J. Pharm. Pharmacol. 1995, 47: 595–600
Received July 21, 1995
Accepted December 13, 1995

Accumulation of 5-Ethyl-2′-deoxyuridine and its 5,6-Dihydro Prodrugs in Murine Lung and its Potential Clinical Application

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Abstract

The accumulation of 5-ethyl-2′-deoxyuridine (EDU), (−)-*trans*-(5*S*,6*S*)-5-bromo-5-ethyl-6-methoxy-5,6-dihydro-2′-deoxyuridine [(5*S*,6*S*)-BMEDU], (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-methoxy-5,6-dihydro-2′-deoxyuridine [(5*R*,6*R*)-BMEDU], (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-2′-deoxyuridine (BEEDU), (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-5′-*O*-valeryl-2′-deoxyuridine (VBEEDU) and (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-3′-5′-di-*O*-valeryl-2′-deoxyuridine (DVBEEDU) in lung and other tissues was investigated in male Balb-C mice following intravenous injection of the corresponding 4-^{14}C-labelled compounds.

EDU showed a rapid distribution into liver and lung immediately after injection, and the overall levels of radioactivity in blood, liver and lung were similar. The distribution of radioactivity in lung after injection of [4-^{14}C](5*S*,6*S*)-BMEDU and [4-^{14}C](5*R*,6*R*)-BMEDU were substantially different from one another and also from that of [4-^{14}C]EDU. The radioactivity level present in lung samples after injection of both [4-^{14}C](5*S*,6*S*)-BMEDU and [4-^{14}C](5*R*,6*R*)-BMEDU was substantially higher than that in blood samples. Radioactivity levels present in lung samples taken at 18 min after injection of [4-^{14}C]BEEDU were significantly higher ($P < 0.05$) than those for liver and blood samples. Although the radioactivity present in lung samples after injection of [4-^{14}C]VBEEDU was significantly higher ($P < 0.05$) than those of liver and blood samples, [4-^{14}C]VBEEDU did not provide a higher radioactivity level in lung samples than did [4-^{14}C]BEEDU. The level of radioactivity in lung samples following injection of [4-^{14}C]DVBEEDU was also higher than that of blood samples. EDU undergoes glycosidic bond cleavage to form EU in lung following intravenous injection into Balb-C mice.

The concentrations of EDU and 5-ethyluracil (EU) following intravenous injection of EDU, and its prodrugs BEEDU and VBEEDU, were quantitated in lung and blood samples. In contrast to lung samples, EU was not detected in blood samples at 120 min post injection of EDU. The concentrations of both EDU and EU in lung tissues after injection of BEEDU and VBEEDU were substantially higher than those in blood samples.

Herpes simplex virus (HSV) causes a variety of infections in man including topical, systemic and respiratory tract infections (Straus 1985; Nahimas et al 1989; Inglis 1993; Portolani et al 1993). HSV is reported to be the most frequently isolated pathogen from the lungs of patients with severe respiratory distress. A mortality rate of 7–71% was reported for HSV-positive patients with complicated pneumonia who were being treated with assisted ventilation (Prellner et al 1992). However, it appears that HSV-infection of the respiratory tract in neonates, young adults and immunocompromised adults is more important (Koskiniemi et al 1989; Ryan & Doody 1992; Whimbey & Bodey 1992; Schuller et al 1993).

5-Ethyl-2′-deoxyuridine (EDU) is a non-mutagenic pyrimidine nucleoside with known antiviral activity against several species of HSV (De Clercq & Shugar 1975; Cheng et al 1976; Davis et al 1978, 1979). EDU is currently used as a topical dosage form for treatment of local HSV infections (De Clercq & Walker 1986; Sacks et al 1991). However, EDU has some clinical limitations including its pharmacokinetic properties which are less than ideal. Recently, several 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrugs to EDU were developed for in-vitro and in-vivo investigations. Some of these prodrugs showed improved site delivery and pharmacokinetic parameters relative to EDU (Cheraghali et al 1994a, b). We now report the accumulation of EDU and its 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrugs, in the lungs of male Balb-C mice.

