Use of CT-PET imaging in investigation of pyrexia of unknown origin

Sir,

Pyrexia of unknown origin continues to intrigue and elude clinicians, providing challenging clinical conundrums (Knockaert et al, 2003; Varghese et al, 2010). The use of computed tomography-positron emission tomography (CT-PET) imaging in pyrexia of unknown origin is not well established (de Kleijn et al, 1997). Published case series suggest it has very low diagnostic yield in patients without raised inflammatory markers (Bleeker-Rovers et al, 2009; Varghese et al, 2010).

The authors retrospectively reviewed the contribution of CT-PET scans to diagnosis of pyrexia of unknown origin at the Hospital for Tropical Diseases, London, from 2005–10. Thirty-three HIV negative patients (mean age 56 years, 21 male) had CT-PET imaging; 19 were inpatients and 14 were outpatients. Thirty patients (91%) had had previous imaging during investigation of pyrexia of unknown origin, including cross-sectional CT in 18 (54%). Final diagnoses were two cases of malignancy, nine which had an inflammatory or autoimmune basis, eight were infection, five were 'other', and nine were inconclusive (three patients died during evaluation). *Table 1* details the role of CT-PET in diagnostic evaluation.

The data involved a heterogeneous group, requiring a systematic exhaustion of tests, and these patients were often managed over long time periods with trials of therapies. CT-PET seemed to have been used as a last resort when conventional imaging was inconclusive and the clinician was debating the use of invasive tests. In this setting, a tertiary care centre in an inner-city location, CT-PET contributed minimally to diagnosis of pyrexia of unknown origin. Although 73% had an abnormal CT-PET, in only one patient (8%) did the new findings actually provide a diagnosis, and CT-PET made no contribution to diagnosis in patients with normal inflammatory markers. While it could be argued that CT-PET had use as a rule-out investigation, in the absence of any noted benefit and with significant cost, this should be interpreted cautiously.

The strength of these data is that they were based on detailed, chronological, case-record-based analysis of the contribution of CT-PET scanning to diagnosis. Undeniably, it was a small sample, and causes of pyrexia of unknown origin for which CT-PET has particularly high diagnostic yield over other cross-sectional imaging, e.g. large vessel vasculitis, were not represented in this group. Patients with pyrexia of unknown origin are a variable case-mix, and this may affect the investigations required. There is also disparity in access to CT-PET. In a tertiary centre, such as ours, patients with pyrexia of unknown origin have already been subject to extensive imaging. Further, there are limitations in making assessment based on a retrospective review. In this audit, the indications for CT-PET were determined from scan request forms as well as documentation in the notes. Similarly, conclusions made by the team and investigations that followed were dependent on this documentation.

These results and review of the literature emphasize the need for larger, prospective studies of the use of CT-PET in pyrexia of unknown origin, and sub-groups for which it has a particular role. These should objectively assess clinically relevant contributions to better inform diagnostic algorithms.

On reflection, a multidisciplinary approach (including infection specialists and nuclear medicine specialists) should improve decision making regarding the role of CT-PET in individual patients. There is a clear role in patients with contraindications to contrast. It has a very low yield in patients with normal inflammatory markers (Knockaert et al, 2003; Varghese et al, 2010). While current guidelines recommend CT-PET late in the diagnostic pathway, as followed in the authors' practice, prospective studies should explore the role of CT-PET as a first-line investigation in distinct pyrexia of unknown origin syndromes (Royal College of Radiologists, 2010; Varghese et al, 2010).

Table 1. Key findings

Patients (number)	Abnormal CT-PET No. (%)	Nodal uptake No. (%)	Other uptake No. (%)	Invasive investigations No. (%)	New findings from CT-PET (not identified on previous imaging) No. (%)	New finding deemed to be the cause of the PUO No. (%)
All patients (33)	24 (73)	15 (46)	15 (46)	14 (42)	13 (39)	1 (8)
Raised inflammatory markers (24)	20 (83)	12 (50)	11 (46)	12 (50)	11 (46)	1 (9)
Normal inflammatory markers (9)	4 (45)	3 (33)	4 (44)	2 (22)	3 (33)	0 (0)

CT-PET = computed tomography-positron emission tomography; PUO = pyrexia of unknown origin

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Sleep-induced hypoxaemia: remember medroxyprogesterone and acetazolamide

Sir,

The article by Zhang et al on sleep-related hypoxaemia in chronic obstructive pulmonary disease (COPD) (vol 74(9), 2013, p. 497) discusses some more commonly used pharmacological treatments for hypoxaemia. However, another three drugs have been studied in the context of sleep-related hypoventilation and are worth mentioning.

