Regular review

Clinical applications of nuclear medicine

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The use of nuclear medicine in paediatrics has experienced a rapid and continuous development over the past 15 years, despite the introduction of computed tomography, echography, and magnetic resonance.

Nuclear medicine is based on the principle that a radioisotope is an unstable substance that gives off energy at a particular level as it decays into a stable compound. The ability to 'label' certain radioisotopes allows a minute quantity of this isotope to be specifically directed at one cell type or organ so that functional images result.

This specific uptake may compensate the lack of resolution compared with other imaging techniques. For instance, the selective uptake of technetium ^{99m}Tc labelled dimercaptosuccinic acid (DMSA) by the tubular cells allows the recognition of focal areas of pyelonephritis, which can be missed by ultrasound or intravenous urography. Iodine 123 (^{123}I) labelled metaiodobenzylguanidine (MIBG) is selectively taken up by the chromaffin tissue, allowing the detection of neuroblastoma metastases, which are not seen by other techniques. Beside the morphological aspects the selective uptake or excretion, or both, of a tracer by an organ makes it possible to quantify one or more functions related to this organ. Nuclear medicine procedures are safe, minimally invasive, and generally expose the child to a very low radiation dose.

Patient preparation

Most radioisotope examinations do not require any patient preparation. In dynamic renal scintigraphy a well hydrated child is not only a happy cooperative child but hydration also permits optimum analysis of the renal scan. When searching for the presence of ectopic gastric mucosa the child must have nothing orally for 4 hours before the examination.

Sedation is rarely used in most paediatric institutions and also in those adult centres geared to carry out a considerable number of studies in children.

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Radioactive tracers

The general principle that radiation has to be kept at the lowest possible level has meant that those isotopes commonly used have a short half life (for example, ^{99m}Tc =6 hours or ^{123}I =13.3 hours) and emit gamma rays at an appropriate level for a gamma camera. The ability to label ^{99m}Tc with various different specific non-toxic chemicals has allowed most examinations requiring nuclear medicine in paediatrics to concentrate on investigating various aspects of renal function, pulmonary perfusion, and disorders of the skeleton as well as the reticuloendothelial system. In addition, imaging of the gut and thyroid gland as well as congenital heart disease have all benefited from the use of ^{99m}Tc . Labelling of white blood cells with a ^{99m}Tc complex is also now available.

Radiation

'As compared to ionizing radiation used externally in diagnostic radiology, the use of radiopharmaceuticals results in internally absorbed doses delivered at much lower dose-rates, which generally are considered to have less biological effect.' This quotation is from the radiation protection body of the United States (National Council on Radiation Protection and Measurements. N°73,1983) and should encourage the use of nuclear medicine in paediatrics.

Low irradiation, no sedation of the patient, and absence of appreciable side effects characterise the radionuclide techniques, which provide useful morphological and functional information and are particularly well adapted to the paediatric patient.

Table 1 Tracers used in renal and urinary tract disorders

Tracers	Physiology	Indications
Diethylene triamine penta-acetic acid—technetium 99m Hippuran 123 I	Eliminated only by glomerular fraction	1,2,3,4,6
	Eliminated by tubular secretion (80%) and glomerular filtration (20%)	1,4
Edetic acid—chromium 51	Eliminated only by glomerular filtration—not suitable for in vivo measurements	3
Dimercaptosuccinic acid—technetium 99m	Uptake by the tubular cells	4,5,6
Pertechnetate technetium 99m	Tracer for bladder filling and voiding	2

Clinical indications

RENAL AND URINARY TRACT DISORDERS (TABLE 1)

Indications¹⁻¹³

(1) A differential diagnosis can be made between urinary obstruction and atonic dilatation from the renogram obtained with 99m Tc labelled with diethylene triamine penta-acetic acid (DTPA) or 123 I Hippuran; parameters of whole kidney and cortical transit can be derived as well as response to frusemide.¹⁻³

(2) Diagnosis and follow up of vesicoureteric reflux, using either 99m Tc pertechnetate for the direct cystogram, or 99m Tc DTPA for the indirect cystogram; both give a much lower gonadal irradiation than the radiological cystogram.⁴⁻⁶

