# The Global Perspective of Pharmacovigilance in Nuclear Medicine Practice

Medicine has brought enormous benefit to the mankind, but no medicine is absolutely safe at all the time in all individuals for whom it is prescribed.[1] Thalidomide tragedy is a grim example of it and will always remain a blot on the face of medical science. That tragic incidence was a watershed moment for drug regulation and forced the regulatory agencies to make the drug approval process more stringent. Following that incidence, the US Congress passed the Kefauver–Harris amendment, and several European countries established regulatory bodies for the premarketing approval of drugs. Since then substantial progress has been made in the drug regulation. The concept of pharmacovigilance and drug safety was initiated to prevent the occurrence of another thalidomide like catastrophe.

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, understanding, and prevention of adverse effects or any other drug-related problems." Currently, the global pharmacovigilance program is coordinated by Uppsala Monitoring Center (UMC), Sweden, with active coordination and cooperation from the member countries.[2] The aim of pharmacovigilance is to improve the patient care and safety in relation to the use of medicines, assessment of benefit and harm, cost-effectiveness and promote awareness, education, and training in pharmacovigilance and its effective communication to the stakeholders such as health professionals and the public. The adverse drug reaction (ADR) is defined by the WHO as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man."[3]

In the last few decades, the branch of nuclear medicine has witnessed rapid growth. The National Health Service data from England suggests that during 1 year in 2015–2016 approximately 560,000 imaging was done with various radioisotopes.[4] It plays a pivotal role in the diagnosis and management of many oncological and non oncological diseases.[5,6] Moreover, in recent few years, many new diagnostic radiopharmaceuticals were discovered and are in clinical use currently, for example, Gallium-68 (Ga-68) DOTATATE, Ga-68 DOTATOC, Ga-68 DOTANOC, and Ga-68 PSMA. Radiopharmaceuticals are also now being used increasingly for the treatment of thyrotoxicosis, thyroid cancer, neuroendocrine tumors, and prostate cancer.[7-9] Many newer therapeutic radiopharmaceuticals have been in clinical use recently, for example, Lutetium (Lu)-177 DOTATATE, Lu-177 PSMA, and Lu-177 EDTMP.[10] Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy.[11] Although safety data of these new drugs are available, there is a lack of long-term data in human. Therefore, it is essential to have pharmacovigilance system in place to report any adverse reaction in due course of practice of these radiotracers.

## Prevalence of adverse reactions to radiopharmaceuticals

The incidence of adverse reactions associated with radiopharmaceuticals is less in comparison to the other classes of drugs used for therapeutic or diagnostic purposes.[12] However, the possibility of an adverse event to radiopharmaceuticals cannot be completely ruled out.[12] In addition, there are several reports of the false-positive effects and drug radiopharmaceuticals interactions exhibited by radiopharmaceuticals.[13-16]

Kenneddy-Dixon *et al*. have done a survey of reported radiopharmaceuticals adverse reaction to the British Nuclear Medicine Society online database from 2007 to 2016. They observed that during this period, 204 adverse reactions were reported. Rash, itching, and vomiting were the three most common adverse reactions reported. The highest prevalence of adverse reaction was noticed with tetrofosmin and oxidronate.[17]

Laroche *et al*. performed the analysis of national pharmacovigilance database in France to find out the adverse reaction to radiopharmaceuticals. There were 304 reports associated with different radiopharmaceuticals. Of these reported cases, 131 (43%) were serious in nature; 12 death, 15 life-threatening complications, 89 required hospitalization, and 15 other conditions. Among the 304 reported cases, 15.8% were associated with the agents used for the therapeutic purpose and 84.2% were with the agents used for diagnostic purpose.[18] For two-third of adverse reactions, 99mTc-oxidronate, 18F-fluorodeoxyglucose, 99mTc-tin pyrophosphate, 99mTc-tetrofosmin, 99mTc-dimercaptosuccinic acid, 99mTc-sestamibi, 201Tl-chloride, and 111 In-pentetate were responsible. In terms of severity of adverse reactions, 86.6% adverse reactions associated with therapeutic radiopharmaceuticals were serious whereas 38.1% serious adverse reaction was reported with diagnostic radiopharmaceuticals. The most common adverse reaction was pulmonary disorders whereas most common adverse reaction reported with diagnostic radiopharmaceuticals was skin disorders.[18] It is possible that most of these adverse

