

pcf3 - Survey of Specialists in Palliative Drugs and Symptom Relief in Palliative Care

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Abstract

A quarter of all prescriptions in palliative medicine are for licensed drugs that are used for unlicensed indications or that are given by an unlicensed route. Such prescriptions may affect two thirds of inpatients in specialist palliative care units.^{1,2} Doctors have been recommended to record in the patient's notes the reason for prescribing outside the licence; to explain, where possible, the position to the patient (and carers, if appropriate) in sufficient detail to allow informed consent to be given; and to inform other professionals involved in the care of the patient of such prescribing, so that misunderstandings are avoided.³ Given the widespread use of drugs outside their licence in palliative care, strict adherence to these recommendations may be impractical. In view of the implications of these recommendations for doctors in palliative medicine and other doctors they advise, a position statement endorsed by the specialty would be helpful. We undertook a survey of current practice to inform the debate.

INTRODUCTION

All 182 palliative care services in the United Kingdom with a medical director or consultant were asked to complete anonymously a postal questionnaire in October 1999 (figure). Informed consent was defined thus: "Patients have been given the information they asked for or need about their treatment in a way they can understand so that whenever possible the patients have understood the nature, purpose and material risks of what is proposed and consent to it before you provide treatment."

One hundred and seventeen questionnaires (64%) were returned. When unlicensed prescribing was limited to consultants, this was generally in the context of a consultant based service. No respondents always obtained written consent to unlicensed use, and only a minority (<5%) always obtained verbal consent, documented unlicensed use in the patient's notes, or informed other professionals of it. The drugs for which these recommended practices were sometimes carried out were ketamine (58 reports), octreotide (19), ketorolac (15), midazolam (10), gabapentin (10), and amitriptylline (10). The only unlicensed drug use for which three of the services sometimes obtained written consent was

gabapentin for neuropathic pain—an indication for which it became licensed in 2000.

Invited comments covered three main themes. Firstly, respondents said that, given the prevalence of unlicensed use, it is impractical to obtain written consent routinely—and that discussion of unlicensed use could create unnecessary anxiety for the patient or carer. Secondly, some respondents sought consent only when prescribing drugs whose unlicensed use was not established in the specialty. Finally, other respondents made no distinction between licensed and unlicensed use and did not obtain verbal informed consent for use of any drug.

Comment

When prescribing drugs for use outside their licence, most specialists in palliative medicine do not routinely obtain verbal or written informed consent, document the reason for unlicensed use in the patient's notes, or inform other involved professionals of unlicensed use. When they do obtain consent, it is likely to be for the use of less established drugs and to be verbal rather than written. Strict adherence to the recommendations is not welcomed by palliative care specialists because of the number of drugs involved and the burden to patients and carers.

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This view is shared by the Royal College of Paediatrics and Child Health—the use of drugs outside their licence is also common in paediatrics—which has stated that in general it is not necessary to obtain the explicit consent of parents, carers, or patients for unlicensed use. The royal college has also stated that NHS trusts and health authorities should support therapeutic practices that are advocated by a respectable, responsible body of professionals.^{4,5}

	Yes	No	
1. Does your service operate a policy on providing information to patients and their carers about the prescribing of licensed drugs for unlicensed uses/routes?	2 (2)	113 (97)	
If 'yes' please provide any details/documentation of any policy your service is operating			
2. Do you limit the prescribing of drugs in this way to consultants only?	20 (17)	93 (79)	
	Always	Sometimes	Never
3. Do you obtain verbal consent from the patient/carers?	5 (4)	62 (53)	45 (38)
4. Do you obtain written informed consent from the patient/carers?	0 (0)	4 (3)	109 (93)
5. Do you document in the notes when you are using drugs outside of their licence and the reasons for this?	6 (5)	48 (41)	58 (50)
6. Do you inform other professionals when using such medication?	7 (3)	80 (68)	25 (21)
If you have answered 'always' to any of the above please provide details/documentation of any policy your service is operating			
If you have answered 'sometimes' to any of the above please answer the following questions			
	No of times		
7. How often have you obtained verbal or written informed consent from patients/carers or documented in the notes the reasons for using licensed drugs for unlicensed uses/routes in the past six months?	0	16 (20)	
	1-3	41 (50)	
	4-6	14 (17)	
	7-10	1 (1)	
	>10	10 (12)	
8. Please list the particular drugs, their use and route of administration			
9. Please add any comments that you may have about the obtaining of informed consent from patients/carers and documenting the use of licensed drugs for unlicensed purposes/routes in relation to your palliative medicine practice			

Figure: Questionnaire on unlicensed use of drugs that was sent to palliative medicine specialists, with numbers (percentages) of responses (n=117) to multiple choice questions

The continuing physical, emotional, and cognitive development in children sets them apart from adults. It influences all aspects of their care, including pharmacological treatment, their understanding of their disease, their communication skills, and their level of dependence.

