Antiviral Research 15 (1991) 1–10
Elsevier.

AVR 00458

Mini-Review

Therapy of viral infections of the central nervous system

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(Received 4 October 1990; accepted 9 October 1990)

Introduction

Viral infections of the central nervous system (CNS) usually represent complications of systemic viral infection. Proper diagnosis and treatment of viral infections of the CNS depend on an understanding of the epidemiology, pathogenesis and clinical features of the potential causes of CNS infection and on an understanding of the special circumstances that govern entry of infectious and therapeutic agents into the CNS.

The endothelial cell tight junctions of the blood-brain barrier restrict access of blood constituents, both soluble and cellular, to the parenchyma of the CNS. The extent of the exclusion is determined for soluble substances primarily by their lipid solubility and the presence of carrier systems (Goldstein and Betz, 1986; Pardridge et al., 1986); for cells by the presence or absence of surface adhesion molecules (Butcher, 1990) and for viruses by surface charge and cellular receptors (Friedemann, 1943; Dropulic and Masters, 1990) and ability to enter with infected cells.

Understanding the entry of substances into the brain also involves an analysis of the barriers between blood and cerebrospinal fluid (CSF) and between CSF and brain parenchyma. CSF is produced by the choroid plexus and passage of substances from blood into CSF occurs across 'leaky' capillary endothelium into the interstitial space and across the tight junctions of the choroidal epithelial cells. Passage is dependent on the size (Felgenhauer, 1974) and charge (Griffin and Giffels, 1982) of the molecule. Once a substance is in the CSF, there is little restriction to movement across the ependyma into the brain parenchyma (Brightman, 1967). For this reason blood-brain barrier penetration of a substance is often assessed by comparing the level in blood to that in the CSF. Since diffusion is a relatively slow process compared to bulk flow of CSF, this may not always be an accurate assessment (Collins and Dedrick, 1983).

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TABLE 1

CNS penetration of antiviral agents

Therapeutic agent	Brain (% extraction)	CSF/plasma (%)	Reference
Acyclovir	–[a]	50	Whitley et al., 1982a; Blum et al., 1982
Amantadine	26	50–60	Spector, 1988; Norris et al., 1990
Dideoxycytidine	<1	20	Yarchoan et al., 1989a, Terasaki and Pardridge, 1988
Dideoxyinosine	–	19	Yarchoan et al., 1989b
Ganciclovir	–	25–50	Fletcher et al., 1986
Interferon	–	<1	Emodi et al., 1975
Ribavirin	<1[b]	40–90	Ferrara et al., 1981; Roberts and Laskin, 1988; Crumpacker et al., 1986
Rimantadine	88	–	Spector, 1988
Vidarabine	–	50–100	Whitley et al., 1980a; Shope et al., 1983
Zidovudine	<1	25–75	Terasaki and Pardridge, 1988; Klecker et al., 1987; Pizzo et al., 1988

[a]No information available.

[b]Percentage of total body drug in CNS.

Entry of pharmacologic agents into the CNS is a major consideration for treatment of CNS infections. Inability to deliver sufficient concentrations of antiviral drugs for therapeutic efficacy is a problem potentially limiting the application of a number of drugs to viral infections of the CNS. Penetration is determined by the size, relative hydrophobicity, and charge of the drug. In general, the smaller, more hydrophobic and more positively charged the agent, the more readily it will enter the CNS. The absolute level of drug will also be influenced by the presence in the CNS of mechanisms for active or passive transport or removal of the compound (Benet and Sheiner, 1985). For instance, entry of nucleosides other than thymidine is aided by an active transport system (Kalaria and Harik, 1986) and entry of compounds ionized at physiologic pH is dependent on their affinity for the weakly basic (drug) carrier in cerebral capillaries (Spector, 1988). In the individual patient, the integrity of the blood-brain barrier, which often changes during the course of infection, may influence drug levels. Table 1 summarizes current knowledge of the CNS penetration of antiviral drugs in use at the present.

