Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care

Mike Bennett Senior Clinical Lecturer in Palliative Medicine, St. Gemma’s Hospice, Leeds, Viv Lucas Consultant in Palliative Medicine and Mary Brennan Specialist Registrar, Garden House Hospice, Letchworth, Andrew Hughes Consultant in Palliative Medicine, St. Oswald’s Hospice, Newcastle-upon-Tyne, Valerie O’Donnell Consultant in Palliative Medicine, Preston Acute Hospital Trust, Preston and Bee Wee Consultant and Senior Lecturer in Palliative Medicine, Countess Mountbatten House, Southampton

Abstract: The management of ‘death rattle’ was reviewed by a task group on behalf of the Association for Palliative Medicine’s Science Committee. Evidence was searched for the effectiveness of various anti-muscarinic drugs in drying oropharyngeal and bronchial secretions in dying patients. Clinical guidelines were constructed based on evidence from volunteer and clinical studies. Death rattle occurs in half of all dying patients and some response occurs in around 80% of treated patients. Clinical studies demonstrate that subcutaneous hyoscine hydrobromide 400 μg is more effective at improving symptoms at 30 min than glycopyrronium 200 μg by the same route. Volunteer studies demonstrate that intramuscular glycopyrronium 400 μg is as effective in drying secretions at 30 min as a dose of 200 μg given intravenously. Duration of response is shortest for hyoscine butylbromide (1 h) and longest for glycopyrronium (more than 6 h). There is insufficient evidence to support the use of one drug over another in a continuous infusion and prescribers should base decisions on different characteristics of each anti-muscarinic drug. Palliative Medicine 2002; 16: 369–374

Key words: anti-muscarinic drugs; clinical guidelines; death rattle

Introduction

‘Death rattle’ is noisy respiration probably caused by turbulent air passing through or over accumulated secretions in the oropharynx or bronchial tree in a patient who is close to death and unable to clear secretions by coughing and/or swallowing.1–3 Air turbulence is dependent on ventilatory rate and airway diameter or, more specifically, resistance. Lack of swallowing and coughing reflexes and a supine or semi-recumbent position can result in secretions pooling in the oropharynx and bronchi. Managing death rattle is likely to depend on reductions in all of the following: salivary and bronchial secretions, ventilatory rate and airways resistance.
Anti-muscarinic drugs have become an established treatment for death rattle based on their demonstrable effectiveness when used during anaesthesia for drying secretions and to attenuate cardiovascular responses at intubation. However, the evidence base to support their use in dying patients was regarded as unknown and this prompted the Task Group to review this area of practice. Task groups have been established by the Science Committee of the Association for Palliative Medicine to review symptom assessment and therapies in relation to a number of areas of palliative medicine.

Methods

A literature search of human studies was undertaken using key words 'death rattle', 'bronchial secretions' and 'anti-muscarinic drugs' of the following databases: MEDLINE express 1985–2001/12, Cimahl 1982–99/11, Serline 1999, Cancer Lit 1997–99/09, Healthstar 1988–99/12 and RCN Journals database 1985–96. A hand search was carried out of Palliative Medicine, Progress in Palliative Care and Journal of Pain and Symptom Management from January 1993 to December 2001. Abstracts of papers were obtained and English language full papers were reviewed if the abstract was relevant to the aims of the review.

The evidence obtained was summarized and graded against criteria described previously,4,5 and these criteria were used to support the clinical guidelines. These grades are:

- Level I: large, randomized, controlled trials with clear cut results and low risk of error;
- Level II: small, randomized, controlled trials with uncertain results and moderate to high risk of error;
- Level III: nonrandomized contemporaneous controls;
- Level IV: nonrandomized historical controls;
- Level V: no controls, case series only.

Results

Pathophysiology of death rattle

Airway secretions are produced from two sources, the salivary glands and the bronchial mucosa, each containing muscarinic receptors. Fluid in the bronchi may also arise from pulmonary oedema and aspiration of food or fluid. There are five types of muscarinic receptor of which only two are involved in airway secretions; M2 on cardiac tissue and airway smooth muscle, and M3 on glandular tissue including salivary glands and airway mucosa.6 M2 receptors in airway smooth muscle act to regulate the response of M3 receptors.7 A dysfunction of M2 receptors (e.g., through infection) can lead to hyperreactivity of M3 receptors, causing secretions and bronchoconstriction. M3 receptors are very sensitive to cholinergic stimulation but M2 are less sensitive.6

