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# Quantitative Distribution of $^{131}$I-labelled Monoclonal Antibodies Administered by the Intra-ventricular Route

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**Abstract**—*In a preliminary study in one patient* [$^{111}$In]*DTPA was injected into the lateral ventricle and at the same time* [$^{99m}$T]*DTPA into the lumbar sac. The* $^{111}$In *distributed freely throughout the CSF but the concentration of* $^{99m}$Tc *in the ventricles remained consistently low.*

*In the second phase of the study three patients with tumours confined to the neuraxis were treated with* 20–50 mCi $^{131}$I*-labelled monoclonal antibodies administered into the lateral ventricle via Ommaya reservoirs. Quantitative distribution of radio-labelled antibody was assessed at intervals up to* 8 *days post injecion. In each case there was rapid distribution to all parts of the neuraxis with* 38–68% *of total CNS counts remaining in the head and* 13–39% *in each of the upper and lower half spine areas. The* $t_{1/2}$ *for total CNS counts were* 31.5, 19.8 *and* 15.5 h. *There was no clear evidence of tumour localization and no neurological toxicity.*

*These patients demonstrate that radiolabelled monoclonal antibodies can be given safely via Ommaya reservoirs and that in order to obtain optimal distribution throughout the CSF this should be the preferred method of administration. Further trials in patients with minimal disease are warranted.*

## INTRODUCTION

THERE HAVE BEEN a number of studies investigating the use of monoclonal antibodies in the treatment of tumours confined to a single body compartment such as the peritoneal or pleural cavity [1, 2]. Injection of antibodies into these compartments may confer a pharmacokinetic advantage compared to intravenous therapy provided the rate of clearance of the antibody from the compartment is significantly slower than from the systemic circulation. Such an advantage has been demonstrated for several chemotherapeutic agents administered directly into the peritoneal cavity [3]. Thus, given adequate distribution, intra-cavity therapy should allow the delivery of higher concentrations of targeted drug or radio-isotope to the tumour than is possible by the systemic route.

Tumours of the brain and spinal cord often remain confined to the neuraxis throughout their natural history and thus administration of drugs directly into the subarachnoid space is an attractive therapeutic option. This method of therapy has been investigated by Coakham and Kemshead [4] and Lashford *et al.* [5] who recently reported promising results of a pilot study of $^{131}$I-labelled monoclonal antibodies in the therapy of leptomeningeal tumours. For such treatment to be maximally effective the drug should distribute freely and uniformly throughout the sub-arachnoid space and in order to achieve this there is evidence that drugs should be administered via the intra-ventricular rather than the lumbar route [6, 7].

In this study we have examined the distribution of two different isotopes administered virtually simultaneously to the ventricular and lumbar CSF and have subsequently obtained quantitative data on the distribution of $^{131}$I-labelled monoclonal antibodies given via the intra-ventricular route.

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## PATIENTS AND METHODS

All patients had frontal ventriculostomies for the administration of the monoclonal antibody immu-

noconjugates. In the first patient a catheter was also inserted percutaneously into the lumbar subarachnoid space. For the pharmacokinetic study in this patient [$^{99m}$T]DTPA (5 mCi) and [$^{111}$In]DTPA (0.5 mCi) were both formulated in normal saline/1% human serum albumin to a volume of 25 ml. Prior to isotope injection 25 ml CSF was removed both from the Ommaya reservoir and the lumbar catheter. The [$^{99m}$Tc]DTPA was then administered as a bolus into the lumbar subarachnoid space and flushed with a further 5 ml saline. Immediately following this the [$^{111}$In]DTPA was administered as a bolus into the Ommaya reservoir and also flushed with 5 ml saline. Sampling of lumbar and ventricular CSF was then performed at intervals up to 24 h. The first 2 ml of each sample was discarded to eliminate errors due to dead space effect. Each aliquot of CSF was then counted for radioactivity in a gamma counter with spill over correction to obtain separate $^{111}$In and $^{99m}$Tc activities. Standard preparations of both injectates were also counted for activity to enable calculation of CSF activity in terms of total injected dose.

