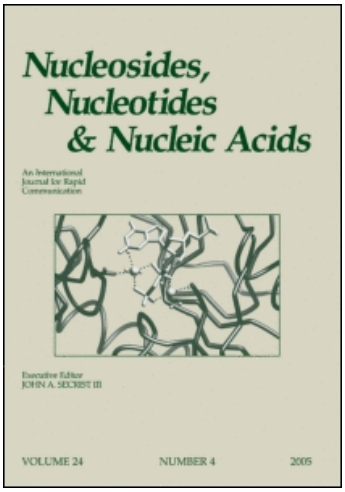

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Biodistribution of [^{77}Br]-5-Bromo-2-Deoxyuridine in Rats

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BIODISTRIBUTION OF [^{77}Br]-5-BROMO-2-DEOXYURIDINE IN RATS

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Abstract: The feasibility of 5-bromo-2'-deoxyuridine as tumour imaging agent for PET studies in comparison with thymidine is discussed.

Treatment of tumours with cytotoxic agents or radiotherapy would be considerably aided by a method by which the effect of such treatment could be evaluated objectively. Such a method should not only measure the caused tumour shrinkage but more importantly the amount of tumour cells capable of re-growth. Since viable cells must contain replicating DNA, comparison of the rate of DNA synthesis before and after treatment by means of a specific DNA precursor would be a good indication.

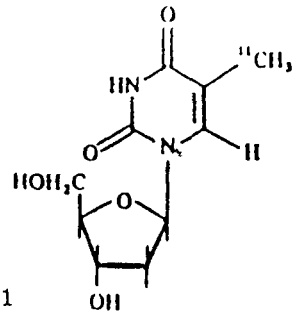

FIG. 1

First we synthesized [^{11}C]-thymidine[1] (Fig. 1) labelled in the methylgroup on the 5-position of the base. Carbon-11 is a positron emitter with a half-life of 20 min and is suitable for detection with positron emission tomography (PET). Ten patients with various types of sarcoma's were selected for [^{11}C]-thymidine uptake studies. Fig. 2 shows a tomographic scan through the brain, 10 min after intravenous injection. Tumour tissue

is clearly visible although activity in normal brain tissue after [^{11}C]-thymidine administration is very low. The radioactivity concentration - time curve for the tumour region, illustrated by Fig. 3 shows a bifunctional profile. After rapid elimination of the tracer (±10 min) the radioactivity level levels of to a plateau This probably represents the degree of [^{11}C]-thymidine incorporation in the tumour DNA. A number of labelled metabolites of [^{11}C]-thymidine could however contribute to the PET image and interfere with the exact interpretation (quantification). These metabolites are now under investigation.

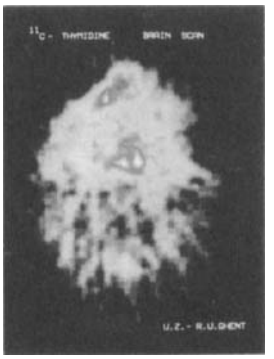

Fig. 2

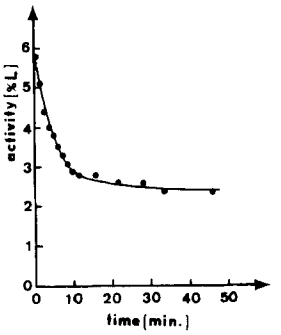

Fig. 3

The short physical half-life of carbon-11 limits its application to short time physiological studies. Therefore [*Br]-5-bromo-2'-deoxyuridine was synthesized. The reaction of 2'-deoxyuridine with radioactive bromine, generated in situ from the oxidation of bromide with N-chloramine T, gave labelled 5-bromo-2'-deoxyuridine with a radiochemical yield of 90 %. The identity of the labelled compound was confirmed with UV, IR and mass spectrometry.

