FABAD J. Pharm. Sci., 37, 43-59, 2012

RESEARCH ARTICLE

Adverse Reactions to Radiopharmaceuticals

Gürhan ABUHANOĞLU*, A. Yekta ÖZER*°

Adverse Reactions to Radiopharmaceuticals

Summary

As the widespread use of radiopharmaceutical drugs as a specific group have recently become a routine, consideration of their side effects, or their adverse reactions as radiopharmaceuticals have started to become very important. The common opinion of the scientists working on the isuue and investigating and gathering the results of the the effects have reported the necessity of keeping these records by a follower. Evaluable results can be achieved through wide use of appropriate reporting systems and forms, manufacturers following and reporting the adverse events more closely and by increasing awareness of the health workers in heath institutios. Thus, major contributions will be provided for positive movements in designing, producing, improving and reducing the adverse effects of new radiopharmaceuticals. The biggest task on this issue, without doubt, will be of the healthcare workers, particularly of the radiopharmacists.

Key Words: *Radiopharmaceuticals, adverse reactions, adverse events.*

Radyofarmasötiklerin Advers Etkileri

Özet

Radyofarmasötiklerin özel bir ilaç gurubu olarak son zamanlarda kullanımının yaygınlaşması ve rutin kullanılır hale gelmesiyle birlikte ilaçlarda yan etki, radyofarmasötikler için ise advers etki olarak nitelendirilen etkiler önemli hale gelmeye başlamıştır. Son zamanlarda konu üzerinde çalışan, etkileri araştırıp derleyen bilim adamlarının ortak görüşü; bu konudaki raporlama sisteminin bir sağlık takipçisi tarafından kurallara uygun bir şekilde tutulması gerekliliği olarak belirtilmiştir. Uygun raporlama sistemlerinin ve formlarının yaygınlaşması, üreticilerin ürünleri ile ilgili advers olayları daha sıkı bir şekilde takibi ve bildirimi ile sağlık kuruluşlarındaki sağlık çalışanlarının bu konudaki duyarlılığının artması sonucunda daha değerlendirilebilir sonuçlar elde edilecektir. Böylelikle yeni radyofarmasötiklerin tasarlanması, üretimi, geliştirilmesi ve advers etkilerinin azaltılması hususlarında pozitif ilerlemeye önemli bir katkı sağlanmış olacaktır. Bu konuda en büyük görev hiç şüphesiz sağlık çalışanları ve özellikle de radyofarmasistlere düşmektedir.

Anahtar Kelimeler: *Radyofarmasötikler, advers reaksiyonlar, advers olaylar.*

Received: 6.3.2013
Revised: 21.6.2013
Accepted: 6.11.12013

* Hacettepe University, Faculty of Pharmacy, Department of Radiopharmacy, 06100, Sıhhıye, Ankara-TURKEY
° Corresponding Author E-mail: ayozer@hacettepe.edu.tr

INTRODUCTION

In this review, it was aimed to review in detail the adverse and unexpected reactions encountered with several radiopharmaceuticals used in nuclear medicine practice. Recognition and classification of adverse reactions, record keeping, and examples to these reactions and related regulations are some of the titles of this review. It is hoped that this review can be successful in catching the attention of the researchers in the radiopharmacy and nuclear medicine fields.

Adverse Reaction/ Adverse Drug Reaction (ADR) means a harmful and unintended response to a human medicine, occurring at doses normally used for the diagnosis or treatment of a disease, or for the restoration, correction or modification of a physiological function. In this context, an adverse reaction is considered as synonymous with suspected adverse drug reaction. **Serious Adverse Reaction** refers to an adverse reaction that causes death, or life-threatening situation, hospitalization or prolonged hospitalization, permanent or significant disability or incapacity, or a congenital anomaly/birth defect. **Unexpected Adverse Reaction** is defined as a reaction, the nature, severity or outcome of which is not consistent with the description used in the product labeling such as Summary of Product Characteristics (SPC) of a medicinal product (1).

As adverse reactions can occur in using of all types of drugs, they are also associated with the use of radiopharmaceuticals, and instead of the term "side effect", which is generally used in common drugs, "adverse reaction", a term with broader sense is used to refer them.

Another definition of adverse drug reaction includes any side effects, damage, toxicity or hypersensitivity reactions that occur during the use of a pharmaceutical drug, as well as undesirable and unexpected pharmacological effects of a medication. The radiopharmaceuticals that are used to diagnose certain medical problems are not administered anticipating a specific pharmaceutical response. The amount of the substance introduced is too little to create this kind of an effect. In addition, radiopharmaceuticals should also have an undesirable but expected radiation effect. However, this reaction caused by radiation may not be observed within a short period, and the effects defined as adverse reactions are nonspecific reactions such as pruritus (itch), urticaria, fever, sweating, nausea, vomiting, low blood pressure, flushing, respiratory disorder, pain, edema. According to the data, the radiopharmaceutical drug groups most frequently reported for adverse reactions are colloids, albumins, phosphates and phosphonates, as well as cisternographic agents.

In this review, we mainly discuss the adverse reactions to radiopharmaceuticals, studies on this topic as well as the prevalence and incidence rates.

Any adverse reaction associated with the use of radiopharmaceuticals should be immediately specified and documented. These reactions should also be reported to the Turkish Pharmacovigilance Center (TUFAM) of the Ministry of Health and to the manufacturer. Adverse drug reaction reporting form is available from the Turkish Pharmacovigilance Center (TUFAM) of the Ministry of Health (1).

An example of this adverse drug reaction reporting form prepared by a manufacturer can be found at the address www.monrol.com.tr (2).

A study on the adverse and false positive reactions to FDG-18, which retrieves 20,000 relevant studies, has revealed that only 1.5% or 300 of these studies contains FDG-18 related adverse reactions. In addition, in the use of FDG-18, an adverse reaction called Sarcoid Reaction may occur. Moreover, it has been reported that false-positive PET scan results could have beeen obtained. For example, some cases of false-positive reaction are related to the breast implants and Teflon. False- positive results were also observed in patients with arthroplasty at the prosthesis sites (3).

It has been reported that some patients with breast carcinoma had developed a type I hypersensitivity reaction (allergy) to intradermal injection of technetium-99m labeled nanocolloidal albumin (4).

A prospective survey performed in 17 nuclear medicine departments in 1996 showed that a prevalence

of 11 events per 105 administrations was obtained (95% confidence limits 3.3-19.2) in Europe. This rate is slightly higher than that obtained in a larger scale study in the United States (2.3 events per 105 administrations, 95% confidence limits 1.2-3.4). The difference has been reported to be due to the algorithm used, the comparative size and time scale of the two studies. The prevalence of adverse reactions included in this study is approximately 1000-fold less than that occurring with iodinated contrast media and drugs (5).

Under the heading of clinical trials, the 65/65/EEC, 75/318/EEC and 89/343/EEC directives for radiopharmaceuticals include rules governing diagnostic/therapeutic efficacy, adverse reactions, initiatives, and dosing (6).

Adverse reactions to radiopharmaceuticals have been reported as follows: more common reactions to Chromic P-32 include anorexia, abdominal pain, diarrhea, nausea and vomiting, weakness and fatigue; less common reactions include severe abdominal pain, severe nausea and vomiting, fever, chills, dry cough, sore throat, chest pain, respiratory disorder, bleeding and bruising. Adverse effects of treatment with sodium iodide I 131 may include loss of taste, dry mouth, stomach irritation, nausea and vomiting, tenderness in the salivary glands or neck. Common side effects of Strontium-89 are Flushing and transient increased bone pain. Less common side effects of Samarium-153 might include irregular heartbeat, temporary increase in bone pain, nausea and vomiting (7).

