

Rabies: a significant palliative care issue

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Over the past 5 years, a palliative care training programme has been developing at San Lazaro Infectious Diseases Hospital, Manila, Republic of the Philippines with the help of a consultative team from Australia and New Zealand. Early in the programme, the terrible plight of rabies patients dying with uncontrolled delirium was identified as a priority need for applying palliative care principles. There is virtually nothing in the literature on the management of dying rabies patients, especially in the context of non-industrialised countries. A management plan was initiated to establish a more effective medication regimen to control the delirium suffered. A study was devised in an attempt to document the symptoms and signs of dying rabies patients, and the effect of the new medication regimen. Many difficulties were encountered in attempting to change practice and in achieving consistency of medication supply. However, eventually, the results of observing 45 patients admitted to San Lazaro Hospital consecutively with a diagnosis of rabies were collected and are reported here. The study recorded the commonest symptoms of rabies patients seen at San Lazaro Hospital and demonstrated the effectiveness of applying basic symptom control principles on reducing their suffering.

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San Lazaro Hospital is the Department of Health Infectious Diseases Hospital in Manila, Republic of Philippines. Over the past 5 years, a palliative care training programme has been developing there with advice from an overseas consultative team from Australia and New Zealand. The goals of the consultative team have been to support San Lazaro staff to: (i) teach and develop the training programme themselves from a Filipino perspective; and (ii) implement palliative care throughout the hospital. A multidisciplinary group was formed which has evolved into the Starfish Palliative Care team led by Dr Ceri Cabanban.

Early in the teaching programme, staff described enormous distress with respect to patients dying from diseases other than HIV/AIDS such as rabies, tetanus, meningitis and tuberculosis to name but a few. Expressed in particular was the terrible plight of rabies patients dying restrained, terrified, aggressive, paranoid and alone in a barred, prison-like room. These horrible deaths were occurring about twice a week.

It seemed clear that rabid patients were experiencing and dying with uncontrolled severe delirium. Although the published literature on rabies contains extensive material on prevention and vaccination, there is virtually nothing on the management of patients dying with rabies in other than intensive care settings in the industrialised world where rabies is a rare occurrence anyway (1–3).

We thus began to look at this from a palliative care perspective at San Lazaro. Managing the delirium with an anti-psychotic medication such as haloperidol seemed the logical cornerstone of care. However, until this time, there was a firm belief that nothing would help. Occasionally, intramuscular diazepam and diphenhydramine was given with little success and the patients strapped to the bed in isolation to await death. Hence, it has been a long journey to change the management of these patients. However, one day, staff decided to manage an 11-year-old boy with haloperidol and the management of rabies changed. He became calm, settled, and was even able to be taken home where he died comfortably. Once staff were convinced to prescribe haloperidol (the most accessible anti-psychotic at San Lazaro), consistent availability has been, and remains, a problem. An alternative regimen was, therefore, suggested

using regular diazepam (as this is consistently available) for when haloperidol treatment was not possible (4–6).

In the absence of published data on dying rabies patients and also to monitor the results of the introduction of regular medication, an observational study was designed. Staff changes and many logistic difficulties delayed the study and made accurate data collection difficult. However, finally, the results of observation of 45 consecutive patients admitted to San Lazaro Hospital have been collected and are reported here.

RABIES

Rabies is a fatal, acute encephalomyelitis and remains one of the commonest viral causes of death in the non-industrialised world. Previously unvaccinated patients with rabies have 100% mortality and without palliation die agonising deaths (4,7).

Accurate data on the world-wide incidence of rabies are scarce with estimates between 40,000 and 100,000 cases annually. Most occur in the non-industrialised world as a result of bites from domestic or feral animals, usually dogs. The incidence in the industrialised world is very low; for example, the US reported 1–2 cases annually in the 1990s. Most human cases in the industrialised world follow exposure to wild animals, *e.g.* bats (2,4,7).

