EDITORIAL

# The Infiltrated Radiopharmaceutical Injection: Risk Considerations

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**J Nucl Med 1991; 32: 890–891**

During the course of a typical diagnostic workup and treatment for a significant illness, a patient may receive an average of three to four intravenous injections, one of which is likely to be a radiopharmaceutical. With consent given for "a little stick" and "maybe a little burning sensation," we otherwise tend to take for granted *risk-free* parenteral drug administration as part of the health care process. The potential diagnostic benefit of the injected drug makes the personal cost of the anticipated transient discomfort acceptable, or at least tolerable. Although it is presumed that intravenous administration of a radiopharmaceutical is always successful, this is not necessarily the case. In this issue of *JNM*, Breen and Driedger bring attention to the risk of local radiation injury from an extravasated dose (*1*).

Perhaps the most easily quantifiable cost of such an incident to the patient is the unexpected local absorbed radiation dose, compounded in this case by the concern associated with unanticipated technical failure of the procedure, loss of diagnostic information or therapeutic value, and the delay in realizing its failure. To minimize this cost, we offer two approaches: (a) rational anticipation and safety preparation for an unlikely technical failure, and (b) understanding the relationship between cost, benefit, and probability of technical failure of the procedure.

Most diagnostic nuclear medical tests employ radiopharmaceuticals that emit gamma photons, since these emissions can be detected externally. For certain therapeutic purposes, particulate-emitting radiopharmaceuticals are often employed. A number of gamma-emitting radiopharmaceuticals also emit particulate radiation ($\beta^-$, $\beta^+$ particles (positrons), internal conversion and Auger electrons) as well as low-energy x-rays that contribute the greater fraction of the radiation dose without any clinical diagnostic benefit. Iodine-131 is still commonly used and clearly falls in this category but can nevertheless be safely administered in relatively small amounts for diagnostic evaluation (*2*). There has been no systematic attempt to determine the probability of occurrence of extravasated radiopharmaceuticals commonly used in the clinical setting. However, a number of recent studies have brought attention to the problem of radiation burden, the radiobiologic effects of which are quantifiable. Minsky et al. (*3*) estimate the local dose from an extravasated injection of $^{32}P$ for treatment of polycythemia vera. They point out the importance of (a) biologic clearance and (b) the assumed volume and uniformity of distribution of the extravasated radiopharmaceutical in estimating the local radiation burden. On the basis of measurements made in an animal model, Castronovo et al. (*4*) conclude that the radiobiologic risk associated with radiation burdens of commonly used radiopharmaceuticals extravasated into a 5-g mass is below that needed to produce severe skin reactions. Shapiro et al. (*5*) propose a simple expression for the worst case estimate of radiation dose resulting from extravasation, namely the product of specific activity, the ratio of measured clearance half-life to physical half-life, and the radionuclide specific dose factor. Table 1, modified from Shapiro et al. (*5*), gives the specific dose factor, $d$, and maximum radiation dose estimates, $D$, for typical total amounts of activity, $A$, of some common radionuclides extravasated into 0.5- and 1.0-ml volumes of distribution.

Taking into account the observed clearance half-life and the assumption made by Driedger and Breen (*1*), the values for $^{131}I$ in Table 1 agree roughly with their estimate. The potential of such radiation injury clearly calls for more extensive considerations of risk involved. The consequences of an unforeseen technical failure which results in a local absorbed radiation dose and injury is an outcome cost *in excess* of that of the decision not to do the test. There is a simple relationship between the excess cost of failure, the probability of failure, and the net benefit of the test (*6,7*). If overhead cost is small compared to the cost of failure, for probabilities of failure less than about 0.1 (10%), the greatest acceptable (or "break-even") failure cost-to-net benefit ratio increases by ten-fold as the probability of failure decreases by ten-fold. In other words, the product of excess cost of failure and the probability of failure must be less than the net benefit of the test. For example, a cost of technical failure of no greater than

Received Feb. 15, 1991; accepted Feb. 15, 1991.
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**TABLE 1**
Maximum Radiation Dose Estimates*

| Radionuclide | *d* | *A* | *D* (0.5 ml) | *D* (1.0 ml) |
|---|---|---|---|---|
| $^{18}F$ | 1352 | 10 | 270 | 135 |
| $^{67}Ga$ | 9715 | 5 | 972 | 486 |
| $^{99m}Tc$ | 321 | 20 | 128 | 64 |
| $^{111}In$ | 7532 | 2 | 300 | 150 |
| $^{123}I$ | 1144 | 2 | 46 | 23 |
| $^{131}I$ | 114026 | 1 | 2280 | 1140 |
| $^{201}Tl$ | 9467 | 2 | 378 | 189 |

* Units of *d*: (rad.ml/mCi) or (cGy.ml/37MBq); *A*: mCi or 37 MBq; *D*: Gy or 100 rad.

about 100 times the test's net benefit is acceptable if the probability of failure is 1%. Although small extravasated amounts may well occur with higher probability in specific instances, this is very likely an overall upper limit in practice.

As with other uses of radioactivity, there is no substitute for prudent safety measures in administration of the radiopharmaceutical, such as using a catheter in the case of administrations for which accidental extravasation may lead to residual radiation injury. Monitoring the site immediately after injection can serve not only as an *ex post facto* means of reducing personal concern in the event of failure, but also provide useful information towards remedial emergency action, such as applying hot compresses to increase local biologic clearance.

The principal consideration we face in making any choice under uncertainty is: Does the *benefit* of the successfully accomplished test outweigh the cost of incurring a safety risk? The two types of quantities involved in optimizing any decision are: (a) average costs and benefits (negative costs) and (b) the probabilities that will be incurred. The choice of units in which to quantify costs and benefits, whether absorbed radiation dose, monetary units, lost or gained lifetime, etc., will never meet with uniform satisfaction. Nevertheless, unexpected costs associated with ignorance of risk are generally greater than anticipated costs associated with rational understanding, i.e., knowledge of risk involved as well as of benefit. In our view, such costs are always reduced a priori by realistic awareness of risk and of benefit thoughtfully conveyed in advance, appropriate precautions taken to minimize risk, and expedient remedial measures taken in the event of failure.


## ACKNOWLEDGMENTS

The author wishes to thank Drs. R.J. Callahan and F.P. Castronovo, Jr. for useful discussions.


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