In the second part of the study three patients were treated with $^{131}$I-labelled monoclonal antibodies administered via the intra-ventricular route. The patients treated all had progressive disease having failed conventional therapy. Informed consent was obtained according to standard MRC practice.

*Antibody preparation*

In patient 1, a man with an HCG-producing teratoma, antibodies directed against HCG (SB10 and W14) were used [8]. The remaining two patients had the immunoreactivity of tumour cells obtained from the CSF tested against a panel of antibodies. The antibody with the most specific reactivity with the patient's tumour cells and the least cross reaction with normal CNS tissue was chosen. In patient 2 the antibody used was UJ13A [9] and in patient 3 MEL14 [10]. Antibodies were labelled with $^{131}$I using a modified chloramine-T technique [11] to a specific activity of 5–15 μCi/μg of protein. Before injection the preparation was passed through a 22 μm filter to ensure sterility. The antibody was administered within 4 h of labelling in order to minimize radiolytic damage and decay.

*Patient preparation*

Thyroid blockade involved the administration of potassium iodide 120 mg tds commencing 3 days prior to therapy and continuing for 4 days followed by 60 mg bd for 11 days. In addition potassium perchlorate 200 mg bd was given starting 1 day prior to treatment and continuing for 4 days in total.

The antibody was administered as a bolus injection into the Ommaya reservoir after the removal of an equal quantity of CSF and was followed by a 2 ml saline flush.

*Study of distribution and data analysis*

Distribution was studied using an IGE Gemini 700 Gamma Camera and data analysis performed on an IGE Stat II nuclear medicine computer using standard 'areas of interest' methodology. Scintigraphic counts were assessed over the head, upper half spine (to mid-thoracic region) and lower half spine at intervals up to 8 days following therapy.

The half life of total neuraxis counts was obtained by the expression:

$$t_{1/2} = 0.693/2.303 \times \text{slope}.$$

## RESULTS

*Comparison of distribution after lumbar and intra-ventricular injection*

Figure 1(A) shows the percentage of $^{111}$In per gram of CSF detected in the CSF sampled from the Ommaya reservoir and lumbar catheter following injection into the right lateral ventricle. There is a rapid initial fall in the ventricular concentration followed by an equally rapid rise in the lumbar CSF concentration. The latter exceeds the ventricular CSF concentration at approximately 6 h following intraventricular administration implying effective CSF distribution.

Figure 1(B) shows the CSF concentrations of $^{99m}$Tc in the ventricular and lumbar CSF following injection into the lumbar sub-arachnoid space. There is a steady decline in the lumbar CSF concentration but only a minimal rise in ventricular CSF concentration which never achieves the levels obtained in the lumbar sub-arachnoid space.

*Quantitative distribution of $^{131}$I-labelled monoclonal antibodies*

*Patient* 1. This 34-year-old man with a testicular teratoma developed cerebral metastases 6 months after completion of initial chemotherapy. On 29/3/88 he received 50 mCi $^{131}$I-labelled SB10 + W14, both monoclonals directed against HCG. At that time his CSF HCG was 18,000 iu/l and the serum HCG was 245 iu/l. No therapeutic effect was seen and on 14/4/88 the CSF HCG was 17,020. This patient experienced headache for 2 h after the administration of the immunoconjugate but no side-effects attributable to the antibody were recorded.