reactions could be Type II (idiosyncratic/hypersensitivity) reactions since low doses of radiopharmaceuticals are used for diagnostic and therapeutic purposes. Drug-radiopharmaceutical interactions such as those with the antiseptic povidone-iodine and chlorhexidine can also lead to adverse reactions due to the release of free pertechnetate.[19] In addition, such interactions in conjugation with previous procedures (radiotherapy, dialysis, and surgery) can lead to unanticipated or altered biodistribution of the radiopharmaceutical agents and may have a significant clinical impact on safety, scan interpretation, and diagnostic imaging accuracy.[20] In a survey done by Silberstein in the United States about the prevalence of adverse events to radiopharmaceuticals from 2007 to 2011, they reported a prevalence rate of 2.1/100,000 with no death or hospitalization.[21] Another survey done by Silberstein and Ryan with 18 collaborating institutes over 5 years found that no patient had experience severe adverse reaction to the radiopharmaceuticals.[22] In Japan, an annual survey running since 1975, has reported an incidence of 1.4 ADRs per 100,000 cases in 2015. Most of the ADRs were allergic reactions or vasovagal episodes, associated with $^{131}$I-iodomethylnorcholesterol and $^{99m}$Tc-HMDP.[23]

A review of published literature on adverse effects of radiopharmaceuticals reported prevalence rates of adverse reactions due to radiopharmaceuticals ranging from 0 to 25 cases per 100,000 administrations, indicating the variability in reporting in different settings. This study also reported that while the use of Technetium-99m was associated with mild adverse reactions, F-18 fluorodeoxyglucose use was associated with more severe adverse reactions.[19]

## Global scenario of adverse reaction reporting associated with radiopharmaceuticals

Despite the existence of a robust pharmacovigilance system in many countries, adverse reaction to radiopharmaceuticals is not encouraging. Unlike the drugs, the reporting system of radiopharmaceuticals is not uniform and varies from country to country.[10]

In the United States, the adverse reaction reporting program for radiopharmaceuticals is jointly supported by the American Society of Nuclear Medicine and the US Pharmacopeia Convention. The reports of adverse reaction to radiopharmaceuticals are collected by the American Society of Nuclear Medicine.[23]

In the United Kingdom, the UK Radiopharmacy group acts as the coordinator for the collation of data pertaining to adverse reactions. They also collate the data related to defective radiopharmaceutical products. They have developed separate adverse reaction reporting and radiopharmaceutical defects report form. After collecting the data, they scrutinize it diligently and inform the UK nuclear medicine community about the potential adverse reactions and drug interactions. They also publish it annually in the *European Journal of Nuclear Medicine and Molecular Imaging*.[24]

In France, radiopharmaceutical is defined as drug and monitoring of adverse events carried out by the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé). Like that of adverse events reporting of drugs, any adverse event due to pharmaceuticals can be reported to the nearest regional center of pharmacovigilance.[19]

Spanish researchers have created an open-access portable database called Datinrad (http://www.radiopharmacy.net/datinrad.html). This database allows entry, storage, and retrieval of radiopharmaceutical interactions with drugs or other agents and adverse effects of radiopharmaceuticals and can act as an easy-to-use reference tool for nuclear medicine specialists.[26]

In Turkey, any adverse events due to radiopharmaceuticals can be documented and reported to the Turkish Pharmacovigilance Centre as well as to the manufacturer.[27]

## Indian perspective

With the incidence of cancer and other non communicable diseases increasing exponentially in India, the use of radiopharmaceuticals used in their diagnosis and management has also increased significantly. Surprisingly, there is no published study available in the public domain regarding the prevalence of adverse events to radiopharmaceuticals in India.