Rabies is caused by a Lyssavirus, a member of the Rhabdoviridae family. It is transmitted by the introduction of saliva from infected animals, *i.e.* through bites, scratches, licks on broken skin and contact with mucous membranes. After entry through a skin break or mucous membrane, the virus replicates in the muscle cells, infects the muscle spindle and then the nerve innervating the spindle. Further replication occurs in these neurons and the virus spreads centrally towards the central nervous system. Virus may be present in dorsal root ganglia within 72 h of inoculation. However, if anti-rabies immunoglobulin and active immunisation are given in time, virus may be prevented from spreading to the nervous system and disease prevented. Once virus has entered the peripheral nerve, however, disease is inevitable. After spreading centrally to the spinal cord the virus spreads throughout the central nervous system and then centrifugally out to the rest of the body via peripheral nerves. Viral shedding from sensory nerve endings in the oral mucosa as well as replication in the salivary glands produces high concentrations of virus in the saliva.

Although post-bite vaccination may be available, many patients do not seek help through ignorance, fear, folk beliefs and overwhelming poverty (4–6)

Clinical manifestation

The incubation period for rabies is, on average, 30–90 days but may be from a few days to several years (4,7).

The early clinical features of rabies are non-specific influenza-like symptoms and localised paraesthesia, pain and pruritis at the bite site. Later, the clinical picture evolves into two forms – the encephalitic ('furious') form in about 80% of

patients or the paralytic ('dumb') form. The features of encephalitic rabies include the hallmark symptoms of hydrophobia and aerophobia, dysphagia, a delirium, including aggression, disorientation, hallucinations, hyper-excitability and confusion, seizure activity and autonomic dysfunction. Paralytic rabies is characterised by ascending paralysis.

With both forms, cardiac arrhythmias and coma intervene and death is inevitable within a few days, usually within 72 h of onset of clinical features.

STUDY METHOD

Forty-five consecutive patients admitted to San Lazaro Hospital with a diagnosis of rabies were observed. The following information was recorded:

1. *Sex and age of the patient.*
2. *Symptoms*

The presence and severity of the following symptoms were recorded: hydrophobia, aggression, hyper-excitability, aerophobia, disorientation, hyper-vigilance, difficulty swallowing, hallucination, hyper-salivation, anxiety/fear, seizure activity, and restlessness/agitation.

The severity of each symptom was graded: none (0), mild (1), moderate (2), severe (3), and very severe (4). This information was to be recorded at least every 4 h.

3. *The medications given and time given*

The planned regimen was:

Haloperidol 5 mg subcutaneously (s.c.) or intramuscularly (i.m.) every hour for at least three doses or until the patient was calm. Then haloperidol 5 mg s.c. or i.m. regularly q4h–q6h and PRN.

Diphenhydramine 50–100 mg i.m. q4h–q6h.

The doses were reduced for children.

If haloperidol was not available, then the following regimen was used:

Diazepam 20 mg i.m. q2h.

Diphenhydramine 50–100 mg i.m. q4h–q6h.

The doses were again reduced for children. Diphenhydramine had been used previously as a sedative. It was retained in the regimen for its potential effect on salivation.

4. *Time of admission and time of death or discharge home.*

RESULTS

There were 45 patients observed; 31 were male and 14 female. The age distribution was: 4–15 years (10 patients), 16–30 years (9 patients), 31–45 years (11 patients), and 46–62 years (15 patients). The median age was 39 years.

The time observed ranged from 1.5–46 h with a median of 12 h. Four patients were taken home and two of these

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are known to have died peacefully at home. There is no information about the other two patients after discharge.

The patients essentially fell into three groups depending on the medications received:

Group 1 22 patients who received haloperidol and diphenhydramine.

Group 2 14 patients who received diazepam and diphenhydramine when haloperidol was not available.

Group 3 9 patients who received a combination of haloperidol and diazepam plus diphenhydramine.

Group 1: patients receiving haloperidol and diphenhydramine

Hydrophobia, aerophobia and difficulty swallowing

For all 22 patients, these symptoms either did not change or changed minimally, maintaining a score of 2 or 3 during the period of observation.

