

Consensus for nuclear pharmacist management and clinical use of radiopharmaceuticals in China

Abstract

Radiopharmaceuticals play a critical role in modern medicine for diagnosing or treating human diseases. Pharmacy administration and pharmaceutical care carried on by department of pharmacy in medical institutions comprise the important component of clinical medical work. In *Drug Administration Law of the People's Republic of China* (newly revised in 2019), radiopharmaceuticals are classified as one kind of drugs under control management due to the radioactive property. However, the current situation that nuclear medicine department instead of pharmacy department takes charge of the drug management as well as the entire clinical course of radiopharmaceuticals alone, exists in almost all the medical institutions of China, resulting in some incompliance with related law, regulations or standards, and sometimes potential risks. Moreover, with the great government encouragement for the development of radiopharmaceuticals and increasing clinical needs for radiopharmaceuticals in China, more radiopharmaceuticals will be available and widely used in medical institutions. Thus, a full-time pharmacist (nuclear pharmacist) should be staffed to be involved with the entire process of radiopharmaceuticals used in nuclear medicine department. Correspondingly, the working system and a proper training or certification mechanism for a nuclear pharmacist should be established promptly and properly.

Introduction

Radiopharmaceuticals, referring to one kind of special drugs labelled with radioisotopes, are the fundamental element of nuclear medicine for diagnosing or treating human diseases ^[1]. On one hand, the radioisotopes emit radiations that could be detected by imaging modalities, like single-photon emission computed tomography (SPECT) or positron emission computed tomography (PET), to achieve early and noninvasive diagnosis according to the radiopharmaceuticals' distribution and quantification of tissue uptake in human body ^[2]. On the other hand, the radioisotopes emit radiations with high linear energy transfer to destroy the targeted malignant and other rapidly proliferating cell populations, to achieve precise treatment ^[3]. Thus, radiopharmaceuticals play a critical role in modern medicine.

Medical application of radiopharmaceuticals began in the 1920s ^[4]. Though the research and production of medical radioisotopes and radiopharmaceuticals in China began in the 1950s ^[5], great progress on the development has been made during the course of more than half a century ^[6]. The National Medical Products Administration (NMPA) of China in the *Opinions of the NMPA on Reforming and Improving the Management System for Radiopharmaceuticals' Evaluation and Approval* in 2023 pointed out that radiopharmaceuticals play a special important role in the diagnosis and treatment of cardiovascular, cerebrovascular and central nervous system diseases, as well as malignant tumors, etc., and it is encouraged to develop new and promising radiopharmaceuticals to meet the clinical needs ^[7]. Thus, with the encouragement and support of Chinese government as well as the work done by academic groups and associations, radiopharmaceuticals in China have a very bright future ^[8], and more radiopharmaceuticals would be applied in medical field.

Radiopharmaceuticals firstly included in *Chinese Pharmacopoeia* was in the 1977 edition ^[7], and began to be classified as one kind of drugs to be under special management in 1985 ^[9]. In 1989, the State Council of China further promulgated the *Measures for the Control of Radioactive Drugs* (revised in 2017) for radiopharmaceuticals, which stated that medical institutions must obtain "Radiopharmaceuticals Using License" prior to use radiopharmaceuticals. Furthermore,

in 2011, the *regulations on the administration of pharmaceutical affairs in medical institutions* announced that radiopharmaceuticals could be purchased and dispensed by nuclear medicine department, which declared that radiopharmaceuticals became the only kind of drugs not supplied by the department of pharmacy ^[10]. Notably, the above regulations further declare the specialties of radiopharmaceuticals distinguished from other drugs.

In China, *Drug Administration Law of the People's Republic of China* states the general principle for the administration of pharmaceutical affairs in medical institutions that medical institutions should be staffed with qualified pharmacists or other pharmaceutical technicians to be responsible for the drug management, prescription review, drug dispense and providing guidance of rational use of drugs, etc ^[9]. While, a current situation that nuclear medicine department instead of department of pharmacy takes charge of the whole process administration of radiopharmaceuticals exists in almost all the medical institutions of China. Obviously, the current situation is not in compliance with the mentioned regulations, and even might bring a negative effect to promote the application and development of radiopharmaceuticals as well. Thus, in the medical institutions of China, it is an urgent need that a full-time pharmacist joins the nuclear medicine department to integrate the pharmacy and nuclear medicine teams.

In some developed countries, like America, the services supplied by nuclear pharmacists had been accepted as routinely as were those of a staff pharmacist in any hospital before 2000 ^[11]. While, due to the differences between China and other countries, including some laws or regulations regarding radiopharmaceuticals, the pharmacy practices for a nuclear pharmacist in China may differ from those in other countries. Herein, the following is a general introduction to the job responsibilities of a nuclear pharmacist in China.

Job Responsibilities of a Nuclear Pharmacist

Supervising the management of radiopharmaceuticals

For the medical radiopharmaceuticals contain the radioisotopes with a relative short physical half-life, it is announced in *Regulations on the Administration of*

Pharmaceutical Affairs in Medical Institutions that nuclear medicine department could purchase and dispense the radiopharmaceuticals ^[10]. Besides, as mentioned before, the types of radiopharmaceuticals used in clinic are depended on the class level of “Radiopharmaceutical Using License” that the medical institutions hold. Thus, the radiopharmaceuticals used in medical institutions would have two sources, either purchased from pharmaceutical companies or prepared by the nuclear medicine department.