Documentation of Adverse Reactions:

An Adverse Reactions Report Form and A Radiopharmaceutical Defects Report Form can be filled online on the website of The British Nuclear Medicine Society (BNMS) (https://www.bnms.org.uk) (8).

The article, "Guidance for Nuclear Medicine Staff on Radiopharmaceuticals Drug Interaction", published by the Radiopharmacy Center of the Nuclear and Energy Research Institute (IPEN), Brazil, points out that there is inadequate and less feedback on drug interactions related to radiopharmaceuticals while more publications and information are available on adverse reactions end. The review emphasizes the importance of documentation and reporting of drug interactions with radiopharmaceuticals while it suggests that nuclear medicine staff should be provided with more guidance on the issue (9).

A review of the literature from 1957 to January 2009 was carried out and the results were published, which found six cases of adverse reactions with radiopharmaceuticals: 2 cases with F-18 fluorodeoxyglucose (FDG) and 4 cases with technetium Tc-99m. Among the 4 cases of adverse reactions with 99mTc, one subject that received Tc-99m labeled sestamibi developed anaphylactic reactions. Moreover, eight cases with false positive reactions were found with FDG (10).

In addition, the researchers called Machado and Santos, who have searched for studies reporting adverse reactions to radiopharmaceuticals by reviewing publications from prominent data banks such as MEDLINE, EMBASE, International Pharmaceutical Abstracts and Science Citation Index. They have found that 5-year studies reported prevalence rates of adverse reactions due to radiopharmaceuticals ranging from 0 to 25 cases per 100,000 administrations. This study also revealed that the majority of adverse reactions associated with Tc-99m were simple and harmless complications. Similarly, a few adverse reactions with FDG have been reported (11).

Spicer et al, in their study, determined the adverse allergic reactions to Tc-99m-MDP as rash and skin eruption. The agent causing the reaction was found to be the organic phosphate MDP (12).

Published by Kusakabe et al, the 29th report on survey of the adverse reaction to radiopharmaceuticals, which was based on responses obtained from 975 institutions among 1263 nuclear medicine institutions, thirty-two cases of adverse reactions were reported. While 1,189,127 radiopharmaceutical administrations were reported, the incidence of adverse reactions per 100,000 cases was 2.7. In addition, three cases of defect products were reported, and the incidence of defect products per 100,000 cases was 0.3 (13).

In a study of 1996, Silberstein and Ryan analyzed 783,525 radiopharmaceuticals and 67,835 nonradioactive drug administrations. They determined that 10 of the 18 adverse reactions to radiopharmaceuticals were insignificant. No patient experiencing an adverse reaction to a radiopharmaceutical required hospitalization or had significant sequelae. Reproducibility of the adverse reactions algorithm was validated by independent evaluation of 30 adverse reaction reports from the U.S. Pharmacopeia-Society of Nuclear Medicine adverse reaction reporting system. All adverse reactions to 49 commercially available radiopharmaceuticals were tabulated and referenced there (14).

The researchers note that radiopharmaceuticals have gained more importance in France since 1992, and very few adverse reactions to radiopharmaceuticals with a rate of 1 to 6 reactions per 100,000 injections have been reported. A prospective survey was performed from November 1993 to May 1995 (during 18 months) in the Department of Nuclear Medicine of the University Hospital in Toulouse. There were 14,794 injections of radiopharmaceuticals (99mTc-phytate, 99mTc-microspheres of serum albumin, 99mTc-dimercapto-succinic acid (DMSA), 99mTc-hydroxymethyldiphosphonate (HMDP), 99Tc-colloid, 99mTc, 99mTc-sestamibi, Thallium-201). Three side effects were reported: one case of necrosis at the injection site, one case of vomiting and one case of dizziness. All the cases occurred with Tc99m-pyrophosphate. According to the World Health Organization's definition, the first side effect was classified as 'serious'. The causal relationship was unlikely for the first and second case and probable for the third. The outcome of these side effects was always favorable (15).

In the section of radiopharmaceuticals, American Cancer Society's web site reports the adverse reactions associated with radiopharmaceuticals that are used for treatment, such as Strontium-89, Samarium 153, I-131, P-32 radio labeled antibodies (16).

The majority of the studies included in the medical review (found on FDA's website, under the Development & Approval Process (Drugs), on the effectiveness of F-18 FDG used in positron emission tomography (PET) reported that no adverse reaction occurred (17).

Stockel et al reported a case of an anaphylactic reaction (anaphylactic shock) following administration of 125I- and 131I-o-iodohippurate in a 32-year-old woman (18).

In the study on the safety of FDG-18, the researchers examined the studies and the reports on the issue of adverse reactions and false-positive reactions, and they suggested the issue should be followed consistently, and cases as many as possible, should be reported (3).

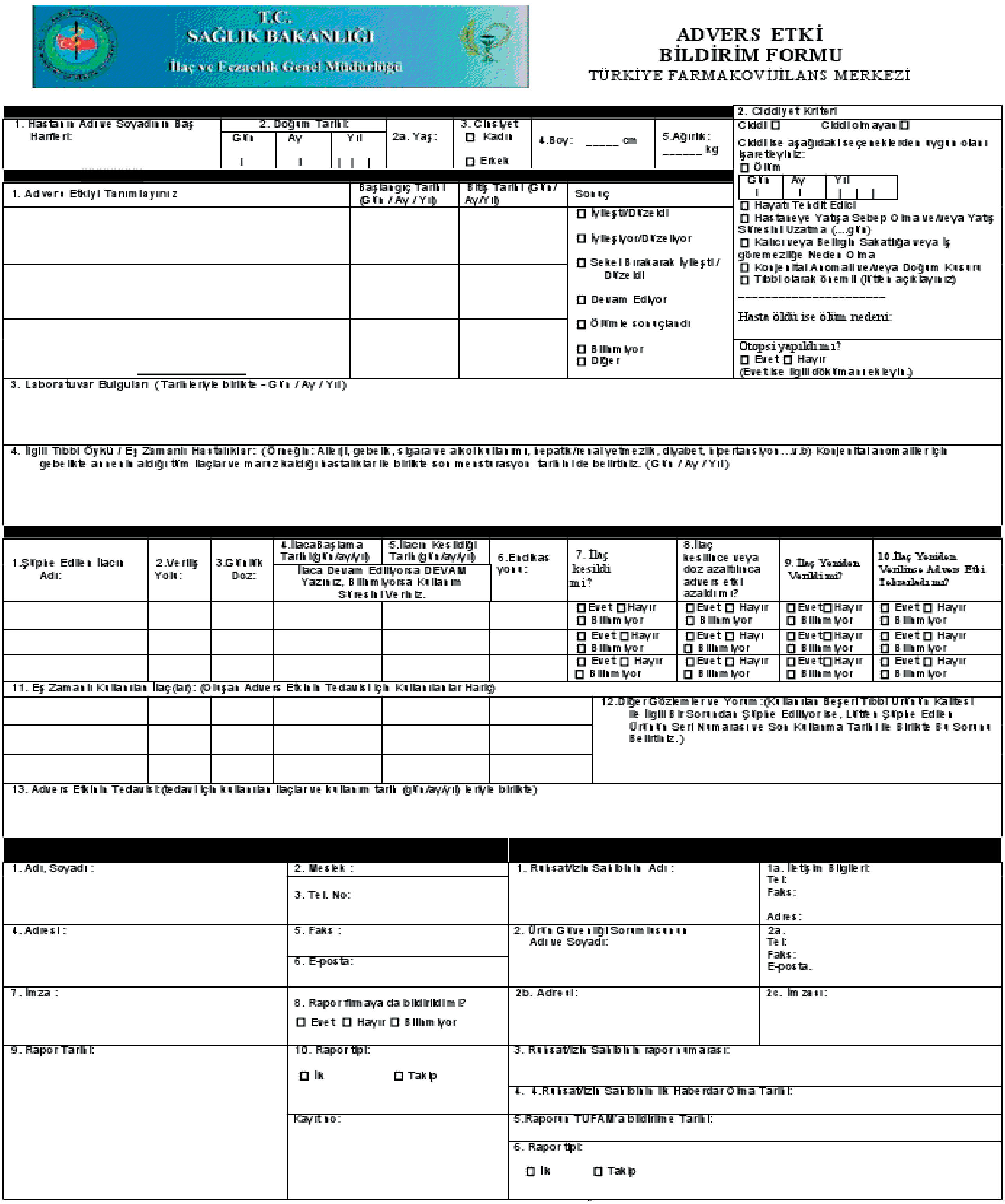
Table 1. Adverse Reactions to Radiopharmaceuticals (14)

