《研究速報》

^{99m}Tc-(Sn)-Pyridoxylidenetryptophan:

A Potential Hepatobiliary Radiopharmaceutical of Rapid Hepatobiliary Transport and Low Urinary Excretion

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I. Introduction

Although the diagnosis of hepatobiliary disorders using ^{99m}Tc-(Sn)-pyridoxylideneisoleucine [^{99m}Tc-(Sn)-PI] or ^{99m}Tc-HIDA has been widely accepted in many clinical sites, there still exists a demand for new agents of rapid hepatobiliary transport and low urinary excretion. It has been reported that the urinary excretion of ^{99m}Tc-(p-butyl) IDA is significantly small compared with other available agents; the slowness of its hepatobiliary transport, however, deters people from adopting this agent in routine diagnosis[1].

Our efforts have been focusing on the ^{99m}Tc-(Sn)-pyridoxylidene-aminate system to find better hepatobiliary agents, and this rapid communication presents the results of preliminary studies on ^{99m}Tc-(Sn)-pyridoxylidenetryptophan [^{99m}Tc-(Sn)-P.Trp], one of the promising agents of rapid hepatobiliary transport and low urinary excretion.

II. Materials and methods[2]

2.1 Preparation of Sn-pyridoxylidenetryptophan (Sn-P.Trp) reagent

The preparation was analogous to that reported for Sn-pyridoxylideneisoleucine (Sn-PI)[3,4]. Mixing a solution of pyridoxal hydrochloride-stannous chloride-ascorbic acid (70.0, 2.0 and 4.0 μmol/m*l* each) with an equivalent volume of tryptophan-sodium hydroxide solution (70.0 and 130.0 μmol/m*l* each) gave a bright yellow reagent of Sn-P.Trp (pH 8.65).

2.2 Preparation of ^{99m}Tc-(Sn)-pyridoxylidenetryptophan [^{99m}Tc-(Sn)-P.Trp]

^{99m}Tc-(Sn)-P.Trp was prepared by mixing 1.5 m*l* of the freshly prepared Sn-P.Trp reagent with 1.5 m*l* of ^{99m}Tc-pertechnetate saline solution (5–10 mCi, obtained by MEK extraction in our laboratory), and then warmed for two min in a boiling water bath[5]. The viscosity of the solution increased moderately on cooling to room temperature, due to the formation of a fluidal gel; but this change caused no physical nor physiological trouble for the ordinary i.v. administration using a syringe with needle. No precipitation of crystalline substance was observed. Thus prepared ^{99m}Tc-(Sn)-P.Trp was stable at room temperature for more than 48 hours.

2.3 Preparation of ^{99m}Tc-(Sn)-PI, ^{99m}Tc-HIDA and ^{99m}Tc-(p-butyl)-IDA

The preparation of ^{99m}Tc-(Sn)-PI has been described previously[3-5]. The kit reagents of Sn-HIDA and Sn-(p-butyl) IDA were obtained commercially (CIS-Sorin), and the ^{99m}Tc-labeling was performed according to the manufacturer's indications.

2.4 Evaluation of labeling efficiency

The labeling efficiency for each preparation was evaluated chromatographically using a silica gel plate developed with methanol: water: methylethylketone (9:1:10 v/v)[4].

2.5 In vivo distribution study in rats

The procedures were identical to that reported previously[3,4]. Female Sprague-Dawley rats (8–9 weeks old, weighing 190–250 g) were used in this study.

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Table 1 Organ distribution of ^{99m}Tc-(Sn)-P. Trp in rats*

Organ	Time after i.v. administration					
	5 min	10 min	20 min	40 min	60 min	120 min
Liver	13.77±2.87	5.51±1.03	1.99±0.39	1.26±0.28	0.90±0.09	0.69±0.13
Small intestine	66.89±5.26	79.98±3.03	87.23±2.27	90.64±1.68	91.96±1.37	93.26±0.86
Large intestine	0.49±0.13	0.15±0.03	0.07±0.02	0.03±0.01	0.03±0.00	0.02±0.01
Stomach	0.11±0.06	0.03±0.01	0.02±0.01	0.01±0.01	0.00±0.01	0.01±0.00
Spleen	0.03±0.00	0.02±0.01	0.00±0.00	0.01±0.01	0.00±0.00	0.00±0.00
Lung	0.46±0.09	0.34±0.06	0.18±0.06	0.11±0.03	0.06±0.03	0.03±0.01
Heart	0.07±0.04	0.04±0.02	0.02±0.02	0.00±0.00	0.01±0.01	0.00±0.00
Kidneys	0.97±0.12	0.80±0.10	0.62±0.09	0.55±0.11	0.52±0.14	0.48±0.12
1 m*l* Blood**	0.24±0.04	0.15±0.03	0.09±0.02	0.05±0.01	0.04±0.00	0.03±0.00
Carcass	13.26±1.98	9.68±0.83	6.37±0.60	4.46±0.27	3.68±0.24	2.86±0.17
Urine	0.71±0.21	1.20±0.14	1.52±0.16	1.76±0.11	1.92±0.15	2.13±0.14

* Mean results for four rats±1 s.d. Data are expressed as % of total administered dose.
** Normarized to the body weight of 200 g.