Fluoxetine (at a dose of 60 mg for only 3 days) has been used to improve hypoventilation via reduction of rapid eye movement-related hypoventilation in asymptomatic obese patients, without COPD (Kopelman et al, 1992). Fluoxetine significantly increased the minimum oxygen saturation recorded (fluoxetine 81% *vs* control 73%; $P<0.05$). The total apnoea/hypopnoea index fell in six subjects with fluoxetine. In five of the six the improvement was associated with the abolition of rapid eye movement sleep. Total sleep time and quality were not affected by fluoxetine. General use is limited by side effects including sexual dysfunction, nausea, insomnia and behavioural disorders.

Acetazolamide (a carbonic anhydrase inhibitor) has been used in patients with respiratory failure resulting from lung disease as a short-term treatment when there is associated metabolic alkalosis, often caused by loop diuretic acting as a respiratory stimulant via generation of a metabolic acidosis. In a placebo-controlled study (Gulsvik et al, 2013), at a dose of 250 mg three times daily, for 5 days, it improved PaO_2 significantly by 1.41 kPa (compared to 0.81 kPa in control group). Acetazolamide is often considered an adjunct with non-invasive ventilation concurrently or in place of this as a short-term measure. It is important to monitor renal function. While these data are interesting, a review of existing studies on acetazolamide (Bales and Timpe, 2004) did not show any longer term benefits on morbidity, mortality or quality of life in COPD patients although short-term improvements in ventilator parameters and arterial blood gases have been reported.

Finally, medroxyprogesterone (30 mg twice daily) has been used as a respiratory stimulant working via progesterone receptors in the hypothalamus in patients with COPD. Short-term results are encouraging but there are no long-term data to support benefits in morbidity, mortality or quality of life in COPD (Bales and Timpe, 2004). A short-term comparative study (Wagenaar et al, 2003) between medroxyprogesterone and acetazolamide in patients with COPD favoured the latter slightly in ability to improve daytime PaO_2 and reduced time with nocturnal desaturation but with similar reductions in day and night time $PaCO_2$.

It is worth remembering the potential short-term value of medroxyprogesterone and acetazolamide that might be better tolerated (metabolic acidosis and renal failure aside with the latter) than oral theophylline. Evidence for fluoxetine is very limited in COPD, and adverse central effects are more problematic. Longer-term studies are still not available to show a clear benefit on mortality, but such drugs might be useful in COPD patients who cannot tolerate non-invasive ventilation or where there are no other therapeutic options.

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Sir,

Dr Medford has highlighted some constructive points. Pharmacological therapies which may ameliorate some of the factors contributing to hypoxaemia during sleep in patients with COPD are an alternative approach. Some medications, including theophylline, long-acting β-agonists, and long-acting anticholinergics such as ipratropium bromide or tiotropium, are accepted therapies for nocturnal hypoxia in COPD. Combined use of oxygen therapy and pharmacological therapies not only improved nocturnal hypoxia but also lowered $PaCO_2$ in previous studies.

As Dr Medford mentioned, fluoxetine has been used to improve hypoventilation via reduction of rapid eye movement-related hypoventilation in asymptomatic obese patients, without COPD (Gulsvik et al, 2013). While the racemic mixture of fluoxetine has certain advantages, its disadvantages are also obvious, with headaches, nervousness, anxiety and insomnia reported as adverse effects. Other disadvantages are its long half-life and long duration of action.

Short-term medroxyprogesterone therapy effectively improved ventilation and decreased $PaCO_2$ in patients with COPD (Saaresranta et al, 2002). Combined treatment with medroxyprogesterone acetate and acetazolamide for 2 weeks in hypercapnic patients with COPD normalized arterial blood gas values and improved nocturnal oxygen saturation and the chemical drive with a relative modest increase in minute ventilation. The combination of medroxyprogesterone acetate and acetazolamide is more beneficial than with either drug alone (Wagenaar et al, 2002). It remains to be established whether long-term combined treatment in hypercapnic patients with COPD will postpone long-term oxygen therapy or non-invasive ventilation, or even improve life expectancy. Another study reported that oral steroid therapy in stable COPD improved nocturnal oxygen desaturation and increased total sleep time. Although there are no relevant data, a similar improvement might be expected with inhaled corticosteroids (Sposato et al, 2007).

Safety is an important concern when considering pharmacological treatment for sleep-induced hypoxaemia in patients with severe COPD. Knowledge about pharmacological treatments and other interventions may direct a better prognosis that is worthy of further research.

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