RADIOPHARMACEUTICAL	TRADE NAME	SIDE EFFECTS-COMMENT AND OTHER REACTIONS
Co-57 Cyanocobalamin	Rupratope-57 Dicopac Kit	N/A N/A
Cr-51 Sodium Chromate	Chromitope	Erythema, rash, hypertension, tachycardia, diaphoresis
F-18 Fluoxyglucose, FDG Fluorodeoxyglucose		N/A
Fe-59 Ferrous Citrate		N/A
Gallium Ga-67 Citrate	Neoscan	Nausea, vomiting, erythema, redness, Diffuse rash, itching, hives / urticaria, respiratory reaction, tachycardia, syncope, weakness, dizziness, vertigo, swelling of the face, metallic taste, dyspnea, Salty Taste

RADIOPHARMACEUTICAL	TRADE NAME	SIDE EFFECTS-COMMENT AND OTHER REACTIONS
In-111 Cabromab Pentetit	ProstaScint	Increased bilirubin, hypotension, hypertension, injection site reactions, elevated liver enzymes, itching, fever, rash, headache, myalgia, asthenia, thigh sensitivity, short breathing, taste changes, HAMA Production by the receiver
In-111- Indium Oksikinolon, Oxin		Fever, Diffuse rash, itching, hives / urticaria
In-111-DTPA Pentetate	MPI-DTPA	Fever, nausea, vomiting, erythema, flushing, itching, hives / urticaria, cardiac arrest, hypertension, headache, aseptic meningitis, death 20 minutes after the injection
In-111-Pentetriotit	Octreoscan	Fever, nausea, erythema, flushing, hypotension, Bradycardia, dizziness, vertigo, headache, excessive sweating, arthralgia, and asthenia, anemia
In -111- Satumomab Pendetit	Oncoscint CR/ OV	Chills, fever, nausea, erythema, flushing, diffuse rash, itching, chest pain, jam or a feeling of heaviness, hypertension, hypotension, dizziness, vertigo, headache, excessive sweating, arthralgia, and asthenia, confusion, diarrhea, hypothermia, Bradycardia, Vasodilatation, Angioedema, HAMA Production by the receiver
I- 123 –Iobenguan MetaIodoBenzylGuanidin, MIBG		Nausea, erythema, flushing, hypertension, respiratory reaction, syncope or weakness, dizziness, vertigo, tachypnoea
I-123-OrthoIodoHippurate Sodium	Nephroflow, Nephropure	Nausea, Vomiting, Diffuse rash, itching, hives / urticaria, hypotension
I-123 Sodium Iodide		Nausea, Vomiting, Diffuse rash, itching, hives / urticaria, chest pain, jam or a feeling of heaviness, respiratory reaction, tachycardia, syncope, weakness, headache, tachypnea, parosmia
I-125 Iodinated Albumin (IHSA, Iodinated Human Serum Albumin)		Diffuse rash
I-125-Sodium Iotalamat	Glofil	N/A
I-131-Iobenguan MetaIodoBenzilGuanidin,MIBG		Erythema, flushing, dizziness, metallic taste, tingling sensation on the face and arms
I-131-Albumin	RISA, Radiodinated Serumalbumin, Megatope	N/A
I-131-OrthoIodoHippurate	Hipputope, Hippuran	Nausea, vomiting, itching, hives / urticaria, hypertension, respiratory reaction, tachycardia, syncope, weakness, excessive sweating, anaphylaxis, facial edema, dyspnea, cold sweating, paleness, amaurosis fugas
I-131 Sodium Iodide	Iodotope	Chills, nausea, vomiting, itching, hives / urticaria, chest pain, feeling of heaviness, tachycardia, headache, dizziness
I-131-6-Beta Iodomethyl-18-Norcholesterol	NP-59	Nausea, vomiting, erythema, flushing, chest pain, feeling of heaviness, hypertension, respiratory reaction, tachycardia, dizziness, headache, excessive sweating, swelling of the face, abdominal pain, metallic taste, dull tongue, dyspnea

RADIOPHARMACEUTICAL	TRADE NAME	SIDE EFFECTS-COMMENT AND OTHER REACTIONS
Kr-81m Krypton		N/A
N-13 Ammonia		N/A
P-32 Chromic Phosphate Suspension	Phosphocol	Chills, fever, nausea, vomiting, chest pain, jam or a feeling of heaviness, respiratory reaction, abdominal pain, dyspnea, sore throat, cough, Pleuritis, Myelosuppression
P-32 Sodium Phosphate		Myelosuppression, Bone Pain
Rb-82 Rubidium		N/A
Sm-153 Lexidronam	Quadramet	Myelosuppression, Bone Pain
Sr-89 Strontium Chloride	Metastron	Chills, fever, Myelosuppression, Bone Pain
Tc-99m Albumin Colloid	Microlite	Chills, nausea, erythema, rash, Diffuse rash, pruritus, hypertension, hypotension, respiratory reaction, tachycardia, dizziness, vertigo, excessive sweating, anaphylaxis, abdominal pain, Myelosuppression (Dissolved Albumin Injection contains MDP and could cause anaphylaxis)
Tc-99m Albumin (HSA-Human Serum Albumin)		Chills, fever, erythema, flushing, diffuse rash, hypotension, tachycardia, dizziness, vertigo, swelling of the face, tachypnea, malaise, dyspnea
Tc-99m Arcitumomab	CEA-Scan	Transient eosinophilia, nausea, bursitis, urticaria, pruritus, headache, fever, Grand Male, HAMA Production
Tc-99m Bicisate Dihydro Chloride (Etil Sisteinat Dimer, ECD)	Neurolite	Nausea, Diffuse rash, chest pain, jam or a feeling of heaviness, respiratory reaction, seizures, Syncope or weakness, dizziness, vertigo, fever, cyanosis, and asthenia, various Neurological Adverse Effects on the underlying disease, visual hallucinations, Parosmi, Cardiac Disorder, Respiratory arrest
Tc-99m Disofenin	Hepatolite	N/A
Tc-99m Eksametazim (HexaMethylPropylen Amine Oxin, HMPAO)	Ceretec	Fever, Erythema, Redness, Diffuse Skin rash, hypertension, Hypotension, Respiratory Reaction, Seizures Excessive sweating, cyanosis, anaphylaxis, swelling of the face, abdominal pain, dyspnea, Myoclonus (marked WBC)
Tc 99m Gluceptate	Glucoscan, Technescan Gluceptate	Chills, nausea, erythema, Redness, Diffuse rash, hives / urticaria, respiratory reaction, tachycardia, seizures, dizziness, vertigo, headache, excessive sweating
Tc-99m Lidofenin	Technescan HIDA	Chills, nausea,
Tc-99m Macroaggregated Albumin (MAA)	AN-MAA Gluceptate Macrotec, MPI-MAA Pulmolite, Technescan MAA	Chills, nausea, erythema, redness, Diffuse rash, itching, hives / urticaria, cardiac arrest, chest pain, jam or a feeling of heaviness, Hypertension, hypotension, Respiratory Reaction, Tachycardia, Syncope or weakness, excessive sweating, Syanozis, anaphylaxis, metallic taste, dyspnea, sore throat, foot numbness, parosmia

