

Continuous deep sedation for patients nearing death in the Netherlands: descriptive study

Judith Rietjens,¹ Johannes van Delden,² Bregje Onwuteaka-Philipsen,³ Hilde Buiting,¹ Paul van der Maas,¹ Agnes van der Heide¹

EDITORIAL by Murray and colleagues

¹Department of Public Health, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, Netherlands

²Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, Netherlands

³Department of Public and Occupational Health, Institute for Research in Extramural Medicine, VU University Medical Centre, 1081 BT Amsterdam, Netherlands

Correspondence to: J Rietjens
j.rietjens@erasmusmc.nl

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ABSTRACT

Objectives To study the practice of continuous deep sedation in 2005 in the Netherlands and compare it with findings from 2001.

Design Questionnaire study about random samples of deaths reported to a central death registry in 2005 and 2001.

Setting Nationwide physician study in the Netherlands.

Participants Reporting physicians received a questionnaire about the medical decisions that preceded the patient's death; 78% (n=6860) responded in 2005 and 74% (n=5617) in 2001.

Main outcome measures Characteristics of continuous deep sedation (attending physician, types of patients, drugs used, duration, estimated effect on shortening life, palliative consultation). Requests for euthanasia.

Results The use of continuous deep sedation increased from 5.6% (95% confidence interval 5.0% to 6.2%) of deaths in 2001 to 7.1% (6.5% to 7.6%) in 2005, mostly in patients treated by general practitioners and in those with cancer (in 2005, 47% of sedated patients had cancer v 33% in 2001). In 83% of cases sedation was induced by benzodiazepines, and in 94% patients were sedated for periods of less than one week until death. Nine per cent of those who received continuous deep sedation had previously requested euthanasia but their requests were not granted. Nine per cent of the physicians had consulted a palliative expert.

Conclusions The increased use of continuous deep sedation for patients nearing death in the Netherlands and the limited use of palliative consultation suggests that this practice is increasingly considered as part of regular medical practice.

INTRODUCTION

Debate surrounds the conditions under which continuous deep sedation until death is medically indicated and the way it is performed. An expert group recommended that to warrant sedation at the end of life, the patient's condition should be irreversible and advanced, with death expected within at most one to two weeks.¹ Benzodiazepines should be the drug of first choice, hydration should be offered to sedated patients only when the benefit will outweigh the harm, and advice from palliative care specialists should be sought

before sedation. There is debate over when this practice is ethically acceptable. Is it slow euthanasia or is it a palliative intervention that should be clearly distinguished from euthanasia?

In 2001, a study in six European countries showed that continuous deep sedation until death was used in 2.5-8.5% of all deaths.² For the Netherlands the estimated proportion was 5.6%.² Another study in the Netherlands in 2001 found the proportion to be 10%.³

The main findings of a study we conducted in 2005 to evaluate the enactment of the Dutch Euthanasia Act were a modest decrease in the rates of euthanasia (from 2.6% of all deaths in 2001 to 1.7% of all deaths in 2005) and an increased application of continuous deep sedation until death (from 5.6% in 2001 to 7.1% in 2005).⁴ This paper compares consecutive data from 2005 with those from 2001.

METHODS

Study design and data collection

In 2005, we created a stratified sample of death certificates from the central death registry of Statistics Netherlands.⁴ We assigned all 43 959 deaths that occurred between August and November 2005 to one of five groups, according to the circumstances of death. See bmj.com. The 2001 study was similar,⁵ and further details have been described elsewhere.^{4,5}

Questionnaire

For all sampled cases reported as not sudden, we asked the attending physician to fill in a four page written questionnaire about the medical decision making that had preceded death. Of the 6860 questionnaires sent out, 5342 were completed and returned (78% response). The response percentage in 2001 was 74% (n=5189).

The 2005 questionnaire contained additional questions about aspects of medical care and treatment before the patient's death and the presence of symptoms, despite possible treatment, during the last 24 hours of life. It also asked whether an expert in palliative care was consulted during the month before death. Physicians were asked to estimate the effect on life shortening, if any, of the decision making before death.