After purification, the produced [*Br]-5-bromo-2'-deoxyuridine was injected intravenously into male Wistar albino rats through the jugularis vein. At different time intervals (0.5; 2; 6; 24; 48 h) the animals were killed by ether anaesthesia. The organs were removed, blotted to minimize adhering blood, weighed and counted in a well counter. The radioactivities were corrected for decay. The amount of radioactivity within a given tissue has been expressed as a ratio of the administered dose (normalized tissue concentration). The biodistribution showed an

TABLE 1
Biodistribution of radioactivity in rat tissue after intravenous injection of [*Br]-5-bromo-2'-deoxyuridine.

Tissue	0.5h	2h	6h	24h	48h
BLOOD	2.6±0.8*	1.9±0.4	2.1±0.4	2.0±0.5	1.9±0.4
HEART	0.4±0.2	0.5±0.2	0.4±0.1	0.3±0.2	0.5±0.1
BOWELS	1.1±0.2	0.9±0.1	1.1±0.2	0.9±0.1	0.4±0.2
STOMACH	1.2±0.3	1.4±0.5	1.7±0.7	1.4±0.6	1.1±0.5
LIVER	1.1±0.1	1.1±0.2	0.8±0.1	0.9±0.2	0.9±0.2
SKIN	1.5±0.1	1.4±0.1	1.3±0.2	1.3±0.1	1.1±0.2

* Mean ± Standard Deviation

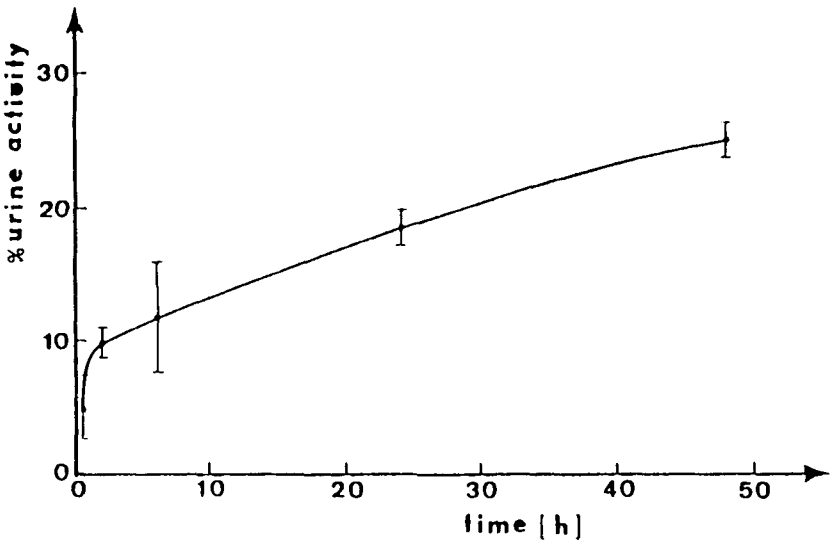

FIG. 4

important uptake of radioactivity in the skin, the stomach, the liver and the bowels. The results are summarized in Table 1.

The specific activities of other tissues like fat, muscles, ... were extremely low. The elimination curve (Fig. 4) was best described by a bi-exponential function. A part of the injected [*Br]-5-bromo-2'-deoxyuridine was excreted very rapidly. The remainder was found to have a half-life of approximately 37h, which is in good agreement with the literature value for bromide[2].

Since it is well known that in vivo dehalogenation can occur, a biodistribution experiment for *Br-bromide was carried out. Rapid accumulation of the *Br in the skin, stomach, lungs and liver, was found while activity in other tissue like the bowels remained low.

In spite of the rather important loss of label, we still observed marked incorporation in fast dividing tissues (like the bowels) which could not be caused by free bromide. Therefore we believe that 5-bromo-2'-deoxyuridine labelled with Br-75 ($t_{1/2}$= 1.6 h) could be an interesting compound for tumour imaging and study of cell activity in vivo using PET. In view of the longer half-life of Br-76 ($t_{1/2}$= 16h) and its emission of high energy γ rays, Br-76 is not as suitable in this research area.

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