RADIOPHARMACEUTICAL	TRADE NAME	SIDE EFFECTS-COMMENT AND OTHER REACTIONS
Tc-99m Mebrofenin	Choletec	Hives / Urticaria
Tc-99m Medronat (MDP, Methylene Diphosphonate)	Osteolite, Technescan-MDP, AN-MDP, MPI-MDP	Chills, fever, nausea, vomiting, erythema, redness, diffuse rash, itching, hives/urticaria, cardiac arrest, chest pain, feeling of heaviness, hypotension, hypertension, respiratory reaction, tachycardia, seizures, Syncope-Weakness, dizziness, Vertigo, headache, excessive sweating, anaphylaxis, abdominal pain, metallic taste, asthenia, injection site pain-fever, photophobia, death due to cardiac arrhythmias
Tc-99m Mertiatide (MAG3, Mercaptoacetyl] glycyl] glycyl] glycine	Technescan MAG3	Nausea, vomiting, erythema, redness, syncope or weakness, sore throat
Tc-99m Oxidronate (HDP, hydroxymethylene diphosphonate)	Osteoscan HDP	Nausea, vomiting, erythema, redness, Diffuse rash, chest pain, jam or heavy feeling, heartburn, seizures, excessive sweating, swelling of the face, itching
Tc-99m Diethylenetriamine Penthaacetic acid (DTPA)	Technescan DTPA AN-DTPA MPI-DTPA Tecniplex	Chills, nausea, erythema, redness, Diffuse rash, itching, hives / urticaria, hypertension, hypotension, respiratory reaction, tachycardia, syncope or weakness, headache, cyanosis, anaphylaxis, arthralgia, injection site pain and burning, wheezing: (Intrathecal Acquisition of Trisodium Salts Causes Neurological Signals)
Tc-99m Pyrophosphate (PYP) and Sodium Pyrophosphate	Pyrolite, Technescan PYP, Phosphotec, MPI, Pyrophosphate, AN Pyrotec Ultratag	Chills, fever, nausea, vomiting, erythema, rash, diffuse rash, pruritus, urticaria, chest pain, feeling of heaviness, hypotension, respiratory reaction, syncope or weakness, dizziness, vertigo, pain at the injection site, tinnitus
Tc-99m Sestamibi	Cardiolite, Mirluma	Nausea, erythema, redness, Diffuse rash, pruritus, headache, metallic taste, tingling, seizures
Tc-99m Sodium Pertechnetate	Minitec, UltratechKow	Chills, nausea, vomiting, diffuse rash, itching, seizures, headache, metallic taste, tingling
Tc-99m Succimer (DMSA, DiMercaptoSuccinic Acid)	MPI-DMSA, Nephroscint	Nausea, erythema, redness, syncope or weakness, Abdominal Pain
Tc-99m Sulfur colloid	AN- Sulfur Colloid, TechneColl, TcSC, Tesuloid	Chills, fever, nausea, vomiting, erythema, redness, diffuse rash, itching, hives / urticaria, cardiac arrest, chest pain, feeling of heaviness, hypotension, hypertension, respiratory reaction, tachycardia, bradycardia, seizures, syncope or weakness, dizziness, vertigo, headache, excessive sweating, cyanosis, anaphylaxis, arthralgia, injection site pain-fever, wheezing, dyspnea, choking sneezing, itchy throat, paraesthesia, weakness
Tc 99m Tetrofosmin	Myoview	Angina, Hypertension, Torsades de Pointes (heart disease), vomiting, abdominal sensitivity, allergy, hypotension, dyspnea, metallic taste, burning sensation in the mouth, irregular smell, mild leukocytosis
Tl-201 Thallium Chloride		Fever, erythema, redness, diffuse rash, pruritus, hypotension
Xe-127 Xenon		N/A
Xe-133 Xenon		N/A



T.C.
SAĞLIK BAKANLIĞI
İlaç ve Eczacılık Genel Müdürlüğü

ADVERS ETKİ
BİLDİRİM FORMU
TÜRKİYE FARMAKOVİJİLANS MERKEZİ

1. Hastanın Adı ve Soyadının Baş Harfleri:
2. Doğum Tarihi: Gün / Ay / Yıl
2a. Yaş:
3. Cinsiyet: ☐ Kadın ☐ Erkek
4. Boy: _____ cm
5. Ağırlık: ______ kg

2. Ciddiyet Kriteri
Ciddi ☐ Ciddi olmayan ☐
Ciddi ise aşağıdaki seçeneklerden uygun olanı işaretleyiniz:
☐ Ölüm (Gün / Ay / Yıl)
☐ Hayatı Tehdit Edici
☐ Hastaneye Yatışa Sebep Olma ve/veya Yatış Süresini Uzatma (....gün)
☐ Kalıcı veya Belirgin Sakatlığa veya İş göremezliğe Neden Olma
☐ Konjenital Anomali ve/veya Doğum Kusuru
☐ Tıbbi olarak önemli (Lütfen açıklayınız)
Hasta öldü ise ölüm nedeni:
Otopsi yapıldı mı?
☐ Evet ☐ Hayır
(Evet ise ilgili dökümanı ekleyin.)

1. Advers Etkiyi Tanımlayınız
Başlangıç Tarihi (Gün / Ay / Yıl)
Bitiş Tarihi (Gün / Ay / Yıl)
Sonuç
☐ İyileşti/Düzeldi
☐ İyileşiyor/Düzeliyor
☐ Sekel Bırakarak İyileşti / Düzeldi
☐ Devam Ediyor
☐ Ölümle sonuçlandı
☐ Bilinmiyor
☐ Diğer

3. Laboratuvar Bulguları (Tarihleriyle birlikte - Gün / Ay / Yıl)

4. İlgili Tıbbi Öykü / Eş Zamanlı Hastalıklar: (Örneğin: Alerji, gebelik, sigara ve alkol kullanımı, hepatik/renal yetmezlik, diyabet, hipertansiyon...v.b) Konjenital anomaliler için gebelikte annenin aldığı tüm ilaçlar ve maruz kaldığı hastalıklar ile birlikte son menstrasyon tarihini de belirtiniz. (Gün / Ay / Yıl)

1. Şüphe Edilen İlacın Adı:	2. Veriliş Yolu:	3. Günlük Doz:	4. İlaca Başlama Tarihi (gün/ay/yıl)	5. İlacın Kesildiği Tarih (gün/ay/yıl)	6. Endikasyonu:	7. İlaç kesildi mi?	8. İlaç kesilince veya doz azaltılınca advers etki azaldı mı?	9. İlaç Yeniden Verildi mi?	10. İlaç Yeniden Verilince Advers Etki Tekrarladı mı?
			İlaca Devam Ediliyorsa DEVAM Yazınız, Bilinmiyorsa Kullanım Süresini Veriniz.						
						☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor
						☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor
						☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor	☐ Evet ☐ Hayır ☐ Bilinmiyor

11. Eş Zamanlı Kullanılan İlaç(lar): (Oluşan Advers Etkinin Tedavisi İçin Kullanılanlar Hariç)

12. Diğer Gözlemler ve Yorum: (Kullanılan Beşeri Tıbbi Ürünün Kalitesi ile İlgili Bir Sorundan Şüphe Ediliyor ise, Lütfen Şüphe Edilen Ürünün Seri Numarası ve Son Kullanma Tarihi ile Birlikte Bu Sorunu Belirtiniz.)