*Patient* 2. This 6-year-old girl had a primitive neuroectodermal tumour involving the posterior part of the left frontal lobe diagnosed in November 1986. In May 1988 she relapsed with progression of the primary on CT scan and large numbers of malignant cells in the CSF. On 7/6/88 she received

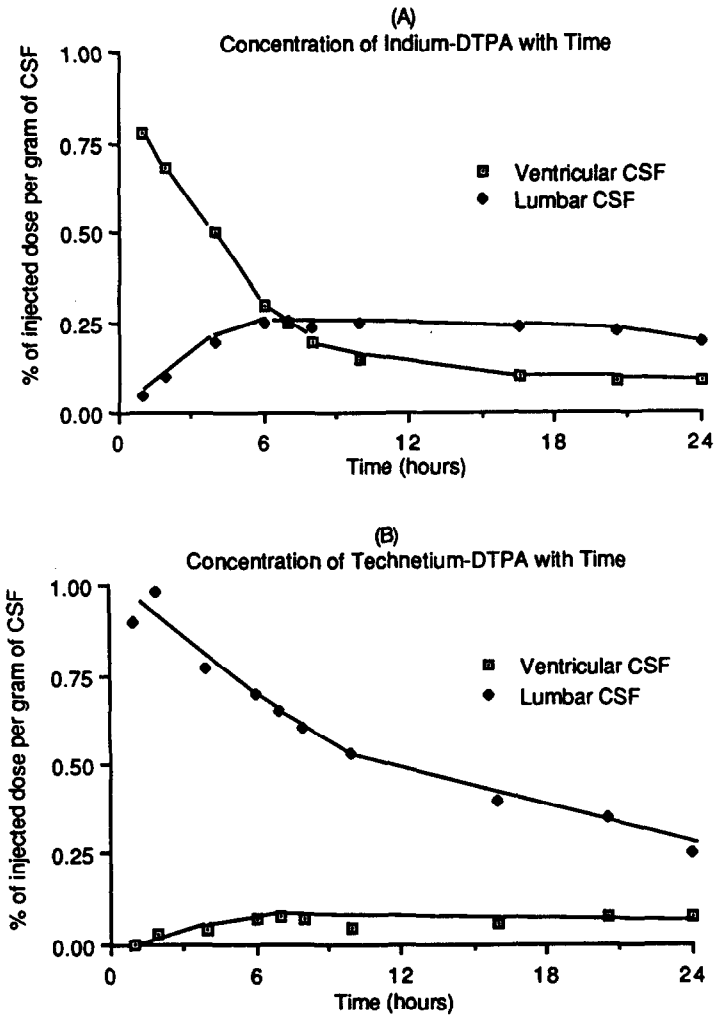


*Fig. 1. Concentrations of indium-DTPA (A) and technetium-DTPA (B) with time following intraventricular (indium) and lumbar (technetium) injection.*

20 mCi $^{131}$I-labelled UJ13A. No acute side-effects were seen but there was no symptomatic or objective improvement.

*Patient* 3. This 22-year-old man was found to have a medulloblastoma involving the posterior fossa in March 1985. He relapsed in October 1987 and by June 1988 he had developed multiple cord lesions resulting in cord compression and an abnormal myelogram. On 6/7/88 he was treated with 40 mCi $^{131}$I-labelled MEL14. Again there were no toxic effects and no therapeutic benefit was seen.

In all three patients the use of the Ommaya reservoir allowed the antibody conjugate to be administered easily and with minimal delay. No spillage or leakage was documented.

*Scintigraphy*

Figure 2 shows the distribution of counts between the brain, upper half spine and lower half spine at the times indicated on the graph. As can be seen there was rapid distribution of radiolabel to all parts of the neuraxis although the proportions in each area remained constant as decay occurred with time (Table 1). Activity was somewhat slower in reaching the lower half spine in patient 3 reflecting the block to free flow of CSF in this patient. The sites of blockage can be seen in Fig. 3 compared to the more uniform distribution in patient 1.

The $t_{1/2}$ for total neuraxis counts was 31.5 h for patient 1, 15.5 h for patient 2 and 19.8 h for patient 3 (Fig. 4).

No convincing evidence of localization of antibody to known tumour sites was seen.

