THE USE OF TECHNETIUM $99m$ AS A CLINICAL TRACER ELEMENT

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THE VARIETY of radioactive tracer chemicals currently available for medical use is almost embarrassingly large and is still increasing. The value of any proposed new isotopes should therefore be carefully considered. No apology however, need be made for the introduction of Technetium $99m$ by Scheer and Maier-Borst (1963) also by Harper, Beck, Charleston and Lathrop (1964), since this substance has many advantages in its application to scanning and in the observation of transients. (Clark, Deegan, McKendrick, Herbert and Kulke, 1965).

It has been evident for some time that many radioisotopes in common use in medicine are not best suited for scanning purposes. The ideal radioactive agent should usually conform to the following criteria:—

- (a) The gamma ray energy should be such as to permit easy collimation without too much absorption in tissue and at the same time deliver the lowest radiation dose. The optimum energy is then within the range 80-200 Kev.
- (b) Beta emission and conversion electrons should preferably be absent as they increase the radiation dose without contributing to the scan.
- (c) The half life should be a few hours only, permitting biological equilibrium in the body to be obtained with the smallest radiation dose. At the same time this will allow the background to be sufficiently reduced for further tests to be carried out in a few days.
- (d) The radioisotope should be available carrier free or at least in high specific activity to avoid toxic or hypersensitivity reactions.

A radioisotope with these properties may be administered in millicurie quantities with a hazard no greater than that of conventional X-ray investigations. Since Technetium $99m$ epitomises these criteria it seemed worthy of further investigation as a tracer isotope. It will be shown that multimillicurie doses may safely be used to obtain high counting rates which can give results of high statistical significance.

Production and Physical Properties

Tc^{99m} is most conveniently produced carrier free as a pertechnetate (TcO_4) in isotonic saline from a Mo^{99} generator which has a half-life of 67 hours. These generators in which the Mo^{99} is incorporated in an alumina column, are regularly available from the Radiochemical Centre, Amersham, England and other suppliers.

Tc^{99m} decays to Tc^{99} by isomeric transition with a half-life of 6.0 hours emitting a 0.140 MeV gamma ray which is 8-11% converted (Strominger, Hollander and Seaborg, 1958). Tc^{99} itself decays by beta emission to stable Ru^{99} , and has a half-life of 2.1×10^5 years so that only millimicrocurie quantities of the isotope are produced by a tracer dose. The Specific Gamma Ray Emission Γ is 0.61 r/mc at 1 cm, and the half-value layers in lead and water are 0.026 cms and 5.0 cms respectively.

Since the gamma ray energy is near that which gives minimum Γ and there is no beta emission, adequate counting rates can be obtained with a comparatively small radiation dose. Conventional instruments give efficient collimation, but due to the low gamma ray energy, shielding and collimator length may be reduced to make a high sensitivity lightweight detector (Harper, Beck and others, 1964).

Metabolism

After some initial experiments on rats, three human subjects were investigated and some results of plasma clearance tests are presented in Fig. 1. Two of the subjects received approximately two millicuries of Tc^{99m} as pertechnetate in isotonic saline by intravenous injection while the same dose was given orally to a third. After two hours the plasma concentration was in each case between 3% and 5% per litre and the mean long term component was 3.5% per litre with a half clearance time of 9 hours.

Urine excretion was approximately 30% at 24 hours and 40% at two days while 10% had been collected in the faeces in two days. (Fig. 2). This is in agreement with the results of Sorensen and Archambault (1963 and 1964), who

FIG. 1.—Plasma clearance of Tc^{99m}. O. Intravenous administration. X. Oral administration.

recovered 58% in the urine and 24% in faeces after three days, and also with Harper, Lathrop, McCardle and Andros (1964) who found 50% total excretion in 1.8 days with 10%-15% in the stools. The activity remaining in the body should be obtainable by subtracting the total known excretion from 100% and this is shown in Fig. 3. The biological half-life is approximately 60 hours.