Delirium

All 22 patients scored 0 for aggression and disorientation and 21 scored 0 for hallucinations throughout the observed period. For anxiety/fear, 14 scored 0 throughout, three went from 2 to 0, and three from 1 to 0, one went from 3 to 1, and one from 2 to 1. Restlessness/agitation was the most likely to receive a score during the period of observation but was also consistently reduced. Five patients scored 0 throughout, eight reduced scores by 2 or more to 0, two from 1 to 0 and five went from 3 to 1. Three patients recorded increases of 1–2 grades when haloperidol was interrupted but reduced again when it was re-introduced. All patients were scored 0 for confusion and hyper-vigilance and only two had scores for hyper-excitability.

Hyper-salivation

Seven patients had a score of 0 throughout the period of observation. Six had a score reduction (four patients going from 2 to 1 and two patients from three to 2). Seven patients maintained the same score and one became worse.

Seizure activity

No patients were recorded as showing any seizure activity.

Group 2: patients receiving diazepam and diphenhydramine

Hydrophobia, aerophobia and difficulty swallowing

Ten patients scored 3 throughout the period of observation. Four recorded increasing scores reaching 3 before death.

Delirium

For aggression, 13 patients had scores of 0 throughout and one a score of 3 throughout. For disorientation and hallucinations, all 14 patients scored 0. For anxiety/fear,

four patients scored 0, two scored 1 and two had scores of 2 throughout. Five scored reductions of 1 down to 2 and 1, while one increased from 1 to 2. For restlessness/agitation there were no patients scoring 0 in this group. Two scored 3 throughout and two went from 2 to 3 and one from 1 to 2. Six patients reduced their scores by 1 down to 2 or 1 and two reduced from 4 to 2. These patients scored consistently higher than the haloperidol group with respect to anxiety/fear and restlessness/agitation. It was observed that when diazepam was given sufficiently frequently (*i.e.* q2h) and in higher dose (20 mg compared to 10 mg), these symptoms were improved but did not achieve the low scores of the haloperidol group. No patients recorded scores for hyper-vigilance and hyper-excitability and only one recorded a score of 1 for confusion.

Hypersalivation

One patient recorded 0 throughout. Three patients had worsening scores and nine maintained the same score. One score was reduced.

Seizure activity

No patients were recorded as showing any seizure activity.

Group 3: patients receiving diazepam and haloperidol together with diphenhydramine

Hydrophobia, aerophobia and difficulty swallowing

Six of these patients maintained scores of 3 for all three symptoms throughout. Two patients worsened to scores of 3 for all 3 symptoms. One patient worsened to 2 for hydrophobia and three for difficulty in swallowing.

Delirium

Three patients received 1 dose of diazepam prior to haloperidol. All three achieved reduced scores similar to the haloperidol-only group. One of these patients went home and there is no information available about his death. One patient received 2–3 doses of diazepam with no change in his anxiety/fear or restlessness/agitation. These symptoms settled once haloperidol was introduced. One patient received one dose of haloperidol followed by one dose of diazepam when haloperidol was unavailable. There was no change in his symptoms. When haloperidol was re-introduced, his restlessness/agitation score was reduced from 3 to 1. One patient received haloperidol hourly for 3 doses and then q4h to 21 h with a reduction in his scores of aggression from 3 to 0, disorientation 2 to 1, anxiety 3 to 0, and restlessness/agitation 3 to 1. When haloperidol was not available, diazepam was given. Restlessness/agitation increased from 1 to 2.

Two patients were given diazepam when they appeared not to be settling with haloperidol. The first had scores of 0 for aggression, disorientation and anxiety, but 3 for restlessness/agitation. One dose of diazepam was given and then haloperidol recommenced. Restlessness was then reduced

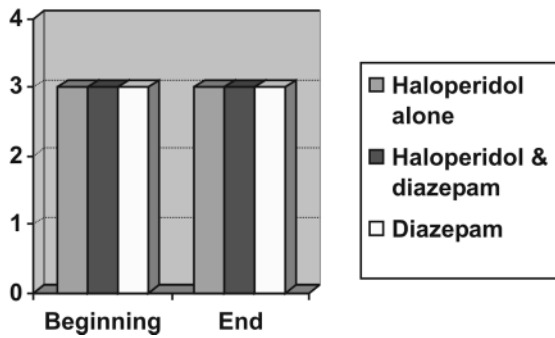


Fig. 1. Hydrophobia (all patients).

