Association of Delirium Symptoms with Medication in Terminal Cancer

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Background

- Delirium is a severe and frequent complication in terminal cancer.
- Delirium is reported to be associated with opioids, benzodiazepines, corticosteroids and co-analgesics.
- However, there is a lack of prospective data to confirm this hypothesis.

Objective

To describe the association between the use of medications with delirium symptoms in terminal cancer

Methods

- 1516 patients in 7 palliative care units in Canada, who survived longer than 48 hours, were followed prospectively from October 2001 to January 2005 from admission until patient's death
- The Confusion Rating Scale (CRS; Fig 1) was used for delirium screening and monitoring
- Daily equivalent of opioids (morphine SC), benzodiazepines (lorazepam PO), and corticosteroids (dexamethasone PO), as well as frequency of prescription of co-analgesics was used for analysis

Fig 1. Confusion Rating Scale (CRS)

Date (month, day)									
	N	D	E	N	D	E	N	D	E
Disorientation									
Inappropriate behavior									
Inappropriate communication									
Illusions/Hallucinations									
Score									

If N.E., write : a = natural sleep; b = pharmacological sedation; c = stupor or coma; d = other reason

CRS procedure
N = Night; D = Day; E = Evening
Code each of four behaviors as follows:
0 = behavior not present during the shift
1 = behavior present at some time during the shift, but mild
2 = behavior present at some time during the shift, and pronounced

Results

- 701 patients free of delirium at admission developed significant delirium symptoms (CRS score > 2) before death, for an incidence of 46,2%
- Average stay was longer for patients with significant delirious symptoms
- Higher ECOG scores revealing lower functional status were associated with fewer delirium symptoms
- Past history of delirium was associated with significant delirium symptoms
- Opioids and co-analgesics (anticonvulsivants, ketamine, others) were associated with more delirium symptoms
- Higher benzodiazepines dosage was associated with fewer delirium symptoms
- Only benzodiazepines showed a significant correlation in survival analysis
- Few patients had formal psychiatric diagnosis and there was no association observed between delirium symptoms and psychiatric diagnoses

Table 1. Socio-demographic data of patients

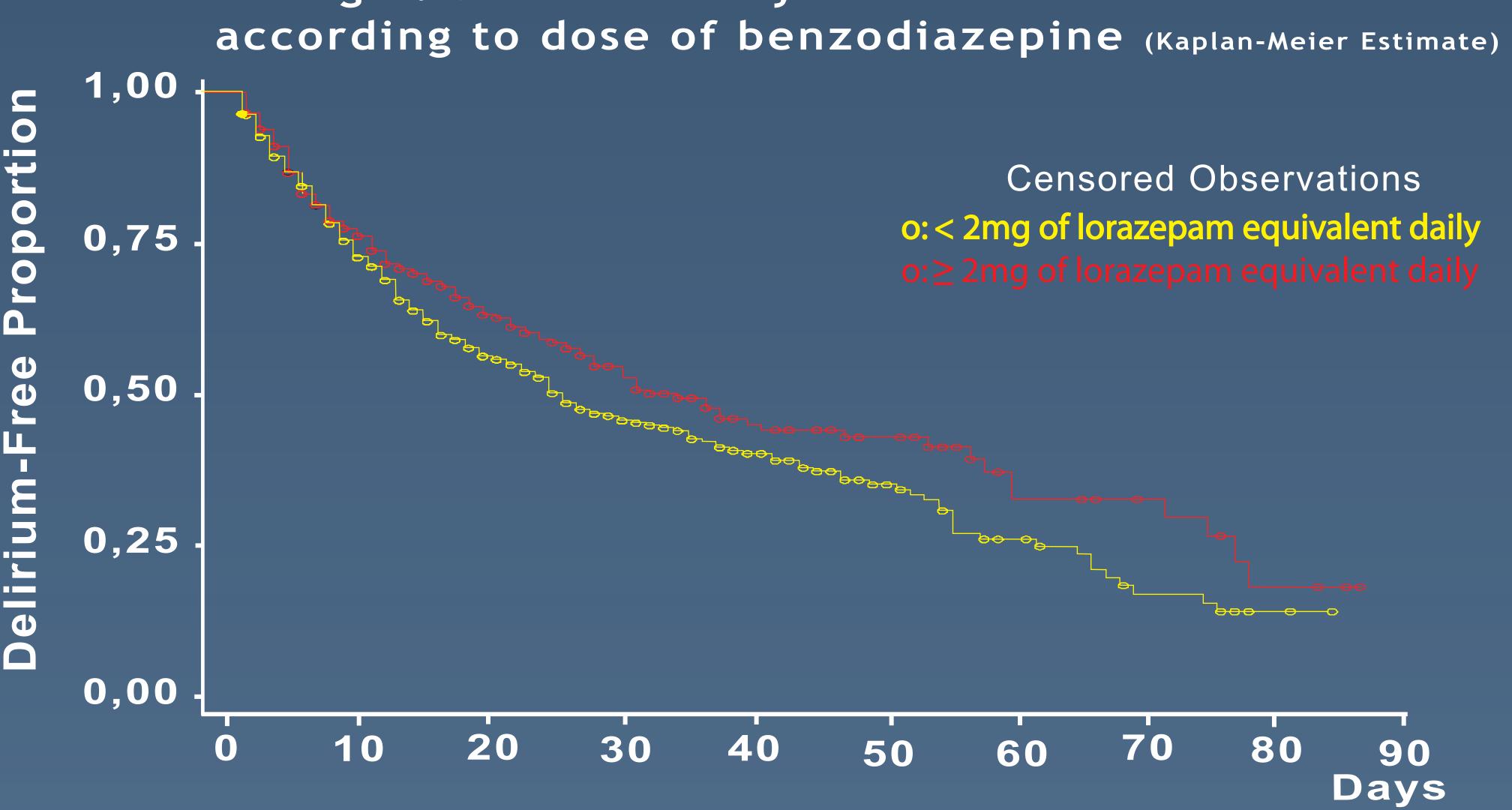| Characteristics	delirium-free patients; n= 815 (std)	delirious patients; n= 701 (std)	p value
Age (year)	68,3 (13)	68,6 (13)	NS
Length of stay/survival (day)	16,0 (15,4)	26,6 (20,3)	< 0,001
Sex (women)	54,7%	52,6%	NS
At least 50% of time confined to bed (ECOG 3-4)	88,8%	86,9%	< 0,001
Primary site			
Trachea, bronchus, lungs	189 (23,2%)	183 (26.1%)	NS
Digestive track	140 (17,2%)	126 (18,0%)	NS
Colon & rectum	110 (13,5%)	101 (14.4%)	NS
Genital and urinary tract	105 (12,9%)	89 (12,7%)	NS
Breast	79 (9,7%)	67 (9,6%)	NS
Prostate	37 (4,5%)	18 (2,6%)	0,04
Others	155 (19,0%)	117 (16,7%)	NS
Past history of delirium			
Yes	87 (10,7%)	126 (18,0%)	< 0,001
None	440 (54,0%)	339 (48,4%)	< 0,001
Unknown	288 (35,3%)	236 (33,7%)	NS