13. Advers Etkinin Tedavisi (tedavi için kullanılan ilaçlar ve kullanım tarih (gün/ay/yıl) leriyle birlikte)

1. Adı, Soyadı:
2. Meslek:
3. Tel. No:
4. Adresi:
5. Faks:
6. E-posta:
7. İmza:
8. Rapor firmaya da bildirildi mi? ☐ Evet ☐ Hayır ☐ Bilinmiyor
9. Rapor Tarihi:
10. Rapor tipi: ☐ İlk ☐ Takip
Kayıt no:

1. Ruhsat/İzin Sahibinin Adı:
1a. İletişim Bilgileri: Tel: Faks: Adres:
2. Ürün Güvenliği Sorumlusunun Adı ve Soyadı:
2a. Tel: Faks: E-posta.
2b. Adresi:
2c. İmzası:
3. Ruhsat/İzin Sahibinin rapor numarası:
4. Ruhsat/İzin Sahibinin İlk Haberdar Olma Tarihi:
5. Raporun TÜFAM'a bildirilme Tarihi:
6. Rapor tipi: ☐ İlk ☐ Takip

Figure 1. Adverse Reactions Reporting Form (19)

Recently, the following of information has been required to be included in the Summary of Product Characteristics (SPC), by the Ministry of Health: (20)

Undesirable effects

This section should provide comprehensive information based on all adverse reactions (ADRs) from

clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product with at least reasonable suspicion and on a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. In this context, all adverse reactions should be included in the SPC if they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.

It is important that the whole section should be worded in concise and specific language and it should not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability. Statements on lack of proof of causal association are not helpful and should not be included.

In order to provide clear and readily accessed information, it should be structured according to the following recommendations:

a. A general description will be necessary for most products. It should state what the most serious and/or most frequently occurring ADRs are. It should be placed before the detailed and specific information presented in the table (s) (see below b.). This description, which should be as brief as possible, should start by providing an estimate of the overall percentage of the treated patients expected to experience adverse reactions. This information must be consistent with the figures presented and must not contain general statements such as 'well tolerated', 'ADRs are normally rare' etc. Examples of acceptable statements (addressing overall and organ specific frequency related to the target population) are given below:

"Approximately 15% of the patients can be expected to experience adverse reactions. These are mainly dose dependent and due to the pharmacologic effects of the medicinal product." or

"ADR are rare (<1/1,000). At the beginning of therapy, epigastric pain, nausea, diarrhea, headache or vertigo may occur: these reactions are usually mild and disappear within a few days even if treatment is continued (see also section (c) below)."

"The most common ADRs reported are dizziness and headache, both occurring in approximately 6% of patients."

"About 30% of the treated patients experience adverse reactions: they usually occur within the first three months after the start of the therapy. Dose-related ADR, such as gastrointestinal reactions and headache, can sometimes be alleviated by reducing the dose (see also section (c) below."

b. A single table of adverse reactions should be used according to the MedDRA (Medical Dictionary for Regulatory Activities) system organ class. The system organ classes should be presented in the order shown in Annex 2. Adverse reaction descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. Generally, any ADR should be assigned to the most relevant SOC related to the target organ. For example, 'Liver functions test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'. Within each system organ class, the ADRs should be ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

The names used to describe each of the frequency groupings should follow standard terms established in each official language. Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.

The expressions isolated/single cases/reports should not be used. If for a specific ADR a frequency cannot

be estimated or a frequency category not be chosen an additional category frequency 'not known' may be added.

The choice of the frequency category to which any ADR will be assigned is based on frequency of data derived from a study (clinical trial or epidemiological study) designed in such a way that when a specific adverse event had been reported in a patient, it would have been detected within the defined observation period, reported, and assessed at least as a 'possible' reaction. This generally requires the use of adequate data collection and causality evaluation methods. In this situation, it is possible to calculate a point estimate of the crude incidence rate and its confidence interval, using standard statistical methods and taking into account the nature of the data (numerator, denominator, time dimension). The point estimate should be used to allocate an ADR to a frequency category.

If the choice of the frequency category is based on more than one suitable study, the category representing the highest frequency should be chosen unless application of a more specific method for detection of the ADR has been applied and thus resulted in an estimate of clearly higher validity, e.g. an integrated analysis across the suitable studies. The category to be chosen for each ADR should not be representing differences (calculated against placebo or other comparator) but crude incidence rates.

The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. If it is decided that an ADR detected by spontaneous reports should be included, each adequately designed study where this ADR could have been detected should be reviewed. If no valid estimate of the incidence rate can be derived from these studies, it has to be classified as 'Not known'. When various galenical/pharmaceutical formulations of a medicinal product are available, appropriate clinical trial data for suitable formulations may be combined for the assessment of frequency categories (e.g. various oral or enteral formulations). This would aim to obtaining results that are more robust. In the case of different modes of application (e.g. enteral versus parenteral versus inhalation etc.), these should be dealt with separately.

A tabulation of ADR frequency estimates from clinical trials, stated as a fraction expressed per 1,000 exposed patients (incidence rates, related confidence intervals), which do not serve the purpose of assignment to the defined frequency categories may only be included when it is of particular relevance to the patient and/or prescriber to be informed of certain risks and related frequency estimates. In these cases, it is preferable that the data should be based on pooled study results or large targeted studies performed under actual market conditions.

When data come from a placebo-controlled trial or a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline incidence rate, and if the ADR is considered important, the background incidence may be provided in a footnote, or results may be presented as an added column or in a separate table.

In the exceptional instances, where frequencies that are more precise are stated, the figures should be annotated with a footnote describing how the data were obtained. The methods used to derive the figures will vary but must be appropriate to the circumstances. The annotation might read, for example:

"Excess incidence compared with placebo in pooled data from clinical trials involving x patients taking the medicinal product and y patients taking placebo, where the placebo incidence was z",

"Incidence of the suspected adverse reaction in an observational post study in x patients".

If there are only a few adverse reactions in total in this section, tabulation by system organ class may be unnecessary.

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and 'see section c)' should be included as a footnote.

c. This section should include information characterizing individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information may describe for example reversibility or time of onset the severity, duration of reaction, mechanism of the reaction (if of clinical relevance), or dose relationship. Mention should be made here of any differences between different dosage forms in respect of adverse reactions. In the case of combination products, a statement should be included in this section pointing out which particular adverse reactions are usually attributable to which component of the combination, where known.

Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur (if of particular importance) should be mentioned and cross-referenced here.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to the following section.

d. This section should include adverse reactions, which apply to the therapeutic chemical or pharmacological class-adverse reactions of very low frequency or with delayed onset of symptoms which may not have been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class. The fact that this is a class attribution should be mentioned.