Characteristics of continuous deep sedation in 2005*. Figures are percentages† of physicians

	General practitioners	Clinical specialists	Nursing home physicians	All physicians
Drugs administered:				
Benzodiazepines	42	13	44	30
Benzodiazepines and morphine	44	60	43	51
Benzodiazepines and other drugs	1	3	2	2
Morphine	11	16	10	13
Morphine and other drugs	2	3	0	2
Other drugs	0	5	0	2
Palliative consultation in last month before death	20	2	5	9
Artificial nutrition or hydration withheld during sedation	95	30	98	66
Duration of continuous deep sedation:				
0-24 hours	43	50	42	47
1-7 days	52	38	58	47
1-2 weeks	3	7	0	4
>2 weeks	2	4	0	2
Estimated shortening of life‡:				
None or <24 hours	57	73	64	65
1-7 days	27	17	18	20
1-4 week	6	3	1	4
>1 month	0	3	4	2
Unknown/missing	9	5	13	9
Preceded by request for euthanasia, not granted	16	4	9	9

*Concerns all cases of continuous deep sedation (n=521).

†Weighted for sampling fractions, non-response, and random sampling deviations.

‡Refers to all medical decision making about end of life.

Analyses

The percentages reported were weighted to adjust for differences in the sampling fractions and for differences in response rates in relation to the patient's sex, age, marital status, region of residence, and place and cause of death. See bmj.com. After adjustment, we extrapolated the percentages to cover a 12 month period to reflect the 136 402 deaths in the Netherlands in 2005. We compared the prevalence of symptoms in patients for whom continuous deep sedation had been started during the last 24 hours of life with the prevalence of symptoms in all patients in whom death was not sudden.

RESULTS

Of all patients who died in 2005, 8.2% (95% confidence interval 7.6% to 8.9%) were continuously and deeply sedated until death. In 7.1% (6.5% to 7.6%) of deaths, such sedation was provided in conjunction with decisions that potentially hastened death (such as decisions to withhold potentially life prolonging treatments), which is a significant increase compared with the 5.6% (5.0% to 6.2%) in 2001. This increase was significant among general practitioners: 3.9% (3.3% to 4.7%) in 2001 *v* 6.6% (5.7% to 7.6%) in 2005. Compared with the other specialties, in 2005 the percentage of continuous deep sedation was highest (10%, 8.7% to 11.5%) in patients attended by clinical specialists.

Sixty one per cent of patients who received continuous deep sedation were aged <80 years, while 51% of all deaths in the Netherlands were in those aged

<80. In 2005, 47% (42% to 52%) of patients who received continuous deep sedation had cancer, compared with 33% (28% to 38%) in 2001. In general practice, the proportions of those with cancer were 72% in 2005 and 69% in 2001. Among clinical specialists, continuous deep sedation was also commonly used for patients with cardiovascular diseases (19%). Nursing home physicians used continuous deep sedation for patients with cardiovascular diseases (24%) and diseases related to the nervous system (12%).

For 47% of all patients who received continuous deep sedation, the sedation was started in the last 24 hours before death. Most patients had more than one symptom, and 74% experienced symptoms that are common indications for sedation—that is, pain, dyspnoea, confusion, or anxiety. Sedated patients had more symptoms than other patients who did not die suddenly and more often experienced dyspnoea, pain, and anxiety.

The table examines the characteristics of the practice of continuous deep sedation in 2005. No comparable data were available from 2001. In 83%, continuous deep sedation was induced with benzodiazepines often combined with morphine. Morphine was used without benzodiazepines in 15%, most often by clinical specialists. Palliative consultation in the month before death was quite rare (9%), and most often sought by general practitioners (20% of cases). Palliative consultation was positively related to the use of benzodiazepines (whether or not combined with other drugs) ($P<0.01$). In two thirds of cases, physicians estimated that the effect of the decision making before death on shortening life was 24 hours or less. In 9% of the cases, the decision to use continuous deep sedation was preceded by an explicit request from the patient to end his or her life by means of euthanasia or assisted suicide, which was not granted.