The Indian Pharmacopoeia Commission (IPC) has included 19 radiopharmaceuticals in IP-2014 and another 10 in the Addendum 2015.[28] In India, radiopharmaceuticals use is regulated under the provision of the Drugs and Cosmetics Act, 1940 and Rules 1945.[29] The suspected adverse events due to radiopharmaceuticals can be reported like that of any other drugs. The health and family welfare ministry, Government of India, launched Pharmacovigilance Programme of India (PvPI) in 2010 under the aegis of Central Drug Standard Control Organization to detect and spontaneously report ADR in India. IPC works as the National Coordination Centre (NCC) for PvPI is also an active contributor to the international database of ADR maintained by UMC, Sweden.[30]

## The procedure for reporting an adverse reaction

The suspected adverse reaction to radiopharmaceuticals can be reported voluntarily by nuclear medicine specialist or nuclear pharmacist or any other paramedical workers to the nearest ADR monitoring centre (AMC). If the institute is a medical college hospital, then it can be reported to the pharmacovigilance center of the institution. The Medical Council of India has made it mandatory for every medical college to have a pharmacovigilance center. A reporting

format, two pages ADR reporting form, has been prepared by PvPI which contains all information regarding the patient, adverse events, regulator, and reporter. The duly filled and signed form can be sent to the nearest AMC. AMC does the casualty assessment using the WHO-UMC scale and sends the analyzed form to NCC through the ADR database. NCC periodically reviewed the reports received from the different AMC across the countries. These reports also send to the global pharmacovigilance database managed by the UMC.

## Conclusion

Radiopharmaceuticals used have increased tremendously over the years for diagnosis and treatment of many diseases. Despite this, there is a meager amount of data available regarding the adverse effects associated with radiopharmaceuticals. At present, many adverse effects associated with radiopharmaceuticals are not reported due to the lack of awareness about the reaction, improper reporting system, and overall poor reporting culture. Whereas reporting of adverse effect and sharing of information may minimize the incidence of adverse effects associated with radiopharmaceuticals. Hence, the need of the hour is to increase the awareness of adverse effects reporting among the nuclear medicine specialists and other paramedical workers by concerted effort.