Parents are usually the main carers for children, with care taking place at home. They and the child’s siblings will need support throughout the child’s illness and their bereavement.

Often, many professional and voluntary agencies are involved, as skill in different aspects of paediatrics and palliative care is needed. Care in hospital, care at home, respite care, and education all need to be coordinated, and community paediatric nurses often do this as key workers.

Many children have prolonged illnesses; an integrated approach is then required, with a gradual change in the emphasis of care between treatments aiming to cure or prolong life and palliative care, rather than one having rigid boundaries.

Although palliative care for children is a relatively young specialty, its importance is being increasingly recognised. The Royal College of Paediatrics and Child Health has established a special interest group to promote the best possible care and develop medical training. Similar commitment exists in nursing. The voluntary sector contributes heavily, particularly with children’s hospices, and government help has come through the “Diana nurses” project. Life threatening conditions for which treatment is available but may fail—for example, cancer

Conditions in which premature death is expected but long periods of intensive treatment to prolong good quality life are anticipated—for example, cystic fibrosis, HIV infection/AIDS

Progressive conditions that may extend over many years and for which no curative treatment is available—for example, Batten disease, mucopolysaccharidoses

Conditions with severe disability that, although not progressive, lead to extreme vulnerability and in which premature death is likely—for example, cerebral palsy.

Children than adults die, they also require palliative care. I am writing on behalf of the Palliative Care Working Group of the Royal College of Paediatrics and Child Health, which wants to alert readers to some of the special needs of children.^{1-2,1-3}

The illnesses from which children die are different from those from which adults die, and paediatric palliative care has emphasised the importance of developing services for children other than just those with cancer.

of both species showed similar responses. At a concentration of 0.02 mM Ag(I), most cells of *C. maltosa* lost their membrane potential within 2 min, whereas 0.02 mM Hg(II) had a negligible effect on membrane potential even at 15 min. The percentage of depolarized cells increased gradually after 15 min. At concentrations below 0.02 mM, the percentage of depolarized cells in Ag(I) reached a plateau (84%) within 15 min, but the percentage of depolarized cells in Hg(II) continued to increase with time (Fig. (Fig.2B).2B).

