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Review

Veterinary nuclear medicine

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Introduction

The veterinary use of radionuclide techniques dates back to the mid-sixties [1, 2], but its more extensive use dates back to the past two decades. In Central and Eastern Europe, it is still in its infancy with only one large research centre, in Budapest, Hungary.

Veterinary nuclear medicine is focused mainly on four major issues: bone scintigraphy — with the majority of applications in horses, veterinary endocrinology — dealing mainly with the problems of hyperthyreosis in cats and hypothyreosis in dogs, portosystemic shunts in small animals and veterinary oncology, however, most radionuclide techniques applied to humans can be applied to most animals.

There is little awareness of the usefulness of radionuclide studies in veterinary practice among the nuclear medicine community. Therefore, we decided to describe some of its applications.

Clinical applications

Bone scintigraphy

Its main objectives are horses, dogs, and to a lesser extent, cats. The demand for advanced and correlative imaging methods in equine medicine is growing. Scintigraphy can provide unique information about the physiological status of an animal that cannot be discerned by other imaging modalities. The crucial problem in horses, where traditional radiographic techniques may not be sufficient, are leg and neck bone lesions, in the second row a veterinary oncology.

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Orthopaedic applications

Bone scintigraphy offers the major advantage of increased sensitivity over standard radiographic imaging. Except for consistent identification of bone cysts, most of the pathological changes to the horse's musculoskeletal system that might cause lameness can be detected using bone scans. Many acute bone diseases can be diagnosed by scintigraphy that cannot be discerned by radiographs until the condition has become chronic. Because of their body size, these conditions may not be diagnosed in horses at all. Scintigraphy in horses offers the other major advantage of affording accurate imaging of the upper limbs, pelvis, and vertebral column without general anaesthesia. Therefore, it has the final advantage of increased safety over conventional radiography because it eliminates the need to perform general anaesthesia to study these areas. A second major benefit of scintigraphic imaging is to differentiate mixed lameness conditions, in which the component of bone disease must be separated from that of soft tissue to arrive at a rational course of treatment or prognosis. Finally, for athletic horses suspected of having lameness due to localized myositis, scintigraphy not only allows confirmation of muscle inflammation, but also identifies the injured muscle bellies reasonably and accurately, so that specific local treatment may be given. Nuclear imaging of equine skeletal disease is an option that should be employed more frequently by equine practitioners for diagnosis of difficult lameness cases. The technique is safe and comparatively inexpensive when one considers the total expense of multiple examinations or radiographic surveys of patients without conclusively diagnosing the source or sources of skeletal pain. This is particularly true when a horse owner becomes dissatisfied and enlists the services of one or more other veterinarians. The equine specialist will maintain better client rapport if he or she suggests referral of the horse to a veterinary medical teaching centre or private clinic where scintigraphic imaging can be carried out, rather than having the client become frustrated and seek another opinion elsewhere [3].

An important cause of lameness in horses, where scintigraphic imaging may be considered, can be stress fractures of legs [4]. Stress fractures of scapula with positive RN and negative radiographic imaging also can be met [5].

Lameness detection is also a major problem of, so-called, veterinary sports medicine, i.e. evaluating the problems of equine (or canine) athletes. It should be remembered, however, that the poor performance of animal athletes could be the result not only of orthopaedic problems, but also of upper and lower airway function disturbances, which result in increased resistance to airflow — a major cause of poor racing performance. Scintigraphic imaging modalities can be used to evaluate both global and regional lung function in cases of suspected pneumonia, chronic obstructive pulmonary disease or emphysema. Nuclear medicine studies can often offer some help in these situations [6]. In some cases, bilateral lameness can be the result of aortoiliac thromboembolism, detectable with first-pass radionuclide angiography [7].