Table 2. Mean daily doses of medication from admission until either patients death (delirium-free population) or incidence of significant delirium symptoms (delirous population)

Medication	mean daily doses (std)		
	delirium-free population	delirious population	p value
Opioids	98,7 (262,7)	136,3 (362,0)	<0,001
Benzodiazepines	4,1 (8,7)	2,2 (2,5)	<0,001
Corticosteroids	9,4 (6,6)	9,6 (6,2)	NS
Antipsychotics	1,6 (1,5)	1,7 (1,7)	NS

Table 3. Proportion of patient with specific pharmacological delirium risk factor

pharmacological risk factor	delirium-free population	delirious population	Odd Ratio (p value)
≥ 90 mg Opioids	0,227 (0,37)	0,331 (0,41)	1,52 (p<0,001)
≥ 2mg Benzodiazepines	0,253 (0,33)	0,273 (0,33)	0,71 (p=0,009)
≥ 15mg Corticosteroids	0,110 (0,26)	0,100 (0,24)	0,87 (p=0,42)
Received co-analgesics	0,161 (0,33)	0,203 (0,35)	1,74 (p<0,001)

Fig 2. Survival analysis of delirium occurence according to dose of benzodiazepine (Kaplan-Meier Estimate)

Censored Observations
o: < 2mg of lorazepam equivalent daily
o: ≥ 2mg of lorazepam equivalent daily

Discussion

- While no formal diagnostic instrument could be used in this population, relationship between CRS scores and variables were consistent even if different CRS thresholds were used, and thus they were considered a valid proxy to detect significant hyperactive delirium symptoms
- The positive relationship between delirium symptoms and opioids or co-analgesics confirms previous observations, thought it did not hold in survival analysis
- The reported positive relationship between corticosteroids and delirium symptoms could not be observed
- The inverse relationship with benzodiazepines and ECOG score may reveal underdiagnosis of hypoctive delirium which might have been missed by the CRS

Conclusions

- Opioids and co-analgesics were associated with delirium
- The inverse correlation with benzodiazepines remains surprising and may be related to confounding variables, including underdiagnosis of hypoactive delirium
- Analysis of delirium risk factors in terminal cancer remains a complex and challenging task

References

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