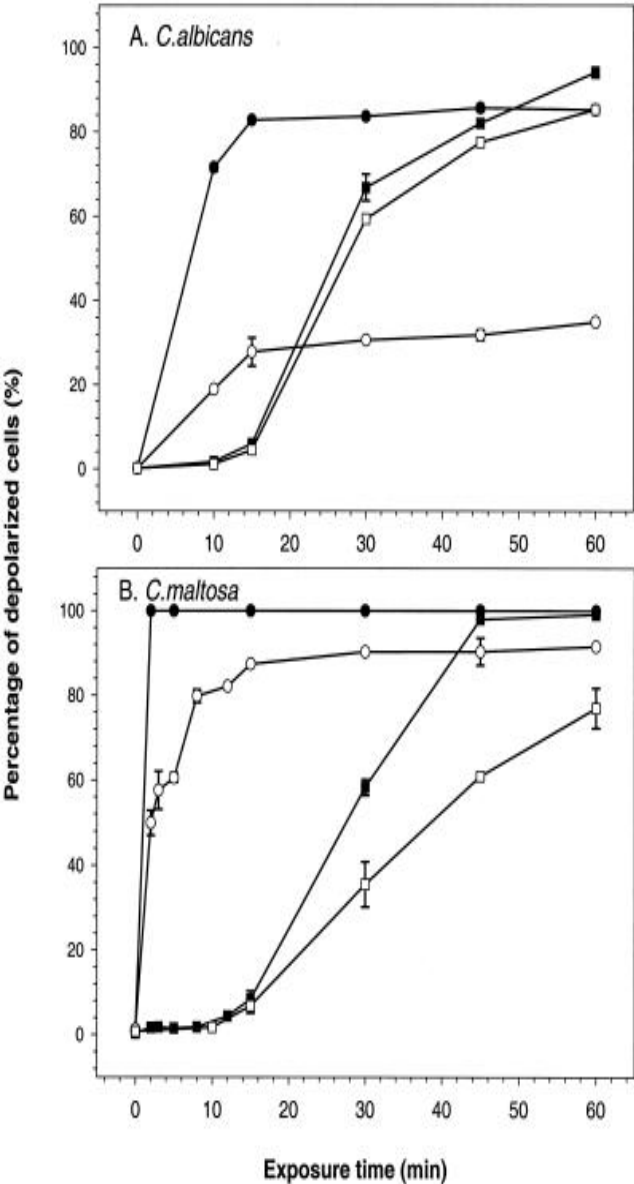


FIG. 2: (A) Depolarization with time of cells of *C. albicans* in 0.002 mM Ag(I) (●, 3.65×10^6 cells ml⁻¹; ○, 7.38×10^6 cells ml⁻¹) and 0.016 mM Hg(II) (■, 3.65×10^6 cells ml⁻¹; □, 7.38×10^6 cells ml⁻¹). (B) Depolarization of *C. maltosa* (2.33×10^6 cells ml⁻¹) in Ag(I) (●, 0.020 mM; ○, 0.004 mM) and Hg(II) (■, 0.020 mM; □, 0.010 mM). Each data point represents the average obtained from duplicate independent assays.

asterisks, MMP-9; open circles, MMP-13. Inhibition is expressed as percentage activity, when 0–11 μM calprotectin is present. Each point represents the mean of duplicates.

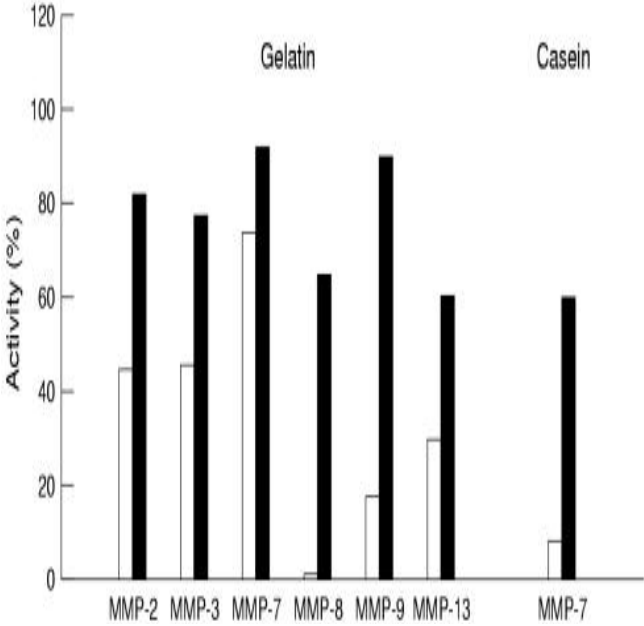


Figure 3: Relative activities of metalloproteinases in the gelatinolytic and caseinolytic microwell assays, when incubated with 11 μM calprotectin and 1 μM (open bars) or 100 μM (closed bars) zinc. The figures are expressed as percentage activity compared with activity without calprotectin.

Discussion

Our results show that modifications of the method described by Rucklidge and Milne allow the quantitative determination of MMP activities. This method avoids the use of radioactive isotopes and different substrates can be used. Furthermore, the assay system is simple and sensitive, allowing detection of 3 ng/ml or less. However, this method is more time consuming than a recently described method using biotinylated gelatin.¹⁴ Another aspect is that some substrates, such as collagen, may be altered and less available for enzymatic degradation as a result of the coating process or exposure to paraformaldehyde. For instance, collagen type 1 (from calf skin, Fluka, Buchs, Switzerland) was almost completely converted into gelatin, which was shown by the fact that it was rapidly degraded by trypsin (data not shown).