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## References

1. Available from: http://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/why-pharmacovigilance/. [Last accessed on 2018 Jul 16].
2. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en. [Last accessed on 2018 Jul 18].
3. Available from: http://www.apps.who.int/medicinedocs/en/d/Jh2992e/2.htm. [Last accessed on 2018 Jul 18].
4. Diagnostic Imaging Dataset Annual Statistical Release. NHS England; 2015/16. Available from: http://www.england.nhs.uk/statistics/wpcontent/uploads/sites/2/2015/08/AnnualStatistical-Release-2015-16-DID-PDF-1.5MB.pdf. [Last accessed on 2018 Jul 15].
5. Yeong CH, Cheng MH, Ng KH. Therapeutic radionuclides in nuclear medicine: Current and future prospects. J Zhejiang Univ Sci B 2014;15:845-63.
6. Alazraki NP. Radionuclide imaging in the evaluation of infections and inflammatory disease. Radiol Clin North Am 1993;31:783-94.
7. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: Effects, side effects, and factors affecting therapeutic outcome. Endocr Rev 2012;33:920-80.
8. Elisei R, Agate L, Mazzarri S, Bottici V, Guidoccio F, Molinaro E, *et al*. Radionuclide Therapy of Thyroid Tumors. In: Strauss H, Mariani G, Volterrani D, Larson S. (editors) Nuclear Oncology. Switzerland Springer, Cham; 2017. p. 1197-1241.
9. Giovacchini G, Giovannini E, Riondato M, Ciarmiello A. Radiopharmaceuticals for the diagnosis and therapy of neuroendocrine differentiated prostate cancer. Curr Radiopharm 2017;10:6-15.
10. Yordanova A, Eppard E, Kürpig S, Bundschuh RA, Schönberger S, Gonzalez-Carmona M, *et al*. Theranostics in nuclear medicine practice. Onco Targets Ther 2017;10:4821-8.
11. Nyakale N, Lockhat Z, Sathekge MM. Nuclear medicine-induced allergic reactions. Curr Allergy Clin Immunol 2015;28:10-7.
12. Hesslewood SR, Keeling DH. Frequency of adverse reactions to radiopharmaceuticals in Europe. Eur J Nucl Med 1997;24:1179-82.
13. Bernardo-Filho M, Santos-Filho S, Moura E, Maiworm A, Orlando M, Penas M, *et al*. Drug interaction with radiopharmaceutical: A review. Braz Arch Biol Technol 2005;48:13-27.
14. Santos-Oliveira R, Smith SW, Carneiro-Leão AM. Radiopharmaceuticals drug interactions: A critical review. An Acad Bras Cienc 2008;80:665-75.
15. Hladik WB 3rd, Nigg KK, Rhodes BA. Drug-induced changes in the biologic distribution of radiopharmaceuticals. Semin Nucl Med 1982;12:184-218.
16. Santos-Oliveira R. Undesirable events with radiopharmaceuticals. Tohoku J Exp Med 2009;217:251-7.
17. Kennedy-Dixon TG, Gossell-Williams M, Cooper M, Trabelsi M, Vinjamuri S. Evaluation of radiopharmaceutical adverse reaction reports to the British Nuclear Medicine Society from 2007 to 2016. J Nucl Med 2017;58:2010-2.
18. Laroche ML, Quelven I, Mazère J, Merle L. Adverse reactions to radiopharmaceuticals in France: Analysis of the national pharmacovigilance database. Ann Pharmacother 2015;49:39-47.
19. Santos-Oliveira R, Machado M. Pitfalls with radiopharmaceuticals. Am J Med Sci 2011;342:50-3.
20. Vallabhajosula S, Killeen RP, Osborne JR. Altered biodistribution of radiopharmaceuticals: Role of radiochemical/pharmaceutical purity, physiological, and pharmacologic factors. Semin Nucl Med 2010;40:220-41.
21. Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia committee of the society of nuclear medicine. J Nucl Med 1996;37:185-92.
22. Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 1996;37:185-92.
23. Subcommittee for Safety Issues of Radiopharmaceuticals, Medical Science and Pharmaceutical Committee, Japan Radioisotope Association, Matsuda H, Uehara T, Okazawa H, Mizumura S, Yokoyama K, *et al.* The 38th report on survey of the adverse reaction to radiopharmaceuticals (The 41st survey in 2015). Kaku Igaku 2017;54:509-19.
24. Silindir M, Ozer AY. Adverse reactions to radiopharmaceuticals (ARRP) particularly to Technetium radiopharmaceuticals. FABAD J Pharm Sci 2008;33:109-17.
25. Available from: https://www.bnms.org.uk/adverse-event/defect-reporting/adverse-event-reporting-information.html. [Last accessed on 2018 Jul 16].

26. Gómez Perales JL, Martínez AA. A portable database of adverse reactions and drug interactions with radiopharmaceuticals. J Nucl Med Technol 2013;41:212-5.
27. Abuhanoglu G, Ozer AY. Adverse reactions to radiopharmaceuticals. FABAD J Pharm Sci 2012;37:43-593.
28. Kumar R, Kalaiselvan V, Kumar R, Verma R, Singh GN. Pharmacovigilance in radiopharmaceuticals. Indian J Nucl Med 2016;31:89-92.
29. Available from: http://www.cdsco.nic.in/writereaddata/Notice%20Radio-harmaceutical.pdf. [Last accessed on 2018 Jul 16].
30. Meher BR, Joshua N, Asha B, Mukherji D. A questionnaire based study to assess knowledge, attitude and practice of pharmacovigilance among undergraduate medical students in a tertiary care teaching hospital of South India. Perspect Clin Res 2015;6:217-21.



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