Bone scintigraphy may also be used in the detection of occult lameness in dogs [8]. Scintigraphy has also gained wide acceptance in diagnosing elbow dysplasia. The term elbow dysplasia encompasses a variety of developmental abnormalities that affect the elbow. Some of the more common conditions referred to as elbow dysplasia include dissecant osteochondrosis, non-united anconeal process, fragmented coronoid process and premature closure of the ulna. Scintigraphy helps to diagnose joint incongruity that has not yet developed into a condition that is detectable by radiography. In addition, scintigraphy has proven helpful in localizing lesions in the shoulder, elbow, stifle, and tarsal joints associated with osteochondrosis and osteoarthritis [9]. In some cases, radionuclide technique could be used in disorders secondary to vertebral column lesions; for example there are reports on scintigraphy performed in bulls with decreased libido due to painful lesions of the vertebral column. Radiographic evaluation of vertebral skeletal problems in mature bulls is limited because of high body mass. Bone scintigraphy helped to determine the location of vertebral column lesions and facilitate localized treatment [10]. Scintigraphy should be considered in all cases of animal lameness which cannot be diagnosed by conventional methods. This technique is also useful as an early indicator of the disease, not only as a method of "last hope" [11].

Oncologic bone scintigraphy applications

In veterinary oncology, the principal goal is the detection of osteosarcoma [12–16]. In limb sarcoma, both radiography and scintigraphy tend to overestimate its extent when compared with histopathologic macro-slides of the same lesions. Nuclear scintigraphy overestimates tumour extent to a larger degree than does radiography. Although radiography is a more accurate method of measurement of the extent of distal radius osteosarcoma, scintigraphy may provide a larger margin of safety for determining the site of proximal osteotomy during a limb-salvage procedure. However, caution should be exercised when utilizing scintigraphy, because this method may overestimate the length of radius involved to such an extent as to cause the surgeon to believe that a patient is not a suitable limb-salvage candidate [13].

An interesting finding is the extra-skeletal accumulation of osteotropic radiotracers of osteosarcomas in cats and dogs [14–16]. This might have some therapeutic importance, as the therapeutic radiotracers: strontium-89 and samarium-153-EDTMP were also showed to accumulate in extraosseous sarcomas [17].

The detection of primary and metastatic osteosarcoma has been also attempted with immunoscintigraphy using F(ab')2 fragments of osteosarcoma-associated monoclonal antibody TP-1 [18].

Veterinary oncology

Oncophilic agents such as 99m-technetium MIBI and DMSA(V) have proven to be useful in detecting lymphomas and malignant schwannomas [19].

As in humans, there is a proven usefulness of sentinel node detection in oncologic patients [20]. Balogh et al proved the superiority of pre-operative RN sentinel node detection (89%) and intraoperative radioguided surgery (97%) over blue-dye technique (77%).

Veterinary endocrinology

Most nuclear medicine procedures in this field are related to thyroid gland diagnostics and therapy, both in dogs and cats. Hyperthyroidism is a crucial problem in cats, and hypothyroidism in dogs.

Feline hyperthyroidism was first described in 1979 and is a relatively common disease. Its symptoms and signs are, as in humans, chronic weight loss, intermittent dyspnoea, chronic diarrhoea, hyperactivity and weakness [21]. Diagnosis, as in humans, is based on palpation, scintigraphy and ultrasound. Management, again as in humans, is either with thyreostatic agents, surgical or with radioiodine, and sometimes even with ethanol ablation.

Thyroidal isotope uptake and scintigraphy

Uptake of radioactive iodine (131-I or 123-I) and 99m-technetium as pertechnetate is increased in hyperthyreoidal cats [22, 23]. Qualitative scintigraphic imaging is a useful procedure to determine unilateral or bilateral involvement, alterations in the position of thyroid lobes, the site of hyperfunctioning accessory or ectopic thyroid tissue, or distant metastases from a functioning thyroid carcinoma [24]

Radioiodine treatment

Radioiodine therapy of hyperthyroidism in cats is a very important issue. It is considered to be the safest, simplest and most effective therapy of feline hyperthyroidism [23].

