

Irradiation of Volunteers in Nuclear Medicine

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The preliminary assessment of many radiopharmaceuticals is often carried out with the help of "normal volunteers". These volunteers are drawn from the general public, are fully informed of the procedure to be performed and its attendant risks, and in many cases are compensated financially for their trouble. The cooperation of such people is of vital importance to the full understanding of the normal kinetics and metabolism of many new radiopharmaceuticals. The restrictions on the choice of normal volunteers, and the radiation dose limits which must be observed are not explicitly defined in any of the current guidelines, and in this paper we propose a rationale, based upon available information, which sets acceptable limits for volunteers, and provides a framework within which scientists and physicians can work.

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The International Commission on Radiological Protection (ICRP) offers general guidance regarding the use of ionizing radiations that may involve the exposure of both workers and members of the public. This guidance can be summarized by three basic requirements (1), whereby:

1. All exposures must result in an overall net benefit (Justification).
2. All exposures should be kept As Low As Reasonably Achievable (ALARA), social and economic factors being taken into account (Optimization)
3. Dose limits specified by the ICRP should not be exceeded.

These guidelines form a coherent and rational framework for radiation protection practice and have been incorporated, or are currently being proposed, into formal legislation throughout the world (2-4). Although the ICRP has also addressed the topic of irradiation of volunteers in research, including nuclear medicine, the nature of the advice is extremely general (5,6). The onus for determining which research practices are deemed "acceptable" is placed on the institution where the irradiation is to take place, as advised by an appropriate expert body and subject to local and national regulations. Unfortunately, regulations do not generally consider this topic and the corresponding

"expert bodies" have little in the way of objective and explicit guidance. This not only renders their task very difficult, but is also likely to result in marked differences from one institution to another. This paper tackles the question of exposure of volunteers in nuclear medicine and proposes an operational scheme that is in keeping with the spirit of the recommendations of the ICRP as listed above. The proposed scheme is designed to be sufficiently detailed for use by any medical institution involved in research. The adoption of this scheme would enable nuclear medicine research to be performed, including the exposure of volunteers, in a rational and consistent manner.

Nuclear Medicine Dosimetry

The most appropriate dosimetric parameter for risk estimation and risk intercomparison purposes in radiological investigations is the effective dose equivalent, which was introduced by the ICRP in 1977 (1). This parameter, which is normally denoted as H_E , enables disparate radiation doses (e.g., external and internal) to differing body organs and tissues, to be combined on a unified scale. Furthermore, an absolute level of risk of $1.65 \times 10^{-2} \text{ Sv}^{-1}$ can also be applied when the H_E value relates to a typical adult working population (1). The use of the effective dose equivalent offers numerous advantages. These include the introduction of a single parameter, based on radiation risk, which enables any diagnostic procedure involving ionizing radiations to be intercompared with any other (ionizing radiation) procedure, or with legal radiation dose limits for occupationally exposed personnel and members of the pub-

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lic. In addition, a direct comparison is also possible between the diagnostic procedure H_E and natural background (or variations in natural background), using the same single, and thereby readily comprehensible, scale. These advantages have resulted in the H_E concept being used, for example, in computed tomography (CT) where a head scan on a second generation EMI 5005 results in an H_E value of 0.84 mSv (84 mrem) (7). The effective dose equivalent has also been introduced into nuclear medicine with H_E values per unit administered activity comprehensively compiled by Johansson et al. (8). Translating these latter values into actual patient doses encountered in a typical North American department results in an average nuclear medicine procedure or dose equivalent of 4.6 mSv (460 mrem) (9).

This study also showed that low dose procedures included technetium-99m macroaggregated albumin (^{99m}Tc]MAA) (1.3 mSv), technetium-99m sulfur colloid (1.4 mSv) and iodine-123 (^{123}I) thyroid uptake studies (0.54 mSv) whereas high dose procedures included ^{99m}Tc]pertechnetate (8.4 mSv), indium-111 white blood cells (12 mSv) and gallium-67 (^{67}Ga) (34 mSv). In terms of population doses, a detailed analysis of the average patient dose (H_E) from nuclear medicine procedures in the province of Manitoba, Canada, during the period 1981–1985 showed the mean patient H_E to be relatively constant in time at 5.2 mSv (520 mrem) (10). Thus it is evident that an average nuclear medicine procedure is associated with a H_E of ~ 5 mSv (500 mrem) with the highest dose procedures approaching, but generally not exceeding, 50 mSv. These patient H_E 's in nuclear medicine can be directly compared to the proposed legal dose limit of 50 mSv for occupational exposure in the US (4), the current legal dose limit of 5 mSv for members of the public (3), the average value for natural background (H_E) of 2 mSv in North America (11) and the per caput dose value of 0.91 mSv from medical exposure in the US (12).