Any undesirable event warnings necessary for excipients or residues from the manufacturing process should be included (20).

In the prospectus of DTPA KIT by a manufacturer reads as follows: "It is stated in the literatures that vasomotor problems related to Tc-99m-DTPA usage may occur, but there is no information about its frequency. The observed symptoms include skin reactions and decrease in blood pressure. There are more serious problems reported to arise from misformulation and misadministration in the application of DTPA aerosol and intrathecal (into cerebrospinal fluid) injection. Exposure to ionized radiation may initiate the formation of cancer. Tc-99m-DTPA should be applied only in the cases where the benefit expected from the application can meet the potential damage (justification principle) and so that the radioactivity amount to be applied is the lowest dose possible to provide the result expected from the application (As Low As Reasonably Achievable) as in the application of all radiopharmaceuticals. The long-term animal experiments concerning that Tc-99m-DTPA influences the fertility and/or may have carcinogenic effect in men and women are not available in literature."

Instructions for use of FDG kit by the same company include the following information. "According to the current data, no side effects or adverse events which would require the termination of PET scanning have been reported. However, rare and transient hypotension, hypo-or hyper-glycemia and increase in alkaline phosphatase have been reported."

In the SPC of MDP kit by the same company, it is stated, "the adverse reactions related to the administration of Tc-99m-MDP, such as various allergic dermatological reactions, low blood pressure, nausea, vomiting and fever, have been reported in the literature. Exposure to the ionized radiation may induce cancer formation. As for all radiopharmaceutical administrations, Tc-99m-MDP should be administered only if the expected benefit is higher than the potential damage (justification principle) and in such a manner that the amount of radioactivity to be implemented will be as low as reasonably achievable for the result expected from the administration. The long-term animal experiments concerning that Tc-99m-MDP influences the fertility and/or may have carcinogenic effect in men and women are not available in literature."

The SPC of I-131 capsules manufactured by the same company indicates that "hypothyroidism may develop in late period in connection with dosage in therapy of hyperthyroidism with I-131 as well as hypoactive thyroid symptoms including change in the menstruation period, lack of motion control, dry and blistered skin, headache, muscle pain. Also, reactions such as hyperhidrosis, fever, increase in the heart rate, fatigue and perturbation may occur.

In addition, following the therapy of thyroid cancer, gastritis and discoloration or blood in feces, cough, fever or shivering, back pain, dysuria, rubescence, abnormal bleeding or bruises may be observed."

The prospectus of Tl-201 solution for injection manufactured by the same firm says, "Possible side effects reported on Tl-201 scintigraphy are fever, diffuse skin redness, rash, allergic reactions such as erythema, and vasovagal reactions. Additionally, local radiation necrosis associated with paravenous injection may develop. Reported adverse reactions include nausea, vomiting, diarrhea, hypotension, sweating, hiccups, blurred vision, shivering, and fever" (21).

In the prospectus for Ga-67 kit by another company, it is stated, "Like all medicines, GA-67-MM-1 can cause side effects for patients hypersensitive to any of the ingredients. Intravenous administration of gallium [^{67}Ga] citrate has been reported to provoke adverse reactions of an anaphylactoid nature (estimated incidence of 1 to 5 per 100,000 administrations). The symptoms are generally mild being characterized as a warm sensation, generalized flushing, cutaneous erythema, pruritis and/or urticaria. Exposure to ionizing radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations, the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred" (22).

While adverse reactions were previously included in the prospectus of the drug in the abovementioned way, the new regulations require them to be listed as follows:

The radiopharmaceutical company's prospectus for 99Mo/99mTc generator indicates that "Undesired effects are listed according to the following level of frequency:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/1, 000 to <1/1,000), very rare (≤1/10,000), unknown.

The adverse effects reported following the application of sodium pertechnetate (99mTc) intravenously are listed below though the level of frequency is not known:

Nervous system disorders:
Coma

Cardiac disorders
Cardiac arrhythmia

Vascular diseases
Vasodilatation

Skin and subcutaneous tissue disorders
Urticaria
Facial edema
Itching

As in all radiopharmaceuticals, it should be administered to the patient if the benefit of application of sodium pertechnetate (99mTc) is more than the risk of ionizing radiation. In this case, the minimum dose should be applied to protect against radiation and to get the optimum result.

Exposure to ionizing radiation may trigger cancer or may lead to hereditary disorders. These adverse effects may arise with the low dosage used for nuclear medicine researches and little application.

The dosage used in nuclear medicine researches for diagnosis purpose is less than 20 mSv. It may be applied at higher doses depending on the clinic conditions.

Regarding MIBI kit, the adverse effects are classified in the same firm's prospectus according to following frequency:

Very common (≥1/10); common (≥1/100 to ≤1/10); not common (≥1/1000 to ≤1/100); rare (≥1/10.000 to 1/1000); very rare (≤1/10.000); unknown.

Gastrointestinal disorders
Uncommon:
Metallic taste, bitter taste in mouth

Rare:
Dry mouth

Skin and subcutaneous tissue disorders
Rare:
Irritation and itch on skin
Inflammation and edema at the injection site

Other effects
Common:
Fever
The following serious hypersensitivity reactions have been reported very rarely following the second injection of 99m Tc-Sestamibi.

Shortly after the injection;
Neurological system
Very rate:
Dizziness
Feeling of faint

Cardiovascular system
Very rare:
Arrhythmia

Gastrointestinal tract
Very rare:
Stomachache
Vomiting

Within 2 hours after injection;
Cardiovascular system
Very rare:
Hypotension
Bradycardia

Gastrointestinal system
Very rare:
Vomiting

Other
Very rare:
Weakness
Respiration disorder"

In the package leaflet of DMSA kit, it is stated, "Like all medicines, MON.DMSA KIT can cause side effects for the patients hypersensitive to any of the ingredients.

Please tell your doctor if you notice any of the following cases:
- Nausea
- Vomit
- Stomach ache
- Fever
- Irritation on skin

These are the slight adverse effects of Tc-99m-DMSA."

The package leaflet of NaF-18 solution for injection by the same company says: "There is no report on side effects observed upon administration of sodium fluoride (18-F). Since the amount of substance administered is very low, the main risk is due to radiation. Exposure to the ionized radiation may cause cancer or genetic defects.

The experiences show that the possibility of observing such kind of undesired effects with regard to the procedures in which nuclear medicines are used is very low due to the low doses administered. The dosage used in nuclear medicine researches for diagnosis purpose is less than 20 mSv" (23).

Regarding the adverse reactions associated with Zevalin-R kit for radiopharmaceutical therapy, the prospectus states: "Many of the patients may be expected to experience adverse reactions.

The frequency of the following adverse events, regardless of the reason, (10% = very often; 1%–10% = often; 1% = rare) are based on data from clinical trials.

Hematologic adverse reactions:

Hematological toxicity has been very commonly observed in clinical trials, and is dose limiting. Median time to blood platelet and granulocyte nadirs were around 60 days after start of treatment. In clinical trials with the indication of relapsed and refractory NHL, grade 3 or 4 thrombocytopenia was reported with median times to recovery of 13 and 21 days and grade 3 or 4 neutropenia with median times to recovery of 8 and 14 days.

Infections and infestations:
During the first 13 weeks after treatment with Zevalin, patients very commonly developed infections. Grade 3 and grade 4 infections were reported as common. During follow-up, infections occurred in common. Of these, grade 3 was common, grade 4 uncommon.