Enteroviruses

Enteroviruses are the most common causes of CNS viral infection and cause both meningitis and encephalitis. Poliovirus infection of the CNS can cause meningitis, encephalitis (principally in infants) or the more classic picture of 'poliomyelitis' with predominant infection of the motor neurons of the spinal cord or brain stem. The paralysis is typically flaccid and asymmetric and may progress over several days. Echoviruses are disproportionately isolated from cases of meningitis and encephalitis and infrequently from cases of paralysis (Moore, 1982). Meningitis due to Coxsackie or echovirus is usually benign with symptoms lasting only a few days and an uneventful recovery. More serious disease occurs with perinatally acquired

infection (Modlin, 1986; Kaplan et al., 1983) or with deficiencies of immunoglobulin synthesis (McKinney et al., 1987). In the latter instance CNS infection is usually manifested by chronic meningitis, encephalitis and slowly progressive neurologic deterioration. Therapy in the immunocompetent individual is supportive. Hypogammaglobulinemic children with chronic enteroviral meningoencephalitis have improved with systemic and intrathecal antibody treatment (McKinney et al., 1987; Erlendsson et al., 1985). No drug has yet proven useful.

Arboviruses

The arthropod-borne viruses (arboviruses) include the togaviruses, flaviviruses and bunyaviruses. All are important causes of epidemic encephalitis in certain parts of the world and have a seasonal occurrence. Typically, days after the bite of an infected mosquito or tick there is a prodromal illness followed by the onset of confusion, obtundation and coma. Seizures are common, particularly in children. No successful specific antiviral therapy has been identified for CNS infection and the mainstay of treatment remains vigorous supportive therapy including respiratory assistance, maintenance of salt and water balance, and control of seizures and increased intracranial pressure (Johnson, 1989).

Rabies virus

Rabies is an important human disease in countries where canine rabies remains endemic. The prodromal phase often includes abnormal sensation at the site of the bite followed by signs and symptoms of neurologic disease. For the encephalitic form this includes periods of hyperactivity, seizures, hallucinations and disorientation accompanied by hydrophobia and aerophobia leading to coma and death. Approximately 20% of individuals have a paralytic illness that may be confused with the Guillain-Barré syndrome. The most important treatment is that given prior to the onset of symptoms and as soon after exposure as possible. This post exposure prophylaxis includes thorough cleansing of the wound, administration of rabies immune globulin (20 IU/kg) and intramuscular administration of rabies vaccine (Baer and Fishbein, 1987). The only survivors of clinically evident rabies received prophylaxis prior to the onset of symptoms (Bernard and Fishbein, 1990). Once neurological symptoms have appeared no intervention has been demonstrated to be of use (Maton et al., 1976; Gode and Raju, 1977; Merigan et al., 1984).

Arenaviruses

Arenaviruses have distinct geographic distributions and induce chronic infection in their natural rodent hosts. In humans neurologic disease is usually a late manifestation of a typically biphasic illness. Immune serum is effective therapy

for Junin virus infection, but may predispose to late neurologic disease (Maiztegui et al., 1979). Intravenous ribavirin therapy (1 g q6h × 5 d followed by 0.6 g q8h × 6 d) is efficacious for treatment of systemic lassa fever (McCormick et al., 1986) but has not yet been systematically applied to the treatment of lymphocytic choriomeningitis, Junin or Machupo virus infections.