(3) When overall clearance has to be assessed instead of undertaking a creatinine clearance an accurate glomerular filtration rate may be obtained using two or three blood samples 2-4 hours after an intravenous injection of 99m Tc DTPA or chromium-51 edetic acid (51 Cr EDTA). This latter technique is more accurate and easier to perform, it does not require urine collection and is useful in those diseases affecting the kidneys symmetrically.⁷

(4) Quantitation of individual kidney function. This is generally obtained from the early phase of a 99m Tc DTPA or a 123 I Hippuran renogram, or from the 99m Tc DMSA uptake. This is indicated in the preoperative and postoperative evaluation of uropathies and certain nephropathies, which may affect the kidneys asymmetrically.^{8,9}

(5) Precise topographical definition of parenchymal damage (acute and chronic pyelonephritis, trauma), kidney site, and morphology (pelvic kidney, transplant, horseshoe) using 99m Tc DMSA static images.^{10,12}

(6) *Aetiology of hypertension.* Detection of the pyelonephritic scars of vesicoureteric reflux, using 99m Tc DMSA (fig 1).¹⁰⁻¹² Detection of renovascular hypertension by combining a 99m Tc DTPA renogram with the pharmacodynamic effect of captopril.¹³

Fig 1 shows a 5 year old boy who presented in mild chronic renal failure with polyuria and polydipsia. There was a history of recurrent urinary infections that had not been investigated. The intravenous urogram (not shown) failed to show a right kidney and demonstrated a poorly functioning left kidney with abnormal calyces. This 99m Tc DMSA scan shows a high background activity. The left kidney is functioning better than the right (R) and focal defects are noted in the lower pole of the left kidney. The right kidney is seen to contribute 31% to overall function despite not being seen on the urogram. Comment: This child was found to be suffering from reflux nephropathy and shows the sensitivity of the DMSA scan in identifying func-

Fig 1

Table 2 Tracers used in pulmonary diseases

Tracers	Physiology	Comments	Indications
Macroaggregates—technetium 99m or human albumin microspheres—technetium 99m Krypton gas 81m	Regional perfusion	High quality static images, can be done at all ages, cheap and easy	1,2,3,4,5,6
	Regional ventilation	High quality static images during normal breathing through a mask, low sensitivity below 1 year of age for subsegmental defects, expensive, requires high organisation	
Xenon gas 133	Regional ventilation	Low quality static images after single breathing, needs patient's cooperation (patients must be older than 6 years), inexpensive	1,2,3,4,5,6
Millimicrospheres aerosols—technetium 99m	Regional ventilation	Still requires extensive standardisation	6

tioning renal parenchyma and focal defects within the kidney.

PULMONARY DISEASES (TABLE 2)

Indications¹⁴⁻¹⁸

- (1) To confirm or exclude the diagnosis of regional lung disease in the presence of normal or equivocal films from chest x rays (foreign body, bronchiectasis, aspiration pneumonia, small lung, hyperlucent lung). Furthermore, to select patients who should undergo more invasive investigations (bronchoscopy, bronchography) (fig 2). For instance, the probability of having bronchiectasis or a foreign body is very low in the presence of a normal scan.
- (2) To evaluate function in the rest of the lungs before surgical removal of a lobe (bronchiectasis, sequestration).
- (3) To detect intrapulmonary shunts and other vascular anomalies before angiography is performed (a negative result on scintigraphy could avoid angiography).
- (4) To follow up severe disease, like cystic fibrosis, or bronchiectasis, or sequelae of viral pneumonia.
- (5) To detect pulmonary embolism or primary artery disease—this needs combined ventilation and perfusion studies.
- (6) To evaluate mucociliary clearance.

