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Pathogenesis of Drug Resistant Clinical HSV-2 Isolates in the Guinea Pig Model of Genital Herpes. N. Bourne, LR Stanberry, J Ireland and DI Bernstein. Childrens Hosp Res Fdn and Gamble Inst Med Res, Cincinnati, OH, USA.

Acyclovir (ACV) resistant HSV isolates are becoming increasingly common in immunocompromised subjects and have recently been reported in immunocompetent patients. We therefore evaluated the pathogenesis of several ACV resistant isolates in the guinea pig model of genital herpes, the model which most closely resembles human disease. We initially examined six clinical HSV-2 isolates with thymidine kinase (TK) activities ranging from 2-3.6%. All isolates were plaque purified twice in the presence of ACV prior to use. Guinea pigs were inoculated intravaginally with 3.5-5.7 log 10 pfu derived from two plaques from each isolate. All isolates caused primary and recurrent gental skin disease. Recurrences ranged from a mean of 0.3 $\pm$ 0.3 to 7.3 $\pm$ 0.6 lesion days from days 15-42 post viral inoculation. The two isolates producing the most severe disease produced peak vaginal virus titers, primary disease severity, and recurrent disease frequency comparable to that seen with our standard ACV sensitive HSV-2 ACV resistant strain MS. Inoculum virus and virus obtained from recurrent lesions and from latently infected dorsal root ganglia are being evaluated for TK activity by plaque autoradiography. We also examined disease caused by one foscarnet resistant isolate and one dual resistant isolate. The foscarnet resistant isolate produced very severe acute disease at inocula from 3.7-5.7 log 10 pfu. The dual resistant virus produced very mild primary disease in about 50% of animals but no recurrences. These experiments demonstrate that TK deficient viruses can produce acute disease and can reactivate to cause recurrent disease. These viruses should prove valuable for evaluating new antiviral agents with in vitro activity against drug resistant viruses.

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Civamide (CIV) Treatment of Primary and Recurrent Experimental Genital Herpes. N Bourne, DI Bernstein and LR Stanberry, Children's Hospital Research Foundation, University of Cincinnati, Cincinnati, OH, USA.

Capsaicin, the irritant compound in hot peppers, affects sensory neuron function and the pathogenesis of HSV infection. CIV, the cis-isomer of capsaicin is less irritating but is neuroactive. Using the guinea pig model of genital HSV-2 infection we evaluated the effect of different intravaginal treatment regimens of 1.25% CIV begun 24 hrs post inoculation [PI]) on primary and recurrent infection. All regimens significantly reduced the severity of primary infection as measured by the area under the lesion score-day curve [AUC] and reduced the frequency of subsequent recurrences.

CIV treatment[a]	Mean AUC($\pm$SE)	Mean Recurrences($\pm$SE)[b]
Untreated	4.76 (0.46)	9.75 (0.90)
BID X 10d	1.21 (0.32)	3.08 (1.39)
QD X 10d	2.21 (0.73)	4.38 (1.17)
QD X 5d	2.20 (0.42)	3.07 (0.64)
QD X 3d	1.73 (0.55)	4.53 (1.16)
QD X 1d	2.14 (0.64)	4.53 (1.16)

[a] beginning 24 hrs PI; [b] for days 15-63 PI

Treatment of latently infected animals (BID X 10d) beginning 21d PI also reduced the frequency of recurrent disease (4.0+0.7 v 9.1+0.9; $p < 0.01$; d22-63PI), however, treatment during primary infection tended to produce a more prolonged reduction in recurrences. The effectiveness of even brief treatment with civamide suggests that it may be useful in the treatment of primary and recurrent HSV infections. Plans for clinical evaluation of CIV are under discussion.