Retroviruses

The retroviruses human T lymphotropic virus (HTLV)-1 and human immunodeficiency virus (HIV) are often associated with neurologic disease. For both, the latent period between infection and onset of neurologic symptoms can be months to years. HTLV-1 causes progressive spastic paraparesis and this shows some improvement with steroid treatment (Osame et al., 1987). Neurologic disease in those infected with HIV is frequent and the clinical manifestations are varied (McArthur, 1987). Meningitis occurs early while dementia and myelopathy are found at late stages of the disease. Effective penetration of thymidine analogs, such as zidovudine and dideoxyinosine, into the CNS has not been established (Table 1). Like thymidine, these drugs have no affinity for the nucleoside transport systems located within the blood-brain barrier (Terasaki and Pardridge, 1988) but are effectively transported into the CSF. However, they equilibrate poorly with brain interstitial fluid (Klecker et al., 1987; Pizzo et al., 1988; Spector and Berlinger, 1982). Nevertheless, several studies suggest that for adults oral (200 mg q4h) or, for children, intravenous (0.9–1.4 mg/kg/h) zidovudine is useful in treatment and possibly prevention of late neurologic disease (Pizzo et al., 1988; Schmitt et al., 1988; Portegies et al., 1989). The efficacy for neurologic disease of the lower doses of zidovudine (100 mg q4h) currently advocated for systemic therapy of HIV infection or of the many other therapeutic agents currently being tested in this disease is not yet clear.

Herpesviruses

Herpes simplex virus (HSV)-1 and HSV-2 are regularly found latent in sensory ganglia but symptomatic CNS infection is unusual. Encephalitis occurs as a consequence of perinatal infection with either virus and during primary or reactivated HSV-1 infection later in life. The incubation period of neonatal infection is 1–3 weeks and the most frequent initial manifestations of infection are lethargy, failure to feed, skin lesions and fever. Nearly 50% of infected infants with disseminated HSV are premature. In the neonate HSV-2 causes more severe neurologic disease than HSV-1 with more seizures and more CNS damage. In the untreated neonate the mortality is 74% and 50% of the survivors have significant residual morbidity. Both vidarabine (15 mg/kg/day) and acyclovir (500 mg/m^2 q8h) are effective therapies (Whitley et al., 1980b; 1986b). Because of problems with latent infection and recurrent reactivation with continued neurologic deterioration (Gutman et al., 1986) the recommended duration of therapy should be lengthened from the 10 days

originally recommended to at least 14 days.

Among adults in the USA HSV is the most common form of endemic fatal encephalitis. It occurs equally in both sexes and at all times of the year. Over 95% of cases are caused by HSV-1 while HSV-2 is more often associated with meningitis. Encephalitis may be a manifestation of primary infection (children and young adults) or reactivated infection (older adults). Temporal lobe localization is characteristic and the disease progresses from behavioral abnormalities and seizures to coma over days to weeks. The mortality of untreated disease is 70%. Treatment with vidarabine (15 mg/kg/day) decreases overall mortality to 30–40% at 1 month and 40–50% at 6 months (Whitley et al., 1981). Treatment with acyclovir (10 mg/kg q8h) is more effective, decreasing overall mortality to 13% at 1 month and 28% at 6 months with approximately 50% of survivors returning to normal function. The earlier treatment is begun in the course of the disease, the better the outcome (Whitley et al., 1986). The optimal duration of therapy has not been established. Several patients have relapsed after 10 days of treatment (Van Landingham et al., 1988; Rothman et al., 1988) so at least 14 days of treatment is probably necessary (Whitley, 1988). Animal studies using combined vidarabine and acyclovir show enhanced antiviral activity compared to either drug alone (Park et al., 1984), but controlled data from patients are not yet available.