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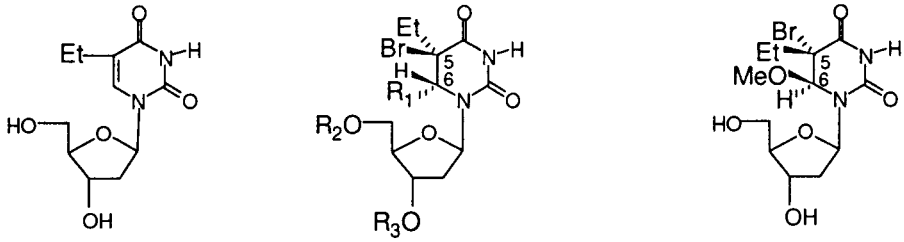
Materials and Methods

5-Ethyl-2′-deoxyuridine (EDU) and 5-ethyluracil (EU) were purchased from the Sigma Chemical Co. (−)-*Trans*-(5S,6S)-5-bromo-5-ethyl-6-methoxy-5,6-dihydro-2′-deoxyuridine [(5*S*,6*S*)-BMEDU], (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-methoxy-5,6-dihydro-2′-deoxyuridine [(5*R*,6*R*)-BMEDU], (+)-*trans*-(5R,6R)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-2′-deoxyuridine (BEEDU), (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-5′-*O*-valeryl-2′-deoxyuridine (VBEEDU), (+)-*trans*-(5*R*,6*R*)-5-bromo-5-ethyl-6-ethoxy-5,6-dihydro-3′-5′-di-*O*-valeryl-2′-deoxyuridine (DVBEEDU) (Fig. 1) and the 4-^{14}C-labelled analogues of these compounds were synthesized according to the



EDU (5R,6R)-BMEDU; R_1=MeO, R_2=R_3=H (5S,6S)-BMEDU

(5R,6R)-BEEDU; R_1=EtO, R_2=R_3=H

(5R,6R)-VBEEDU; R_1=EtO, R_2=Valeryl, R_3=H

(5R,6R)-DVBEEDU; R_1=EtO, R_2=R_3=Valeryl

FIG. 1. Structures of EDU and its 5,6-dihydro prodrugs (5S,6S)-BMEDU, (5R,6R)-BMEDU, BEEDU, VBEEDU and DVBEEDU.

methods described previously (Cheraghali et al 1994a, b). Male Balb-C mice (20–22 g) were purchased from the University of Alberta Health Science Laboratory Animal Services Facility. Three animals were used in each experiment. All animal studies were performed according to the Canadian Council on Animal Care Guidelines, with review and approval of protocols by the University of Alberta Health Sciences Animal Welfare Committee.

The biodistribution of [4-^{14}C]EDU and its 4-^{14}C-labelled 5,6-dihydro prodrugs described above were determined after injection of the test compound [126 kBq (3·4 μCi) mixed with 0·2 mmol kg^{-1} of non-radioactive compound for a final specific activity of 31·5 MBq mmol^{-1}, dissolved in 100 μL dimethylsulphoxide-water (50 : 50 v/v)] into the lateral tail vein of mice. Animals were killed by carbon dioxide asphyxiation and tissues, including liver, blood and lung, were excised at 3, 8, 18, 30, 60, and 120 min post injection. The weights of samples collected from each tissue were limited to a maximum 180 mg of wet tissue, or 100 μL blood, to ensure complete combustion and quantitative trapping of [^{14}C]CO_2. Samples were air dried at room temperature (21°C) for at least three days to ensure quantitative combustion using an OX-300 Harvey Biological Material Oxidizer. The [^{14}C]CO_2 produced upon combustion and oxidation of the radioactive tissue samples was trapped in 15 mL Carbon-14 Cocktail (Harvey Co.). These solutions were then counted using a Beckman LS9000 liquid scintillation counter.

The biotransformations of EDU, BEEDU and VBEEDU were investigated in male Balb-C mice after intravenous injection of 0·4 mmol kg^{-1} of the test compound into the tail vein. The test compound was dissolved in 0·1 mL water : polyethylene glycol (PEG) 400 (40 : 60 v/v). Animals were killed by carbon dioxide asphyxiation at 2, 5, 10, 20, 30, 60, 90 and 120 min post injection of the test compound. Whole lung and blood samples (about 0·7 mL obtained via cardiac puncture) were collected. The blood samples from each mouse were extracted by shaking the whole blood sample with methanol (2 mL) using a mechanical shaker for 15 min. Lung samples from all three mice were pooled and homogenized in a mechanical homogenizer using 5 mL physiological saline. Either this mixture, or the mixture from blood samples, was centrifuged for 10 min at 1000 g and the supernatant fraction was then filtered through a Sep-Pak (C18, Waters Millipore) cartridge. Each Sep-Pak cartridge was preconditioned by washing with 3 mL methanol. The filtrate from the supernatant was dried under a stream of nitrogen gas and the residue obtained was dissolved in 400 μL methanol.