Secondary malignancies:
Myelodysplastic syndrome (MDS) /acute myeloid leukemia (AML) has been reported in four out of 211 patients assigned to treatment with Zevalin. The risk of developing secondary myelodysplasia or leukemia following therapy with alkylating agents is well known. Since all of these patients had previously received treatment regimens including alkylating agents, available results provide insufficient data on whether Zevalin contributes to an increased risk of MDS/AML, or on the extent of risk" (24).

The scientists examining Nanocoll-R, Tc-99m labeled nanocolloidal albumin used for sentinel node identification, reported that it might lead to allergic reactions such as Type-1 hypersensitivity reaction (25).

In their scientific review, Atak and Ozer provided a definition for adverse reactions to radiopharmaceuticals, gave solid examples, and by examining notifications and reports on this issue, they emphasized the importance of evaluating these reports (26).

Silindir and Ozer published a review examining adverse reactions particularly encountered in the studies of Tc-99m radiopharmaceuticals, and they concluded the reporting and documenting of adverse reactions by nuclear medicine staff or radiopharmacist are of great importance in reducing the incidence of ARRPs and preventing misdiagnosis (27).

Keeling explained the adverse reactions to radiopharmaceuticals by classifying as hypersensitivity reactions (skin reactions, anaphylactic shock, vasovagal reactions), pyrogenicity and sterility induced problems of products. In addition, he specified the incidence of reactions by particularly evaluating the reports on colloids, albumin particles, phosphates and phosphonates, DTPA and other radiopharmaceuticals, which were found in the reporting system (28).

In another Sampson study; adverse reactions to radiopharmaceuticals are comparatively few in numbers. Various estimates quote an incident rate of 1 to 6 reactions per 100,000 injections. Other figures quoted are 1 in 800 for the bone-seeking radiopharmaceutical methylene diphosphonate, and 1 in 400 for the lung visualisation agent macroaggregated albumin. The very low numbers of reported adverse effects probably reflect the tiny amounts of material which are used in the formulation of radiopharmaceuticals. Adverse reactions to radiopharmaceuticals are usually mild and transient and require little or no medical treatment. A few reactions involve respiratory or circulatory collapse or loss of consciousness. Several fatalities have been reported with the liver scanning agent 99mTc (technetium 99m) -albumin colloid. Clinical manifestations may be categorised under the headings of vasomotor effects i.e. faintness, pallor, diaphoresis or hypotension, and anaphylactoid effects such as nausea, dermographism, wheezing, bronchospasm, erythema and pruritus. The most prominent group of radiopharmaceuticals that have been reported to produce adverse events are the diphosphonates, which are used for scanning the skeleton. Typical diphosphonate reactions include erythema (especially over the extremities), nausea, vomiting and malaise. The onset of reaction is usually 2 to 3 hours after injection. The second group of radiopharmaceuticals which give rise to adverse events are the colloids, which are used for liver and spleen scintigraphy. Typical colloid reactions include pallor, nausea, flush and pulse changes. Adverse events may also occur as a result of the patient's medication interfering with the disposition of the radiopharmaceutical. Although not usually hazardous or dangerous, such events may be so pronounced that a marked deviation in the expected pharmacokinetics may occur. Drug interactions can be conveniently categorised under the headings of unusual handling of the radiopharmaceutical because of pharmacological action, genuine in vivo interaction between the medication and radiopharmaceutical, drug-induced disease and interaction between the radiopharmaceutical and catheters or syringes. The most serious drug

interactions are those where the patient is taking cortisone or cytotoxic agents prior to tumour scintigraphy. Other important effects occur in patients undergoing bone scanning who are receiving iron preparations. Nifedipine has been reported to produce quite severe problems in scanning, including difficulties in the radiolabelling of red cells (for cardiac scintigraphy), and other effects where the drug appears to prevent the transport of bone-seeking materials into the skeleton. Many drugs alter hormonal status and these effects may produce marked deviations from the expected biodistribution. Diethylstilbestrol (stilboestrol), digitalis, gonadotrophins, phenothiazines and cimetidine all increase estrogen levels in high doses (29).

Torizuka et al, Technetium-99m-DTPA-galactosyl human serum albumin (99mTc-GSA) is a new radiopharmaceutical which binds to the asialoglycoprotein receptors located specifically on the hepatocytes. Phase I study of 99mTc-GSA was performed on seven normal volunteers, who were intravenously injected with 185 MBq (5 mCi) and 1-10 mg of 99mTc-GSA. None of the adverse reactions, abnormal findings of laboratory test and anti-99mTc-GSA antibody production was recognized. The livers were clearly visualized in all subjects. In the pharmacokinetic analyses on five subjects, 99mTc-GSA was rapidly taken up by the livers immediately after the injection and was slowly excreted through the biliary tracts and the urinary tracts. Dose-dependency which is a specific feature for the receptor-mediated agents was observed; the blood clearances of 99mTc-GSA were prolonged in proportion to the injected ligand doses. These results suggest that 99mTc-GSA may be a potential agent for evaluating hepatic functions based on the hepatic receptor quantities (30).

The another study on new radiopharmaceutical Tc-99m Ethambutol (EMB) is a specific tuberculosis imaging agent. No adverse reactions were observed. The present study states that developed 99mTc -EMB has high potential to qualify as a specific tuberculosis imaging radiopharmaceutical and is safe for human use (31).

Ronald et al's guideline was developed by the SNM to describe important factors common to most nuclear medicine procedures. It is intended to guide nuclear medicine practitioners in establishing policies and procedures for the use of radiopharmaceuticals in clinical practice. This guideline is intended to be concordant with the regulations of the Nuclear Regulatory Commission and other state and federal government agencies. Adverse reactions associated with administration of radiopharmaceuticals should be investigated and documented. Serious adverse reactions and problems with products should be reported to the appropriate individuals and entities (32).

Oliveira et al's reviews are about radipharmaceuticals drug interactions. They say: 'The purpose is to provide a reference on drug interactions that could inform the nuclear medicine staff in their daily routine. Efforts to increase adverse event reporting, and ideally consolidate reports worldwide, can provide a critically needed resource for prevention of drug-radiopharmaceuticals interactions (33).

According to Hladik and Norenberg, problems associated with the clinical use of radiopharmaceuticals can usually be classified into one of four categories: unusual imaging results, adverse reactions, unique difficulties encountered in special patient populations, and quality assurance failures. In this study, each of these problem areas are briefly described and a guide for troubleshooting such problems is presented (34).

Hesse et al report cause for concern adverse events in nuclear medicine in their review. New challenges in CT and MRI contrast agents, therapeutic radiopharmaceuticals and WHO definitions are presented (35).

Salvatori et al. analysed further considerations on adverse reactions to radiopharmaceuticals in Europe, Japan and USA. Using these results, Hesse et al harmonized a strong action by the EANM, through the restoration of the annual reports from the EANM database, in collaboration with the national societies of nuclear medicine could reverse the present trend in underreporting of adverse reactions to radiopharmaceuticals (36).

CONCLUSIONS

Based on the above-mentioned reports and evaluations of adverse drug reactions, we can conclude that further severe, not frequent, adverse events in the administration of radiopharmaceutical products might continue to occur. The important thing is that the relevant staff should immediately document such reactions as soon as the event occurs. With the increased functionality of clinical pharmacy and radio-pharmacists on this issue, the interpretability and statistical analysis will certainly allow for better assessments. The importance of reporting such adverse events by the manufacturer, practitioners and patients using the forms specifically developed for this purpose, some of which have been provided in our publication, is increasing every day. The regular documentation and recording of such reactions as well as evaluation of the results will make a great contribution to the development of better radiopharmaceuticals with less adverse effects.

