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Enhanced serum concentrations of Ara-C using suppositories containing tetrahydrouridine as a deamination inhibitor of Ara-C

G. G. LIVERSIDGE*, T. NISHIHATA†, K. K. ENGLE‡ AND T. HIGUCHI†, †*Pharmaceutical Chemistry Department, University of Kansas, Lawrence, Kansas 66045, ‡INTERx Research Corporation, Lawrence, Kansas 66044, USA*

Rectal bioavailability of Ara-C (serum AUC 4 h: 65 μg h^{-1} ml^{-1}) administered in a suppository formulation containing tetrahydrouridine (a deamination inhibitor) and sodium salicylate (an adjuvant) to dogs was better than that from a suppository formulation without tetrahydrouridine (serum AUC 4 h: 18 μg h^{-1} ml^{-1}).

Ara-C (1-β-D-arabinofuranosylcytosine) has been administered by slow intravenous infusions for the treatment of lymphatic cancers (Goodell et al 1970; Bickers et al 1974) due to its poor absorption in the gastrointestinal tract (Wan et al 1974). We have reported (Nishihata et al 1986) that, on rectal administration, Ara-C in a microenema containing either the adjuvants 5-methoxysalicylate or glycerol monooleate–glycerol (1 : 1 v/v) in rats shows preferential absorption into the lymphatic system. Thus, rectal administration provides a non-invasive method of targeting the drug to the site of action with a consequent reduction in systemic side effects.

Here we report the effects of suppositories containing the adjuvants sodium salicylate (300 mg) with or without 1(-β-D-ribofuranosyl)-4-hydroxy tetrahydro-2[1*H*]-pyrimidine, (3,4,5,6-tetrahydrouridine, THU) on the serum levels of Ara-C and its major metabolite Ara-U (1-β-D-arabinofuranosyluracil) in adult beagle dogs.

The deamination of Ara-C to a biologically inactive product Ara-U by pyrimidine nucleoside deaminase (cytidine aminohydrolase) has been studied both in-vitro (Camiener 1967a, b; Camiener & Smith 1965; Loo et al 1965) and in-vivo (Camiener 1968; Dedrick et al 1973). Ho & Frei (1971) and Wan et al (1974) have reported that the disappearance from plasma of Ara-C was biphasic with a short-life of 11 min and a longer half-life of 111 min. They also demonstrated dose-related pharmacokinetics which indicated that the deamination of Ara-C was a saturable process. The deamination process can be partially inhibited by THU (Camiener 1968). Furthermore, it has been reported by Camiener (1968) that THU shows no noticeable toxic effects in rats, mice, monkeys and dogs. Thus, we would expect to see elevated serum Ara-C levels and reduced Ara-U levels from suppositories containing THU. However, such observations were not seen.

Methods

Suppository preparation. Ara-C (Upjohn), 33 mg, and where appropriate THU (Sigma), 1 mg, were dissolved in 260 μl distilled water. To the solution was added molten Witepsol S55 (Dynamit Nobel), 700 mg, with thorough mixing. To the mixture was added sodium salicylate (99% + Aldrich), 300 mg, in 25 mg amounts each of which was thoroughly dispersed in the mixture before the next addition. The molten mass was then cooled with stirring until just above the solidification point and poured into a 1 g suppository mould and the product stored for 24 h before administration. For i.v. injections, 30 mg of Ara-C was dissolved in 1 ml of distilled water.

Five normal, healthy beagle dogs, 10·6 to 14·5 kg were used with a period of one week between successive drug administrations. The animals were fasted with free access to water for 24 h before use. Suppositories were inserted to a depth of 4 cm from the outer rectal sphincter, and blood samples were taken from the cephalic vein at the following times: 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 min. Blood was withdrawn at the same times after intravenous administration of Ara-C; the i.v. injection was administered in the cephalic vein

* Present address & correspondence: Smith Kline & French F112, 1500 Spring Garden Street, Philadelphia, PA 19101, USA.

