

PET/CT Newsletter is a free publication dedicated to informing and educating medical professionals on the topic of molecular imaging. Thank you for your interest and we hope you find our newsletter stimulating and informative.

Table of Contents

Prognosis accuracy improves with PET/CTp 1

Test shines a light on why you're in pain.....p 2

C-11 PiB PET shows treatment success for Alzheimer's.....p 3

Case Study of the Month p 4-5

JNM: NanoPET/CT valuable in preclinical researchp 6

DOTA-NOC-PET/CT aids tumor treatment.....p 6

Surgical alternative for mesothelioma?p 7

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Positron Emission Tomography (PET) is a non-invasive diagnostic imaging procedure that can provide unique information for accurate TNM staging. Many cancers exhibit increased glucose metabolic rates which can be identified with PET via the radio-pharmaceutical ¹⁸F-FDG. Since changes in glucose metabolism often occur before changes in anatomy (e.g. tumor growth), PET can often identify the presence of disease earlier than other anatomic imaging techniques. Early disease identification is particularly critical during the assessment of nodal involvement or the determination of the presence of metastatic disease.

In The News

Mesothelioma Prognosis Accuracy Improves with PET/CT 'Delayed Phase'

*By Fred Park
survivingmesothelioma.com
November 16, 2011*

More research has confirmed the value of FDG-PET/CT technology for predicting treatment response in mesothelioma – especially when the scan is conducted in two phases.

Positron emission tomography (PET) is a nuclear medicine imaging technique that produces three-dimensional images of functional processes in the body. When the molecule FDG (fluorodeoxyglucose, a type of sugar) is used as the tracer, PET allows doctors to 'see' metabolic processes as they are happening. Because metabolism is often higher in cancer cells, FDG-PET has proven to be a useful tool for diagnosing mesothelioma, the asbestos-linked cancer. When FDG-PET is combined with computed tomography (CT), another powerful imaging test, the resulting images contain even more potentially crucial diagnostic, staging and prognostic information for mesothelioma.

Now, a study conducted in Japan and published in the international medical journal *Oncology Reports* has found that FDG-PET/CT may be even more effective for determining mesothelioma prognosis when used in a particular way. The researchers reviewed the FDG-PET/CT results of 31 patients who had been confirmed as having mesothelioma. While 30 (97%) of the patients showed abnormal cellular uptake of the FDG when they were scanned 1 hour after being injected with the FDG tracer, one did not. The results of scans done at 60 minutes are referred to as 'early phase' results.

But when the same scan was administered 2 hours after the injection (called 'delayed phase'), all 31 mesothelioma patients were found to have

abnormal scans. Furthermore, the abnormal FDG uptake values at the delayed phase were higher in every patient than they were at the early phase. The delayed phase scan also found metastasis to the lymph nodes in 7 (23%) patients and to other areas in 8 (26%) mesothelioma patients. The researchers concluded that an abnormal FDG uptake value in the delayed phase "is a more reliable prognostic factor than in the early phase".

In another recent wide-ranging assessment of the FDG-PET/CT technique in *Molecular Imaging and*

Biology, a group of Indian researchers conceded that "disease prognosis... is an evolving area where this modality has demonstrated significant promise" and that dual time point and delayed imaging may improve the technology's effectiveness for this purpose. If the results of the Japanese study are confirmed in further studies, it suggests that mesothelioma doctors who use FDG-PET/CT scans should rely more heavily on the uptake values seen in the delayed phase of the

test, rather than the early phase, in determining the patient's prognosis.

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Basu, S, "Current Evidence Base of FDG-PET/CT Imaging in the Clinical Management of Malignant Pleural Mesothelioma: Emerging Significance of Image Segmentation and Global Disease Assessment", October 2011, *Molecular Imaging and Biology*, pp. 801-11.



Test that shines a light on why you're in pain

By Rachel Ellis
Mail Online
November 15, 2011

Doctors have developed a new technique which allows them to 'see' pain for the first time. The technology could provide relief for some of the 10 million Britons whose lives are blighted with chronic pain from conditions such as arthritis, cancer, back conditions and headache.

Diagnosing the cause of pain is notoriously difficult — because doctors have to rely solely on the patient's description, in many cases it's impossible to pinpoint exactly which part of the body is causing the discomfort.