Justification

The first step in the ICRP radiation protection scheme is the requirement for a given practice to be justified. For a medical research project involving the exposure of normal volunteers to radiopharmaceuticals, this process can be conveniently considered in two distinct stages—an ethics committee approval of the overall research project and informed consent by the individual volunteer.

Ethics committee approval. All medical research projects involving human "volunteers" require prior formal approval by an ethics committee. With respect to nuclear medicine research projects, an ethics committee would be requested to address two specific questions. The first regards the overall merit of the research project to ensure that its design is appropriate for the task in hand and that the scientific objectives are deemed worthwhile. The second question should be aimed at

ensuring that any volunteer's radiation exposure is minimized, which would obviously require input from appropriately qualified professionals (discussed below in the "Optimization" subsection). It is clearly important to have suitable ethics committee clearance on the two questions addressed in this section before an exposure of a volunteer to ionizing radiation in the course of medical research could be deemed justifiable.

Informed consent. In addition to an ethics committee approval, it is important that volunteers are willing to participate in a research study which will expose them to ionizing radiation. Although the radiation doses normally encountered in nuclear medicine are relatively low (see "Dose Limits" section), there is considerable controversy regarding the corresponding risks (13). It is, however, customary to work on the assumption that the stochastic risks are linearly proportional to the radiation dose, with no threshold, as recommended by the ICRP (1). This inevitably involves the volunteer undertaking an (assumed) risk with no resultant *direct* benefit even though it could be reasonably argued that individuals benefit indirectly as members of society from the medical/scientific advances brought about by the research being undertaken. In this situation, it is necessary that the nature, and purpose, of the research project are explained to the volunteer. This should include a specific statement regarding the magnitude of any radiation exposure and the resultant radiation risks arising from this exposure. The radiation doses could be compared with other exposures normally encountered in society (e.g., natural background, medical exposures, occupational dose limits) and the resultant risks could also be compared with those normally encountered in society (e.g., smoking, driving automobiles, occupational safety). An essential component of any radiation exposure to volunteers in medical research is the signing of an informed consent form which includes a summary of the estimated radiation doses and the corresponding radiation risks.

Optimization

It is important to ensure that the ALARA principle is strictly adhered to, since it is generally considered to be the key aspect in radiation protection practice, *including* all medical exposures (14–16). For medical research purposes, however, it is clearly both impractical and undesirable to develop the kind of sophisticated cost-benefit optimization schemes that are proliferating in many fields of radiation protection practice (17). Optimization should involve the professional judgement of, for example, a certified nuclear medicine physician and a certified medical physicist. This judgement would ensure that the proposed procedure, including the *amount* of activity to be administered, is sufficient to provide the desired medical information. It is assumed here that, adequate preliminary animal studies have been performed which have established a

well understood kinetics and biodistribution of the proposed radiopharmaceuticals.

The question of the acquisition of the same information by increased imaging times rather than increased dosage must be handled on a case by case basis, keeping in mind the ALARA principle. In general, if the study can be performed with increased data acquisition times without adversely affecting the quality of the results then this is clearly the route to take. If, however, such increased times will detract from the study, due to changed distribution during the course of the imaging, or due to patient movement, then higher doses may be necessary, provided these are consistent with the general exposure restrictions proposed here. The estimated radiation dose, together with a statement that the diagnostic procedure has been optimized for the task in hand should be forwarded to the ethics committee prior to the latter granting approval for the project.

Dose Limits

The most difficult aspect of dealing with volunteers exposed to radiation in medical research is the setting of any dose limit(s) above which a practice would be prohibited on the grounds that the radiation risk to the volunteer would be unacceptably high. In this respect, the volunteer may be either a patient or a normal healthy subject, and could also include children.

In addressing the question of a suitable dose limit for a volunteer exposed during a medical research project, the fundamental issue is one of acceptable risk. This is clearly beyond the scope of a purely scientific analysis since it *must* involve the use of value judgements. One possible scheme might be to suggest that a volunteer should be regarded as a member of the public, for whom any "voluntary" radiation exposure for medical research should not exceed the corresponding annual dose limit. Although this approach may offer a superficial appeal, it has two major drawbacks. The first difficulty arises from the fact that the ICRP annual dose limit for members of the public has recently been reduced from 5 mSv yr⁻¹ to 1 mSv yr⁻¹ (18). Given that typical nuclear medicine procedures are associated with radiation doses (H_E) of ~5 mSv (500 mrem) such a proposal is likely to place insuperable obstacles in the way of medical progress in nuclear medicine. Allied with this difficulty, of course, is the fact that ICRP do not regard exposure at the dose limits as acceptable per se, but only boundary conditions that should never be exceeded after a suitable optimization process has been undertaken. Thus the ICRP would not expect actual exposures to members of the public to ever approach the appropriate dose limits, but to be well below the limit. The second difficulty is that annual dose limits for members of the public are examples of *involuntary* risk and are considered acceptable because the corresponding risks are such that members of soci-

ety generally consider such small risks to be of negligible importance. Clearly *volunteers* should not be treated in the same manner.