## DISCUSSION

The first part of this study confirms the advantage of administering drugs directly into the ventricles. Radiolabelled DTPA injected via this route distributed throughout the CSF within 6 h achieving similar concentrations in the ventricular and lumbar areas. However a similar volume of technetium-labelled DTPA injected almost simultaneously into the lumbar space failed to distribute adequately to the ventricles. The design of this study eliminated both inter-patient variation and the use of different

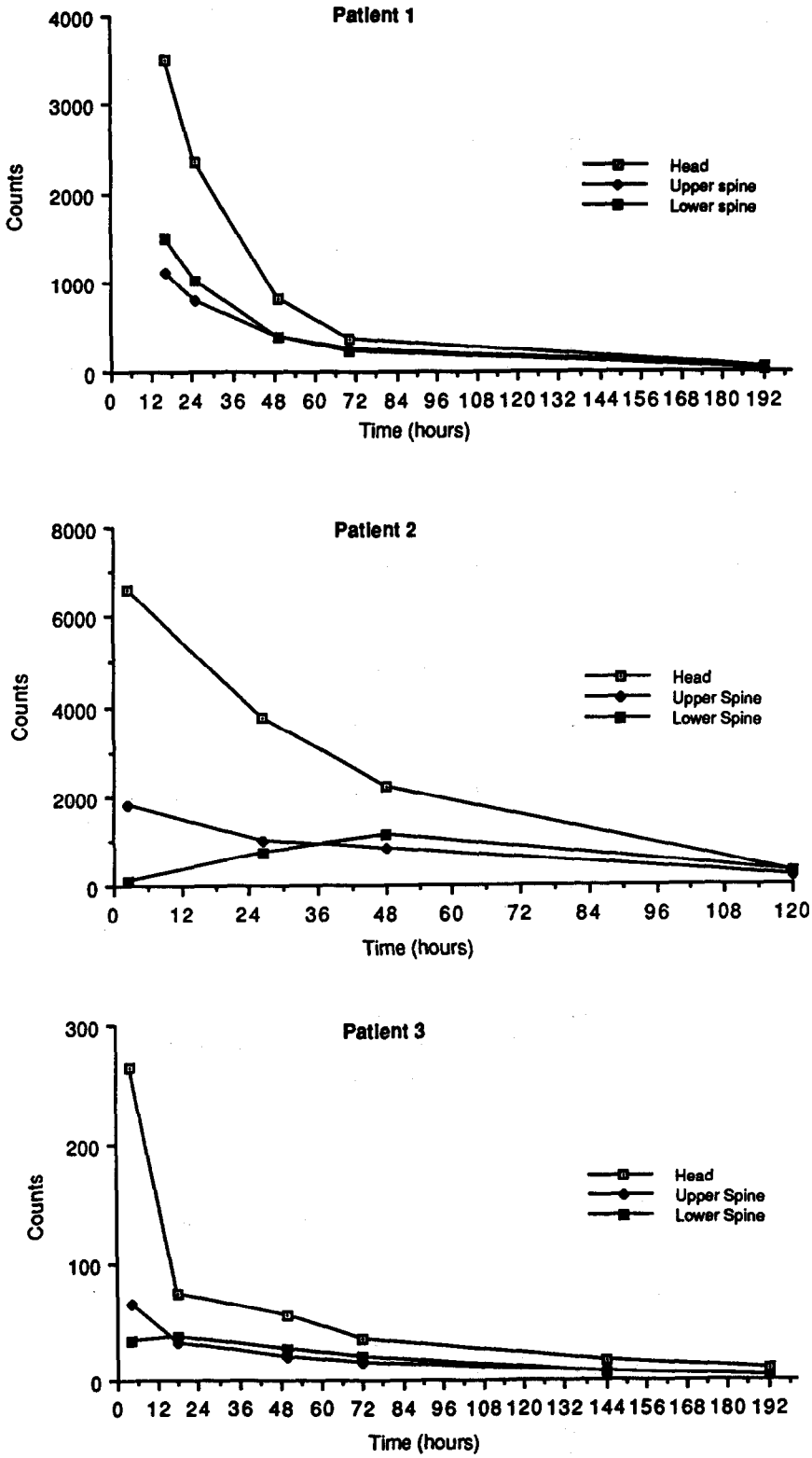


*Fig. 2. Counts obtained over the head, upper spine and lower spine in the three patients treated with $^{131}$I-labelled monoclonal antibodies at sequential time points following injection.*