A 40-μL aliquot of this solution was then subjected to quantitative high-performance liquid chromatography (HPLC) analysis using the HPLC system described previously (Cheraghali et al 1994a, b). All separations and quantitative analyses were carried out using a Waters Radial-Pak C18 reverse phase cartridge column (10 μ, 8 mm × 10 cm) at 25°C with UV detection at 230 nm. The identity of EDU and EU present in the sample was confirmed by comparison of retention times with those of authentic samples. The concentration of each compound in blood, as a function of time, was plotted using the SigmaPlot program (Jandel Scientific). Statistical analysis of the data was carried out using the t-test for independent samples.

Results and Discussion

The distribution of radioactivity after injection of 126 kBq (3·4 μCi; 31·5 MBq mmol^{-1}) of either EDU or its 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrug (BMEDU, BEEDU, VBEEDU and DVBEEDU, Fig. 1) is summarized in Fig. 2. EDU showed a rapid distribution into liver and lung shortly after injection, and the level of radioactivity was slightly higher than that in blood. However, the overall distribution of radioactivity in blood, liver and lung was similar (Fig. 2). Samples taken 3 min after injection of [4-^{14}C]EDU showed 9·6, 9·7 and 8·1% of the injected radioactivity per gram of lung, liver and mL of blood, respectively. The distribution of radioactivity in lung after injection of [4-^{14}C](5*S*,6*S*)-BMEDU and [4-^{14}C](5*R*,6*R*)-BMEDU was substantially different from each other and also from that of [4-^{14}C]EDU. Lung samples taken 8 min post injection of [4-^{14}C](5*S*,6*S*)-BMEDU showed the highest level of radioactivity. However, injection of [4-^{14}C](5*R*,6*R*)-BMEDU provided the highest radioactivity in lung at 3 min post injection. The radioactivity level present in lung samples after injection of both [4-^{14}C](5*S*,6*S*)-BMEDU and [4-^{14}C](5*R*,6*R*)-BMEDU was substantially