MMPs are activators of a broad range of cytokines, including interleukin 1, tumour necrosis factor α, Fas ligand, and transforming growth factor β,^{15–19} and thereby play important roles in regulating processes such as acute and chronic inflammation, tumour cell invasion, apoptosis, and macrophage chemotaxis. Calprotectin may affect various pathophysiological processes by competing with MMPs for zinc. Our study revealed that calprot

ectin inhibits the activity of all the enzymes tested, and that this inhibition was overcome by the addition of zinc. A higher concentration of calprotectin was necessary to inhibit some metalloproteinases than others, regardless of the substrate. In the gelatinolytic assay, MMP-3, MMP-8, and MMP-13 needed a 200–700 times molar excess of calprotectin to give a 50% inhibition. By comparison, up to a 18 000 times molar excess was necessary to give a similar inhibition of MMP-2 and MMP-9.

These results suggest that MMPs have different affinities for zinc, and that calprotectin has an even lower affinity, because a large excess was necessary for inhibition.

Structurally, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13 have one catalytic domain containing the zinc binding site. In addition, MMP-2 and MMP-9 have one zinc binding site closer to the C-terminal, suggesting a higher capacity for binding of zinc. MMP-7, the smallest of the proteins, also has one catalytic domain.¹ Nonetheless, a much higher concentration of calprotectin was needed to inhibit this enzyme than MMP-3, MMP-8, or MMP-13, which suggests that MMP-7 has a higher affinity constant for zinc.

The metalloproteinases are totally dependent on zinc for their enzymatic activities,¹ and our results support the hypothesis that some biological effects of calprotectin are linked to its sequestration of zinc. Sohnle et al showed that calprotectin inhibits microbial activity via a zinc deprivation mechanism,^{8,20} and it has also been shown that the apoptosis inducing activities of calprotectin were inhibited by the addition of micromolar concentrations of zinc.²¹ The concentrations of calprotectin needed to inhibit the MMPs in vitro may be biologically relevant. During bacterial infections, up to 120 ng/μl has been found in plasma.⁴ The release of calprotectin from neutrophils in human peripheral blood may give a concentration of about 20 ng/μl plasma, based on a content of 5 pg calprotectin/cell,²² and 4×10^9 neutrophils/litre blood. Local accumulation of granulocytes corresponding to five times the normal may provide 5 μM calprotectin, which would lower the activity of most of the enzymes by 50% or more, if their concentrations in vivo were similar to those used in vitro. The enormous numbers of leucocytes seen at sites of inflammation have the potential to provide several thousand times higher concentrations of calprotectin.

DISCUSSION

An apparent threshold level of Ag(I) reduced membrane potential and membrane integrity rapidly for the individual cells of *C. albicans* and *C. maltosa*, suggesting that a major target of silver is located in the cell membrane. The absence of such a threshold dose for Hg(II) suggested that the target molecules and their threshold levels of mercury were different from those of silver. Moreover, in Ag(I) solutions, cells lost recoverability at a rate similar to those for cell depolarization and membrane permeabilization, whereas in Hg(II) solutions, loss of cell recoverability preceded the loss of membrane potential and membrane integrity, especially for *C. maltosa*. *C. albicans* retained membrane integrity even after exposure to Hg(II) for 1 h and in this regard differed significantly from *C. maltosa*. A further distinction between the activities of the two ions was the fact that the uptake and binding of Ag(I) by *C. maltosa* were greater and more rapid than those of Hg(II).

Brown and Smith (4) showed by a cytochemical method that the Hg(II) accumulated by *Cryptococcus albidus* was present in various parts of the cell other than the cell wall and membranes. Passow and Rothstein (16) demonstrated that mercury ions caused irreversible membrane damage in *S. cerevisiae*, whereas Bruner (5) found that this metal inactivated the enzymes that are responsible for catabolic metabolism. These reports suggested that mercury ions might interact with a variety of reactive sites in both the cell membrane and intracellular targets. An interaction of Hg(II) with *C. albicans* and *C. maltosa* at multiple sites with disruption of vital cell processes might explain the observed loss of cell recoverability before the loss of membrane potential and membrane integrity. Ag(I) and Hg(II) may act similarly for both yeasts and possibly with different targets, but the more-rapid binding of Ag(I) may overshadow any threshold differences between membrane function and cell recoverability.

We recognize that chemical forms of a metal in solution, which regulate metal binding to the membrane and penetration into the cell, are difficult to identify and vary under different experimental conditions (6, 12). Nevertheless, relative metal toxicity may be assessed from the equivalent biologically active metal concentrations. We found that the percentage of depolarized cells of both species increased with increasing concentrations of metals and generated a sigmoidal dose-response relationship. These sigmoidal curves permitted an estimation of metal concentrations that remained in the supernatants.

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