A wide variety of neurologic complications occur in association with varicella zoster virus (VZV) infection. Complications occur both during primary (varicella) and reactivated (zoster) infection. The most common neurologic complication of varicella is cerebellar ataxia. This disease has a benign course and is thought to be immunologically mediated rather than the result of direct VZV infection of the CNS. Cases of meningoencephalitis and transverse myelitis are often examples of postinfectious encephalomyelitis, an immune-mediated disease, but may be due to direct virus invasion of the CNS. Neurologic complications of zoster include paralysis anatomically associated with the reactivated sensory ganglion, generalized meningoencephalitis, cerebral arteritis, and postherpetic neuralgia. CNS complications of zoster occur in the setting of advanced age and immunosuppression (Jemsek et al., 1983), and rarely in apparently normal individuals. Two neurologic syndromes attributed to VZV, multifocal leukoencephalitis and acute retinal necrosis, occur without evidence of recent VZV infection. Treatment of immunocompromised patients with dermatomal zoster early in disease with natural interferon-α (Merigan et al., 1978), vidarabine (Whitley et al., 1982b), or acyclovir (Balfour et al., 1983) can prevent visceral spread of infection. There are no controlled data on treatment of VZV-induced disease already localized to the nervous system. For complications likely to be due to direct virus infection of CNS (encephalitis, arteritis) acyclovir (500 mg/m^2 q8h) is generally accepted and has been reported anecdotally to be efficacious in acute retinal necrosis (Blumenkranz et al., 1986).

Epstein-Barr virus can cause acute meningoencephalitis as part of infectious mononucleosis. Less than 1% of cases are complicated by overt neurologic problems, but CSF abnormalities occur in up to 25%. Recovery is usually uncomplicated. Acyclovir has had limited use in Epstein-Barr virus-induced infections (Andersson et al., 1986), but treatment for CNS disease has not been established.

Cytomegalovirus (CMV) is an uncommon cause of meningoencephalitis in immunologically normal individuals but has emerged as a significant cause of CNS disease in patients with immunosuppression related to organ transplantation or HIV infection. Acute CMV mononucleosis complicated by meningoencephalitis presents with headache, progressing over several days to confusion, disorientation and seizures. Infants with congenital CMV infection may have microcephaly, seizures, growth retardation, chorioretinitis and intracerebral calcifications. Immunosuppressed adults may present in a subacute fashion with confusion, disorientation and myelopathy. Ganciclovir (5 mg/kg q12h) has been used successfully for treatment of CMV retinitis (Buhles et al., 1988), but its efficacy for more generalized CNS disease has not been established.

Herpes B virus (*Herpesvirus simiae*) is a benign, latent infection in macaques analogous to HSV infection in humans. The virus can be transmitted by the bite of an asymptomatic infected monkey and cause fatal encephalitis in humans. Symptoms usually appear within 1 month of exposure and typically begin with vesicular skin lesions near the site of virus inoculation followed by local neurologic symptoms and encephalitis. The reported mortality is 75%, but early use of acyclovir may be associated with recovery (Centers for Disease Control, 1987).

Slow virus diseases

Chronic progressive CNS infection may be caused by rubella (progressive rubella panencephalitis), measles (subacute sclerosing panencephalitis, SSPE) and the papovavirus JC (progressive multifocal leukoencephalopathy, PML). No accepted treatment is available for any of these infections and therapy is difficult to evaluate because of the rarity of the diseases. Treatment of progressive rubella panencephalitis and SSPE with isoprinosine has been attempted without evident benefit (Wolinsky et al., 1979; Noetzel et al., 1983). In addition, bromodeoxyuridine, iododeoxyuridine, azaguanine, amantadine, interferon, ether, ribavirin, and transfer factor have been used for treatment of SSPE with only anecdotal uncorroborated reports of short-term benefit (Griffith and Ch'ien, 1984; Ogle et al., 1989). Attempted treatment of PML with vidarabine (Rand et al., 1977), cytosine arabinoside (Conomy et al., 1974; Horn et al., 1978) and acyclovir (Berger et al., 1987) has been similarly disappointing.

Summary

The herpesviruses (particularly HSV) are the only CNS viral infections for which reasonably clear guidelines exist for specific antiviral treatment. However, data are also beginning to emerge for specific antiviral therapy of HIV-associated CNS disease despite the lack of a clear understanding of the pathogenesis of the CNS abnormalities. As the pace of antiviral drug development increases it is likely that a wider range of CNS viral infections will be treatable in the future although entry

into the CNS is likely to remain a problem limiting the successful application of many compounds to CNS infection.

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