This makes treatment difficult and can be extremely frustrating for patients, who are left in debilitating pain.

But now researchers from Sweden have come up with a new test which involves injecting special 'markers' into the body; these markers bind to inflamed tissue and light up under a scan. This enables the doctors to see exactly where pain is coming from.

And with more precise information this could mean better treatment for thousands of pain sufferers.

Torsten Gordh, professor in pain medicine at Uppsala University Hospital, who carried out the research, explains: 'Most doctors have help from blood tests and imaging methods like X-ray, CT or MRI scans when diagnosing different diseases. But none of these show pain — it is something that is invisible.'

The test, the culmination of more than ten years of research, is based on a molecule called C-D-deprenyl which collects around inflamed tissue.

Inflammation is the body's natural response to any kind of harm, such as infection, injury or irritants. It occurs when white blood cells and fluid from the blood move into the injured tissues in an attempt to remove whatever is causing harm and initiate the healing process.

Inflammation also releases chemicals that stimulate nerve endings, causing pain — that's why inflamed tissue is seen as a sign that there is pain.

The new pain molecule was first identified in 1997, when doctors discovered it bound to inflamed tissue in the knee of a patient with rheumatoid arthritis. When steroids were injected in the knee to reduce inflammation, levels of the marker also dropped.

The Swedish team has now found a way of tracking this marker using positively charged electrons, called positrons, that light up when seen under a PET (Positron Emission Tomography) scan.



Relief at last? Researchers have developed a new technique that allows them to 'see' pain using a special 'marker' that is injected into the body

The study looked at 22 patients with whiplash neck injuries, and compared them with 14 healthy people.

Each received an injection of the positron-modified pain molecules. All the volunteers then underwent a PET scan immediately afterwards to show where the molecules had collected in the body.

Results showed whiplash patients had significantly higher numbers of the inflammation marker, and the precise area — the soft tissue surrounding the cervical muscles in the neck — was also pinpointed.

While this study looked at patients with whiplash, the test will also benefit patients with other pain conditions.

The study, funded by a Swedish insurance company Alliance Sweden, is still ongoing, and more research needs to be done before the test can become widely available.

Commenting on the research, Dr Michael Platt, a consultant in pain medicine at Imperial College Healthcare NHS Trust



Mesothelioma Radiation 'Boost': A Surgical Alternative?

By Mark Collier Parisi
survivingmesothelioma.com
 November 3, 2011

	Conventional imaging	PET/CT
Primary tumor detection		
Sensitivity	63.8%	78.3%
Specificity	92.5%	92.5%
Positive predictive value	93.6%	94.7%
Negative predictive value	59.7%	71.1%
Accuracy	74.3%	83.5%
Metastases detection		
Sensitivity	81.8%	97.4%
Specificity	100%	100%
Positive predictive value	100%	100%
Negative predictive value	69.6%	94.1%
Accuracy	87.2%	98.2%

DOTA-NOC-PET/CT findings established true positives for primary tumors in 54 patients and true negatives in 37. Three patients had false positives and 15 had false negatives.

The scans localized primary tumors in 18 patients with carcinoid, 15 patients with gastrinoma, four patients with insulinoma, and 17 patients with neuroendocrine tumors not otherwise specified.

Metastases results

DOTA-NOC-PET/CT also was able to detect metastases in 75 (97%) of 77 patients with one or more sites of metastases, with the hybrid modality finding a total of 106 metastatic regions among the 75 patients. The most common site of metastases was the liver, followed by the lymph nodes.

Once again, DOTA-NOC-PET/CT achieved sensitivity, specificity, positive predictive value, negative predictive value, and accuracy equal to or greater than that of conventional imaging. There were true-negative results in 32 patients and no cases of false-positive lesions. Two patients had false-negative results for liver metastases.

Naswa and colleagues also found that there was a "substantial change" in treatment for 21 patients (19%), whereas DOTA-NOC-PET/CT supported treatment decisions in 32 patients (29%).

Six patients (5%) underwent surgery for primary lesions that were not discovered by conventional imaging, including two patients who underwent resection for a primary tumor, and resection for an insulinoma, a glucagonoma, and a gastrinoma that were not seen by other modalities. DOTA-NOC-PET/CT helped determine the proper surgical plans for eight patients.