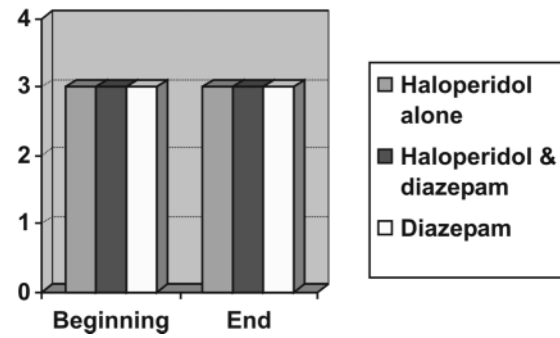


Fig. 2. Aerophobia (all patients).

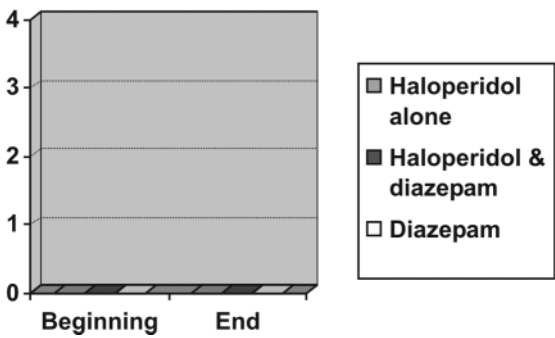


Fig. 3. Aggression/disorientation/hallucinations (all patients).

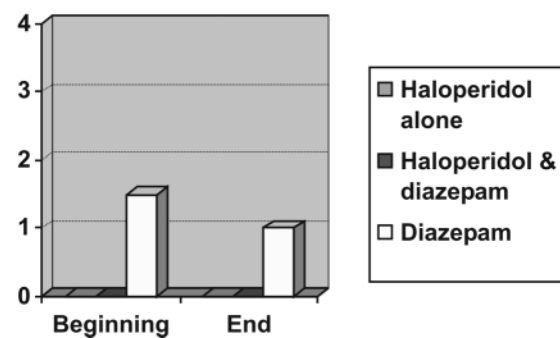


Fig. 4. Anxiety/fear (all patients).

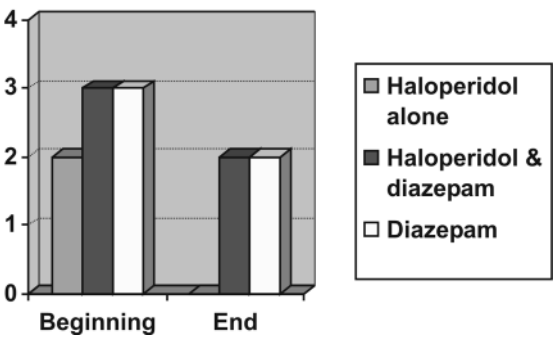


Fig. 5. Restlessness/agitation (all patients).

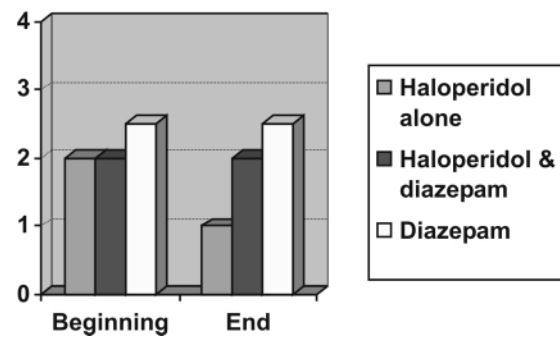


Fig. 6. Hypersalivation (all patients).

from 3 to 2. Although reported as 'not settling' prior to giving the diazepam, the patient was reported as conversing and smiling. The other patient, a 7-year-old boy, showed scores of 3 for anxiety and restlessness after haloperidol 2.5 mg q1h for 3 doses and a score of 2 for aggression. He was then given 1 dose of diazepam 10 mg. It was reported that his aggression seemed reduced with haloperidol but his restlessness remained. He was, however, able to smile and converse. He scored 2, reducing to 1 for hypervigilance.

