Original Article

A low-dose radioisotope procedure for assessment of subcutaneous drug delivery systems used for slow intrathecal infusion of antispasmodic agents

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Study design: Retrospective single centre study.

Objectives: To evaluate a low-dose radioisotope imaging procedure for assessment of implanted intrathecal drug delivery and to compare the radiation dose and diagnostic value of these studies with other reported studies using higher administered radiation dose.

Setting: National Spinal Injuries Centre, Stoke Mandeville Hospital, UK.

Method: A total of 11 spinally injured patients with subcutaneous drug delivery systems and uncontrolled spasm were investigated for catheter failure using a low-dose radioisotope procedure with an administered dose of radioactivity of 40 MBq Technetium-99m.

Results: Loss of catheter patency was demonstrated in six patients, enabling identification of the site of blockage. Catheter patency and subsequent perfusion of CSF (ie normal result) was demonstrated in five patients. Radiation effective dose was estimated at 1.3 mSv per patient study, with a low associated risk of deleterious effect of one in 13,000.

Conclusion: Radioisotope investigation using a reduced administered dose of 40 MBq Technetium-99m DTPA, formulated according to a strict radiopharmaceutical protocol, provides a safe test for assessment of intrathecal drug delivery systems.

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Keywords: spinal cord injury; spasm; intrathecal drug delivery system; radioisotope imaging; radiation dose; baclofen

Introduction

Intrathecal drug administration via an implanted drug delivery device is an established method of providing good and safe control of spasm in patients with spinal cord injury (SCI), if provided by a skilled and experienced team.^{1–3} However, in each individual patient with a decreased response to the drug, it is essential to establish whether there is a mechanical problem with the delivery system, for example, a blockage in the catheter. It is obviously critical to avoid the need for unnecessary revision surgery. Using an isotopic method, a very sensitive and relatively physiological assessment can be made. Previous studies using a radioisotope technique employing either Technetium-99m (Tc-99m) or Indium-111 (In-111) for evaluation of these devices have reported successful diagnostic results but have not included an assessment of radiation dose to the patient.^{4–6} The relative merits of Tc-99m *versus* In-111 have been described elsewhere.⁷

Method

Clinical protocol

By 2001, 190 drug delivery systems had been implanted in 85 patients for control of spasm using a continual slow intrathecal infusion of antispasmodic drugs, in this case baclofen. Approximately 152 of the devices were programmable computerised SynchroMed Model 8626L-18EL systems (Medtronic, Minneapolis, USA), while the remainder were constant flow infusion pumps. Only patients with uncontrolled spasm underwent radioisotope investigation. There were 11 such patients and the studies took place over a 6-year period from 1996 to 2001, under an appropriate diagnostic licence issued by the Administration of Radiopharmaceuticals Advisory Committee of the Department of Health (ARSAC). (The ARSAC is the United Kingdom regulatory authority for use of radioactive materials in patients or volunteers.) Informed consent was obtained from each patient.

Because of the reported risk of adverse effects from intrathecal Tc-99m DTPA, the radiopharmaceutical

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formulation protocol was critically important in order to ensure safety against pyrogens and toxicity.^{7,8} Similarly, it was important to safeguard against possible overdose arising from rapid delivery of the antispasmodic agent during the test. Although the drug could be removed from the pump reservoir, it was not possible to empty the catheter, as the pumps implanted at our centre do not have an access port. Therefore, several days prior to investigation, the reservoir was emptied by percutaneous aspiration and the pump run on saline. This protocol enabled the drug remaining in the pump tubing and catheter to be delivered at a normal therapeutic rate, until the system had been emptied of baclofen. Assuming the sum of pump tubing and catheter volumes is 0.5 ml (the most conservative estimate for safety reasons), the number of days, D , required for its safe emptying can be calculated using the formula

$$D = \frac{0.5}{A} \text{ days,}$$

where A is the total volume (ml) that is usually delivered per day, which in turn can be calculated using the formula:

$$A = \frac{\text{Dose delivered per day in } \mu\text{g}}{\text{Concentration of pharmaceutical in } \mu\text{g/ml}} (\text{ml}).$$

According to our protocol, an isotope activity of 40 MBq Technetium-99m DTPA in 1 ml was administered to all patients via the pump. The isotope was then delivered in two consecutive 0.5 ml 'boluses' delivered at the fastest rate allowed by the device, which on average is 25 min per bolus. The aim was for the first bolus to fill the pump tubing and catheter with isotope, and for the second bolus to deliver isotope into the CSF. Although the timing of subsequent images is not crucial, our protocol used images at 1 h postadministration and delayed images at 3–4 h, to assess whether the system had successfully delivered the isotope to the CSF. All isotope images were acquired on a single-headed gamma camera with general purpose collimator. In patients where a hold up was demonstrated at a particular level, a radioactive marker source was used to identify the level reached by the isotope. An ink mark then made on the patient's skin enabled a radio-opaque marker (eg a paper clip) to be attached to the skin at that level for subsequent plain-film radiography. Comparison of the radiographic and isotopic images allowed a distinction to be drawn between incomplete perfusion of CSF due to catheter blockage, or incomplete perfusion caused by adhesions (generally at the level of the original skeletal injury) preventing further progress of isotope successfully delivered to the CSF.