For five of the eight patients, the additional information provided by PET/CT led to the removal of more primary foci for a complete surgical cure. Additional nodal disease was detected in two patients who underwent complete excisions, while four patients were spared unnecessary surgery because the scans found an advanced stage of the disease.

DOTA-NOC-PET/CT "appears to be a highly sensitive and specific modality in the detection of gastroenteropancreatic neuroendocrine tumors," Naswa and colleagues concluded. "It is better than conventional imaging for this patient population and can have significant impact on patient management."

In addition, a negative finding on DOTA-NOC-PET/CT "can guide the treating physician to choose an alternate form of treatment," they wrote.

For mesothelioma patients who are not candidates for surgery, new research suggests that an escalated dose of radiotherapy in the right place may help slow the cancer's progression.

Mesothelioma, a cancer of the lining around the lungs and other organs, is hard to treat with traditional therapies in part because of its atypical configuration. The cancer tends to spread across the thin, membranous tissue of the mesothelium in a 'sheet' formation, rather than a solid mass. The odd shape of mesothelioma tumors not only makes them difficult to remove surgically, but can also make them challenging to treat with radiation without harming vital organs beneath such as the lungs.

But a group of radiology researchers in Milan, Italy found that, not only did an escalated dose of precision radiation appear to improve overall mesothelioma survival, but it also had a 'significant impact' on localized recurrence of the treated tumor. To conduct their study, the team utilized helical tomotherapy, an advanced method of delivering intensity modulated radiation therapy (IMRT) that is especially well-suited to irregularly-shaped tumors like mesothelioma. When paired with PET/CT imaging, tomotherapy can precisely tailor the radiation dose to a target area while minimizing the damage to healthy tissue around it.

Researchers administered radiation to two groups of 12 mesothelioma patients using PET/CT-guided tomotherapy. The first group was treated with 56 Gy targeted to all areas where cancer was detected, including all positive lymph nodes. The second group received the same dose to the whole pleura, in addition to a simultaneous 'boost' of 62.5 Gy to the positive areas.

No patients in the first mesothelioma group experienced acute or late complications from the radiation, but three patients in the second group did develop pneumonitis that lasted from 2 to 10 weeks. Median survival among patients in the first group was 8 months. Patients whose mesothelioma had been treated with an additional radiation boost had a median survival of 20 months. The difference in relapse rates between the two mesothelioma groups was also significant: 8 months vs. 17 months. Sixteen percent of first group patients experienced a year without local relapse, in contrast to a 1-year relapse-free rate in the second group of 81%.

Helical tomotherapy, as was used in this trial, has been shown in previous studies to be an effective adjuvant therapy after mesothelioma surgery, but few studies have focused on the technology as a primary treatment modality. Although the radiation 'boost' technique is still new and the size of the trial sample was small, the study's authors conclude that the method deserves further study and may offer an important alternative treatment option to mesothelioma patients who are unable to undergo surgical resection.

Sources:

- Fodor, A et al, "PET-guided dose escalation tomotherapy in malignant pleural mesothelioma", October 28, 2011, *Strahlentherapie und Onkologie*, Epub ahead of print.
- Sylvestre, A et al, "Mesothelioma at era of helical tomotherapy: Results of two institutions in combining chemotherapy, surgery and radiotherapy", June 8, 2011, *Lung Cancer*.



¹⁸F NaF bone PET • CT for staging and restaging a patient with prostate cancer

Clinical History

A male patient with newly diagnosed prostate carcinoma was referred for staging evaluation.

Imaging Findings

¹⁸F NaF WHOLE BODY TOMOGRAPHIC BONE IMAGING: 12/6/07

INDICATION: STAGING PROSTATE CANCER

TECHNIQUE*: The patient was injected with 11.2 mCi of sodium fluoride F 18 injection (¹⁸F NaF) intravenously and whole body PET acquisition was performed, followed by low-dose noncontrast coregistration CT.



Fig. 1

IMAGING FINDINGS: There were areas of focally increased uptake present in the cervical and upper thoracic spine, consistent with arthritic change. Similar benign uptake was present in low lumbar facets. Arthritic-related disease was present in acromioclavicular joints.

In the left aspect of the L5 vertebral body, there was a focus of intensely increased uptake corresponding to a 1.0 cm diameter sclerotic lesion, most likely representing blastic metastasis. There were no other areas of abnormal skeletal activity seen to suggest metastatic disease.