A target delivery dose to the thyroid is 150 Gy. The average activity of radioiodine applied varies from 3–5 mCi. It is administered orally, intravenously or subcutaneously. The two latter means of radioiodine administration are preferable, but when compared with i.v. administration, s.c administration of radioiodine appears to be safer to personnel, less stressful to the cats and it is currently the preferred route of administration of radioiodine [25]. Oral administration was attempted, but higher doses are generally required, the risks of radiation spillage are greater and vomiting may occur. Euthyroidism may be attained in over 90% of cases with a single dose ranging from 39 to 222 MBq [23, 27]. Regarding survival time following treatment of hyperthyroidism with radioiodine, 67% of cats were alive and euthyroid up to 33 months after treatment [29]. Many of the remaining cats died due to renal disease, which could be a side-effect of the treatment (see section below). Hypothyroidism and recurrent hyperthyroidism can develop, but seem to be fairly rare; other side effects are minimal [26].

The main drawbacks to widespread use of radioactive iodine treatment in cats are the requirements for special licensing and the need of isolation of the cats following treatment, ranging from a several days to several weeks depending on the dose used and local radiation regulations.

Radioiodine treatment of hyperthyroidism in cats — renal disease as a side-effect

Hyperthyroidism itself can mask underlying renal disease [30]. Also the renal function may further be adversely affected by the induction of euthyroidism and should be carefully evaluated before treatment with radioiodine [23]. Renal-irradiation due to radioiodine renal excretion cannot also be excluded. Renal side-effects care is also required for treatment with anti-thyroid drugs and surgery. A significant decline in renal function may frequently occur after the treatment of hyperthyroidism in cats with previous renal disease, therefore pre-treatment measurement of GFR is valuable in detecting sub-clinical renal disease and in predicting which cats may have clinically important declines in renal function following treatment [30]. In the absence of such estimations, careful evaluation of serum urea and creatinine concentrations and urine specific gravity is required before radioiodine treatment of hyperthyroidism [23].

Radioiodine treatment of hyperthyroidism in cats — radioprotection of staff and environment

Just as in humans, a crucial factor is the radioprotection of staff securing radioiodine-treated cats, due to the radioactivity of the animals themselves and their urine. The effective decay half-time after oral administration of 178 to 204 MBq of 131-I (T1/2E) for surface emissions was 2.19 to 4.70 days, and T1/2E for urine radioactivity was 2.16 to 3.67 days. Surface gamma-radiation emission rates for cats following administration of I-131 appears useful in determining the upper limits (threshold) of urine radioactivity and are a valid method to assess the time at which cats can be discharged after I-131 administration [31]. In the USA, it varies between 3–7 days. In Germany, it requires hospitalization for approximately two weeks, although the practical considerations of radiation exposure of cat owners do not justify this long interval [32]. On the other hand, cats seem to tolerate the period of hospitalisation relatively well.

Hypothyroidism

Hypothyroidism is a relatively frequent disorder in dogs. Underlying causes include thyroid dysgenesis and inherited iodination defects. Scintigraphy readily differentiates between those two conditions because animals with thyroid dysgenesis have minimal uptake of radionuclides in the anatomic region of the thyroid gland, whereas animals with iodination defects have enlarged thyroid lobes with normal or increased tracer uptake [33]. In thyroid carcinoma and associated hypothyroidism, scintigraphy helps to localize the lesion, and thus allows adequate planning for surgical resection and later for post operative evaluation [34]. Radionuclide therapy was also reported in animal thyroid carcinoma [35].

Other endocrine disorders

99m-technetium sestamibi may be use for the detection of a parathyroid adenoma in dogs with primary hyperparathyroidism [36].

Somatostatin receptor scintigraphy using indium In-111 pentatreotide can be performed in APUDoma tumours — this is important, because these tumours, in dogs, have a poor long-term prognosis due to a high rate of metastases and recurrence; staging (and therefore prognosticating) is difficult and usually done at the time of surgery [37, 38].

Cardiology

Equilibrium gated blood pool study proved to be useful in dogs with an X-linked, Duchenne-like, muscular dystrophy involving myocardium, the same as human Duchenne muscular dystrophy [39].

Nuclear scintigraphy with 99mTc-MAA proved to be a quick alternative method to cardiac catheterization in diagnosing right-to-left cardiac shunts and quantification of shunt fraction [40].

In peripheral vessels, first-pass radionuclide angiography proved to be useful in detecting aortoiliac thrombosis [7].

Lungs

Conventional perfusion scintigraphy has the similar indications, acquisition mode and outcomes as in humans [41].