While radiopertechnetate is sufficiently concentrated in the thyroid to produce good scans, the thyroid uptake is small by comparison with radioiodine and it is more rapidly released, the maximum uptake occurring within an hour. One normal showed a peak uptake of 4% (Fig. 3); another had 3% in the gland at three hours. We have not been able to demonstrate protein binding and it appears that the uptake follows a similar pattern to that of the "blocked" gland for iodine (Foss and Herbert, 1952), where the percentage uptake for normals is within the range 2.1%-7.3%. This is also in agreement with observations of Harper, Lathrop, McCardle and Andros (1964) who found that the uptake of Tc^{99m} in normals was 2%.

Brown-Grant (1961) describes the concentration of iodine in the stomach after intravenous injection of iodine. Similarly, if the trunk is scanned after intravenous injection of radiopertechnetate the concentration of Tc^{99m} is clearly seen, first in the stomach and later in

FIG. 2.—Excretion of Tc^{99m}. O. Faeces. X. Urine.

FIG. 3.—Metabolism of Tc^{99m}.
(a) Total retained (whole body)
(b) Stomach.
(c) Plasma clearance (% per litre)
(d) Thyroid.

FIG. 4.—Serial scans of stomach after intravenous injection of Tc^{99m} .

the gut. A series of such scans is shown in Fig. 4. By measuring the density of the stomach scan, subtracting the background over adjacent areas, and then comparing with a standard phantom, it has been possible to make an estimate of the uptake (Fig. 3 and 4). The maximum of 6% occurs at 5 hours and decays with a half-time of 13 hours. It is not known whether this results from secretion in the gastric juices or swallowed saliva, for the concentration in saliva reached 46% per litre at 3 hours and thereafter dropped sharply. Uptake of Tc^{99m} in the parotid and submaxillary glands has been demonstrated by Harper, Beck, Charleston and Lathrop (1964) in their thyroid scans. No other significant concentration has been observed.

Dosimetry

The above information is sufficient to make a fair estimate of the radiation hazard resulting

from a tracer dose of Tc^{99m} . The critical organs appear to be the thyroid and stomach.

In our calculations it has been assumed that the gamma ray energy is 0.140 Mev, the specific gamma ray emission is 0.61 r/mch at 1 cm, and there is 9% electron conversion in which the 0.014 Mev is dissipated as beta like radiation.

Whole body—Uptake 100%; T eff = 0.23 days; w = 70 Kg; g = 125 cms.

$$D \gamma \propto \frac{0.0346 \times 0.61 \times 125 \times 1000 \times 0.23}{70000} = 0.0087 \text{ r/mc.}$$

$$D \beta \propto \frac{73.8 \times 0.140 \times 1000 \times 0.23 \times 0.09}{70000} = 0.0031 \text{ rads/mc.}$$

$$\text{Total effective dose} = 0.0118 \text{ rem/mc.}$$

Calculating as above;

Thyroid (normal)—Uptake = 5%; T eff = 0.14 days; w = 20 g; g = 15 cms.

$$D \gamma \propto 0.11 \text{ r/mc.} \quad D \beta \propto 0.32 \text{ rad/mc.}$$

$$\text{Total dose} = 0.43 \text{ rem/mc.}$$

Stomach—Uptake = 6%; T eff 0.17 days; w = 250 g; g = 94 cms.

$$D \gamma \propto 0.081 \text{ r/mc.} \quad D \beta \propto 0.038 \text{ rad/mc.}$$

$$\text{Total dose} = 0.119 \text{ rem/mc.}$$

FIG. 5.—Hand held collimated scintillation detector for low energy gamma rays.

These values are in reasonable agreement with those of McAfee, Fueger, Stern, Wagner and Migita (1964) who quote 0.011 rads/mc whole body and 0.08 rads/mc for stomach but the thyroid dose is higher than that given by Harper, Beck and others (1964) (0.1 rad/mc).

Measuring and Detecting Apparatus

For dispensing tracer doses, a well-type ionisation chamber Type 1383A with a brass liner has been used and calibrated with a standardised Ce-141 source. In our instrument the sensitivity was 5.1 pico-amps. per millicurie for a 10 ml sample.