There was physiologic activity present in the urinary collecting systems. Review of the coregistration CT scan revealed severe changes of central lobular emphysema and mild prostate enlargement. There was a 2.0 cm benign cyst on the upper pole of the left kidney.

IMPRESSION:

1. There was focal increased uptake in the L5 vertebral body with associated blastic change on coregistration CT, consistent with metastasis from known prostate carcinoma.
2. No other scintigraphic evidence of metastasis was found.
3. Several other areas of arthritic-related activity are present, as detailed above.
4. Additional findings on coregistration CT scan of prostate enlargement, benign left renal cyst, and moderately severe fibro-emphysematous lung disease.

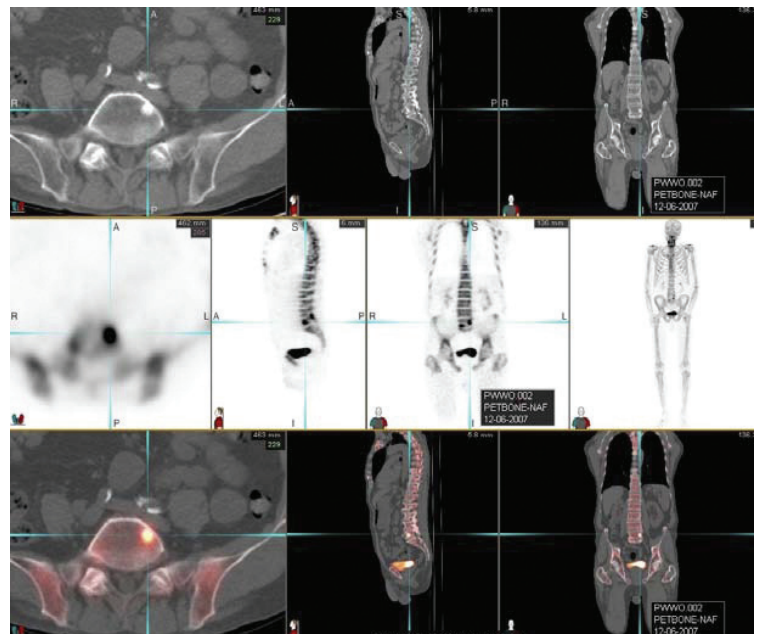


Fig. 2

Treatment

Lupron® therapy

Follow-up Imaging Findings

¹⁸F NaF WHOLE BODY TOMOGRAPHIC BONE IMAGING: 8/21/08

INDICATION: RESTAGING PROSTATE CANCER

COMPARISON: ¹⁸F NaF PET•CT bone scan of 12/06/07, and outside CT 09/17/07

CLINICAL HISTORY: A male patient with history of prostate carcinoma, treated with Lupron for follow-up and restaging.

TECHNIQUE*: The patient was injected with 13.6 mCi of ¹⁸F NaF intravenously and whole body PET acquisition was performed, followed by low-dose noncontrast coregistration CT.



Fig. 3

IMAGING FINDINGS: Since the last bone scan on 12/06/07, the single metastatic focus located in the L5 vertebral body had increased slightly in size, formerly 1.0 cm in diameter, now 1.5 cm in diameter. There was no evidence of other metastatic lesions. There were multiple stable areas of abnormal activity present due to arthritic disease including the L4-5 facets and right L5-S1 vertebral interface, cervical spine including facets C1-2 and C6-7 vertebral body interfaces and both acromioclavicular joints. There was physiologic uptake in both urinary collecting systems.

Discussion

Prostate cancer is the most common malignancy in men. Clinical nomograms based on prostate-specific-antigen (PSA) levels, Gleason score at biopsy, and clinical stage at presentation have been generated for pretreatment risk stratification and prediction of the probability for local recurrence or distant metastatic spread. On the basis of these parameters, patients are categorized at diagnosis as having low-risk or high-risk primary cancer.¹ Patients with low-risk cancer are unlikely to have metastatic bone involvement. Therefore, the routine use of bone scintigraphy for primary staging in all patients with newly diagnosed prostate cancer has been discouraged.¹ Bone scintigraphy is mainly reserved for patients with high-risk cancer, elevated serum alkaline phosphatase levels, bone pain, or equivocal bone lesions.

