Deferoxamine Mesylate Enhancement of $^{67}$Ga Tumor-to-Blood Ratios and Tumor Imaging

Kiyoshi Koizumi, Norihisa Tonami, and Kinichi Hisada
Department of Nuclear Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan

Abstract. To improve the tumor-to-blood ratio in $^{67}$Ga tumor imaging, the effect of administration of deferoxamine mesylate (DFO) was evaluated. DFO improved $^{67}$Ga tumor-to-blood ratios in tumor-bearing rats. Administration of DFO 12 h after $^{67}$Ga injection did not decrease the concentration of radioactivity in the tumor of rats, but administration of DFO 4 h after $^{67}$Ga decreased the concentration of radioactivity in the tumor. Serum unsaturated iron binding capacity in rats was transiently increased by DFO administration, but when DFO was administered before $^{67}$Ga injection the tumor uptake showed rather decreased levels. In human studies, DFO accelerated the excretion of $^{67}$Ga from the blood, but tumor images were not necessarily improved.

Introduction

Deferoxamine mesylate (DFO) is a pharmaceutical that has a strong affinity for ferric ion and induces increased excretion of iron in the urine. It has been reported that the effect of DFO on $^{67}$Ga clearance was observed in experimental animals, and the lesion-to-blood ratios were improved by the administration of DFO in tumor- or abscess-bearing animals [1, 2, 5-8]. However, no clinical application has been reported.

This study was undertaken to determine the optimal interval between IV injection of $^{67}$Ga and IM administration of DFO to enhance effectively the lesion-to-blood ratios in tumor-bearing rats. Furthermore, several clinical applications are reported.

Materials and Methods

Deferoxamine mesylate was provided from CIBA Pharmaceutical Co., and $^{67}$Ga-citrate was supplied from Nihon Medi-Physics Co., and $^{67}$Ga-citrate was supplied from Nihon Medi-Physics Materials and Methods

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Results

Results of biodistribution of $^{67}$Ga-citrate in tumor-bearing rats are shown in Fig. 1. Tumor uptake increased until 3 h after injection, but blood activity decreased during this interval. Therefore the tumor-to-blood ratios increased gradually.

The chromatographic migration pattern of the $^{67}$Ga-citrate mixed with DFO in vitro was different from that of $^{67}$Ga-citrate (Fig. 2). This result showed the strong affinity of $^{67}$Ga for DFO and the possible formation of a $^{67}$Ga-DFO complex. Biodistribution of the $^{67}$Ga-DFO complex in tumor-bearing rats is shown in Fig. 3. Compared with the biodistribution of $^{67}$Ga-citrate, this complex was rapidly excreted through the kidneys and 82% of the administered tracer was excreted in the urine within 3 h after injection.

Table 1A shows the results of a distribution study in which DFO was IM administered 4 h after IV injection of $^{67}$Ga-citrate. The concentration of radioactivity in the tumor gradually decreased. The concentrations in the blood, muscle, and lung decreased rapidly at the early period, but remained at the same levels at the delayed period. The concentration in the liver decreased at first and increased later. An early increase in the concentration of activity in the kidney was observed. Table 1B shows the results of a distribution study at 12 h performed by the same procedure as at 4 h. In comparison with the previous studies, the decrease in the concentration of radioactivity in the tumor was minimal. The concentration in the blood rapidly decreased for 3 h after DFO administration. When DFO was not administered, tumor uptake of $^{67}$Ga gradually increased during 4 to 10 h after the tracer injection, and then gradually decreased during 12 to 24 h. The changes of the concentrations in the tumor and the blood following DFO administration at
Fig. 1. Biodistribution of $^{67}$Ga-citrate in tumor-bearing rats. Tumor uptake increased rapidly until 3 h after injection.

Fig. 2. Chromatographic migration pattern of $^{67}$Ga-citrate is shown in the upper part of the figure (Rf=0). That of $^{67}$Ga-citrate mixed with DFO in vitro is shown in the lower (Rf=0.31).

4 and 12 h after $^{67}$Ga-citrate injection are illustrated in Fig. 4A and B. A similar rapid decrease in the concentration in the blood was observed within 3 h after the DFO administration in both studies, but the changes in the concentration in the tumor were different. There was a gradual decline of the concentration in the tumor when DFO was given 4 h after the $^{67}$Ga injection in comparison with the control group, but it was not reduced when DFO was given 12 h after the $^{67}$Ga injection. The tumor-to-blood ratio was improved from 1.2 to 16.5 at 3 h after DFO administration following 4 h after $^{67}$Ga-citrate injection, and from 2.2 to 29.4 at 3 h after DFO following 12 h after $^{67}$Ga.

Figure 5 shows the results of the effect of DFO dose on tumor-to-blood ratio at 3 h after DFO administration following 4 h after $^{67}$Ga injection. The tumor-to-blood ratio increased from 0.89 at 10 mg/kg up to 12.16 at 200 mg/kg in proportion to the administered dose. When physiological saline was administered instead of DFO, the tumor-to-blood ratio was only 0.61.

The results of the effect of DFO on serum unsaturated iron binding capacity (UIBC) is shown in Table 2. UIBC transiently increased at 1 and 3 h after IM DFO injection.

When DFO was administered at 1 and 3 h before $^{67}$Ga-citrate injection, blood and tumor showed decreased concentrations of radioactivity, and the tumor-to-blood ratios showed rather decreased levels in both cases (Table 3).

In human studies, the effect of DFO on the excretion of $^{67}$Ga from the blood was evaluated by administration of the drug 24 h after the tracer injection. Residual radioactivity of a unit volume of the blood was standardized to the radioactivity at 24 h after the tracer injection as 100% (Fig. 6). Compared with the control group (n=10), the DFO administered group (n=4) showed obviously increased excretion of the tracer from the blood.

The enhancement effect of DFO on clinical tumor imaging was evaluated by obtaining images 24 h after DFO administration which was done 24 h after $^{67}$Ga injection and comparing with the control images which were obtained 24 h after $^{67}$Ga.