One patient received 2 doses of diazepam when a misdiagnosis was contemplated. However, 30 h after admission, his symptoms became more overt. Three doses of haloperidol were given but no scores recorded from that time.

None of the patients in this group recorded scores for confusion or hyper-excitability.

Hypersalivation

Three patients were recorded as having 0 score throughout. Three patients' scores worsened, one remained stable and two were reduced slightly.

Seizure activity

No patients were recorded as showing any seizure activity.

Summary of results

The median scores for significant symptoms at the beginning and end of the periods of observation were calculated for each

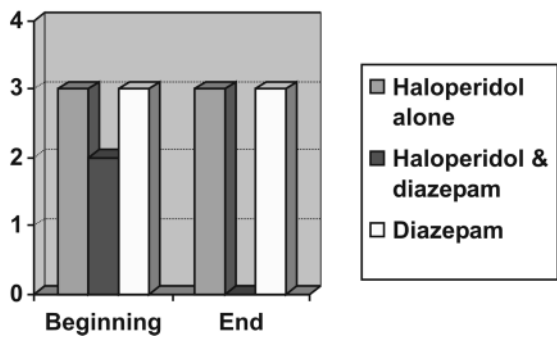


Fig. 7. Aggression/disorientation/hallucinations (excluding those patients who scored 0 throughout the period of observation).

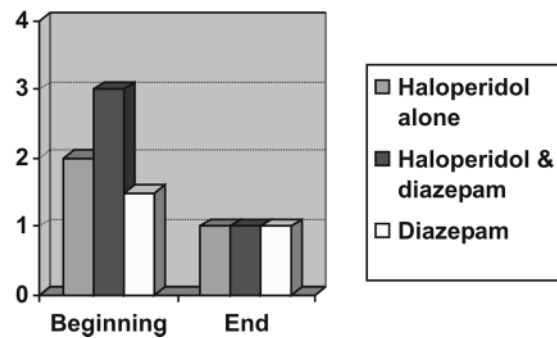


Fig. 8. Anxiety/fear (excluding those patients who scored 0 throughout the period of observation)

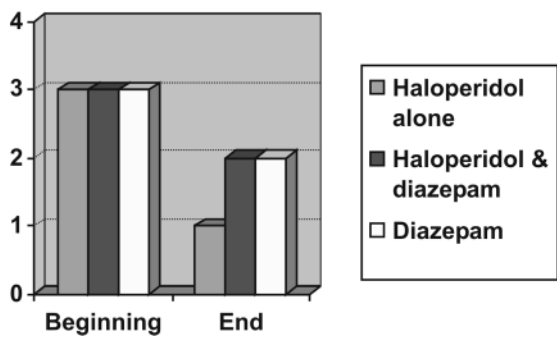


Fig. 9. Restlessness/agitation (excluding those patients who scored 0 throughout the period of observation).

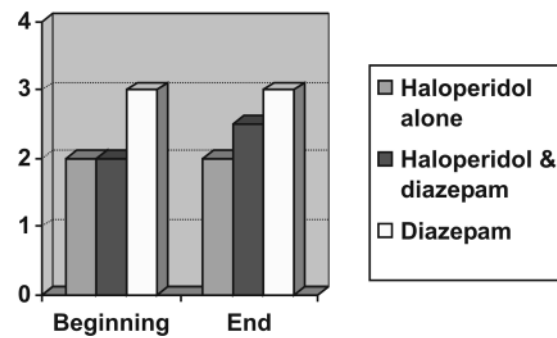


Fig. 10. Hypersalivation (excluding those patients who scored 0 throughout the period of observation).

of the three treatment groups and graphed in an attempt to demonstrate some of the trends and comparisons observed clinically. These are displayed in Figures 1–10. Figures 1–6 include all patients. Figures 7–10 exclude those who scored 0 (and were, therefore, free of that symptom) throughout the course of the observation period. When the patients scoring 0 throughout were excluded, the percentage reduction in median score for each symptom for each group was calculated to demonstrate the effect of medications on established symptoms. These are displayed in Table 1.