Radiation dose calculation

The quantity 'effective dose' provides a measure of the risk associated with a given exposure to radiation, and has been defined by the International Commission for Radiological Protection (ICRP), as the sum of the

radiation doses to the individual organs, weighted according to their susceptibility to radiation-induced harm.⁹ It is a useful quantity that enables direct comparison of the radiation-induced risk from different radiological procedures.

To determine effective dose, a knowledge of doses to individual organs is first required. Organ doses depend on the physical characteristics of the isotope administered (which isotope, its emissions and half-life), its distribution within the body and its biological clearance, reflecting the length of time it resides in particular organs. The techniques, equations and data provided by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine provide a means of calculating such doses. For this study, organ doses were estimated using data from MIRD pamphlet 11, relating to Indium-111 and Technetium-99m,^{10,11} together with published bio-kinetic data from the ICRP.¹²

For any given organ, there were two components to the dose received; firstly, the dose to that organ from isotope within the pump reservoir, and secondly, the dose to that organ from isotope circulating in the CSF. The MIRD data were used to estimate the component resulting from isotope within the pump reservoir, while ICRP bio-kinetic data were used to estimate the component resulting from isotope in the CSF.¹³

The MIRD methodology required slight modification for use in the present study, as it required one of the ICRP organs to be identified as the source organ. Normally, the choice of organ is a straightforward decision, the source organ being taken as the principle organ concentrating the isotope, and therefore usually the organ being imaged. For example, in the case of a thyroid scan, the thyroid itself harbours most of the isotope and is therefore the obvious choice of source organ. However, in our particular patients, the radioisotope resides in an implanted pump, rather than in one of the defined organs. The ovaries were therefore chosen to provide a surrogate source organ for the pump in

Figure 1 Normal study, posterior and L lateral views showing pump (1), ventricles perfused with isotope (2)

Figure 2 Posterior images at 1-h and 4-h postinjection demonstrating a blocked catheter. Sternal notch (1), Iliac crest (2) Level of 8th–9th thoracic vertebrae (3)

determining doses for all organs except the gonads themselves, for which the bladder provided a suitable surrogate. The reason for these choices was that they reflected most closely the anatomical location of the pump, and so enabled a reasonably accurate representation of the geometry pertinent to our patients.

Finally, the MIRD and ICRP components of organ dose were then added together for each organ, before combining all the organ doses, weighted according to the methods described by ICRP, to provide an estimate of effective dose.¹² Using the same methods, the radiation effective doses to patients in drug pump studies conducted elsewhere were also estimated for comparison.

Results

Our clinical results can be summarised as follows: in five patients, the study demonstrated normal pump function and a patent catheter. In six patients a diagnosis of blocked catheter was made, in four of which the isotope did not leave the pump, indicating a proximal block. Figures 1–3 show a series of images demonstrating a normal study (Figure 1), and blocked catheters (Figures 2 and 3).

Figure 3 Posterior images at 1-h, 1-h (shielded pump) and 4-h, demonstrating a proximal catheter blockage. Xiphisternum (1), Iliac crest (2)

In this series, the radiation effective dose was approximately 1.3 mSv for an administered activity of 40 MBq Tc-99m DTPA. The radiation effective doses calculated for previous studies were between 6 mSv for an administered dose of 18.5 MBq In-111^{5,6} and 13 mSv for 400 MBq Technetium-99m⁴ (Table 1). The associated risk of deleterious effect is given by ICRP as approximately 1 in 17,000 per mSv effective dose.¹² Risk factors estimated for this and other studies are summarised in Table 1.

Conclusion

In the six abnormal studies in our series, the isotope test indicated the need for subsequent surgery and careful inspection of equipment. In the five studies where normal pump function and catheter patency was demonstrated, the test results enabled surgery to be avoided.

Although the use of In-111, with its longer half-life, allows the pump to continue to run at its normal rate, the effective dose per patient is high.^{5,6} It is important to minimise radiation effective dose, particularly in this group of patients who tend to be young, and who undergo frequent radiological examination. Further, in

Table 1 Comparison of radiation dose and risk from isotope studies for assessment of subcutaneous drug delivery systems

Study	Number of patient studies	Isotope and radiopharmaceutical	Activity administered (MBq)	Effective dose (mSv)	Estimated risk of cancer induction	Relative risk
Hicks RJ <i>et al</i> ⁴	8	Tc 99m DTPA	400	13	One in 1300	10
Rosenson AS <i>et al</i> ⁵	17	In-111 DTPA	18.5	6	One in 2800	4.6
Le Breton F <i>et al</i> ⁶	1	In-111 DTPA	18.5	6	One in 2800	4.6
This study	11	Tc 99m DTPA	40	1.3	One in 13,000	1

the UK, legislation requires that radiological practitioners adopt strategies for optimisation of patient dose due to medical radiation exposure.¹³ The effective dose per patient for our series was low at 1.3 mSv, compared to what we have calculated for other series (6–13 mSv). These latter effective doses place these radiological studies among the examinations traditionally regarded as the highest dose givers, such as body CT, which typically result in effective doses of 3–13 mSv.¹⁴ However, the effective dose of 1.3 mSv achieved in our study is more akin to lower dose radiographic examinations, such as lumbar spine radiography.¹⁴ The relative risks shown in Table 1 indicate that a four- to 10-fold reduction in radiation risk is possible with a low-dose Tc-99m protocol.

In summary, low-dose radioisotope assessment of implanted drug delivery systems for intrathecal infusion in patients with SCI, using 40 MBq Tc-99m, provides a safe and accurate diagnostic test.

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