The use of the annual dose (H_E) limit for occupational exposure (50 mSv yr⁻¹) as an upper limit for volunteers has a number of attractive features and is recommended for operational use by research institutions. The ICRP justification for this dose limit for occupational exposure was based on empirical evidence that a dose limit of 50 mSv yr⁻¹ actually resulted in average operator doses of 5 mSv yr⁻¹ in the radiation industry. The average radiation risk can thereby be readily computed, using the above mentioned risk factor of 1.65 × 10⁻² Sv⁻¹ which applies to cancer fatalities and serious genetic defects in the first two generations. The resultant average radiation worker risk is below 10⁻⁴ yr⁻¹ and is therefore deemed to be comparable to the measured annual fatality rate in industries that are generally regarded as being "safe". This is clearly analogous to nuclear medicine where the average diagnostic procedure dose equivalent is also ~5 mSv but occasional higher dose studies may approach 50 mSv. The actual risk associated with a radiation dose (H_E) of 5 mSv can also be compared to risks of dying from lung cancer by smoking cigarettes (5 mSv/30 packs of cigarettes) or the risk of dying in a car accident (5 mSv/1,500 miles highway driving) (19). The exclusion of radiation exposures of above 50 mSv to volunteers in a research study may appear to be unduly restrictive because volunteers could be deemed to be free to accept any risk that they freely choose. In general, however, it is difficult to envisage a routine diagnostic nuclear medicine procedure that would incur such a high radiation dose. Nevertheless, this upper limit is considered desirable because it would be difficult for the radiation safety community to justify exposures that are not "permitted" in the course of a year of annual occupational exposure. The one exception that could perhaps be entertained would be the self exposure of a (knowledgeable) researcher who may be deemed to benefit directly and would thereby be exempted from the "volunteer" classification. The philosophy proposed in this report is also entirely consistent with that contained in the Federal Drug Administration Radioactive Drug Research Committee (FDA/RDRC) (20). This suggests that "the subject should receive the smallest radiation dose with which it is possible to perform the study without jeopardizing the benefits to be obtained". This dose can be considered safe up to a maximum of 50 mSv (5 rem) per year.

The question of using children (i.e., subjects under 18 yr old) as volunteers in nuclear medicine is clearly much more problematical because of the increased radiation risks (see below) per unit exposure to children, and the difficulties of obtaining informed consent. The ICRP has suggested that children should only be irradiated if their expected radiation doses are of the

order of one-tenth of the annual dose equivalent limit applicable to members of the public and if valid approval has been given by those legally responsible for such persons (1). There do not seem to be any compelling reasons to depart from this recommendation. This corresponds also to the FDA/RDRC guidelines. However, it is worthwhile to point out that given the current ICRP recommended annual dose limit of 1 mSv yr^{-1} for members of the public (see above), this guidance will effectively prevent the use of children as volunteers in virtually all diagnostic imaging procedures. This in itself should not be a serious impediment to nuclear medicine research since presumably normal adult volunteers could be used for research purposes leaving children to be only exposed during clinical studies alone.

DISCUSSION

The manner of dealing with volunteers in nuclear medicine research that has been proposed in this note is clearly in full accord with the spirit and letter of ICRP recommendations. In addition, it provides explicit quantitative guidance that should benefit individual research institutes in their deliberations on this topic and provides a basis for the consistent treatment of "exposed volunteers" wherever medical research is undertaken. Alternative schemes have been proposed where an overall acceptable risk of 1 in 10^4 , which corresponds to an H_E of 8 mSv, has been suggested together with a variety of modifying factors that depend on the age, sex, and status of the subject (21). These modifying factors differentiate between healthy volunteers and patients, and have volunteers listed in the following four age categories: 15–24 yr; 25–34 yr; 35–49 yr; and ≥ 50 yr. At first glance, this appears to offer a rational framework, since older patients would be "permitted" a higher radiation dose. In practice, however, it is likely to prove cumbersome to administer, difficult to justify the various modifying factors given the large uncertainties in current radiation risk estimates (13), and be unnecessarily restrictive in limiting the (base) exposure to 8 mSv in *all* cases. The advantages of the scheme proposed here are therefore deemed to include simplicity, reduced arbitrariness in the choice of "acceptable" risk, full integration with the well established ICRP recommendations and minimal impedence to legitimate and worthwhile nuclear medicine research.

