Eur J Nucl Med Mol Imaging (2012) 39:1360–1362
DOI 10.1007/s00259-012-2120-1

LETTER TO THE EDITOR

Further considerations on adverse reactions to radiopharmaceuticals

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Received: 9 March 2012 / Accepted: 13 March 2012 / Published online: 20 April 2012

Dear Sir,

We read with great interest the recent editorial by Hesse et al. concerning adverse events (AEs) in nuclear medicine, in which the authors pointed out the clinical implications for the nuclear medicine community [1]. Hesse et al. reported a prevalence of adverse reactions ranging from 1.3 to 11 per 10^5 administrations, inferring these data from three studies [1]. A review of this topic has also recently been published [2]. In order to enrich the evidence-based data available so far, we performed a meta-analysis calculating the pooled prevalence of adverse reactions to radiopharmaceuticals classified as possible or probable, according to the causality assessment proposed by Silberstein and Ryan [3].

A comprehensive computer literature search for relevant large longitudinal studies on adverse reactions to radiopharmaceuticals of the PubMed/MEDLINE, Embase and Scopus databases was performed. The search algorithm was based on a combination of the terms: (a) "PET" or "SPECT" or "scintigraphy" or "radiopharmaceuticals" or "nuclear medicine" AND (b) "adverse reactions" or "adverse events" or "drug interactions" or "adverse effects" or "false positive reactions". No start date or language restrictions were used. The search was run until 29 February 2012. Statistical analyses were performed by means of StatsDirect statistical software.

The comprehensive computer literature search retrieved seven studies [3–9], reporting prevalence rates for adverse reactions to radiopharmaceuticals ranging from 0 to 11 cases per 100,000 administrations (Table 1), with wide 95 % confidence intervals (95 % CI). The pooled prevalence of adverse reactions to radiopharmaceuticals was 1.9 per 100,000 administrations (95 % CI 1.1–2.8 per 100,000 administrations; Fig.1).

The results of our meta-analysis indicate heterogeneity among large longitudinal studies (I^2 >90 %), in particular related to the European study and the high reporting rate in the UK [4], a country historically very sensitive and attentive in pharmacovigilance and post-marketing safety monitoring. Indeed, the new version of the adverse reactions reporting database, very recently implemented by the Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM), matches the one previously operated by the EANM in collaboration with the UK Radiopharmacy Group and hosted by the British Nuclear Medicine Society [10, 11]. Furthermore, the results of our meta-analysis reflect the regularity and the large number of radiopharmaceutical administrations considered in all the reports from Japan [6–9].

We agree with Hesse et al. that the "mild and transient nature of most reactions" and the "confusion in terminology" may contribute to the overall under-reporting [1]. However, other reasons should be taken into account, including physician's anxiety about potential liability, belief that there will be little interest in an already

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Table 1 Prevalence of adverse reactions to radiopharmaceuticals in the included studies

Reference	Year	Country	Adverse reactions	Number of administrations	Prevalence of adverse reactions (per 100,000 administrations)
[3]	1996	USA	18	783,525	2.3
[4]	1997	Europe	8	71,046	11
[5]	1998	USA	0	81,801	0
[6]	2006	Japan	16	1,277,906	1.2
[7]	2007	Japan	19	1,264,098	1.5
[8]	2008	Japan	32	1,189,127	2.7
[9]	2009	Japan	11	1,192,072	0.9

known adverse reaction, concern about the time required to fill in the form, lack of report forms, and misrecognition or lack of recognition of adverse reactions due to delayed appearance outside the nuclear medicine service [3].

Reporting adverse reactions to radiopharmaceuticals in Italy is regulated, as for non-radiolabelled drugs, by the Italian Medicine Agency (AIFA) by means of the National Network of Pharmacovigilance (RNF). Furthermore, it is highly recommended to communicate any adverse reactions to the EANM and Italian Association of Nuclear Medicine (AIMN). As quoted by Hesse et al. [1], updates on post-marketing changes in the benefit/risk ratio for radiopharmaceuticals are provided by AIFA via the "*Nota Informativa Importante*" (NII), a kind of "*Dear Doctor letter*" sent directly to nuclear medicine physicians, available online and distributed by hospitals local pharmacovigilance authorities. During November 2011, AIFA released a NII, issued by the European Medicine Agency (EMA), concerning the potential risk of hypersensitivity reactions and acute hypotension due to human antimouse antibody (HAMA) production of besilesomab (Scintimun) a monoclonal antibody labelled with ^{99m}Tc used to diagnose suspected osteomyelitis [12]. To monitor late adverse reactions, especially those appearing outside the nuclear medicine setting, a form for patient adverse reaction reporting was enclosed with the NII. Despite the efforts of the AIFA and AIMN to improve and facilitate reporting of adverse reactions to and defects in radiopharmaceuticals, this matter continues to be a recognized problem in our country.

In conclusion, we agree with Hesse et al. that a harmonized 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.

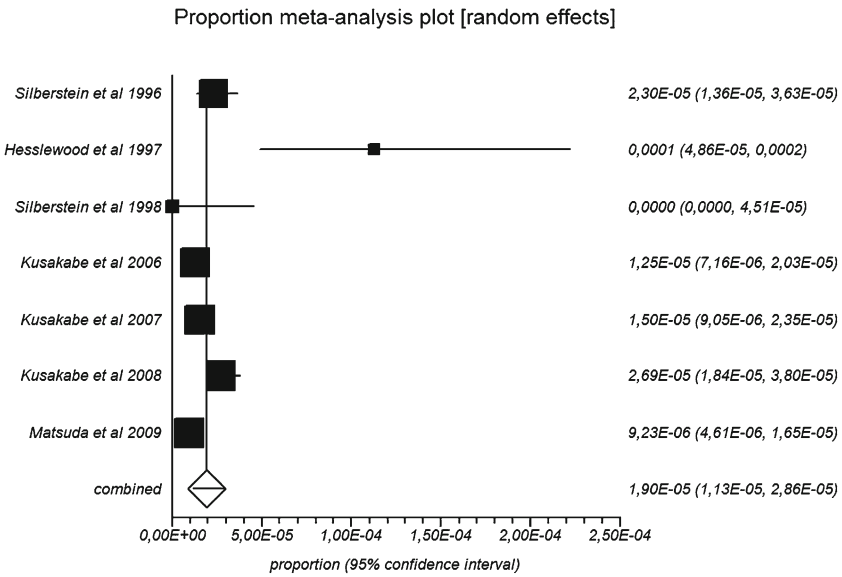

Fig. 1 Plot of individual studies and pooled prevalence of adverse reactions to radiopharmaceuticals, including 95 % confidence intervals (95 % CI). The size of the squares reflects the weight of each study

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