As a nuclear pharmacist responsible for the drug management, it is essential to have a thorough understanding of the various types of radiopharmaceuticals used in clinic. Then, due to the current inadequate hospital information system for radiopharmaceuticals, the nuclear pharmacist should check the clinical usage record of radiopharmaceuticals regularly to ensure that is consistent with the purchased or produced record. Additionally, as for the purchased radiopharmaceuticals, the nuclear pharmacist ought to take part in setting standard purchasing procedures, including the qualification review of suppliers and signing of drug quality-related agreement, etc. As for the produced radiopharmaceuticals, the real records of the production and quality control procedures are necessary to be supervised frequently by the nuclear pharmacist.

Providing pharmacy services of radiopharmaceuticals

Radiopharmaceuticals are applied for diagnostic and therapeutic purposes due to different medical radioisotopes could emit different types of radiations. For the diagnostic purpose, the radiopharmaceuticals are used in small quantities to observe physiological alterations or abnormal distribution in the patients’ body, and the emitted radiations possess lower energy but higher penetrating power. Thus, these radiopharmaceuticals do generally not have a pharmacologic effect ^[12]. While, the therapeutic radioisotopes emit radiations with higher energy that could destroy the niduses and used in larger quantities leading to adverse reactions. In addition, whether the diagnostic or therapeutic radiopharmaceuticals could achieve the efficiency is mainly depended on the uptake of radiopharmaceuticals by the targeted cells. Thus, any drugs or chemical agents which alter the chemical identity of the radiopharmaceuticals and the physiological status of the organ of interest, or compete for binding sites with

radiopharmaceuticals, could be expected to alter the uptake of radiopharmaceuticals [13]. For example, sodium pertechnetate [^{99m}Tc] injection is used as a diagnostic agent for the imaging of thyroid, brain, saladen and ectopic gastric mucosa. Drugs containing iodine and perchlorates can affect the uptake of the radiopharmaceuticals by thyroid and stomach. Then, dexamethasone and glucocorticoids could cause false-negative result, while methotrexate would result in false-positive reaction [14].

As a pharmacist with specialized knowledge in pharmaceuticals, a nuclear pharmacist should possess a thorough understanding of properties and uses of different radiopharmaceuticals, including the mechanism of action, indications and administration dosage, etc. In addition to the above, the radiopharmaceuticals' drug interactions with other drugs and adverse reactions are the main focuses that the nuclear pharmacist should pay attention to. As radiopharmaceuticals are typically administered only once or at very limited number of times to patients, recognition of the interactions could decrease the incidence of misdiagnosis and unnecessary exposure to radiation [13]. Moreover, timely interventions to certain prognosis of the adverse reactions of radiopharmaceuticals could decrease the occurrence of drug-related adverse effects and increase the treatment compliance of patients.

Generally, a nuclear pharmacist should be specialized with pharmacy knowledge and involved in the collaborative practices to provide the medication guidance for the medical team or medication consultation for the patients. In other words, the nuclear pharmacist should assist the doctor to make proper pharmacotherapy decisions, including avoiding the drug interactions, intervening potential adverse reactions as well as prescribing the appropriate off-label use drugs, and provide appropriate patient education and counseling even some necessary pharmaceutical visits.

Participating in clinical trials or investigational radiopharmaceuticals research.

In China, the *regulations on the administration of pharmaceutical affairs in medical institutions* announces that a pharmacist in medical institutions should conduct the research and evaluation on drugs' clinical application based on the clinical practices, and participate in clinical trials or monitoring the safety and efficacy of new drugs [12]. A clinical trial is an important and necessary procedure designed to obtain the efficacy

and safety of an investigational medicinal product before being approved to market. *Technical guidelines for clinical evaluation of radiotherapeutic drugs in vivo* suggests a closer multidisciplinary collaboration is needed during the preparation, implementation and follow-up of radiopharmaceuticals' clinical trial ^[15].

Therefore, a nuclear pharmacist is recommended to be involved with the radiopharmaceuticals' clinical trial, assisting the researchers to record complete drug information that patients medicated, make medication adjustments and schedule a follow-up visit when necessary. More importantly, for diagnostic radiopharmaceuticals are used with microdosing which do not cause pharmacologic effect, new diagnostic radiopharmaceuticals especially the positron emitting tracers could be applied for the phase 0 clinical trial ^[16]. Phase 0 clinical trial is conducted in small number of subjects which could help to obtain the pharmacokinetics and pharmacodynamics data of potential drug candidates in a relatively short time, and positron emitting tracers have been providing an important support for drug development ^[17]. A nuclear pharmacist involved in the research team to assist in the evaluation of investigational radiopharmaceuticals could promote the research and clinical translation of new radiopharmaceuticals. Additionally, a nuclear pharmacist participating in the radiopharmaceuticals' medication in clinic, would have a better understanding of the clinical actual needs for new radiopharmaceuticals and could provide some helpful ideas for the research team.

In brief, a nuclear pharmacist taking participate in clinical trials or investigational radiopharmaceuticals' researches not only could keep continuous striving for self-improvement, but also provide better pharmacy services for the clinic medication of radiopharmaceuticals via a proper and close combination of researches and clinical use, as well as promote the research and clinical translation of new radiopharmaceuticals.

Conclusion

Considering the current condition of radiopharmaceuticals' administration in medical institutions of China with some irrationalities, as well as the widespread applications and rapid development of radiopharmaceuticals, it is necessary and urgent to appeal a

full-time pharmacist (nuclear pharmacist) to join the nuclear medicine department. A nuclear pharmacist would play a crucial role in the entire administration process of radiopharmaceuticals in medical institutions, including supervising the management, promoting the rational clinical applications, decreasing the potential drug-induced risks and assisting in the clinical research of investigational radiopharmaceuticals. Simultaneously, a proper training mechanism and working system for a nuclear pharmacist should be set up gradually.

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