Palliative medicine for the cancer and non-cancer patient

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The importance of palliative and end-of-life care has been recognised with unprecedented Government investment in recent years, linked to the National Cancer Plan. Palliative care beyond cancer has also been highlighted within organ- and specialty-specific National Service Frameworks that set the scene for the document *Building on the best.*[1] This has led to investment in care pathways to improve end-of-life care in all settings, irrespective of diagnosis. Palliative medicine is central to these developments.

Good palliative medicine for all patients requires:

- The recognition and communication that prognosis is short. Prognostication is difficult; however, the question, 'Would I be surprised if this patient died within the next year?' can be a useful prompt to discussion, decision-making and care planning with the patient.
- Collaboration between specialties to evolve effective symptom management and models of care for the increasing number of people living and dying with advanced, progressive disease.
- Well-structured, coordinated and adequately resourced delivery of health and social care.

Prescribing for this group of patients is complex. Disease-modifying treatments may provide good palliation near the end of life for patients with advanced cancer and non-cancer diagnoses, such as cardiac, respiratory and renal failure. Drugs for direct symptom management are also usually needed. However, the balance between potential benefits and burdens of all medical treatment in the palliation of symptoms needs to be clear. This conference focused on the pharmacological management of patients in the palliative phase of their illness from whatever cause.

General pharmacology

Therapeutics in patients with advanced, progressive disease has been poorly researched as patients invariably meet exclusion criteria for clinical trials. Many such patients may be compromised by single organ impairment through to multiple organ failure. Age and cachexia can increase susceptibility to drug side effects. Delirium is prevalent and concordance uncertain. Polypharmacy is rife, sometimes justifiably, with a mixture of disease-modifiers, preventive measures such as PPIs and statins, and palliative care drugs for specific symptoms due to disease or the effects of other medications. As mentioned, therapeutic trials within palliative care are difficult, with ethical and practical barriers to recruitment and high dropout rates. There is a need critically to evaluate the evidence that is available, and to share experience across disciplines to further therapeutics in palliative care.

The individual approach to patients is paramount. In addition to comorbidities and polypharmacy, there is the challenge of route of drug administration when swallowing and gut absorption may be limited by weakness, fatigue, dysphagia, nausea and vomiting. Many drugs prescribed in palliative care are for off-license indications, or via off-license routes, with consequences for informed consent. With the administration of multiple drugs in patients with advanced disease the scope for drug interactions and side effects is huge. Symptoms related to drug administration may be missed and attributed to the underlying disease process. A firm grounding in pharmacology and a high index of suspicion are required.

In one study, 50% of hospice inpatients received at least one pair of interacting drugs, and educating prescribers led to fewer unwanted interactions.[2] Similarly, an audit of 160 patients attending palliative daycare found that 25 drug combinations involving 35 patients could have given rise to clinically important interactions.[3] There is the challenge of applying theoretical knowledge of drug metabolising enzyme systems, such as cytochrome P450, to the clinical situation. Some predicted interactions, such as increased sedation with midazolam when coadministered with erythromycin, are clinically significant.[4] Other predicted interactions may or may not be clinically relevant – with over 50 drugs in the *Palliative care formulary*[5] having the potential for interactions via cytochrome P450, and subtle clinical interactions may go undetected in the context of polypharmacy for complex symptoms.

Pain management

Morphine and palliative care are usually taken to be synonymous. Morphine remains the opioid analgesic of choice for moderate to severe cancer pain, but

wide inter-individual variability in morphine absorption and metabolism may lead to a poor analgesic response in up to a third of patients. Other opioids now available in convenient formulations include fentanyl, oxycodone, methadone, hydromorphone and buprenorphine. This has enabled palliative medicine physicians to switch from morphine to other opioids when toxicity or suboptimal analgesia is apparent. There is a growing body of clinical experience to support such practice, but no randomised controlled trials have been done to establish a robust evidence base. Laboratory work is progressing on the pharmacokinetics and dynamics of differing opioids. An observed synergy between opioids, and developments in pharmacogenetics, promise new therapeutic approaches to pain management, with the potential to tailor regimes more effectively for individuals with better analgesia and reduced side effects.

The role for opioids in the management of persistent non-cancer pain has been more controversial. One in five people in the UK have persistent pain, a total of 7.5 million people. The management focus for these patients is pharmacotherapy within rehabilitation. Pain management services cannot handle this volume of patients and there is a need for all health professionals to be trained in the assessment and management of patients with persistent pain. Opioids can provide analgesia, but may not improve quality of life. Problem drug use is uncommon. There are few long-term randomised controlled trials and many unanswered questions. However, there are concerns regarding cognitive, endocrine and immunological effects of long-term opioids, along with impact on driving and social skills.