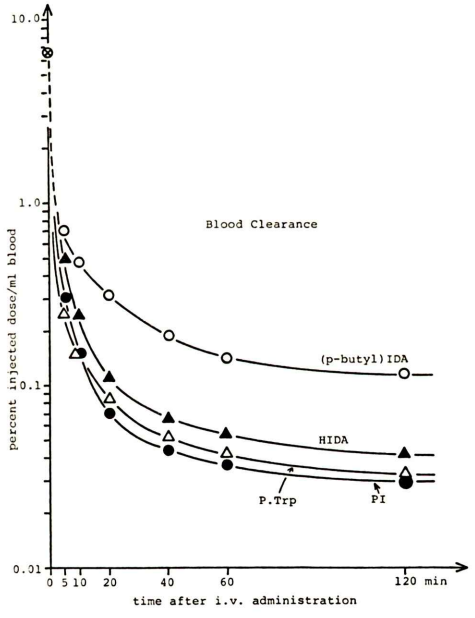

Fig. 1 Blood clearance of radioactivity after i.v. administration of ^{99m}Tc-labeled hepatobiliary agents in rats. Each point represents mean result for four animals. ^{99m}Tc-(Sn)-P.Trp, ^{99m}Tc-(Sn)-PI and ^{99m}Tc-HIDA showed almost similar clearance, while ^{99m}Tc-(p-butyl) IDA showed a relatively delayed blood clearance.

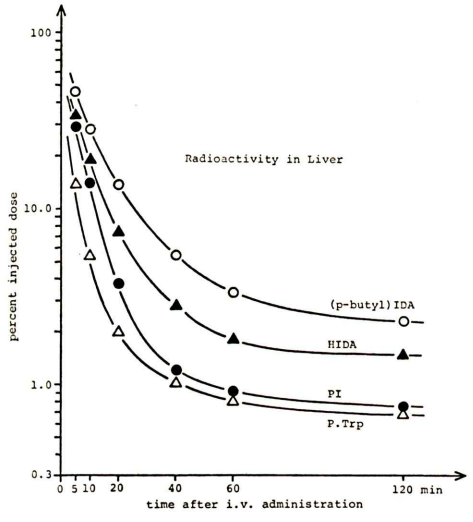

Fig. 2 Radioactivity in liver at various time intervals after i.v. administration of ^{99m}Tc-labeled hepatobiliary agents in rats. Each point represents mean results for four animals. ^{99m}Tc-(Sn)-P. Trp showed a significantly fast disappearance from liver compared with other three agents.

III. Results and discussion

The chromatographic analysis revealed that the labeling efficiency for each preparation was practically 100%; neither unreacted pertechnetate (Rf 0.98–1.00) nor reduced-hydrolyzed technetium (at the origin) was detected in any preparation. The in vivo distribution of each ^{99m}Tc-labeled agent (Table 1, Fig. 1–4) also indicated the absence of pertechnetate and hydrolyzed

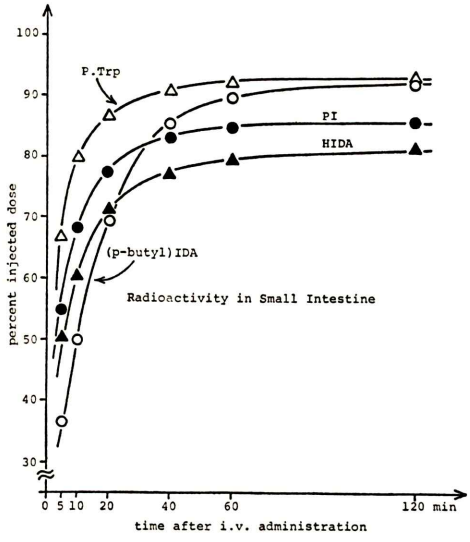

Fig. 3 Radioactivity in small intestine at various time intervals after i.v. administration of ^{99m}Tc-labeled hepatobiliary agents in rats. Each point represents mean result for four animals. ^{99m}Tc-(Sn)-P.Trp showed a significantly rapid biliary excretion into small intestine compared with other three agents.