As most ventilatory disturbances will necessarily and instantaneously be followed by a corresponding perfusion abnormality (adaptation mechanism), most ventilatory diseases (foreign body, cystic fibrosis, etc) can be investigated by either a perfusion or a ventilation scan. On the contrary, vascular disease (embolus, pulmonary artery disease) shows an abnormal perfusion and a relatively normal ventilation scan (mismatching). With a sequestered

segment, the perfusion scan is always abnormal, the ventilation scan may either show a matched defect or may be relatively normal.

Fig 2 shows a 6 year old girl with recurrent moist cough and wheezing episodes. The suspected clinical diagnosis was that of bronchiectasis. (a) The chest radiograph picture shows overinflation of both lung fields as well as the mediastinum displaced to the right with loss of the right heart border. The vessels in the right lung are also diminished compared with that on the left. (b) This shows the ^{99m}Tc macroaggregates perfusion scan. (c) This shows the Krypton—81m ventilation lung scan. These images were obtained in the right posterior oblique (RPO) projection and show a pronounced decreased activity of both isotopes throughout the right lung with total absence of activity in both the upper and lower zones. The left lung shows a segmental defect of both ventilation ($\bar{V}$) and perfusion ($\bar{Q}$) in the upper zone with a generalised decrease of both isotopes in the left lower zone. (R indicates the right side.) Comment: Further investigation confirmed collapse with bronchiectasis in the right lower lobe which was non-functioning on lung scan. The compensatory overinflation of the right upper lobe as well as the left lung have non-perfused and non-ventilated segments. This child was found to be immunologically abnormal and asthmatic.

HEPATOSPLENIC DISORDERS (TABLE 3)

Indications¹⁹

- (1) Jaundice—to exclude biliary atresia in the infant; to assess postsurgical patency of biliary tree; to assess drainage in choledocal cyst and the presence of dilated ducts—for example, Caroli's disease.
- (2) Detection and follow up of space occupying lesions in the liver in combination

Fig 2(a), 2(b), 2(c)

with other techniques (ultrasound, computed tomography).

(3) To detect congenital splenic abnormalities associated with congenital heart disease (asplenia, polysplenia).

(4) To detect splenic trauma, or accessory spleen (idiopathic thrombocytopenic purpura).

GASTROINTESTINAL TRACT DISORDERS (TABLE 4)

Indications²⁰⁻²⁴

(1) Diagnosis and follow up of gastro-

oesophageal reflux (chronic vomiting, recurrent lung infections, near-miss sudden infant death syndrome, etc).²⁰

(2) Study of the oesophageal transit (caustic stricture, peptic oesophagitis, achalasia, neurogenic impairment of the peristalsis, etc).²¹⁻²²

(3) Diagnosis of a Meckel's diverticulum containing gastric mucosa.²³

(4) Evaluation of the gastric emptying time.²⁴

If the diagnosis of ectopic gastric mucosa is made the

perchnetate scan should not be performed during active bleeding as there is the possibility of a false negative result due to dilution or washout of the radioactivity. Premedications such as pentagastrin or cimetidine have been suggested to increase the sensitivity of the perchnetate scan. False negative results have been described (sensitivity~75%); and positive abdominal images have been described in conditions other than Meckel but can generally be differentiated.

SKELETAL DISEASES (TABLE 5)

Indications^{19 25-27}

- (1) To detect primary or metastatic bone malignancies (fig 3).
- (2) To confirm the presence of suspected inflammatory or infective bone lesions with normal or equivocal x ray (osteomyelitis).
- (3) To diagnose avascular necrosis and to follow up revascularisation.
- (4) To diagnose and localise osteoid osteoma.
- (5) To diagnose bone marrow disorders (early diagnosis of metastatic disease and haematological disorders).
- (6) To investigate long term symptoms which

may be skeletal in origin—for example, a limp or backache.