Ventilation/perfusion scintigraphy in horses provides valuable additional information on regional lung function that is not obtainable from conventional thoracic radiographs. This is particularly true of horses with chronic obstructive pulmonary disease and those suspected of having some form of small-airway disease. Findings from horses with chronic obstructive pulmonary disease have improved the understanding of the radiographic patterns of air trapping and vascular distribution, and provided us with a sensitive means of detecting residual bronchial changes in the absence of clinical signs of the disease. Several other scintigraphic parameters such as mucociliary clearance and abscess-avid labelling show promise for future lung imaging on clinical cases, but still require further research to develop appropriate techniques for delivery and image analysis [42].

Gastrointestinal tract and kidneys

GI tract

Probably radionuclide diagnosis of portosystemic shunts (PSSs) in cats and dogs is most important here.

Portosystemic shunts (PSSs) are abnormal venous communications allowing blood in the portal system to enter the systemic venous system directly, without passing the liver. The shunted blood contains abnormally high levels of compounds absorbed from the intestinal tract that are normally removed, detoxified or metabolised by the liver [43]. Shunts are classified as intra- and extra-hepatic, or, alternatively, as congenital or acquired. Most feline congenital PSSs consist of a single large vessel representing a developmental error in which a vascular communication is maintained between abdominal veins derived from the cardinal and vitelline veins. Extrahepatic shunts are located outside the liver parenchyma and most commonly empty into the prehepatic *vena cava*. However, some cats may have atypical PSS connections. The clinical signs in dogs and cats with portosystemic shunts are highly variable, but usually involve poor growth and central nervous system signs of postprandial hepato-encephalopathy. These central nervous system signs may include intermittent disorientation, pacing, circling, tremors and even seizures. Congenital shunts are best managed with surgical intervention, where acquired need medical treatment. To accomplish this task, veterinarians must be able to identify patients in which a PSS is a strong possibility.

Transcolonic portal scintigraphy is a non-invasive method of diagnosing PSS and also allows calculation of the shunt degree, although scintigraphy, unlike jejunal vein portography, cannot aid in precise anatomic shunt localization. With a cat under sedation, 99m-technetium (usually as DTPA compound) is placed into the colon where it is rapidly absorbed into the portal system. In an animal with normal portal circulation, the liver field is the first marked by a radionuclide flow; in PSS, the area represented by a liver is a void, whereas the heart is the first organ illuminated by the radiotracer flow [43].

Surgical options for PSS occlusion include ligation for acute vessel occlusion and for slow vessel occlusion using an ameroid constrictor. The prognosis is based on the degree of shunt occlusion and the ability of the liver to adapt to increased hepatic blood flow [43]. However, post-operation mortality is high.

The opinions on hepatobiliary scintigraphy with HIDA derivates are controversial. Whereas some authors advocate this method in lambs [44], dogs and cats [45], the others say that the method is insensitive in cholangiohepatic lesions [46]. Quantitative hepatobilliary scintigraphy facilitates the interpretation of the study [47].

Kidneys

In cats and dogs, renal insufficiency is relatively frequent. There are number of diseases that can affect the kidneys in animals, which include: infections, neoplasms, cysts, nephrolithiasis, and injury from toxin exposure (glycol antifreeze, aspirin, acetaminophen, ibuprofen), as well as a number of inflammatory diseases (glomerulonephritis, systemic lupus). Diagnosis of kidney disease is difficult in the stage of compensation, and impossible when based solely on routinely performed laboratory tests of blood and urine. As in humans, only scintigraphy allows unilateral assessment of renal function, which is most important in animals with morphologically altered kidneys, such as kidney cysts, hydronephrosis or tumours [48]. Quantitative and qualitative scintigraphic measurement of renal function are presently applied in practice [49]. Determination of the kidney's glomerular filtration rate (GFR) is often taken into account in surgical planning. Only scintigraphy has the ability to measure individual kidney function. It is of importance in case of planned surgical nephrotomy or nephrectomy.

As in humans, nuclear medicine techniques may be useful in evaluating acute renal allograft rejection in dogs and cats, although there is a debate on superiority of scintigraphic over radiographic findings in those patients [50].