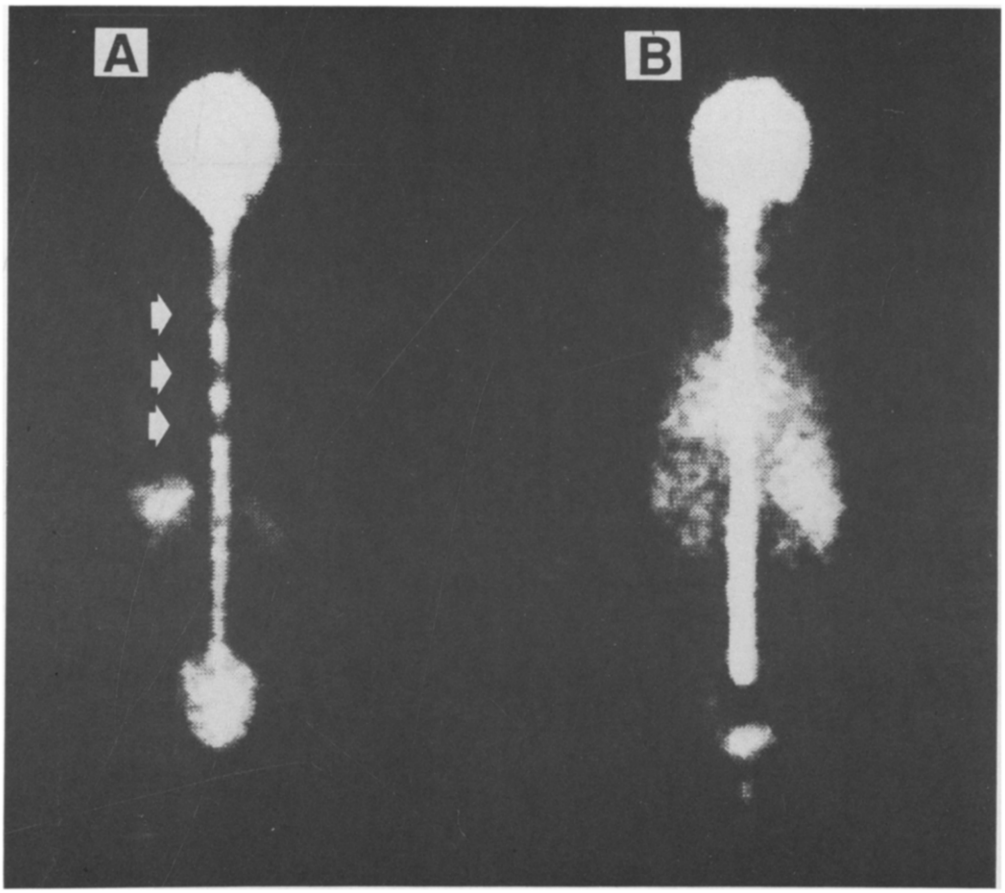


*Fig.* 3. *Distibution of radioactivity in patient* 3 *at* 26 h (*A*) *and in patient* 1 *at* 25 h (*B*) *showing the areas of partial block to CSF flow* (*arrowed*) *in patient* 3.