Normal ^{99m}Tc labelled methylene diphosphonate (MDP) bone scans have been reported in acute septic arthritis and also when osteomyelitis occurs in the young infant. Although uncommon, negative bone scans are seen in older children with osteomyelitis. White blood cells labelled with ¹¹¹Indium are used in some hospitals as a second or third choice investigation for suspected osteomyelitis especially in the newborn where the ^{99m}Tc MDP scan is unreliable in excluding the disease. Scans of white blood cells labelled with ^{99m}Tc hexamethyl propylene amine oxime (HMPAO) require evaluation in septic arthritis and in the young infant with osteomyelitis. ⁶⁷Gallium may also be used as a second choice isotope when the initial bone scan is negative or equivocal. A number of extrasosseous abnormalities may concentrate ^{99m}Tc MDP; this is seen in neuroblastoma, splenic infarction in sickle-cell anaemia, myocardial infarction, soft tissues metastases of Ewing's sarcoma, ectopic calcifications, and in the intestine in necrotising enterocolitis.

Fig 3 shows a 2 year old child who was unwell and was found to be anaemic and hypertensive. The clinical diagnosis was neuroblastoma; this was

Table 3 Tracers used in hepatosplenic disorders

Tracers	Physiology	Indications
Colloid—technetium 99m	Uptake by the reticuloendothelial system of liver and spleen	2+4
Damaged red blood cells—technetium 99m	Selective uptake by the spleen	3,4
Iminodiacetic acid (N substituted)—technetium 99m	Early uptake by the parenchymal liver cell and excretion through the biliary ducts into the duodenum	1

Table 4 Tracers used in gastrointestinal tract disorders

Tracers	Physiology	Indications
Colloid—technetium 99m	Non-reabsorbed or modified in the stomach	1,2,4
Krypton 81 in glucose	Fast disappearance due to the ultra short life of the tracer	2
Perchnetate—technetium 99m	Actively taken up by the gastric mucosa	3

Table 5 Tracers used in skeletal diseases

Tracers	Physiology	Indications
Methylene diphosphonate—technetium 99m	Static image activity dependent upon blood flow and osteoblastic activity	1,2,3,4,6
Colloid—technetium 99m	Taken up by the reticuloendothelial cells of the bone marrow	5
Gallium 67	Non-specific uptake by inflammatory tissue	2
White blood cells—indium III. Hexamethyl propylene amine oxime white blood cells—technetium 99m	Monitoring migratory pattern of the child's white blood cells	2

further suggested by high vanillylmandelic acid concentrations in the urine. (a) This shows the ^{99m}Tc methylene diphosphonate bone scan. This posterior view of the axial skeleton shows abnormal vertebrae with areas of both increased and decreased activity. Abnormal increased uptake of isotope is noted in the left femur. Uptake of isotope by the left adrenal tumour is also noted. (b) This shows the ^{123}I metaiodobenzylguanidine scan. The posterior view of the axial skeleton, pelvis, and femurs show

Fig 3

numerous bony areas taking up the isotope; this is abnormal. Isotope is seen in the left adrenal gland. Activity is also noted in the heart; this is normal. (R indicates the right side.)

THYROID DISORDERS (TABLE 6)

Indications²⁸

- (1) Definition of aplasia/ectopia or normally located gland.
- (2) Evaluation of neck nodules and their relation with thyroidal tissues.
- (3) Diagnosis of nodular lesion in hyperthyroidism as possible hyperfunctioning adenoma (rare in children).

^{131}I Iodine is a well established tracer for assessing thyroid function. It is contraindicated in children because of the high radiation. The alternative tracers are either ^{123}I Iodine or ^{99m}Tc pertechnetate. There are protagonists of each isotope and in the investigation of a thyroid nodule it may be unimportant which tracer is used.

HEART DISEASES (TABLE 7)

Indications^{17 29-31}

- (1) Assessment of left to right heart shunt using ^{99m}Tc pertechnetate.
- (2) Assessment of right to left heart shunt using ^{99m}Tc macroaggregates (MAA).