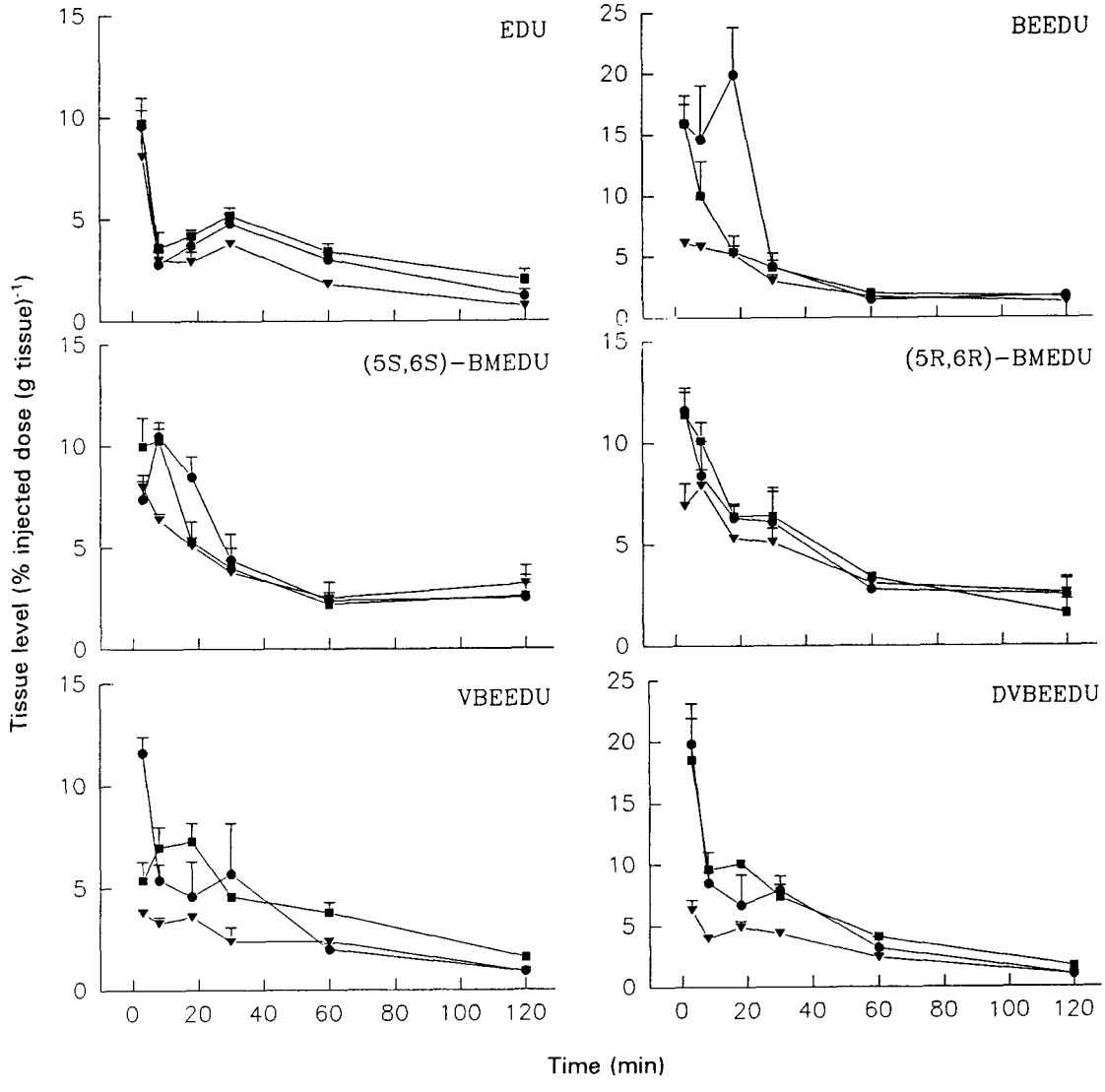


FIG. 2. Percent of injected dose present per gram of lung (●), liver (■) and blood (▼) samples after injection of 126 kBq (3·4 μCi) of 4-^{14}C-labelled EDU, BEEDU, (5S,6S)-BMEDU, (5R,6R)-BMEDU, VBEEDU and DVBEEDU. Values are the mean ± s.e.m. (n = 3).

higher than that of blood samples (Fig. 2). Injection of [4-^{14}C]BEEDU into mice provided a higher radioactivity in lung samples compared with those of EDU and BMEDU diastereomers. Radioactivity present in lung samples taken 18 min after injection of [4-^{14}C]BEEDU was significantly higher ($P < 0{\cdot}05$) than in liver and blood samples at this time interval. Although the radioactivity present in lung samples after injection of [4-^{14}C]VBEEDU was significantly higher ($P < 0{\cdot}05$) that those in liver and blood samples, [4-^{14}C]VBEEDU did not provide higher radioactivity in lung samples than [4-^{14}C]BEEDU (Fig. 2). The radioactivity level present in lung samples after injection of DVBEEDU was similar to that of liver samples. However, lung samples showed a considerably higher percent of the injected dose than did blood samples.

The HPLC analysis results for lung and blood samples after injection of a 0·4 mmol kg^{-1} intravenous dose of either EDU, BEEDU or VBEEDU into mice are shown in Fig. 3. It appears that EDU and EU are the major components present in lung samples. Although the concentration of EDU in lung samples taken 2 min after injection of EDU was substantially lower than that of blood, the concentration of EDU in lung samples obtained at longer times was very similar to that of blood samples. In contrast to lung samples, EU was not detected in blood samples taken at 120 min post injection of EDU. The concentrations of both EDU and EU in lung samples after injection of BEEDU was substantially higher than that of blood samples. In contrast to blood samples, both EDU and EU showed accumulation in lung samples following injection of BEEDU. Lung samples taken after injection of VBEEDU also showed a considerably higher concentration of EDU and EU compared with that of EDU (Fig. 3).