DISCUSSION

In the Netherlands the increase in the use of continuous deep sedation for patients nearing death mostly occurred among general practitioners and clinical specialists, especially for patients with cancer. Patients for whom sedation was started in the last 24 hours of their life more often had dyspnoea, pain, and anxiety than other patients whose death was not sudden. In about four out of every five patients sedation was induced with benzodiazepines. Clinical specialists were more likely than general practitioners and nursing home physicians to use other drugs, mostly morphine. Physicians rarely sought palliative consultation, although this happened more often among general practitioners. In about one in every 10 patients, the use of continuous deep sedation was preceded by a request for euthanasia or assisted suicide that was not granted.

Strengths and weaknesses of the study

The large random samples of death certificates and high response rates in both years ensure generalisability to all deaths in the Netherlands. The study design was similar in both years, and anonymity of patients and physicians was guaranteed which further

strengthened the validity and reliability of our results. In the 2005 questionnaire, there were small adjustments in the wording of the key questions regarding the use of continuous deep sedation. Because we did not change the key elements of our definition (continuous and deep sedation or coma until death) we believe this did not affect our results.

Strengths and weaknesses in relation to other studies

To minimise possible differences in the perception of sedation across the respondents we provided them with a descriptive definition of continuous deep sedation until death. Most other studies use terms such as palliative or terminal sedation, which can have varying connotations and implications for normal practice.

A study performed in six European countries in 2001, found the highest rates of continuous deep sedation were also found among patients who died in hospitals compared with elsewhere (2.9-13.2%), except for Italy, where sedation rates were higher outside the hospital.² Our findings show an increase in the use of continuous deep sedation until death in the studied period, especially among general practitioners. This agrees with results of another Dutch longitudinal study.⁶ Most other studies report the use of continuous deep sedation only for patients with cancer, probably because they were restricted to specific settings such as palliative care units.⁷⁻¹⁰ Also in some other studies, delirium or terminal restlessness, dyspnoea, and pain are frequently mentioned indications for sedation, which agrees with our findings.

We found that 15% of patients were sedated with morphine as a single therapy. Two other nationwide Dutch studies conducted in 2001 and 2005 found somewhat higher levels of use (36%³ and 28%,¹¹ respectively). Similar to our findings, both studies showed that clinical specialists were more likely than general practitioners and nursing home physicians to use morphine for this purpose.^{3,11}

Interpretation

There could be several explanations for the increase in the use of continuous deep sedation until death seen between 2001 and 2005. Physicians and medical authorities have paid more attention to continuous deep sedation and knowledge has increased. From 2002 on, for example, regional cancer centres have published guidelines to improve its application, and in 2005 (after our data collection) a nationwide guideline was released in the Netherlands.¹² The practice of continuous deep sedation until death also recently received a lot of attention in the media. These developments could have led to an increased interest in its use among physicians as well as patients and their relatives.

Continuous deep sedation has possibly increasingly been used as a relevant alternative to euthanasia. The use of euthanasia had decreased from 2.6% of all deaths in 2001 to 1.7% of all deaths in 2005 (a decrease of 1200 cases),⁴ while continuous deep sedation increased by 1800 cases from 5.6% to 7.1%. This increase took place mostly in the subgroups in which euthanasia is most common: patients attended by general practitioners and those with cancer. Of the patients who received sedation, 9% had been refused euthanasia. Although euthanasia and continuous deep sedation generally address different clinical problems,¹³ this suggests that substitution might be possible in some situations. Many Dutch physicians have been found to consider high quality end of life care as an alternative to euthanasia.⁵ We do not know whether such substitution is always in accordance with the patient's wishes and with legal and professional guidelines. For patients with a longer life expectancy at the time that sedation is started, there is a risk that labelling the decision as continuous deep sedation instead of ending of life might serve as a way to evade the procedural requirements for euthanasia. The estimated effect on life shortening, however, was, in most cases, limited. Future studies about medical practices at the end of life should evaluate this in more detail. Our study confirmed the relation between consultation and adequate drug use, and increased use of palliative consultation might improve the clinical performance of continuous deep sedation.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Continuous deep sedation until death is sometimes used in severely suffering patients with refractory symptoms; in the Netherlands use increased from 5.6% of all deaths in 2001 to 7.1% in 2005

Guidelines recommend the use of benzodiazepines for deep sedation, while morphine is usually rejected as a single therapy to attain sedation because of its unpredictable sedative and side effects

Continuous deep sedation and euthanasia are generally used in different clinical situations