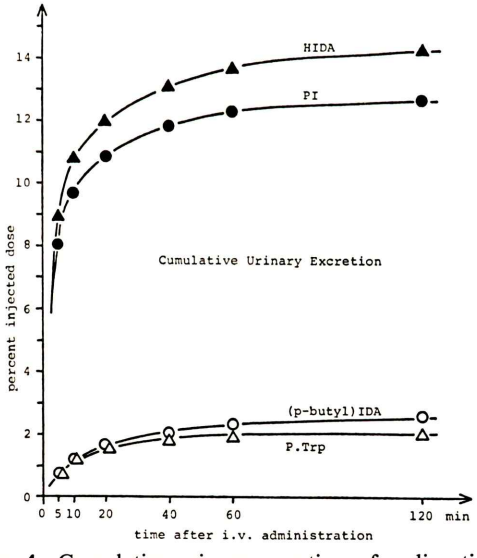

Fig. 4 Cumulative urinary excretion of radioactivity after i.v. administration of ^{99m}Tc-labeled hepatobiliary agents in rats. Each point represents mean result for four animals. The urinary excretion of ^{99m}Tc-(Sn)-P.Trp was slightly lower than that of ^{99m}Tc-(p-butyl) IDA.

technetium in the preparation.

Table 1 shows the distribution of ^{99m}Tc-(Sn)-P.Trp in rats at various time intervals after i.v. administration, and Fig. 1–Fig. 4 illustrate the results of the comparative distribution studies on ^{99m}Tc-(Sn)-P.Trp, ^{99m}Tc-(Sn)-PI, ^{99m}Tc-HIDA and ^{99m}Tc-(p-butyl)-IDA. The blood clearance of ^{99m}Tc-(Sn)-P.Trp was almost identical to those of ^{99m}Tc-(Sn)-PI and ^{99m}Tc-HIDA, and significantly faster than that of ^{99m}Tc-(p-butyl) IDA (Fig. 1). The biliary excretion patterns of these agents can be seen in Fig. 2 and Fig. 3. The excretion of ^{99m}Tc-(Sn)-P.Trp into the bile was significantly faster than those of other three agents, and ^{99m}Tc-(p-butyl) IDA showed the mostly delayed excretion. Wistow et al. also reported a relatively slow biliary excretion of ^{99m}Tc-(p-butyl) IDA in baboons and humans[1]. The urinary excretion rate of ^{99m}Tc-(Sn)-P.Trp was extremely small (Table 1, Fig. 4), whose 2%/two-hour excretion rate is comparable to that of ^{131}I-or ^{123}I-labeled rose bengal[1].

Wistow and his co-workers reported that the increase of the molecular lipophilicity of N-substituted iminodiacetic acid (IDA) derivatives retards the biliary excretion of their ^{99m}Tc complexes, nevertheless the high-lipophilicity is effective in decreasing the urinary excretion[1,6]. Therefore, in the system of ^{99m}Tc-labeled IDA derivatives, the fast hepatobiliary transport seems to be incompatible with the low urinary excretion. On the other hand, the author reports in this communication that ^{99m}Tc-(Sn)-P.Trp undergoes suprisingly rapid biliary excretion which is compatible with its extremely low urinary excretion. It seems that there may exist some differences in the mechanisms of the hepatobiliary transport between ^{99m}Tc-(Sn)-P.Trp and ^{99m}Tc-labeled IDA derivatives, but further precise studies should be done in this respect.

Further works are now in progress including scintigraphic studies using higher animal species, in vivo distribution studies in animals with artificial hepatobiliary disorders. All the results obtained to date strongly suggest the usefullness of ^{99m}Tc-(Sn)-P.Trp as an improved hepatobiliary radiopharmaceutical. Details of the investigation will be reported soon.

Acknowledgments

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要 旨

^{99m}Tc-(Sn)-ピリドキシリデントリプトファン: 尿中排泄が少なく，肝胆道移行が迅速な肝胆道系イメージング用放射性医薬品としての可能性

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スズ還元法によって ^{99m}Tc-(Sn)- ピリドキシリデントリプトファン [^{99m}Tc-(Sn)-P. Trp] を調製し，ラットにおける体内動態を現在臨床に供されている3種のテクネチウム製剤 [^{99m}Tc-(Sn)-PI, ^{99m}Tc-HIDA, ^{99m}Tc-(p-butyl)IDA] と比較，検討した．

静脈内投与後の血中消失率は，^{99m}Tc-(Sn)-PI にほぼ等しく，^{99m}Tc-(p-butyl) IDAに比して有意にや速かであった．肝臓から小腸への移行は極めてや速かであり，^{99m}Tc-(Sn)-PI および ^{99m}Tc-HIDA と比較しても有意に迅速な肝胆道移行を示した．

また，^{99m}Tc-(Sn)-P. Trp の静脈内投与後1時間における尿中への排泄量は投与総放射能の 1.9% と少なく，^{99m}Tc-(p-butyl) IDAの尿中排泄をも下回った．

これらの結果は，^{99m}Tc-(Sn)-P. Trp が (1) 迅速な血中からの消失，(2) 迅速な肝胆道移行，(3) 極めて少ない尿中排泄，という3つの優れた特性を備えた新しい肝胆道系イメージング剤となり得ることを示唆した．

ウキギを用いたイメージング実験，肝障害を生じせしめた動物を用いた検討などを続行中であり，この製剤の有用性を示唆する結果が得られつつある．近々詳報を発表する予定である．

Key words: ^{99m}Tc-(Sn)-pyridoxylidenetryptophan, hepatobiliary imaging agent