Table 6 Tracers used in thyroid disorders

Tracers	Physiology	Indications
Pertechnetate—technetium 99m	Selective uptake by the thyroid gland	1,2,3
Iodine 123	Selective uptake by the thyroid gland and incorporation in thyroid hormones	1,2,3

Table 7 Tracers used in heart diseases

Tracers	Physiology
Pertechnetate—technetium 99m	This isotope will be taken via the right heart to the lungs then to the left heart and on to the systemic circulation. In the presence of a left to right shunt isotope will go from the left heart phase both to the systemic circulation and also back to the lungs. The shunt can be quantified.
Macroaggregates—technetium 99m	The isotope will be trapped in the first capillary plexus and therefore after an intravenous injection all the isotope is normally stopped in the pulmonary capillary bed. In the presence of a right to left shunt the isotope is seen in the systemic circulation—for example, kidneys.
Red blood cells—technetium 99m	As the isotope is attached to the red blood cell mass images of the pulsating heart can be obtained over a period of time in order that ventricular function can be assessed. Changes in function can be measured (ejection fraction).
Krypton gas—181 m	This isotope will come out of solution as soon as it is in contact with air. If the ^{81m}Kr is given by constant intravenous infusion then the isotope will enter the right heart and then the pulmonary circulation. The isotope will freely cross the alveolar membrane and be exhaled so that no isotope will reach the pulmonary veins or left heart normally. Good delineation of the right ventricular structures can therefore be reached, without any superposition of the left heart; this allows a measurement of the right ventricular contractility.

- (3) Assessment of left ventricular function using ^{99m}Tc pertechnetate (first pass) or red blood cells labelled with ^{99m}Tc (equilibrium).
- (4) Assessment of right ventricular function using ^{99m}Tc pertechnetate (first pass) or ^{81m}Kr infusion.

Recent progress in radioactive tracers

LABELLED WHITE BLOOD CELLS USING EITHER $^{111}\text{INDIUM}$ OR ^{99m}Tc HMPAO

Indications³²

- (1) To investigate when pus is suspected at any site (fig 4).
- (2) To investigate pyrexia of unknown origin.
- (3) To investigate inflammatory bowel disease.

Tracers

White blood cells labelled with ^{99m}Tc HMPAO: the labelled white blood cells migrate to the focus of infection/inflammation where they accumulate. If the polymorphs are labelled then one may be able to distinguish active infection from inflammation.

White blood cells labelled with $^{111}\text{Indium}$: this is based on the same technique but gives a high radiation dose to the spleen and bone marrow. It is, however, still the isotope of choice for inflammatory bowel disease.

Fig 4 shows a ^{99m}Tc hexamethyl propylene amine

oxime scan. White blood cells labelled with the isotope were injected: the image at one hour is on the left, the middle image was taken at three hours, and the right hand image at 20 hours. The one hour image shows the spleen and liver with minimal lung activity persisting. The three hour image again shows the liver and spleen with a slight increase of activity in the mediastinum on the right hand side. The 20 hour image shows little activity persisting in the liver; the spleen is still clearly seen. The abnormal mediastinal activity is now quite pronounced. This was due to a mediastinal abscess in a child who had undergone a reoperation for oesophageal atresia and was feverish. (L indicates the left side.)

LABELLED METAIODOBENZYLGUANIDINE (MIBG) USING EITHER ^{131}I OR ^{123}I

Tracer

This tracer, a precursor of noradrenalin, is taken up by the adrenal medulla and also by neuroblastoma and pheochromocytoma even when these tumours are extra-adrenal in origin or spread.

Indications

Diagnosis of neuroblastoma (primary and metastasis) and pheochromocytoma (fig 3).³³

BRAIN BLOOD FLOW TRACERS

Tracers

^{123}I amphetamines and ^{99m}Tc HMPAO.

Fig 4

Physiology

Lipophilic tracers crossing the blood-brain barrier and giving an image of the blood flow.

Indications

Currently under review.

Conclusion

The role of radioisotopes in paediatrics is very specific in providing functional images of various organs. To gain maximum benefit for the patient the use of this technique should be in conjunction with other imaging methods. An abnormality on ^{99m}Tc MDP bone scan necessitates a high quality radiograph of the area; a ventilation/perfusion lung scan should always be accompanied by a chest radiograph. No renal isotope study should be performed without first carrying out an abdominal ultrasound examination.

When appropriately used, radioisotopes provide information that is important for patient care and frequently unavailable by any other technique.

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