REFERENCES

1. T.C. Sağlık Bakanlığı, Türkiye İlaç ve Tıbbi Cihaz Kurumu, Advers Etki Bildirim Formu (TÜFAM). http://www.iegm.gov.tr/Default.aspx? sayfa = anasayfa
2. Eczacıbaşı-Monrol Advers Reaksiyon Bildirim Formu. http://www.monrol.com.tr/advers.asp
3. Santos-Oliveira R, Fleming B. Are Radiopharmaceuticals Safe? The Case of FDG-18. *Adv Pharmacoepidem Drug Safety*, 1: 102, 2012.
4. Chicken DW, Mansouri R, Ell PJ, Kesthgar MRS. Allergy to Technetium-Labelled Nanocolloidal Albumin for Sentinel Node Identification. *Ann R Coll Surg Engl*, 89: 186, 2007.
5. Heeslewood SR, Keeling DH. Frequency of Adverse Reactions to Radiopharmaceuticals in Europe. *Eur J Nucl Med Mol Imag*, 24: 1179-82, 1997.
6. Radyofarmasötikler, EEC Direktifleri, 3AQ20a, 175-84, 1990.
7. Margaret Alic (Ph. D.). Radyofarmasötiklerin Advers Etkileri. www.answers.com
8. The British Nuclear Medicine Society, Advers Reaction Report Form and Radiopharmaceutical Defects Report Form. http://www.bnms.org.uk/adverse-event/defect-reporting/adverse-event-reporting-information.html
9. Oliveira RS. Guidance for Nuclear Medicine Staff on Radiopharmaceuticals Drug Interaction. *Braz J Pharm Sci*, 45: n.4, 2009, ISSN 1984-8250, http://dx.doi.org/10.1590/S1984-82502009000400003.
10. Oliveira RS. Undesirable Events with Radiopharmaceuticals. *Tohoku J Exp Med*, 217: 251-7, 2009.
11. Oliveira RS, Machado M. Pitfalls with Radiopharmaceuticals. *Am J Med Sci*, 342: 50-53, 2011.
12. Spicer JA, Preston DF, Stephens RL. Adverse Allergic Reaction to Technetium-99m Methylene Diphosphonate. *J Nucl Med*, 26: 373-74, 1985.
13. Kusakabe K, Arano Y, Kasagi K, Komatani A, Matsuda H, Maruno H. The 29th Report on Survey of the Adverse Reactions to Radiopharmaceuticals (The 32nd Survey in 2006.) *Kaku Igaku*, 45: 19-35, 2008.
14. Silberstein EB, Ryan J. Prevalance of Adverse Reactions in Nuclear Medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med*, 37 (1): 1064-67, 1996.
15. Bagheri H, Galian ME, Bastie D, Couffignal AL, Tafani JA, Fourcade C, Morena I, Guiraud R, Montastruc JL. Prospective Survey on Adverse Effects of Radiopharmaceuticals. *Therapie*, 51: 550-53, 1996.
16. Radiopharmaceuticals, Last Medical Review, 2011. www.cancer.org
17. Drugs, Development and Approval Process (Drugs), Review of F-18 Fluoro -2-Deoxyglucose (F-18 FDG) Positron Emision Tomography in the Evaluation of Malignancy–August 4, 1999. www.fda.gov
18. Stockel M, Ennow K, Kristensen K, Rodbro P. Anaphylactic Reaction to Orthoiodohippurate. *Eur J Nucl Med Mol Imag*, 8: 89-90, 1983.
19. Türkiye Farmakovijilans Derneği Web Sitesi, Advers Etki Bildirim Formu. http://www.farmakovijilansdernegi.org/UserFiles/File/advers_etki_bildirim_formu_v3_669ea9c.pdf
20. Sağlık Bakanlığı, İlaç ve Eczacılık Genel Müdürlüğü Web Sitesi, Mevzuat, Kısa Ürün Bilgisine Ait Kılavuz, www.iegm.gov.tr
21. Monrol Kit Prospektüsleri, İnter-Med Hastane

Ürünleri Web Sitesi, www.intermed.web.tr
22. Radmed Kit Prospektüsleri, Ga-67 MM-1 Kit Prospektüs Bilgisi, www.radmed.com.tr
23. Monrol Kit Prospektüsleri, Monrol Web Sitesi, www.monrol.com.tr
24. Zevalin Kit Prospektüsü, www.ilacprospektusu.com
25. Dennis WC, Reza M, Peter JE, Mohammed RSK. Allergy to Technetium-Labelled Nanocolloidal Albumin for Sentinel Node Identification. *Ann R Coll Surg Engl*,89: 186, 2007.
26. Atak İE, Özer AY. Radyofarmasötiklerde Karşılaşılan Ters İlaç Reaksiyonları. *Hacettepe Univ J Fac Pharm*, 23: 33-58, 2003.
27. Silindir M, Özer AY. Advers Reactions to Radiopharmaceuticals (ARRP): Particularly to Technetium Radiopharmaceuticals. *FABAD J Pharm Sci*, 33: 109-17, 2008.
28. Keeling DH. Adverse Reactions and Untoward Events Associated with the Use of Radiopharmaceuticals. *Textbook of Radiopharmacy Theory and Practice.* Chapter 15, 289-309, Chapter 34, 431-46, 1994.
29. Sampson CB. Adverse reactions and drug interactions with radiopharmaceuticals. *Drug Safety: an Int J Med Toxic and Drug Exp*, 8 (4): 280-94, 1993.
30. Torizuka K, Ha-Kawa SK, Ikekubo K, Suga Y, Tanaka Y, Hino M, Ito H, Yamamoto K, Yonekura Y. Phase I clinical study on 99mTc-GSA, a new agent for functional imaging of the liver. *Kaku Igaku*, 28 (11): 1321-31, 1991.
31. Namrata S, Bhatnagar A. Clinical Evaluation of Efficacy of 99mTC -Ethambutol in Tubercular Lesion Imaging. Hindawi Publishing Corporation, Tuberculosis Research and Treatment, Volume 2010, Article ID 618051, 9 pages, doi:10.1155/2010/618051.
32. Ronald J. Callahan, Henry M. Chilton, James A. Ponto, Dennis P. Swanson, Henry D. Royal, and Allegra D. Bruce. Procedure Guideline for the Use of Radiopharmaceuticals 4.0. *J Nucl Med Tech*, 35 (4): 272-75, 2007.
33. Oliveira RS, Smith SW, Carneiro-Leao AM. Radiopharmaceuticals drug interactions: a critical review. *An Acad Bras Cienc*, 80 (4): 665-75, 2008.
34. Hladik WB, Norenberg JP. Problems associated with the clinical use of radiopharmaceuticals: a proposed classification system and troubleshooting guide. Find out how to access preview-only content. *Eur J Nuc Med*, 23 (8): 997-1002, 1996.
35. Hesse B, Vinberg N, Berthelsen AK,Ballinger JR. Adverse events in nuclear medicine – cause for concern? *Eur J Nucl Med Mol Imag*, 39: 782–85, 2012.
36. Salvatori M, Treglia G, Mores N. Further Considerations on Adverce Reactions to Radiopharmaceuticals. *Eur J Nucl Med Mol Imag*, 39: 1360-62, 2012.