Herpes simplex virus (HSV) is responsible for respiratory tract infections in man and it is reported that HSV infection of the respiratory tract is more important in neonates, young children and immunocompromised adults than in other populations. Therefore, it is crucial for the antiviral

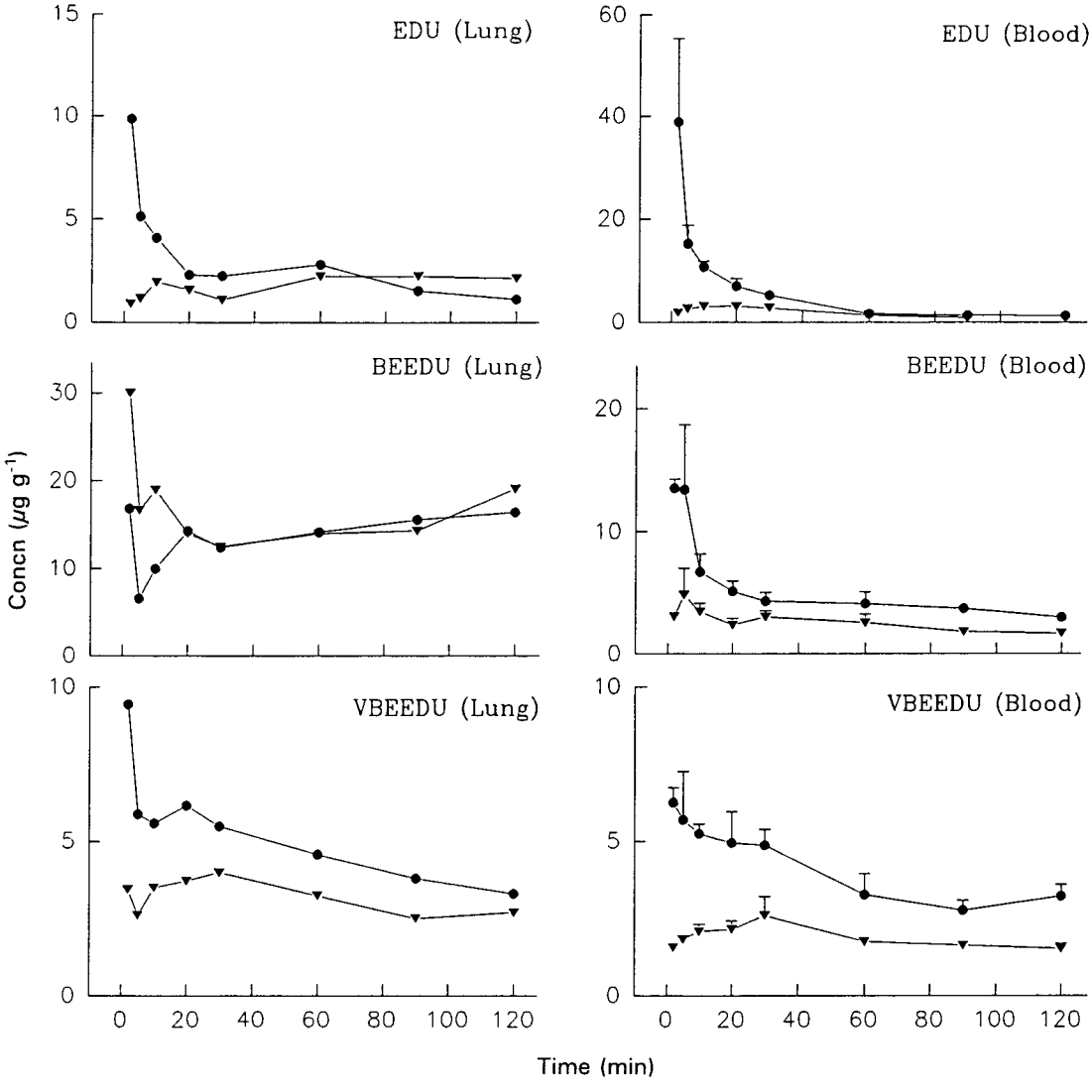


FIG. 3. Concentration of EDU (●) and EU (▼) ($\mu g\,g^{-1}$) of blood and lung samples after injection of a 0·4 mmol kg^{-1} EDU, BEEDU and VBEEDU. Values are the mean ± s.e.m. (n = 3) where applicable.

drug to localize in the virus-infected areas of the lung to effectively treat these patients.