The use of a value of 50 mSv as the H_E dose limit for volunteers implies that only the ICRP stochastic risk factor is being taken into account. For occupational exposure, the ICRP have also introduced a 500 mSv yr^{-1} nonstochastic limit (workers) for the dose equivalent to any individual organ or tissue. It may seem

prudent, therefore, to include this restriction in dealing with volunteers. However, it is important to note that this dose limit is designed to prevent the occurrence of nonstochastic radiation effects (i.e., those with thresholds) which typically required absorbed doses of 20 Gy (2,000 rad) or more for their occurrence, delivered over a short period of time. In practice, it is clear that the overwhelming majority of radiation exposures to volunteers would involve an H_E of the order of 5 mSv where the nonstochastic dose equivalent limit of 500 mSv to an individual organ could not be exceeded. For the small number of instances where the application of a 50 mSv H_E limit to volunteers may theoretically result in the ICRP nonstochastic limit being exceeded, it is nonetheless obvious that the primary ICRP objective of preventing nonstochastic effects will still be achieved. Under these circumstances, the specific adoption of an additional nonstochastic dose limitation for volunteers is superfluous.

The volunteer dose limit of 50 mSv is intended to apply to a given research project in which an individual volunteer may be involved in a number of separate exposures, e.g., serial studies or repeat studies. It is unlikely that such volunteers would be repeatedly exposed in a short period of time in a number of diverse research projects. Although some administrative control may be possible to minimize the likelihood of such repeat exposures, this is considered to be both difficult to achieve in practice and also unnecessary. An individual volunteer who is willing to be exposed to radiation on a regular basis is still unlikely to receive a cumulative radiation exposure in excess of 50 mSv yr^{-1} . Furthermore, the informed consent form clearly specifies the approved volunteer dose limit and its rationale, and this would discourage (though not prevent) individuals exceeding such a limit. Nevertheless, although it may be theoretically possible to exceed this value, the administrative difficulty of achieving this degree of control coupled with the philosophical (and extremely unlikely) problem of preventing individuals from taking calculated risks that they deem worthwhile suggest that the matter can be satisfactorily ignored from the practical radiation protection point of view.

The use of children as volunteers for research purposes is generally considered to be undesirable. In the scheme presented here, it would be effectively impossible to use children as volunteers, except in those cases where the radiation exposures are essentially trivial, i.e., where the radiation exposures are of the order of the variation of the annual exposure from natural background. The radiation risk to children, per unit radiation dose, is higher than for adults for three reasons:

1. Children are more sensitive to radiation.
2. The genetically significant component of a given radiation exposure to children is greater because of their higher mean child expectancy.

3. The long latent period of radiation carcinogenesis (typical mean latent period ~25 yr) means that children are more likely to express an increased carcinogenic risk.

It is of interest to determine whether the effective prohibition of significant exposure to child volunteers could have an adverse effect on medical research as applied to nuclear medicine. The available evidence from a number of research centers suggests that very few children, if any, are used as volunteers and furthermore, this does not appear to have impeded progress in nuclear medicine. The continuation of this approach thus appears to be justified.

An integral part of the scheme proposed here is the obtaining of "informed consent" from the prospective volunteer. There should be little difficulty in explaining to potential volunteers that a typical radiation exposure of 5 mSv (H_E) is "acceptable" in the sense that the risk is negligibly small. To support such an argument, attention could be drawn to the "theoretical" nature of the risk whereby it is extrapolated from observed effects in humans at high doses and high dose rates. Furthermore this typical nuclear medicine radiation dose is one-tenth of the current legal dose limit for occupational exposure and "radiation industries" are deemed to be "safe" by reputable international organizations such as the ICRP. Since some exposures may possibly approach the proposed limit of 50 mSv, obtaining volunteers may become more difficult—but this is surely appropriate since the higher the risk, the lower the number of people who would be prepared to undertake such a risk! The major advantage of maintaining the volunteer dose limit at a value of H_E equal to 50 mSv is that it offers research facilities flexibility in pursuing worthwhile research without unduly infringing on the rights of individuals to act as volunteers, and still satisfying the general ICRP framework for radiation protection practice. The scheme proposed in this note is thus deemed to offer satisfactory radiation protection to volunteers while still enabling medical research to progress in an ethically acceptable manner.

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