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A Rational Approach to the Development of Antiviral Combined Chemotherapy by Reduction in Nucleoside Triphosphates Levels.
S. N. Pancheva. Institute of Microbiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.

An attempt was made to argue a more general concept for development of the rational antiviral combined chemotherapy taking into account that into the cells, the physiological nucleoside triphosphates compete with nucleoside triphosphate analogues in binding to susceptible virus-induced enzymes. The reduction in the intracellular content of the natural substrates could make their direct competitors more effective at the enzyme level. On the basis of this concept a combination of acyclovir (ACV) and ribavirin (Rbv) was applied in vitro and a strong synergistic effect was observed against HSV-1 and pseudorabies virus. A potentiated antiviral effect was also found in vivo, in the experimental HSV-1 keratitis model in rabbits. The antiviral activity of the ACV-Rbv combination was reversed by guanosine. Our results suggest that the reduction in dGTP level accounts for the potentiating effect of Rbv on the antiviral activity of ACV. To confirm this approach we have chosen another combination of agents assuming a similar interaction with the pool sizes of NTPs in the same test system. We have found that the combination of bromovinyldeoxyuridine (BVDU) and amethopterin (Ame) showed a synergistic activity against HSV-1 in cell cultures. The antiviral effect of BVDU-Ame was reversed by thymidine. In this case dTTP could be considered as "key" metabolite responsible for the greater effectivity of the combination.

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Activity of penciclovir and acyclovir in DBA/2 mice infected intraperitoneally with HSV-1 (SC16).
M.R. Boyd, D. Sutton, and R.J. Ashton, SmithKline Beecham Pharmaceuticals, Epsom, Surrey, UK, KT18 5XQ.

Penciclovir (9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine) has comparable activity to acyclovir in cell culture against HSV and VZV. Penciclovir triphosphate in virus infected cells has much greater stability than the triphosphate of acyclovir, leading to more prolonged inhibition of virus replication in cell culture when the extracellular drug concentration is low. We have compared the activities of both compounds in DBA/2 mice infected intraperitoneally with HSV-1 (SC16) by measuring the amount of virus in peritoneal washings. In untreated mice, following an eclipse phase, virus titres are maximum 48 hours after infection and thereafter decline. When given ad libitum in drinking water, penciclovir and acyclovir reduced virus replication to a similar extent even though acyclovir had better oral absorption. In dose response experiments, penciclovir, given as single subcutaneous or intravenous doses 24h after infection, was ten-fold more effective than acyclovir ($p<0.01$ for each). A single subcutaneous dose of penciclovir 5h after infection prevented virus replication for 3 days and was more effective than 3 doses of acyclovir given 1, 5 and 20h after infection ($p<0.05$). The superior activity of penciclovir following discrete dosing is unlikely to be due to pharmacokinetic differences and is probably a reflection of the very stable intracellular triphosphate. The maintenance of high penciclovir blood concentrations is less important than with acyclovir and may lead to a less frequent dose schedule in man.