Salivary glands are innervated by cholinergic nerves, contain M3 receptors and are very sensitive to changes in vagal tone and inhibition. The tracheal and main bronchial glands have a high density of M2 and M3 receptors, with much lower density in smaller airways, in contrast to the distribution of β2 adrenergic receptors.8 Tonic vagal activity regulates basal secretions from the bronchi, which are mixed serous and mucous in nature. Stimulation of the vagus nerve results in an increase in volume of these secretions without overall change in the viscosity.9 However, in one animal study, vagal inhibition only reduced baseline bronchial secretions by 39%, suggesting that other mechanisms are important in their regulation.10 Other influences include α and β adrenergic receptors, cough receptors and inflammatory changes. Anti-muscarinic drugs, thus, have most effect on inhibiting bronchial secretions in response to vagal stimulation rather than on influencing baseline secretory rate.10,11

Cerebral and lung tumours (primary or metastatic disease) appear to predispose to death rattle.2,12 Persistent or refractory death rattle was associated with pulmonary pathology including infection or oedema in the study of Morita et al.12 but not in another smaller study.1 Differences in definitions and measurement techniques used in these studies limit further conclusions.

Pharmacological studies

Anti-muscarinic drugs competitively antagonize acetylcholine at muscarinic receptors without affecting nicotinic receptors.6 These drugs are classed as tertiary or quaternary amines. Hyoscine hydrobromide and atropine are chemically related and are tertiary amines that are readily absorbed across membranes such as the gut wall and blood–brain barrier. Quaternary amines such as hyoscine butylbromide and glycopyrronium are larger molecules and do not cross such membranes easily. Hyoscine is extensively metabolized, but atropine and, in particular, glycopyrronium are excreted largely unchanged in the urine.

Herxheimer and Haefeli examined the effects of subcutaneous (SC) injections of hyoscine butylbromide in 36 healthy volunteers.12 Effects on heart rate, salivary secretion and visual accommodation were assessed using doses of 20, 28, 40 and 56 mg. Effects on heart rate (tachycardia) and secretion peaked at 15–20 min and disappeared by 60 min. Effects on accommodation appeared by 30 min and wore off by 2 h. All effects were dose-dependent. An infusion of hyoscine butylbromide was used to determine the elimination rate, which was calculated at 4.6–6 μg/kg/min. Thus, a healthy 70 kg person can eliminate an infusion rate of 20 mg/h. Single oral doses of hyoscine butylbromide...
Glycopyrronium was given to six volunteers in three doses via the oral, intramuscular (IM) and intravenous (IV) routes. Oral glycopyrronium at 4 and 8 mg produced a significant reduction in salivary secretions between 3 and 6 h postdose. At 6 h, secretion was still only 50% of baseline, and subjectively, effects were felt up to 24 h postdose. The oral/parenteral ratio was calculated as 35:1; that is, 200 µg glycopyrronium IM produces similar effects to 7 mg orally. The IM injections resulted in 85% reduction in salivary secretions at 1–3 h with significant reduction at 6 h and again, subjectively, effects were felt beyond 8 h. The IV injections produced effects similar to IM injections, but peak effects generally appeared at around 30 min with IV compared to 1 h with IM. Thereafter, duration of action was similar between the two. Doses of 400 µg of glycopyrronium IM, however, produced effects at 30 min similar to 200 µg IV. Effects on sweating mirrored those on salivation with around 70% reduction in active sweat glands at 6 h after 4 or 8 mg of glycopyrronium orally. No significant effects were seen on heart rate and pupil size at the doses used.

Mirakur and Dundee studied six further volunteers given three doses of glycopyrronium and atropine at weekly intervals and effects on heart rate, salivary secretion, sweating and accommodation were assessed for up to 6 h. Doses of atropine at 500 µg, 1 and 2 mg IM reduced salivary secretions by 43%, 72% and 85%, respectively, by 1 h. Statistically significant reduction in salivary secretion lasted for up to 4 h with 1 mg of atropine and throughout 6 h with 2 mg.

Doses of glycopyrronium at 100 and 200 µg IM produced peak effects by 2 h, which lasted for 2 and 4 h, respectively. However, a dose of 400 µg IM produced peak effects at 1 h with significant reduction in salivary secretions between 1 and 6 h and this drug was calculated as being overall 5.6 times more potent than atropine. Average maximal reductions in secretions were 43%, 74% and 94%, respectively, for the three doses. Significant tachycardia resulted from atropine for 1–4 h in contrast to glycopyrronium, which resulted in 20% reduction in baseline heart rate for the duration of study at higher doses (400 µg or more). Glycopyrronium produced intense and prolonged reductions in sweating compared to atropine. Pupil size was affected by atropine but not by glycopyrronium.