DISCUSSION

As well as the pathognomic symptoms of rabies (*i.e.* hydrophobia and aerophobia), the distressing symptoms of dying

rabies include a severe delirium featuring disorientation, anxiety, hypervigilance, hyperexcitability, confusion together with restlessness/agitation and, at times, aggression.

The elements of delirium appeared to be significantly improved (as demonstrated by the percentage median reduction in symptom scores) or prevented (suggested by patients with scores of 0 throughout) with regular medication, be it haloperidol or diazepam. There were significant numbers of patients scoring 0 for symptoms of delirium throughout especially with respect to aggression/disorientation/hallucination, anxiety/fear and for haloperidol restlessness/agitation. There was 1 patient only in each of the haloperidol and diazepam groups and 2 in the haloperidol/diazepam group with scores for aggression/disorientation/hallucination. The rest all

Table 1. Percentage median reduction of symptoms for each of the treatment groups when those scoring 0 throughout observation are excluded

	Haloperidol	Haloperidol/diazepam	Diazepam
Aggression/disorientation/hallucination (%)	0	100	0
Anxiety/fear (%)	50	67	33
Restlessness/agitation (%)	67	33	33
Hyper-salivation (%)	0	+25	0
Hydrophobia (%)	0	0	0
Aerophobia (%)	0	0	0

scored 0 throughout. Hence, Figure 7 and the percentage median reduction scores for this symptom are misleading.

The 22 patients receiving haloperidol only (with diphenhydramine) all had symptoms of aggression/disorientation/hallucinations, anxiety/fear, and restlessness/agitation considerably improved or controlled. We have been surprised by the relatively low doses of haloperidol that achieved symptom control. Often 10–20 mg in 24 h has been sufficient.

Symptoms were improved with the use of diazepam alone with diphenhydramine but not as consistently or as well as with the haloperidol group, especially with respect to restlessness/agitation. To improve any symptoms with any consistency, diazepam needed to be given every 2 h by painful intramuscular injection. The intravenous route was not considered to be a reasonable, safe option by the treating clinicians.

Seven of nine patients documented as receiving both haloperidol and diazepam also demonstrated the effectiveness of haloperidol in controlling the delirium of rabies. The remaining two were given diazepam when they appeared not to be settling quickly with haloperidol in terms of restlessness and agitation. The other parameters did improve or were controlled.

Interestingly, the scores in all groups for confusion, hyperexcitability hyper-vigilance were usually 0 or very low indeed throughout. This remains unexplained.

Significantly, no patients in any group had improvement in scores for hydrophobia, aerophobia or difficulty in swallowing. However, as these symptoms represent an exaggerated irritant reflex of the respiratory tract with laryngo-pharyngeal spasm, it is certainly not surprising that haloperidol, in particular, had no effect. The terms hydrophobia and aerophobia are in this sense a misnomer and do not represent 'phobia' in the usual sense of the word.

The role of diphenhydramine remains unclear from this study. In the past, diphenhydramine was apparently used for its sedative effect. It has continued to be used more for the potential effect on hypersalivation. Other medications were not used due to lack of availability. Diphenhydramine has been consistently available at San Lazaro Hospital. Its role in rabies management remains unclear.

The introduction of haloperidol in the management of dying rabies patients has demonstrated, very clearly, good symptom management as a fundamental cornerstone of good palliative care. It has made possible, physical and personal care of the patient (hitherto unthinkable for a delirious, aggressive patient) as well as allowing emotional, social and spiritual needs to be addressed. There are many moving stories of families being able, now, to sit with dying rabies patients. Saying goodbyes are possible and much emotional and spiritual healing has been observed. Previously, patients were isolated and strapped to a bed in a barred and locked cell-like room with carers and family scared to approach from fear of being assaulted and infected.

It has been inspirational to see how the staff at San Lazaro can apply palliative care principles holistically in the short time frame allowed by the rapidness of rabies from diagnosis to death.

Tragically, rabies is preventable with animal vector vaccination and post-bite vaccination. Poverty often prevents this. As tragic, is the inability often to achieve consistent supplies of a relatively inexpensive drug such as haloperidol to control the agonising symptoms of those dying with rabies.

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