A review of selected papers in the literature reveals that the accumulation of various nucleosides in lung varies significantly from one nucleoside to another. For example, it was reported that 2–8% of the injected dose of 5-halo-1-(2′-fluoro-2′-deoxy-β-D-ribofuranosyl)uracil and 1-(2′-halo-2′-deoxy-β-D-ribofuranosyl)uracil accumulates in the lung of mice following intravenous injection (Abrams et al 1986; Mercer et al 1987, 1989). 5-Halo derivatives of uracil and 2′-bromo-2′-deoxyuridine and 5-bromo-1-(2′-chloro-2′-deoxy-β-D-ribofuranosyl)uracil also showed up to 8% of the injected dose in lung (Lee 1983). However, it was reported that accumulation of (E)-5-(2-iodovinyl)-2′-deoxyuridine and 5-fluoro-5,6-dihydrouracil nucleosides in lung was less than 1% of the injected dose (Samuel 1985; Visser et al 1989). Acyclovir, which is currently used for the treatment of respiratory tract HSV infections (Ruben & Nguyen 1991), showed a substantially lower radioactivity level in lung relative to blood and liver after administration of [8-^{14}C]acyclovir (Miranda et al 1981). Administration of [2-^{14}C]5-(2-chloroethyl)-2′-deoxyuridine, which is structurally related to EDU, showed higher radioactivity levels in lung relative to that in liver and blood (Szinai & De Clercq 1989). In contrast to other nucleosides, our study and others (Szinai & De Clercq 1989) show that EDU and 5-(2-chloroethyl)-2′-deoxyuridine accumulates in lung to a greater extent relative to blood and liver. More importantly, our study demonstrates that 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro acts as a prodrug for EDU, providing a higher concentration of EDU in lung than does EDU itself.

The 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrug for EDU, described in this investigation, provided higher radioactivity levels in lung than in liver and blood after injection of the 4-^{14}C-labelled compounds. This observation clearly illustrates processes of accumulation or metabolic trapping in lung. It was previously reported that these 5,6-dihydro prodrugs are rapidly metabolized to the parent nucleoside

EDU (Cheraghali et al 1994 a, b). Therefore it was anticipated that the radioactivity present in lung would be primarily due to the presence of EDU or EU. It appears that the high radioactivity level present in lung samples after injection of [4-^{14}C]EDU (Fig. 2) is mainly due to its rapid biodistribution, where the overall distribution of radioactivity in lung, liver and blood samples was very similar. On the other hand, lung samples taken 8 min after injection of [4-^{14}C](5S,6S)-BMEDU and [4-^{14}C](5R,6R)-BMEDU showed a higher accumulation of radioactivity in lung with T_{max} values of 18 and 8 min, respectively (Fig. 2). The level of radioactivity in lung samples taken after injection of [4-^{14}C](5S,6S)-BMEDU was substantially different from that of [4-^{14}C](5R,6R)-BMEDU. This observation indicates that the configuration of the 5,6-dihydro prodrug may also play a role in accumulation of the compound in lung. Lung samples taken after injection of [4-^{14}C]BEEDU showed a considerably higher percentage of the injected dose relative to those for [4-^{14}C]EDU, [4-^{14}C](5S,6S)-BMEDU and [4-^{14}C](5R,6R)-BMEDU. Injection of [4-^{14}C]DVBEEDU, which is a highly lipophilic 5,6-dihydro prodrug of EDU, provided significantly higher radioactivity levels in lung samples than in blood, but not in liver samples (Fig. 2).

To quantitate EDU and EU in lung samples after injection of EDU and its 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrugs, EDU, BEEDU and VBEEDU were injected into male Balb-C mice. The results of these experiments are summarized in Fig. 3. The concentrations of EDU and EU after injection of EDU, BEEDU and VBEEDU were compared in lung and blood samples. The concentration of EDU in lung was substantially lower than that in blood at early time periods after injection of EDU. In contrast to blood, EU showed accumulation in lung samples (Fig. 3), whereas the accumulation of EDU and EU in lung samples, relative to blood, was higher after injection of BEEDU. Lung samples showed a high concentration of EDU shortly after injection of VBEEDU, but there was a rapid decrease 5 min after injection. Lung samples taken after injection of EDU, BEEDU and VBEEDU showed a higher concentration of EU compared with those of blood samples (Fig. 3). The higher concentrations of EU, which is a metabolite of EDU, in lung samples compared with blood samples indicate the pulmonary cleavage of the glycosidic bond of EDU.

