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Therapeutic Implications of The Unusually Long Half-Life of (E)-5-(2-bromovinyl)uracil (Bvura) In Vivo

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THERAPEUTIC IMPLICATIONS OF THE UNUSUALLY LONG HALF-LIFE OF
(E)-5-(2-BROMOVINYL)URACIL (BVUra) IN VIVO

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Summary - The long half-life of BVUra in the plasma permits, on the one hand, the *de novo* formation of the antiviral drug (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd) by a pentosyl transfer, and, on the other hand, the inhibition of the degradation of pyrimidine bases such as 5-fluorouracil (FUra).

In contrast to other pyrimidine bases such as uracil (Ura), thymine (Thy), 5-iodoUra, FUra, which are eliminated from the blood stream within 2-4 hours after their administration, BVUra maintains a constant level of 50-70 μ M in plasma for at least 6 hours. This peculiar behavior is probably due to the lack of degradation of BVUra by the reductive catabolic pathway of pyrimidines.

We have demonstrated that the potent and selective antiherpes agent BVdUrd¹ could be generated from BVUra in the plasma of rats following the administration of pyrimidine deoxynucleosides such as thymidine, 2'-deoxyuridine (dUrd) or other 5-substituted dUrd derivatives; BVdUrd is formed by a deoxyribosyl transfer from the deoxynucleosides to BVUra catalysed by pyrimidine nucleoside phosphorylases.² The generation of the active drug BVdUrd from its inactive metabolite BVUra *in vivo* can be repeated several times after a single administration of BVUra; and this procedure could be useful to potentiate the clinical efficacy of BVdUrd.

In addition, BVUra is an inhibitor of the reductive step of the pyrimidine catabolism and increases the *in vivo* half-life of other pyrimidine bases that are normally rapidly degraded, particularly of FUra; and we have demonstrated that the inhibition of FUra degradation is reflected by an increase of the antineoplastic activity of this pyrimidine analogue.

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