¹⁸F NaF PET•CT has been found to be a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer.² In this case, ¹⁸F NaF PET•CT revealed a lumbar spine prostate metastasis that would have been challenging to pick up on a standard technetium bone scan, and the follow-up PET•CT scan confirmed the initial call.

Data courtesy of Ronald Smith, MD, Providence Western Washington Oncology, Lacey, Washington

References:

1. Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. *Semin Nucl Med.* 2004; 34:274–292.
2. Even-Sapir E, Metser U, et al. The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: 99mTc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, ¹⁸F-Fluoride PET, and ¹⁸F-Fluoride PET/CT. *Journal of Nuclear Medicine* 2006; 47(2):287-297.

* Any of the protocols presented herein are for informational purposes and are not meant to substitute for clinician judgment in how best to use any medical devices. It is the clinician that makes all diagnostic determinations based upon education, learning and experience.

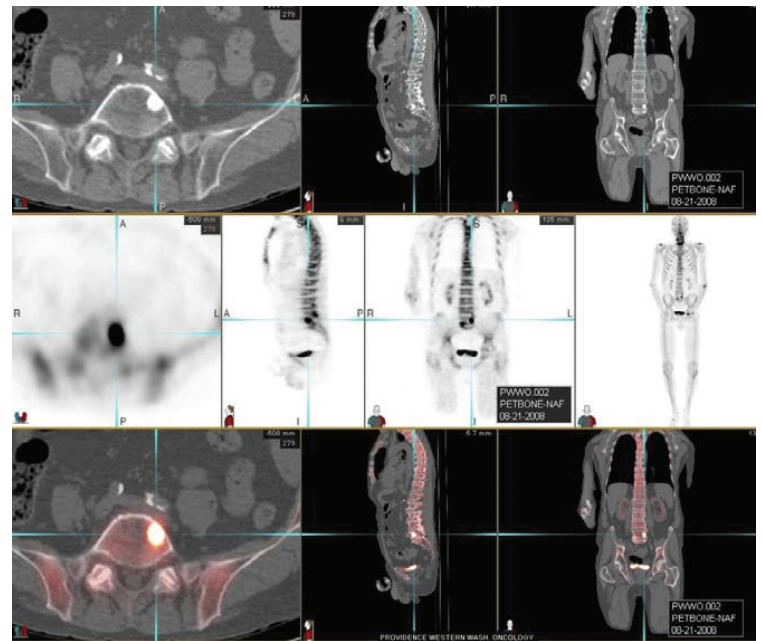


Fig. 4

Review of the coregistration CT scan images demonstrated moderate centrilobular emphysema. A cyst in the upper pole of the left kidney appeared to have resolved.

IMPRESSION:

1. Single focus of blastic metastatic disease, still metabolically active, increased from 1.0 cm to 1.5 cm in size on coregistration CT scan.
2. Various areas of arthritic uptake are present, most pronounced in cervical spine and low lumbar facets.

JNM: NanoPET/CT valuable in preclinical research

*By Brian Dunham
MolecularImaging.net
November 2, 2011*

In a performance evaluation, the National Electrical Manufacturers Association found the NanoPET/CT system to be of significant value in preclinical research, according to an article published in the November issue of the Journal of Nuclear Medicine.

Istvan Szanda, of the division of imaging sciences and biomedical engineering at Kings College London, and colleagues evaluated the spatial resolution, sensitivity, counting-rate capabilities and image quality in the system.

Designed to be compact and allow sequential PET and CT imaging in a single session for small animals, the NanoPET/CT is comprised of 12 detector modules, which are split into groups of three and connected to four analog-to-digital converter cards, which then transfer data to a computer.

"The scanner behaved in a stable fashion throughout all experiments, which were facilitated by the highly flexible data acquisition and readout," the authors wrote. "The energy resolution and temporal resolution are comparable to those of other preclinical PET systems with a similar overall configuration."

Szanda and colleagues noted that the NanoPET/CT's performance parameters were similar or exceeded those of comparable systems, and the spatial resolution is the highest among currently available commercial systems.

"The larger number of detector crystals, arranged with a fine pitch, results in excellent spatial resolution, which is the best reported for currently available commercial systems," the authors wrote. "The absolute sensitivity is high over the field of view. Combined with excellent image quality, these features make the NanoPET/CT a powerful tool for preclinical research."