A putative mechanism for accumulation of EDU and EU after administration of the 5,6-dihydro prodrugs is described in Fig. 4. It appears that the diffusion of EDU and its 5,6-dihydro prodrugs (P-EDU) into the lung is mainly governed by the lipophilicity of these compounds. Therefore, more lipophilic prodrugs (P-EDU) diffuse into lung with higher levels than EDU ($k_1 \gg k_2$). Following their conversion to EDU in lung (k_5), P-EDU provides a high concentration of EDU in lung. However, conversion of P-EDU to EDU in blood (k_4) and subsequent diffusion of EDU into lung (k_2), could also contribute to increasing concentration of EDU inside the lung. The fact that concentration of EU in the lung was much higher than that of blood, after administration of both EDU and P-EDU, indicates that conversion of EDU to EU in the lung (k_7) is more efficient than that in blood (k_6) and also that EU

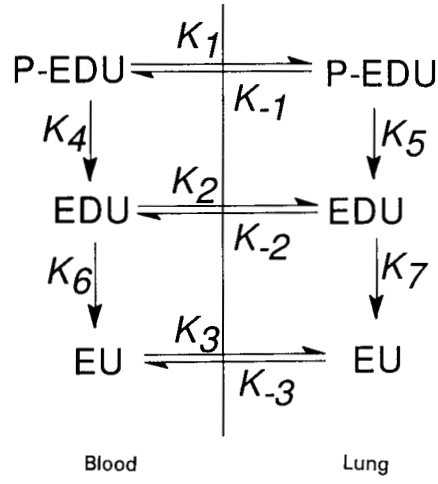


FIG. 4. Putative mechanism of accumulation of EDU, EU and 5,6-dihydro prodrugs of EDU (P-EDU) in murine lung.

does not diffuse in and out of the lung (k_3 and k_{-3}) in significant amounts.

At present, little is known about the metabolic fate of pyrimidine nucleosides during lung passage. To our knowledge, the kinetic parameters for the elimination of most antiviral and anticancer nucleosides by the lung have also not been determined. However, there have been studies which investigated the elimination of 5-fluoro-2′-deoxyuridine (FUDR) from lung tissues. Foth et al (1990) reported that pulmonary tissues possess a marked intrinsic capacity to transform FUDR into 5-fluorouracil (FU). In contrast, the catabolism of FU and 5,6-dihydrouracil was virtually lacking. It has also been reported that FUDR is converted to FU in human lung tissue (Michihiko et al 1990). In normal lung tissue, FUDR undergoes almost complete glycosidic bond cleavage since the nucleoside phosphorylase activity was much higher than thymidine kinase activity in lung (Michihiko et al 1990). The nucleoside phosphorylase activities in lung, colon and liver tissues were found to be much higher than that of plasma. Michihiko et al (1990), therefore, suggested that plasma may not be the most important site for FUDR degradation. The results of the current investigation also clearly indicate that lung is capable of converting EDU into EU.

In conclusion, the results of this study show that a substantial percentage of the injected dose of [4-^{14}C]EDU and its 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrugs localize in lung tissues. Although the lipophilic (5*S*,6*S*)-BMEDU, (5*R*,6*R*)-BMEDU and BEEDU showed a higher radioactivity level in lung samples after injection of the 4-^{14}C-labelled compounds, injection of the more lipophilic [4-^{14}C]VBEEDU and [4-^{14}C]DVBEEDU did not show linear increases in radioactivity present in lung. Although the mechanisms of accumulation have not been resolved, it is concluded that these 5-bromo-5-ethyl-6-alkoxy-5,6-dihydro prodrugs of EDU could serve as good candidates for treatment of respiratory tract HSV infections.

Acknowledgements

We are grateful to the Medical Research Council of Canada

(Grant No. MT-12304) for financial support of this research, to the Iranian Ministry of Health and Medical Education for a PhD studentship to A. M. Cheraghali and to the Alberta Heritage Foundation for Medical Research for a studentship to K. W. Morin. We also thank Professor Yun K. Tam for his critical comments concerning design of the kinetic studies.

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