Pain is not always managed with traditional analgesics. The use of bisphosphonates in the prevention and treatment of bone pain in cancer, osteoporosis and Paget's disease is now well established. As newer and more potent bisphosphonates become available, their efficacy and side effect profile in palliative care needs to be understood. Intravenous pamidronate continues as first-line treatment for malignant hypercalcaemia and bone pain in most palliative care practices, with newer agents such as zoledronic acid reserved for more resistant symptoms.

Emesis

Whilst theoretical models to understand pain are available and are evolving on the basis of laboratory and clinical studies, empirical knowledge of other palliative care symptoms is more limited. For example, effective strategies for managing emesis are applied widely, based on putative emetic pathways and neurotransmitters derived from animal models. Clinical trials of antiemetics are available for postoperative and oncology patients and in pregnancy, but have not been done in palliative care.

Pruritis

Itch is distressing for patients and a challenge for prescribers, being incompletely understood and difficult to treat in many circumstances. Thorough assessment of cause(s) is particularly important. Theoretical models help to inform therapy. The hypothesis that pruritus may be caused by an imbalance between central opioid tone and serotoninergic inhibition provides a rationale for the use of opioid antagonists or selective serotonin reuptake inhibitors (SSRIs) in certain types of pruritus. Antihistamines are not effective in chronic pruritus as histamine is not the causative agent – they merely provide sedation.

Delirium

Delirium is prevalent in elderly and palliative care patients, and is often amenable to prevention and treatment. Antipsychotics and benzodiazepines have a role in both the causation and palliation of delirium, and the relative merits and drawbacks of

Conference programme

- **Palliative care drugs, pitfalls for the unwary**
  Dr Martin Lennard, Reader in Clinical Pharmacology, University of Sheffield
- **Bisphosphonates – from science to practice**
  Dr Catherine Urch, Consultant in Palliative Care, St Mary's Hospital, London
- **Which opioid(s) should we use for pain?**
  Dr Columba Quigley, Consultant in Palliative Medicine, Hammersmith Hospitals Trust, London
- **Opioids for persistent non-cancer pain**
  Dr Karen H Simpson, Consultant in Pain Management, Leeds Teaching Hospitals Trust, Leeds
- **Recent developments in the treatment of pruritus in advanced diseases**
  Dr Zbigniew Zylicz, Consultant in Palliative Medicine, Hospice in the Weald, Kent, and Chair of Palliative Medicine, Nicolaus Copernicus University in Torun Collegium Medicum, Bydgoszcz, Poland
- **Drug handling in end-stage heart disease, reviewing cardiac drugs in the terminally ill (and when to worry about the QT interval)**
  Professor Allan Struthers, Professor of Cardiovascular Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee
- **Drug handling in end-stage kidney disease**
  Dr Joanna Chambers, Consultant in Palliative Medicine, Southmead Hospital, Bristol, and Dr Charles Ferro, Consultant Renal Physician, University Hospital Birmingham NHS Foundation Trust, Birmingham
- **Drug handling in end-stage liver disease**
  Dr Polly Edmonds, Consultant in Palliative Medicine, King's College Hospital, London, and Ms Sarah Stoll, Senior Liver Pharmacist, King's College Hospital, London
- **Prescribing antiemetics, does the science relate to practice?**
  Dr Kathryn Mannix, Consultant in Palliative Medicine, Royal Victoria Infirmary, Newcastle upon Tyne
- **Delirium in palliative care**
  Dr Max Henderson, Honorary Specialist Registrar, Department of Psychological Medicine, King's College Hospital, London

both classes of drug are reasonably clear. However, the keys to success lie in the differentiation of delirium from dementia and depression (particularly when all three elements are not infrequently present), and the identification and reduction of predisposing and exacerbating factors such as visual and hearing impairment, sleep deprivation, dehydration, metabolic factors and polypharmacy. Attention to the global picture has been termed 'evidence-based thoughtfulness' (Max Henderson). Such thoughtfulness has the potential significantly to decrease the incidence of delirium[6] and of sedation, with its attendant ethical and practical implications.

