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Short report

Antibiotics and antivirals do not modify experimentally-induced Creutzfeldt-Jakob disease in mice

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SUMMARY Thiamphenicol, rifampicin, amantadine, cytosine arabinoside and isoprinosine were administered to mice which were inoculated with brain tissue containing Creutzfeldt-Jakob disease (CJD). All the mice developed disease within 3 to 6 months after inoculation. As there was no significant shift in incubation periods among animal groups of each drug administration and non-administration, these compounds had no effect in controlling experimental CJD.

Creutzfeldt-Jakob disease (CJD) is a human disease in a group of "unconventional virus" infections of the CNS that includes kuru in New Guinea, scrapie in sheep and transmissible mink encephalopathy. CJD has been transmitted to chimpanzees and other primates,[1] and recently to small rodents.[2-4] Direct transmission from patients to mice and rats, and successive propagations were carried out for the first time in our laboratory.[4] Using this experimental animal system, we studied the modifying effects of antibiotics and antiviral compounds including amantadine which was reported to have therapeutic effect on CJD patients.[5 6] Other antivirals, including rifampicin, cytosine arabinoside (Ara-C) and isoprinosine (Inosiplex, Viruxan) were also studied. Thiamphenicol was chosen as an example of a broadspectrum antibiotic.

Methods

Thirty mg per kg of Ara-C was injected intraperitoneally three times weekly, while other compounds were dissoved in drinking water and given *ad libitum* until the onset of the illness. Daily doses of thiamphenicol, rifampicin and amantadine were approx. 100, 90 and 160 mg per kg, respectively. Three doses of isoprinosine were shown in the table. Two days after administration of the compounds, white (CF 1, DDD) and black (C57BL) mice were injected intracerebrally 0·01 ml of 10^{-1} dilutions in saline of brain homogenates from affected mice. Mouse passage CJD agents were procured from two patients KF and BY whose clinicopathological details were reported elsewhere.[4 7] Control mice were inoculated with the same homogenates as the test group, though not given the compounds. The experiments were performed on two occasions and after the onset of clinical symptoms, all animals were killed for pathological verification of the diagnosis.

Table *Treatments and incubation periods (days: $M \pm SD$)*

A

Treatment	*CF 1 mouse/KF**	*C57BL mouse/KF*	*C57BL mouse/BY*
Brain emulsion	124.7±8.4(9)	166.4±3.3(5)	143.5±2.2(4)
+Thiamphenicol	137.0±12.1(6)	160.8±10.4(5)	145.8±2.3(5)
+Rifampicin	122.4±1.2(6)	166.4±3.3(5)	148.2±3.9(5)
+Amantadine	128.0±9.4(4)	166.4±3.3(5)	145.8±4.3(5)
+Ara-C	121.8±7.2(6)	164.6±3.8(5)	143.8±2.7(5)

B

Treatment	*CF 1 mouse/BY*	*CF 1 mouse/KF*
Brain emulsion	124.0±10.4(5)	104.2±14.8(5)
+Isoprinosine 100mg/kg/day	123.8±9.0(5)	
+Isoprinosine 300mg/kg/day	126.0±11.4(5)	113.4±15.6(5)
+Isoprinosine 600mg/kg/day		115.4±11.3(5)

*Inoculated animal/CJD patient ( ) Number of animals

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Results

All the animals developed the disease after the incubation periods shown in the table. None of the compounds produced a statistically significant shift in the incubation periods. A distinct sign in the diseased mice was plasticity of the body and tail, as noted previously.[4] Spongiform change and proliferation of astrocytes were common pathological findings, though the distribution of the lesion in mice depended upon which of the two CJD agents had been inoculated. There was no distinct difference between clinicopathological features of control and test groups.

Discussion

Unconventional properties of the mouse passage CJD agents had been inoculated.[7] There was no previously and the infectivity titre (LD_{50}) was between 10^7 and 10^8 per gram of mouse brain.[8]

Recently, amantadine has been administered to CJD patients and improvement or delayed worsening of clinical symptoms has been described.[5,6] In this experiment, however, no difference was found between test and control animals. As there was no major shift in the incubation period, the administered compounds had no effect in controlling experimental CJD. Hitherto, antiviral compounds have not been tested systematically in experimental CJD, due to limitations of susceptible animal species and long incubation periods. In our experiments, the disease was induced in the mice within 3–6 months after intracerebral inoculation, thus making it feasible to carry out further systemic studies of this morbid disease.

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