Harper, Beck and others (1964) have shown that optimum collimation for brain scanning is obtained at a gamma ray energy of about 100 Kev. By using a $\frac{1}{4}$ " thick NaI crystal with a 180 hole focussed collimator $\frac{3}{4}$ " thick we have made a detector which is lighter and cheaper than the conventional detectors for medium energy, yet for the same resolution the sensitivity is increased by a factor of 5. Since only a comparatively thin crystal is required, CsI may also be used. A hand held scintillation detector with a simple collimator suitable for measuring transients is shown in Fig. 5. This particular counter weighs only 4 lbs. compared with nearly 1 cwt. which is necessary to provide similar collimation for I^{131} .

Clinical Application of Technetium-99m

The clinical uses of this new isotope are

FIG. 6.—Comparison of thyroid scanning with Tc^{99m} and I^{131} .

self-evident from the above considerations and our expectations have been borne out in practice.

- (a) *Thyroid studies:* For the reasons already stated massive quantities relative to I^{131} can safely be administered and sufficient isotope accumulates in thyroid cells to yield very accurate thyroid scans. In scanning a small organ the low energy monochromatic radiation of Tc^{99m} , yields much superior scans than can be obtained with I^{131} . This fact is illustrated in Fig. 6 which compares a thyroid scan with I^{131} with a scan using Tc^{99m} in a gland containing functioning adenomata, normal tissue and inactive cysts. The isotope is therefore of use to determine the position, size and shape of the thyroid gland preoperatively or for calculation of I^{131} dosage in thyrotoxicosis, to determine retrosternal extension of the thyroid gland and to determine the position of any ectopic thyroid tissue. Its reliability in the diagnosis of tumours has not yet been fully determined, but it appears to be of the same order as I^{131} . Some concentration of the isotope does occur in malignant conditions of the thyroid, but it is not to the same extent as the concentration in normal thyroid tissue, and it is not yet clear whether this represents active isotope trapping by the neoplastic cells, or is non-specific and due to a breakdown in blood-tissue barrier in the tumour. Functioning thyroid metastases will concentrate Tc^{99m} but apparently not to any greater extent than would be expected from metastases of other origins. Harper, Lathrop and others (1964) quote the thyroid uptake of Tc^{99m} in hyperthyroid individuals as 6-30% which might suggest that it is suitable for use as a thyroid function test. This has not been confirmed in our studies and indeed it would be surprising on theoretical grounds if this were possible as technetium uptake can only represent the size and vascularity of the gland and the size of the iodide compartments of the body, and high uptakes might be expected equally from puberty goitres, iodide deficiency goitres, and thyrotoxic goitres. The great value of Tc^{99m} in thyrotoxicosis is that it enables scans to be performed routinely in all cases without any great radiation exposure to the individual or to the population. Thus using I^{131} , 50 μ cs needs to be administered to obtain uptake and survey studies, yielding thyroid doses of the order of 50 rems and whole body and gonad doses of 0.025 rems. Using Tc^{99m} for survey, 10 μ cs I^{131} is sufficient for uptake studies giving a large reduction in exposure, whilst for the combination of 10 μ cs of I^{132} and 1 mc Tc^{99m} the dosages are reduced to 0.5 rem (thyroid) and 0.01 rem (whole body). Both isotopes can be given coincidentally if a gamma ray spectrometer is used for the uptake measurements.
- (b) *Brain tumour localisation:* The use of Tc^{99m} as pertechnetate has been reported by Harper, Beck and others (1964) and Anger, Van Dyke, Gottschalk, Yano and Scheer (1965). McAfee, Fueger and others (1964) prefer this isotope to most other agents. Although the radiation energy is suitable for brain scanning and very high counting rates are obtainable, retention of the isotope in tumours may not be prolonged and it is necessary to scan at a time when the level of isotope in the circulating blood is high. This obscures localisation in parts of the base and occipital regions of the brain in a manner resembling the scan produced by R.I.¹³¹S.A. It is possible that a more suitable technetium compound would give improved results.
- (c) The observation of transients in a small volume of tissue presents collimator problems similar to those of scanning. Clark and others (1965) have shown that the increased counting rate and improved collimation achieved by using Tc^{99m} as pertechnetate instead of I^{131} has increased the accuracy of the detection of intra-cardiac shunts by external counting over a lung field. Pertechnetate clears too rapidly from the blood for use in cardiac output measurement, but Tc^{99m} albumin, which has been prepared by Stern, Zolle and McAfee (1965) would be eminently suitable for this purpose.
- (d) Multimillicurie quantities of technetium may be safely injected rapidly to act as a radioactive bolus, yielding a high count rate. This could be of value in the study of dynamic processes with scintillation cameras as described by Bender and Blau (1963) and Anger (1965).

