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IN VIVO ANTIHERPETIC ACTIVITY OF DEOXYTHYMIDINE

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Cytostatic effects of high deoxythymidine concentrations of the order of 10^{-3}M in vitro have been well documented (1, 2, 3, 4). Also in tissue cultures its virostatic activity against THEILER's Virus, a ribovirus, has been reported (5). No reports, whatsoever, describing in vivo inhibition of virus multiplication by this compound have so far come to our notice. This paper describes the effect of deoxythymidine on experimental herpes keratitis in rabbit and also its effect on the mortality rate of herpes keratitis infected hamsters.

According to our earlier experiments with rabbits, lower deoxythymidine concentration (0.5%; 0.4 ml injected subconjunctively and assisted with eye drops during the day time only) remarkably enhanced the development of the herpes keratitis. Moreover, some increase in the mortality rate of the infected animals was recorded (6, 7).

In present studies, however, with higher deoxythymidine concentrations, a therapeutic effect is achieved when subconjunctive injections of 0.4 ml 4% deoxythymidine were applied on three consecutive days and eye drops of the same strength continued

for a total of 10 days. On the 13th day post infection this treatment yielded 80% corneal healings (deoxythymidine/control p=0.01). In the control group only 20% healings were recorded. The comparative examination with 5-iodo-2'-deoxyuridine, applied twice daily as a 0.2% ointment for 10 days, showed a therapeutic effect in 60% of the infected animals (IDU/control p=0.02; IDU/d-thymidine p=ns). Prolongation of the subconjunctive d-thymidine treatment beyond the three injections to the infected animals produced toxic side effects to cornea. In respect to local toxicity, the infected cornea reacts towards the d-thymidine in a different manner than the scarified non-infected one because, according to present observations, subconjunctive treatment with 4% d-thymidine for 12 day neither influences the regeneration of experimentally damaged cornea nor is capable of producing lesions to normal healthy cornea.

In further experiments the effect of intraperitoneal d-thymidine injection was studied in herpes keratitis-infected hamsters. In these animals casualities occur regularly following intracorneal herpes infection thereby allowing a quantitative evaluation of the antiviral activity (8). As shown in table 1 d--thymidine significantly reduces the mortality rate of the infected animals when compared with that of the non-treated controls.

In an experiment with hamsters the animals were infected with a sublethal virus dose. In this case in the 10 control animals herpetic lesions appeared primarily along the eye lids only approximately 30 days after the infection. Later on they spread over the whole face. During an observation period of 5 months the lesions healing at one place kept recurring at the other

sites. In none of these animals complete regressions were seen.

Table 1: EFFECT OF I N T R A P E R I T O N E A L D-THYMIDINE TREATMENT ON MORTALITY RATE OF HERPES KERATITIS-INFECTED HAMSTERS

mg/kg/day	Total dose mg/kg	day 30 survivors	day 30 casualities	n	P_0
0 = controls	-	11 (55%)	9 (45%)	20	-
200 (10 days before infection)	2000	6 (60%)	4 (40%)	10	ns
100 (10 days before and after infection)	2000	8 (80%)	2 (20%)	10	ns
200 (10 days before and after infection)	4000	8 (80%)	2 (20%)	10	ns
200 (10 days after infection)	2000	8 (80%)	2 (20%)	10	ns
400 (10 days after infection)	4000	9 (90%)	1 (10%)	10	0.1
400 (10 days before and after infection)	8000	10 (100%)	0	10	0.02

P_0 = Significances against 0 hypothesis

In the d-thymidine group only one of the 10 animals treated intraperitoneally for 10 days (400 mg/kg) developed minute lesions temporarily. No lesions were observed during the complete observation period of 5 months in the remaining 9 animals.

In experimental studies so far such a course of herpes infection has not been reported. It is believed here that this test might also enable evaluation of virostatic activity of compounds of low potency which in the mortality test (8) might prove to be relatively ineffective.

Following this experimental virostatic activity the effect of d-thymidine has been evaluated in the clinical treatment of dendritic herpes keratitis. So far, in 20 patients treated with 3% eye drops, therapeutic value of d-thymidine has been evidenced.

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