DOTA-NOC-PET/CT aids neuroendocrine tumor treatment

*By Wayne Forrest
AuntMinnie.com staff writer
November 10, 2011*

PET/CT scans with the radiotracer gallium-68 (Ga-68) DOTA-NOC are "highly sensitive and specific" for detecting gastroenteropancreatic neuroendocrine tumors, outperforming conventional imaging such as CT, ultrasound, and MRI, according to a study published in the November issue of the American Journal of Roentgenology.

The research, led by Dr. Niraj Naswa from the department of nuclear medicine at All India Institute of Medical Sciences, also found that the information gleaned from Ga-68 DOTA-NOC-PET/CT can significantly affect patient treatment for the neuroendocrine tumors (AJR, Vol. 197:5, pp. 1221-1228).

Gallium-68 DOTA-NOC binds to somatostatin receptors, which are found on the surface of neuroendocrine tumors. By injecting the tracer into patients, PET/CT scans can be used to visualize the tumors.

CT, ultrasound, and MRI historically have been used to diagnose gastroenteropancreatic neuroendocrine tumors, with MRI being the most sensitive for detecting liver metastases, which can be difficult to localize because of their small size, the authors noted.

Subjects and methods

The prospective study enrolled 109 patients with gastroenteropancreatic neuroendocrine tumors who were evaluated with Ga-68 DOTA-NOC-PET/CT between October 2007 and September 2010. The researchers included only the initial PET/CT studies -- not any follow-up exams -- in their analysis.

The results were analyzed based on staging the disease in patients with confirmed neuroendocrine tumors, detecting recurrence in patients who had been treated for neuroendocrine tumors, and diagnosing neuroendocrine tumors in patients suspected of having the disease.

Naswa and colleagues also sought to compare PET/CT results with conventional imaging modalities to determine whether the results of Ga-68 DOTA-NOC-PET/CT would alter patient treatment plans.

The scans were performed on a dedicated PET/CT scanner (Biograph, Siemens Healthcare), with an injected dose of 132 MBq to 222 MBq of Ga-68 DOTA-NOC. PET/CT scans were performed after a 45- to 60-minute uptake period.

Two experienced nuclear medicine physicians evaluated the DOTA-NOC-PET/CT images and were blinded to the findings of structural imaging. Positive findings on the scans were localized to anatomic images from the unenhanced CT portion of the scan. The criterion for correct detection was both positive DOTA-NOC uptake and the correct anatomic localization of the tumor.

Primary tumor results

A review of the images found that DOTA-NOC-PET/CT detected primary tumors in 57 (79%) of 72 patients, with a total of 67 primary tumors localized in the 57 patients. The most common site of primary tumor was the pancreas. PET/CT was unable to localize primary tumors in the remaining 15 patients.

The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of DOTA-NOC-PET/CT for primary tumors was equal to or surpassed that of conventional imaging in all five evaluations.

and the Wellington Hospital, London, says the scan is an interesting step forward in pain management which could lead to better treatment for a whole range of patients.

'This test gives us more of an idea of what targets to aim for and may enable us to treat it better in the early stages with medication, steroid injections or physiotherapy, so that it doesn't turn into a long-term problem.

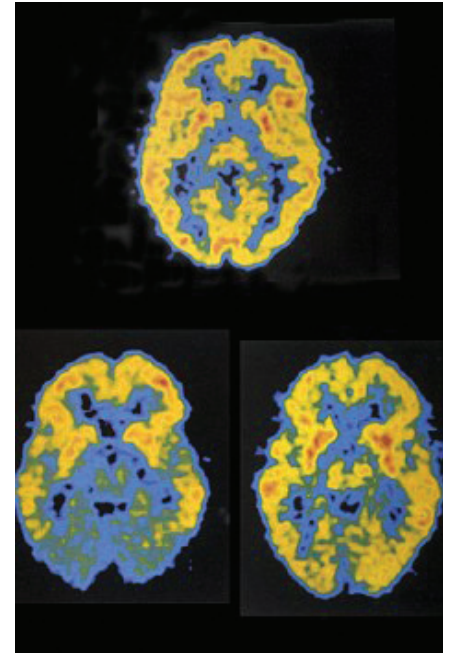
'In the future and with more research, it may be possible to use this test for other chronic pain conditions.'