WHAT THIS STUDY ADDS

The increase in the use of continuous deep sedation until death in the Netherlands was mostly because of an increase in use by general practitioners, especially for patients with cancer

Of the physicians who used continuous deep sedation, 15% used morphine and no benzodiazepines and 91% did not consult a palliative care expert

The use of euthanasia decreased while the use of continuous deep sedation increased, especially in subgroups in which euthanasia is most common; and 9% of patients who received continuous deep sedation had previously asked for euthanasia but their requests were not granted

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Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study

Henrik Toft Sørensen,¹ Steffen Christensen,¹ Frank Mehnert,¹ Lars Pedersen,¹ Roland D Chapurlat,² Steven R Cummings,³ John A Baron⁴

EDITORIAL by Majumdar

¹Department of Clinical Epidemiology, Aarhus University Hospital, 8000 Aarhus C, Denmark

²INSERM Research Unit 831, Université de Lyon, Department of Orthopedics and Rheumatology, Hôpital E Herriot, Lyon, France

³San Francisco Coordinating Center, San Francisco, CA, USA

⁴Departments of Medicine and Community and Family Medicine, Dartmouth Medical School, Hanover, NH, USA

Correspondence to: H T Sørensen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark
hts@dce.au.dk

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ABSTRACT

Objective To assess the association between atrial fibrillation and flutter and use of bisphosphonates for osteoporosis among women.

Design Population based case-control study, using medical databases from Denmark.

Setting Northern Denmark.

Participants 13 586 patients with atrial fibrillation and flutter and 68 054 population controls, all with complete hospital and prescription history.

Main outcome measure Adjusted relative risk of atrial fibrillation and flutter.

Results 435 cases (3.2%) and 1958 population controls (2.9%) were current users of bisphosphonates for osteoporosis. Etidronate and alendronate were used with almost the same frequency among cases and controls. The adjusted relative risk of current use of bisphosphonates compared with non-use was 0.95 (95% confidence interval 0.84 to 1.07). New users had a relative risk of 0.75 (0.49 to 1.16), broadly similar to the estimate for continuing users (relative risk 0.96, 95% confidence interval 0.85 to 1.09). The relative risk estimates were independent of number of prescriptions and the position of the atrial fibrillation and flutter diagnosis in the discharge record, and were similar for inpatients and outpatients.

Conclusion No evidence was found that use of bisphosphonates increases the risk of atrial fibrillation and flutter.

INTRODUCTION

Bisphosphonates are widely used to treat osteoporosis after the menopause.¹ Recently an international trial reported that the bisphosphonate zoledronic acid substantially reduced the risk of fractures² but unexpectedly was associated with serious atrial fibrillation.² A reanalysis of an earlier placebo controlled clinical trial of zoledronic acid showed similar rates of atrial fibrillation in the two groups,³ but a reanalysis of a third

trial found a trend towards an increased risk of atrial fibrillation among patients treated with oral alendronate compared with placebo.⁴ We investigated whether bisphosphonates are associated with a risk of atrial fibrillation and flutter.

METHODS

We carried out this population based case-control study using databases from four northern Danish counties, with a combined population of 1.7 million (about 30% of the Danish population). We used the personal identifier assigned to each Danish citizen⁵ to link records to people across all the Danish medical registries and databases. Because bisphosphonates are primarily used by women we focused our study on Danish women.

Cases and population controls

To identify incident cases of atrial fibrillation and flutter we used computerised data from the Danish National Registry of Patients. For each hospital admission since 1977 (since 1995 for hospital outpatient visits and emergency room visits) the registry records the civil registration number of the patient; dates of admission and discharge; surgical procedures, and up to 20 discharge diagnoses, coded by doctors (international classification of diseases, eighth revision until the end of 1993 and the 10th revision thereafter).^{6,7} We searched the registry for patients with discharge codes for atrial fibrillation and flutter. These were coded separately in ICD-8 but together in ICD-10. We therefore studied atrial fibrillation and atrial flutter as one end point.

We chose cases who had a first diagnosis during 1999-2005 because the availability of computerised prescription data for people living in the four counties has been complete since 1998. In this way we had at least a year of prediagnosis prescription history for all cases.

For each case we used risk set sampling to select five controls matched on age, sex, and county, and assigned