused by Hantaan virus, a member of the family

Bunyaviridae) when that disease has occurred in China. Presently, ribavirin is utilized as a major chemotherapeutic agent against complicated respiratory syncytial virus infections in infancy and early childhood. When children, particularly with congenital heart disease or bronchopulmonary dysplasia, develop RSV infections like bronchiolitis or pneumonia they may have a protracted course and mortality may ensue. Ribavirin is given to these infants by aerosol and results in a high concentration of the drug in airways and alveolae. Serum accumulation of the drug is prevented by aerosol administration. This effect has been proven beneficial in two double-blind studies. The aerosol is administered either by mask, mist tent or a mouth piece. A specific ventilation device has been designed to administer small sized particle aerosols containing ribavirin to the airways and alveoli of children. Aerosolized ribavirin also ameliorates influenza A and B viral infections in young adults. It is not known whether influenza A or B viral pneumonia could be influenced by ribavirin given by this route. The major toxicity of ribavirin relates to the fact that it selectively affects erythroid cells in the bone marrow and peripheral circulation and it accumulates in the cell as ribavirin trisphosphate. This interferes with the formation of guanosine triphosphate and deoxyguanosine triphosphate and there is a maturation arrest of the red cell precursor and an element of hemolysis if ribavirin levels in serum are excessive. The correct use of ribavirin depends upon an accurate and rapid diagnosis of RSV infections by detecting viral antigen in respiratory secretions by either ELISA or immunofluorescent antibody tests. Some authorities think that the drug may be being used too frequently in some hospitals at the present time and the therapy should be reserved for infants with underlying cardiac and lung disease or those who might have excessive morbidity from the infection.

Recently, ribavirin has been studied to determine if the progression of patients with ARC to AIDS could be delayed. Although the study suggested an effect, on further review of the data it was found that the majority of patients with low initial CD4 counts had been placed by random assignment into the placebo arm of the study. This problem with randomization essentially mitigated the results of the study and as a consequence the drug will have to be restudied in order to see whether or not it has a clinical effect in HIV infections. In tissue culture, ribavirin and AZT are antagonistic to each other. It is thought that ribavirin inhibits the phosphorylation of AZT to AZT-TP, the active form of the drug, probably by increasing deoxythymidine triphosphate levels, resulting in a feedback inhibition of thymidine kinase. The effects of ribavirin against Lassa fever and against Korean hemorrhagic fever should be important to persons in countries where these diseases are endemic and to U.S. citizens who may incur these diseases while abroad on travel or in the Armed Services. A major difficulty in the development of ribavirin has been with management personnel who have but with few exceptions not pursued valid clinical studies with the drug to satisfy the efficacy and safety requirements of the FDA.

INTERFERON

Discovered in 1957 by Drs. Isaacs and Lindenmann, interferon once noted just for its antiviral activity has also been found to have cell anti-proliferative and immunomodulatory activities. Initially conceived of as

a single substance, there are now known to be families of interferon: alpha interferon (IFN-α), beta interferon (IFN-β) and gamma interferon (IFN-γ) (Table 1).

Table 1

Characteristics of human interferons

Type	Alpha (leukocyte)	Beta (fibroblast)	Gamma ("immune" or "class II")
Produced by	Peripheral leukocytes	Fibroblasts	Lymphocytes
Inducing agent	Virus infection, dsRNA	Virus infection, dsRNA	Mitogens (nonsensitized lymphocytes); specific antigens (sensitized lymphocytes)
Number of genes	14	At least 2; possibly 5	1
Presence of introns	No	No	Yes
Chromosomal location	9	9,2,5	12
Size of primary protein (number of amino acids)	166	166	166
Length of signal sequence (amino acids)	23	21	20
Size of actual protein (number of amino acids)	143	145	146
MW	17,000	17,000	17,000
Glycoprotein	No	Yes	Yes
Stability at pH 2	Yes	Yes	No
Activity in the presence of SDS	Yes	Yes	No

Table 1: Joklik, 1985

There are at least 14 interferon molecules that belong to the alpha interferon or leukocyte interferon family. As many as five molecular species may belong to the beta-interferon or fibroblast interferon family. Only one gamma interferon or immune interferon exists. The molecules in each of these families are related to each other but are different from ones in the other families. Alpha interferon is antigenically distinct from beta and gamma interferon and assays have been set up to measure alpha, beta and gamma interferons based upon differences in antigenicity of the individual molecules in each family. Alpha and beta interferons are considered to be closer to each other and distant from gamma interferon in that about 40% of the DNA coding for alpha interferon is homologous with that coding for beta interferon and only about 20% of the DNA coding for gamma interferon has been found homologous with either alpha or beta interferon. The molecules in each family generally have a molecular weight of 17,000 and approximately 143 amino acids. A leader sequence of 23 amino acids is cleaved before secretion from the cell of origin.