*Table* 1. *Proportion of counts per area for each patient*

| | Time of gamma scan following isotope injection | | | | | |
|---|---|---|---|---|---|---|
| Patient 1 | 16 h | 25 h | 49 h | 70 h | 192 h | 264 h |
| Head | 0.57 | 0.56 | 0.52 | 0.44 | 0.40 | 0.41 |
| Upper spine | 0.18 | 0.19 | 0.24 | 0.30 | 0.36 | 0.39 |
| Lower spine | 0.42 | 0.24 | 0.23 | 0.26 | 0.23 | 0.19 |
| Total CNS counts | 6131 | 4175 | 1583 | 828 | 126 | 53 |
| Patient 2 | 4 h | 28 h | 50 h | 72 h | 144 h | |
| Head | 0.73 | 0.52 | 0.54 | 0.50 | 0.56 | |
| Upper spine | 0.18 | 0.22 | 0.19 | 0.21 | 0.23 | |
| Lower spine | 0.09 | 0.25 | 0.25 | 0.28 | 0.20 | |
| Total CNS counts | 364 | 144 | 102 | 72 | 30 | |
| Patient 3 | 2.5 h | 26 h | 48 h | 120 h | | |
| Head | 0.77 | 0.68 | 0.53 | 0.38 | | |
| Upper spine | 0.21 | 0.18 | 0.20 | 0.24 | | |
| Lower spine | 0.01 | 0.13 | 0.26 | 0.37 | | |
| Total CNS counts | 8488 | 5451 | 4148 | 688 | | |

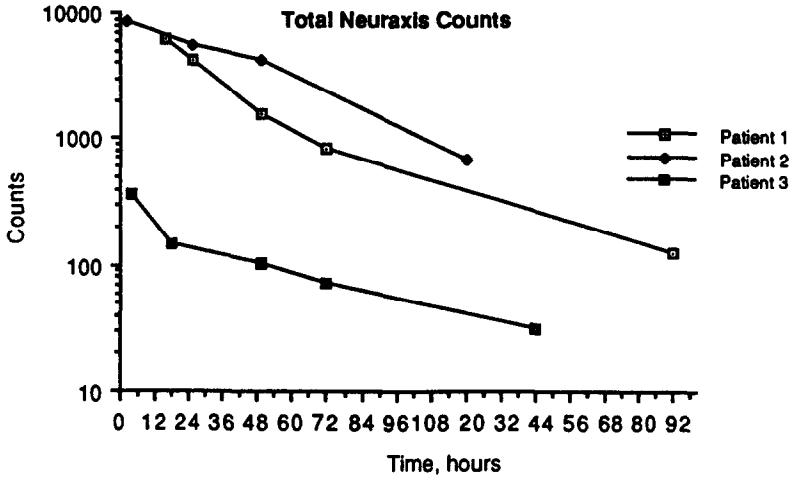


*Fig.* 1. *Decay of total neuraxis counts in the three patients treated with* $^{131}$I*-labelled monoclonal antibodies.*

volumes of injectate as potential sources of bias. These are criticisms that have been levelled at previous studies [6, 7].

The second part of the study shows that the distribution of radiolabelled monoclonal antibody occurs rapidly to all parts of the neuraxis following administration via the intra-ventricular route. In all three patients the quantitative distribution of antibody followed a similar pattern with approximately 50% of the total counts from the neuraxis being localized to the head and 18–30% to each of the upper and lower spine areas. Since there was no clear evidence of localization to tumour-bearing sites and no neurological toxicity it is likely that this pattern of distribution reflects the volume of CSF in these areas rather than binding to normal neural tissue.

In the patient with the spinal block there was delay in flow of antibody to the lower spine but by 26.5 h the quantity of irradiation detected from this region was similar to that in the patients where no block existed. This suggests that it may not be necessary to administer antibody above and below any potential block. Radiation administered in this manner has the advantage of restricting the depth of penetration of the radiation and thus limiting normal tissue damage. However the corollary of this is that only superficial tumours of small diameter are likely to be treated effectively. Two of the three patients described had bulk disease present on CT

scanning and thus the lack of therapeutic effect was not surprising.

In conclusion administration of radiolabelled antibody by the intra-ventricular route has been shown to result in rapid distribution to the entire neuraxis even in the presence of a partial spinal block. In addition there was no sign of acute or late neurological complications. Moreover the available evidence suggests that for the treatment of established meningeal tumour involvement this is the optimal mode of administration. Further studies of this type of therapy in patients with minimal disease are warranted but its value in the presence of bulk tumour is doubtful.

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