Palliation of organ failure

Symptoms such as breathlessness, fatigue, weakness, nausea and pain are common in patients with end-stage organ failure. Pharmacological management requires disease-modifying drugs to address the underlying cause and medication to palliate residual symptoms. Evidence for the specific use of drugs in this context is limited. This is particularly true of 'cinderella symptoms' such as fatigue and weakness, which have only become the focus of palliative care research in more recent years, and for which simple pharmacological solutions are unlikely to be found.

Heart failure

Greater collaboration between specialists in heart failure and palliative medicine is beginning to bear fruit regarding the safe and effective use of opioids in the relief of breathlessness. Palliative medicine physicians offer specialist skills in symptom assessment and in the creative administration of medication to patients in whom gastrointestinal absorption may be poor. Cardiologists can advise on which palliative care drugs are likely to be tolerated by patients with heart failure. For example, depression is underdiagnosed and undertreated in this group. Treatment of depression would improve if the diagnostic skills of palliative care were combined with the knowledge of which antidepressants would be least likely to impair cardiac function. There is now some evidence to suggest that sertraline is well tolerated and imipramine is relatively contraindicated.[7,8]

Rationalisation of drugs is important to minimise tablet burden and potential drug interactions. Many drugs may be safely stopped in patients nearing the end of life. Drugs such as statins clearly provide little benefit for patients with a short prognosis. Antihypertensives may be stopped in patients who have had significant weight loss and whose blood pressure has fallen as a result. Regular review of all drugs is good medical practice, but is of particular importance to patients at transition points in their illness. Clear communication with patients regarding cessation of drug treatment is, however, vital.

The fine balancing of benefits and burdens of treatment in end-of-life care is illustrated by drugs that affect the QT interval. Certain highly effective drugs in symptom management, such as cisapride, have been withdrawn because of the demonstrable dangers of QT prolongation in pooled data from large populations. While safety is paramount, certain well-informed patients at the end of life might opt for optimal management of vomiting above and beyond any potential risk of cardiac arrhythmia. However, as availability of such drugs becomes restricted, their production in time becomes unprofitable. Research into the safety and efficacy of such drugs in palliative care would also require rigorous justification.

Renal failure

Chronic kidney disease is prevalent and underdiagnosed. The incidence of renal impairment in palliative care patients is unknown, but is likely to be high, and it may increase side effects to common drugs, particularly opioids. All professionals prescribing in palliative care need a firm grasp of the physiology of end-stage renal disease, including the impact on all organ systems, so that prescriptions are appropriate in terms of drug, dose and route. Guidelines on prescribing in renal disease are available, however consensus is lacking.[9]

Better tolerated alternatives to the usual first-line analgesics, antiemetics and other palliatives are usually available. Even so, regular and frequent assessment and review are necessary for the safe and effective titration and substitution of drugs and to ensure that drug side effects do not outweigh the relevant symptoms in need of palliation. To this end, timely communication between potential prescribers is vital.

Within renal medicine, work is progressing on models of care for patients with end-stage renal disease. Traditionally, the emphasis has been on dialysis or transplantation, and the third treatment arm of conservative management has received little systematic attention. The need to develop conservative management options for patients with end-stage renal disease is pressing in light of a lack of evidence of clear benefit from dialysis or transplantation in this group.[10] Symptoms such as pain are common and psychosocial needs are likely to be prevalent. The assessment, review and management of these patients require a network of suitably trained professionals across care settings.

Liver failure

Patients with end-stage liver disease as a consequence of chronic liver disease (CLD), large volume metastases, or primary liver cancer on the background of CLD, receive care from a variety of disciplines. The extent of liver damage is difficult to define on the basis of liver function tests. The INR and serum albumin are probably the most sensitive indicators. No drugs can be considered to be well tolerated and the approach to symptom management has to be of accurate assessment of causes of symptoms, the initiation of low doses of appropriate palliatives, with cautious dose titration according to response and side effects. Regular review is essential and where possible, non-drug approaches to symptom management should be tried. Once on board, drugs are hard to eliminate, so prescriptions need careful thought.

Conclusion

Prescribing effectively in palliative care necessitates a mature understanding by the physician of the likely prognosis of the

patient. Only in this context can treatments be individualised with a true understanding of the relative benefits and burdens. Rationalisation of medication is essential and all unnecessary drugs should be stopped. This is likely to happen in a stepwise fashion as illness progresses. The approach must be pragmatic in the absence of a good evidence base in this context. Crucially, the goals of treatment should be understood by all prescribers for each patient. This requires good communication between all relevant clinical teams and primary care and the advent of non-medical prescribing makes this more of a challenge. Medication essential to good symptom management must be reviewed regularly as symptoms, goals and physiology change with advancing disease.

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