TABLE 1
COMPARISON OF Tc^{99m} WITH IODINE ISOTOPES.
RADIATION DOSES.

	Tc^{99m}	I^{123}	I^{125}	I^{131}	I^{132}
Thyroid dose rem/mc injected	0.43	108	1200	1900	20
Whole body dose rem/mc injected	0.012	0.038	6.0	2.7	0.12

TABLE 2
COMPARISON OF Tc^{99m} WITH IODINE ISOTOPES.
DATA RELEVANT TO SENSITIVITY AND COLLIMATION.

	Tc^{99m}	I^{123}	I^{125}	I^{131}	I^{132}
H. V. L. in Sodium iodide (mm)	3.0	3.5	0.32	14	28
H. V. L. in lead (mm)	0.26	0.35	0.026	3	7
Relative weights of collimators for 1" crystal. (transmission 0.1%)	1	1.4	0.09	23	92

- (e) Gastric scans. If technetium is actively secreted by gastric mucosal cells, then useful scans may be feasible. Normal gastric scans have been made but positive pathological scans have not yet been attempted.
- (f) Placentography. Excellent scans of the placenta have been made by McAfee, Stern, Fueger, Baggish, Holzman and Zolle (1964) using Tc^{99m} tagged albumin.

Comparison with Other Radioisotopes

As Tc^{99m} has been used for scanning the thyroid gland, it is instructive to compare its properties with I^{125} , I^{131} and I^{132} , all of which are in common use for thyroid studies. I^{123} (Myers and Anger, 1962) has also been included as its emissions are most like those of Tc^{99m} and if this radioisotope becomes readily available it should be the agent of choice for thyroid scanning, combining optimum physical properties with true iodide metabolism. For brain scanning, placentography and other applications where iodide is not specifically required, Tc^{99m} has the advantage of a much smaller thyroid and whole body dose.

The data relevant to radiation dose are shown in Table 1 and it will be seen that while tracer doses of I^{125} and I^{131} should be kept much less than 1 millicurie, severely limiting the counting rate obtainable for scanning purposes, multi-millicurie doses of Tc^{99m} may be safely given.

In Table 2 the data relevant to detector sensitivity and collimation are given including relative weights of typical collimators. The high penetration of I^{132} makes it unsuitable for any but the crudest collimation, while for the low energy radiations of Tc^{99m} , I^{123} and I^{125} the weight of lead screening can be less than 1/20 of that for I^{131} . Also crystals of a few millimetres thickness can provide adequate detection efficiency, resulting in a reduction in the cost and a further reduction in weight of collimators. With the thickness required Caesium iodide crystals have been used with advantage.

Summary

The physical properties, metabolism and radiation dose of Tc^{99m} are discussed and compared with those of I^{123} , I^{125} , I^{131} and I^{132} .

It is shown that with Tc^{99m} the highest "in vivo" counting rates are obtained for a given internal radiation dose, so that measurements of high statistical accuracy may safely be made.

The gamma ray energy is near optimum for scanning and the observation of transients allowing light-weight collimators to be used.

While Tc^{99m} tagged albumin is considered superior to R.I.S.A. for applications such as brain scanning, placentography and the measurement of cardiac output, I^{123} if it becomes available will be preferable for thyroid scanning.

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