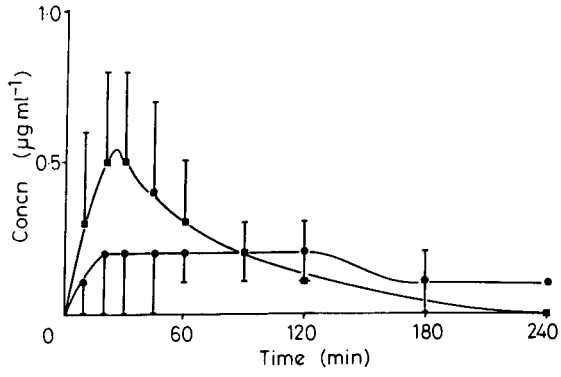

FIG. 1. Serum levels of Ara-C (■) and Ara-U (●) after rectal administration of a suppository. (±s.d. for n = 5).

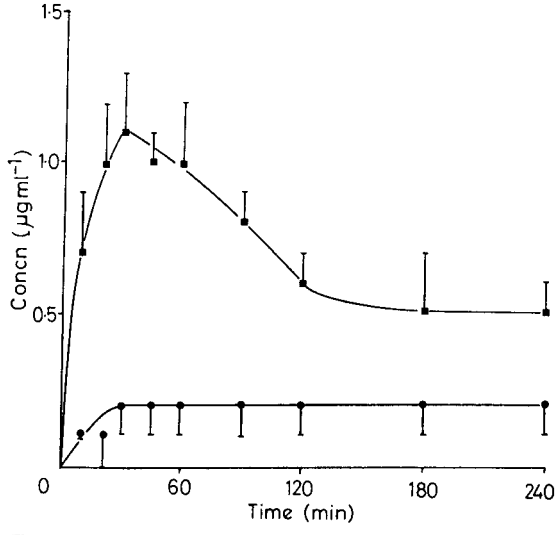

FIG. 2. Serum levels of Ara-C (■) and Ara-U (●) after rectal administration of a suppository containing THU. (± s.d. for n = 5).

not being used for sampling. Serum was analysed for Ara-C and Ara-U according to Liversidge et al (1983).

Results and discussion

Figs 1 and 2 show the effects of the two formulations containing 30 mg of Ara-C on serum, Ara-C and Ara-U, the only difference being that one formulation included 1 mg THU (Fig. 2). The areas under the serum concentration-time curve (AUC 4 h) up to the last measured time (4 h) were calculated using Simpson's Rule. The AUCs after i.v. administration were 285 μg h^{-1} ml^{-1} for Ara-C and 65 μg h^{-1} ml^{-1} for Ara-U; after rectal administration in the formulations containing THU, the AUC 4 h were 65 and 18 μg h^{-1} ml^{-1}, respectively, and after rectal administration in the formulations without THU, 18 and 14 μg h^{-1} ml^{-1}, respectively. The AUC, for the intravenous administration of Ara-C is 100%, while that for the formulation containing THU is for Ara-C 23% and for Ara-U 55%, and that for the formulation that does not contain THU is Ara-C 6% and Ara-U 44%. Thus, the serum Ara-C levels are much higher (383%) when THU is incorporated, however, the Ara-U level is also higher (20%). The Ara-U levels would be expected to be the lowest for the formulation containing THU. We hypothesize that the increased levels of Ara-U may be attributed to deamination occurring at two sites, the rectal membrane and in the blood. While the high concentration of THU at the membrane may significantly inhibit deamination, permitting a greater quantity of Ara-C to pass into the blood, once in the blood stream, the Ara-C is subjected to greater enzymic deamination leading to enhanced levels of Ara-U.

The low serum availability (23%) from suppositories containing THU may be explained by the preferential absorption of Ara-C into the lymphatic system. We have shown in rats (Nishihata et al 1986) that lymphatic concentrations of Ara-C are greater than serum concentrations when the drug is administered rectally rather than intravenously. With rectal administration, there is a good correlation between serum and lymphatic concentrations. Thus, the total availability (blood and lymph) will be greater than that indicated by comparison of AUC's with intravenous administration. Compared with the findings of Camiener (1968) and Dedrick et al (1973), deamination activity is lower in dogs than in man or monkeys and we would expect a much greater effect of THU-containing suppositories on the serum levels of Ara-C in both of these species and the suppository formulation containing THU to provide a useful alternative to slow intravenous infusions of Ara-C.

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