Meanwhile, research has also shown that a herb widely used for its sedative effects can be effective for period pain.

The new study, being reported in the International Journal of Gynecology & Obstetrics, involved 100 women, half of whom took valerian root pills three times a day for three days at the onset of menstruation, for two consecutive cycles, while the other half took a placebo sugar pill.

Pain was assessed using a scoring system. At the start of the trial, the pain experienced by the two groups was the same.

Results show that the pain score dropped from 7.45 points to 1.99 in the second cycle among women taking the herb, which is a flowering plant that grows throughout Europe. In the placebo group, the pain score went down from 7.07 to 4.41. Just how it works is not clear, but one theory is valerian relaxes muscles, which reduces pain.



Scan: The scientists have found a way of tracking the molecule marker which bind to inflamed tissue. They then show up under light, which could result in better treatment for patients.

C-11 PiB PET shows treatment success for Alzheimer's disease

By Wayne Forrest
AuntMinnie.com staff writer
October 10, 2011

Using PET imaging with the radiopharmaceutical carbon-11-labeled Pittsburgh Compound B (C-11 PiB), researchers found that treatment with the antibody gantenerumab appeared to reduce amyloid levels in the brains of Alzheimer's patients, according to a report published online October 10 in Archives of Neurology.

Gantenerumab is a human anti-amyloid-beta monoclonal antibody currently in clinical development for the treatment of Alzheimer's disease by F. Hoffmann-La Roche Neuroscience and GE Healthcare. In previous studies, gantenerumab has bound in vivo to amyloid-beta plaques in mice. Five months of treatment with gantenerumab significantly decreased the amyloid plaque load in the mice.

The ability to reduce amyloid-beta plaque levels in the brain could help decrease or slow the progression of Alzheimer's disease and dementia, as amyloid plaque is associated with the advance of both neurological conditions.

In this study, two consecutive cohorts of patients with mild-to-moderate Alzheimer's disease received two to seven infusions of intravenous gantenerumab (60 or 200 mg) or placebo every four weeks. In addition, brain tissue from two patients with Alzheimer's was obtained during tumor surgery and was coincubated with gantenerumab as an ex vivo study (Arch Neurol, October 10, 2011).

The levels of amyloid-beta in the brain were measured using C-11 PiB with PET (Ecat Exact HR+, Siemens Healthcare). C-11 PiB binds to amyloid in neural tissues and can be used to evaluate changes in amyloid levels.

PiB-PET was instrumental in a recent study that concluded passive immunization can reduce brain amyloid levels in vivo after 18 months of treatment, according to the authors. The approach was also less likely to induce severe neuroinflammation. PiB-PET has also demonstrated that it can be used to detect high concentrations of amyloid plaques during the early stages of Alzheimer's disease.

In the current study, lead author Dr. Susanne Ostrowitzki, from Hoffmann-La Roche, and colleagues determined the reduction in amyloid-beta plaque was directly related to the size of the gantenerumab dose. The mean percent change from baseline difference relative to placebo in cortical brain amyloid level was -15.6% for patients receiving 60 mg of gantenerumab and -35.7% for those receiving 200 mg of gantenerumab.

The efficacy of gantenerumab was also seen in the mean percent change from baseline compared to total PiB signal, at 11% for the placebo group, 2.1% for the 60-mg group, and -9.4% for the 200-mg group.

"Our study demonstrates that two to seven months of treatment with gantenerumab led to dose-dependent amyloid reduction in the brains of patients with Alzheimer's disease," the authors wrote. "Additionally, our findings in the placebo-treated patients support previous reports indicating that amyloid load continues to increase in many patients with mild-to-moderate Alzheimer's disease."

It is still unclear whether any reduction in brain amyloid levels will translate into clinical efficacy, Ostrowitzki and colleagues added. A phase II clinical trial is under way to investigate whether a clinical benefit can be achieved in gantenerumab-treated patients with Alzheimer's disease.

The research is supported by F. Hoffmann-La Roche. Several authors, including Ostrowitzki, are full-time employees of Roche/F. Hoffmann-La Roche. Study co-author Lennart Thurfjell, PhD, is a full-time employee of GE Healthcare.



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PET/CT NEWSLETTER

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