Infection and inflammation

99mTc-HMPAO-labelled leukocytes scintigraphy is an effective tool for the diagnosis of orthopaedic infection as a cause of lameness in horses [51].

99mTc-HMPAO-labelled leukocytes were also used in assessing small intestinal malabsorption in horses. Intestinal uptake of activity was detected in 12 of the 17 cases, but in none of the control horses. The technique was therefore specific for intestinal pathology, but failed to detect some horses that might have had intestinal pathology. No indications of the horses' specific pathology were obtained, and their prognosis or response to treatment could not be predicted [52].

99mTc-labeled radiopharmaceutical ciprofloxacin can be used in dogs to reveal the site of an infection [53].

Imaging — miscellanea

Some data might be available from feline hysteroscintigraphy. These findings demonstrated that fluids or particles deposited in the vagina of the cat could be transported into the uterus during some stages of the oestrous cycle. The fluoroscopic and scintigraphic techniques may be further modified to permit more detailed studies of uterine contractile patterns and sperm transport in the feline female reproductive tract. The information on cervical patency is also of value for the development of techniques for artificial insemination in this species, and should also be studied in the ovulatory cycle [54].

Radionuclide therapy

Radionuclide therapy of hyperthyreosis in cats is reviewed above. High fixed doses (more than 1000 MBq) were used in cats after surgical removal of thyroid carcinoma [55].

Bone and joints

153-Sm-EDTMP has been experimentally used in veterinary medicine for more than a decade to treat bone tumours and to provide bone pain palliation [56, 57]. Lattimer and co-workers, after extensive studies in normal dogs [56], applied 153-Sm-EDTMP in forty dogs with bone tumours [57]. Bone pain palliation occurred in most cases. Remarkably, there were complete regressions of some tumours. During the following years, Milner and co-workers from South Africa [58], and Moe and Aas from Norway applied 153-samarium in treating osteosarcomas [59, 60]. Their results include the complete regression of tumours in 2 out of 9 treated dogs. However, in other patients, the palliative effect of radionuclide therapy could sparsely be documented.

Radionuclide synovectomy may be applied in horses with good results, although a "flare" phenomenon may last for up to 72 hours [61]. In animals, radiosynovectomy using 166-holmium ferric hydroxide macro-aggregate or 153-samarium bound to hydroxyapatite microspheres and 90-yttrium silicate may be considered as a supportive therapeutic option for inflamed joints with synovial lining hyperplasia. It should preferably be used in combination with pharmacological treatment and/or physical therapy in cases of osteoarthritis prior to surgery or joint replacement [62].

Ophtalmology

Corneal pannus was shown to respond to radiation therapy with Sr-90, and long-term benefits can be achieved. Side effects are minimal. Optimal sequencing of therapy and dosage still has to be examined [63]. Good results were reported following the implantation of gold-198 seeds with 65 Gy by local delivery in cat's eyelid carcinoma [64].

Radionuclide therapy — varia

Attempts were made to treat essential thrombocytaemia, with promising results [65].

Staff and equipment

Veterinary dedicated medical equipment dates back to the eighties [66]. It required a specially constructed gantry, with a head on a long arm, to enable the imaging of heads and legs in horses. Today, now that nuclear medicine department are numerous, either in veterinary hospitals or outpatients practices, there exists dedicated veterinary PET equipment, with large stationary gantries enabling large animals to be scanned. On some occasions, gammacameras originally suited for humans are regenerated and reconstructed for animal studies either by extension the arm of the gammacamera's head or by constructing a special large gantry to enable the study of large animals.

Radioprotection of veterinary staff is not a major problem within the legislated limits for whole body doses, caution should be paid to secure radioactive waste secondary to urine radionuclide excretion [67].

Concluding remarks

As shown above, veterinary nuclear medicine is an interesting entity, covering most fields of interest of radionuclide diagnostics in humans. Veterinary nuclear medicine is very popular in the USA and its popularity in Europe is growing. As mentioned in the introduction, in Central Europe it is not very popular, and scientific activity is in fact limited the to the group of Dr. L. Balogh from Budapest. This situation should be changed for the benefit of local nuclear medicine communities.

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