A study in patients undergoing caesarian section showed that IM hyoscine hydrobromide readily produces effects on salivation between 1 and 3 h postdose. In contrast to atropine, hyoscine hydrobromide produced bradycardia at clinical doses and central nervous system side effects were frequently seen, though not specified.

Clinical studies
The majority of clinical studies are hampered by lack of standardized dosing regimens and inadequately detailed measurement of response.

Observational studies of dying patients report that around 41–92% develop death rattle. However, larger prospective studies (around 200 patients or more) have reported the incidence to be 44–56% (mean 44.4%, n=949). The mean [median] onset before death is 57 [23] h. Anti-muscarinic drugs, mainly hyoscine hydrobromide, were given to 34–92% (mean 73%, n=700) of patients who develop death rattle. Overall, the effectiveness of anti-muscarinic drugs in these observational studies lies between 48% and 92% (mean 79%, n=239), suggesting that refractory death rattle occurs in 21% of patients who initially present with this symptom or 10% of all dying patients. Nursing interventions alone (repositioning the patient, oropharyngeal suction) improved symptoms in 31% of patients in one study.

A recent study compared the effectiveness of hyoscine hydrobromide, hyoscine butylbromide and glycopyrronium in controlling death rattle in 101 patients divided into three groups. A single SC dose of any of the drugs led to an improvement in 35–54% of patients (hyoscine butylbromide 20 mg: 54% improvement; glycopyrronium 200 µg: 46%; hyoscine hydrobromide 400 µg: 35%). The use of glycopyrronium resulted in 49% of patients remaining symptom-controlled within the first three doses compared to 32% controlled with hyoscine hydrobromide. These differences were not assessed statistically. Reassurance and support combined with symptom improvement relieved the distress of relatives on 90% of occasions.

Back et al. have directly compared the effects of SC hyoscine hydrobromide 400 µg and glycopyrronium 200 µg in 108 and 62 patients, respectively. Noise levels were recorded following drug administration. They showed that significantly fewer patients had symptom improvement at 30 min postinjection in the glycopyrronium group than the hyoscine group. However, at 1 h and at the final recording before death, there was no difference in effectiveness between the two drugs. Furthermore, patients treated with glycopyrronium had significantly higher noise scores than the hyoscine group at baseline (79% versus 56% at level 2 or 3, \(P=0.027\)). There was no significant difference in the use of sedatives such as midazolam or levomepromazine (either by dose or number of injections) between the two groups. In this nonrandomized sample, however, significantly more patients given glycopyrronium
required diamorphine by injection compared with patients treated with hyoscine hydrobromide (72% versus 52%), although the indications for diamorphine were not stated.

Cowl et al. assessed the efficacy of atropine and glycopyrronium when used during bronchoscopy in a double-blind, placebo-controlled trial in 217 patients. Two observers estimated the effects of the drugs on bronchial secretions and found no difference between active drugs and placebo. This might seem to support the pathophysiological model where muscarinic mechanisms determine salivary secretion more than bronchial secretion. However, the medications were given between 15 and 45 min prior to bronchoscopy and this short interval may have been inadequate to judge the peak effects of the anti-muscarinic drugs.

Summary of the evidence

Pharmacodynamics
Low doses of anti-muscarinics will readily inhibit salivary secretion. Nonmuscarinic mechanisms are important in regulating baseline (resting) bronchial secretions and, therefore, the clinical effects of anti-muscarinic drugs on these will be less than on salivary secretions. Bronchial secretions that occur in response to vagal stimulation are only inhibited using higher doses of anti-muscarinics (Level II).

In general, the IV route results in faster onset but shorter duration of action than the IM route in the inhibition of salivary secretions. In volunteer studies, both parenteral hyoscine butylbromide and hyoscine hydrobromide have a rapid onset of action (approximately 20 min after IM injection) but short duration of effect (less than 1 h for butylbromide and 2–3 h for hydrobromide). In contrast, peak effects of IM or SC glycopyrronium occur after 1–2 h and are dose-dependent, with 50% reduction in salivary secretions still apparent 6 h postinjection. Higher doses of glycopyrronium IM produce similar effects at 30 min to lower doses given IV (Level II).

Evidence of benefit
Clinically, around three-quarters of patients with death rattle receive anti-muscarinic drugs and beneficial responses are seen in 80% of patients treated. About 20% of patients with this symptom do not benefit from these drugs possibly due to bronchial secretions formed in response to infection or pulmonary oedema. Higher response rates are seen in patients where anti-muscarinic drugs are combined with interventions such as suctioning or turning the patient from supine to lateral position, or sitting up (Level V).