Interferon is induced by either live or inactivated viruses, double-stranded RNA or by other stimuli. Induction involves host cell DNA to be

derepressed so that interferon message is transcribed, translated and interferon released from the cell. Interferon then has to react with a cell receptor to exert its activity and for the antiviral state to become manifest. Alpha and beta interferon probably share parts of a common receptor while gamma interferon has a different receptor. Once ligand-receptor interaction has occurred, the DNA of the cell is derepressed to transcribe certain RNA messages which are then translated and result in the antiviral state. It is not clear what constitutes the total panorama of the antiviral state but two enzymes are produced which then have important functions as inhibitors of macromolecular synthesis. An enzyme is induced that is a protein kinase; it phosphorylates protein synthesis initiation factor eIF2 which is essential for protein manufacture. Another enzyme produced is 2,5-oligo A synthetase. This enzyme produces a variety of oligo adenylate residues which are joined by phosphodiester linkages at the 2' and 5' groups of the ribose sugar moiety. This is an unusual configuration since in RNA and DNA the linkages are phosphodiester bridges between the 3' and 5' portions of ribose or deoxyribose. The induction of oligo A sequences induces the formation of a endonuclease which is non-selective in its capacity to degrade other RNA messages. Viral RNA messages are degraded and this contributes to the antiviral state. Although the induction of a protein kinase and 2,5-oligo A synthetase are correlated with the antiviral state, most authorities think that this may be only a partial answer to explain the activities of interferon. Interferon also inhibits cell proliferation and has immunomodulatory activities. T-suppressor cytotoxic cells, T-helper cells, macrophages, natural killer cells and B lymphocytes are affected. Although leukocyte interferon has been prepared through the Finnish Red Cross blood banking system, it was only with the introduction of recombinant DNA technology that large quantities of alpha, beta and gamma interferon have been able to be made. Alpha and beta interferon are now easily made in prokaryotic cells and these preparations can be purified so that there are many million units of activity per microgram of protein.

As interferon becomes more easily available, there will be increasing opportunities to apply these molecules in human medicine. Alpha interferon has been approved by the FDA to be safe and effective treatment of hairy cell leukemia and Kaposi's sarcoma. Like all antiviral substances discovered to the present, interferon is virustatic and not virucidal. Once interferon is stopped, recurrences may occur. In terms of viral disease, it is known that leukocyte interferon is effective in the therapy of complicated varicella zoster virus infections in immunocompromised patients. It has been utilized effectively prophylactically to prevent symptomatic cytomegalovirus infections in the post renal transplant period. It can also prevent herpes simplex virus infections. The reasons why interferons are not utilized for these particular purposes at present time is that these preparations are expensive, have side reactions which can be severe, some are antigenic and there are other substances that can accomplish the same goals with lesser cost and toxicity. Side effects of interferon include fever, chills, fatigue, malaise, tachycardia, myalgias and headache. There can be an effect on gastrointestinal and central and peripheral nervous system function, cardiovascular effects, and hepatic dysfunction. Hematologic disturbances can also occur. In contrast, the effects of acyclovir on varicella zoster virus infections are quite potent, the side-effects minor and the cost is small. There is no necessity to use interferon for VZV

infections. It may be that interferon will find its role in viral infections as an adjunct to other therapies. It may be able to be used with AZT in AIDS. A trial in progress involves giving IFN-ß to patients with HIV infections who cannot tolerate full doses of AZT. Interferon has been approved by the FDA as effective therapy in condyloma accuminata. These lesions are caused by human papilloma viruses (HPV) and in some patients are considered to be precursors of genital tract malignancy. The application of systemic and local, intralesional interferon aids in the therapy of this common disorder. Some condylomas are quite large and may obstruct orifices. It is possible that interferon could reduce lesion size sufficiently so that it could act as definitive therapy or it may make it more approachable by other modalities such as surgery, cryosurgery, electrocautery or laser therapy. The action of interferon on hepatitis, chronic active hepatitis and persistent antigenemia is complex, actively being investigated at this time and beyond the scope of this review.

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