Response rates have been assessed by a subjective decrease in noise levels with some efforts to measure audibility at different distances from the patient. An audit has demonstrated that reducing death rattle helps to reduce relatives’ anxiety (Level V).

Evidence of harm
Glycopyrronium has little effect on heart rate and visual accommodation at lower doses (200 μg) but higher doses (400 μg) result in bradycardia at 6 h postdose (20% reduction in heart rate). Hyoscine butylbromide results in tachycardia in a dose-dependent fashion (20% increase in heart rate at 20 mg, 50% increase at 56 mg) while doses of 200 μg of hyoscine hydrobromide cause bradycardia. Both hyoscine hydrobromide and atropine cross the blood–brain barrier and can cause confusion. All anti-muscarinic agents cause dryness of the mouth and can precipitate retention of urine (Level III).

Comparison of agents
Glycopyrronium 200 μg SC appears to be less effective at drying secretions than hyoscine hydrobromide 400 μg at 30 min. However, in volunteer studies, 400 μg of glycopyrronium IM produced effects at 30 min similar to IV administration of 200 μg. There remains a lack of conclusive evidence of comparative efficacy of different anti-muscarinic drugs in a clinical setting and, therefore, no particular regimen can be determined to be optimal. Each drug has some unique properties (speed of onset, duration of action, effects on the central nervous system) that can confer an advantage or disadvantage over another drug. Glycopyrronium appears to have greater cardiovascular stability and longer duration of action, whereas hyoscine hydrobromide has a shorter onset and duration of action but can result in sedation, which may be desirable, or agitation, which may not. It is not known if these latter pharmacological differences are clinically relevant in the dying patient (Level IV).

Clinical guidelines for the use of anti-muscarinic drugs in the management of death rattle

Indications
Patients at the extreme end of life with noisy respiration due to salivary or bronchial secretions collecting in the oropharynx.

Regimens
The optimal drug regimen has not been determined and prescribers should be aware of the different characteristics of anti-muscarinic drugs. Their use, however, should not divert attention away from the use of potentially helpful nonpharmacological interventions or from effective communication with relatives and carers. While evidence exists for single doses of anti-muscarinic
drugs, no evidence has been found to guide doses used in SC infusions. The following guidelines are, therefore, based on the duration of action of single doses and take account of unwanted effects at higher doses.

1) Hyoscine hydrobromide 400 μg SC injection: review response after 30 min and, if effective, consider 1.2–2.0 mg continuous SC infusion over 24 h (assuming a single dose of 400 μg would produce effects lasting between 5 and 8 h).

2) Glycopyrronium 200 μg SC injection: review response after 1 h. Doses of 400 μg are likely to produce faster results at 30 min. Depending on prognosis, further injections or continuous SC infusion at 1.2–2.0 mg over 24 h can be considered (assuming a single dose of 400 μg would produce effects lasting between 5 and 8 h).

3) Hyoscine butylbromide 20 mg SC injection: review response after 30 min. Assuming a single dose of 20 mg would produce effects lasting for 1 h, a SC infusion of over 400 mg would need to be given over 24 h. This is substantially higher than doses used in current clinical practice.

4) The use of atropine has not been considered in the literature and no recommendations can be given for its use in managing death rattle.

Response
Response to anti-muscarinic drugs is likely in around 80% of treated patients. The duration of response to single SC injections is expected to be shortest for hyoscine butylbromide (less than 1 h) and longest for glycopyrronium (6 h). Patients with predominantly salivary secretions may have greater benefit than those with bronchial secretions. There is a risk of causing excessive mouth dryness when prescribing anti-muscarinic medication (though this may not be an issue in unconscious patients) so the burdens and benefits for individual patients need to be assessed.

Additional measures
Repositioning of the patient to a lateral or more upright position to promote drainage of secretions can be effective. Anti-muscarinic drugs do not remove existing secretions, so gentle suctioning of the oropharynx may need to be considered if secretions have accumulated.

Key recommendations for research
1) Develop a greater understanding of the pathophysiology of death rattle, e.g., the relative contributions of salivary and bronchial secretions to the development of symptoms.

2) Compare efficacy of different anti-muscarinic drugs.
3) Investigate role of suction in management of death rattle.

Acknowledgement
The Task Group is very grateful for Dr Ian Back’s expert commentary on this report.

References


