European Journal of Internal Medicine 78 (2020) 121–126

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Anticholinergic drug exposure at intensive care unit admission affects the occurrence of delirium. A prospective cohort study

Ariël M. Vondeling[a,b,*], Wilma Knol[b], Toine C.G. Egberts[d], Arjen J.C. Slooter[c]

[a] Department of Geriatric Medicine, Diakonessenhuis Utrecht, the Netherlands
[b] Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons (EPHOR), University Medical Centre Utrecht, Utrecht University, the Netherlands
[c] Department of Intensive Care Medicine and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[d] Department of Clinical Pharmacy, University Medical Center Utrecht & Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Delirium
Intensive care
Critical care
Anticholinergics
Cohort studies
Survival analysis

ABSTRACT

Background: Anticholinergic drugs may increase the risk of delirium in non-critically ill patients, but it is unclear whether exposure to these drugs is also a risk factor for Intensive Care Unit (ICU) delirium. In this study the hypothesis was tested that anticholinergic drug exposure at ICU admission increases the risk to develop delirium during ICU stay, particularly in patients with advanced age and severe sepsis.

Methods: A prospective cohort study was performed in the mixed 32-bed medical-surgical ICU of the University Medical Center Utrecht, the Netherlands in the period from January 2011 till June 2013. Included were non-neurological patients that were consecutively admitted for more than 24 hours. The presence of delirium was evaluated each day using a validated algorithm based on the Confusion Assessment Method for the ICU (CAM-ICU), the initiation of delirium treatment as well as chart review by researchers. Anticholinergic drug exposure at ICU admission was assessed using the Anticholinergic Drug Scale (ADS). To evaluate the association between anticholinergic drug exposure at ICU admission and the risk of developing delirium, we performed multivariable competing risk Cox proportional hazard analysis corrected for confounding factors.

Results: Approximately half (47%, n = 513) of the 1090 included patients developed delirium during ICU admission. The absolute risk for delirium development increased with more anticholinergic drug exposure: 42% in patients with ADS score = 0, 49% in patients with ADS score = 1, and 53% in patients with ADS higher than 1. Taking competing events (death and discharge) and potential confounding factors into account, the subdistribution hazard ratio (SHR) was 1.13 (95% CI: 0.91-1.40) for ADS score = 1 point and 1.35 (95% CI: 1.09-1.68) for ADS ≥ 2 compared with an ADS score = 0 (no anticholinergic drug exposure). The effect was strongest during the first days of ICU admittance and was strongest in patients above 65 year without severe sepsis and/or septic shock (SHR 2.15, 95% CI 1.43-3.25).

Conclusions: Anticholinergic drug exposure at ICU admission increases the risk of delirium in critically ill patients. This effect was most pronounced in patients older than 65 years without severe sepsis and/or septic shock, and declining over time.

1. Background

Delirium frequently complicates Intensive Care Unit (ICU) stay [1,2]. The costs accompanying delirium are high [3], mainly due to an increased length of stay both in the ICU and in the hospital [1,4,5]. In addition, delirium is a burden for patients and a risk factor for long-term cognitive impairment [6].

Although several delirium risk factors have been described, it is incompletely known which patients are particularly at risk to develop delirium [7,8]. Medication with anticholinergic effects is presumed to be a precipitating factor based on the central cholinergic deficit hypothesis [7,9]. The presumed reduction in acetylcholine activity in

Abbreviations: ACH, Acetylcholine; ADS, Anticholinergic Drug Scale; APACHE IV, Acute Physiology and Chronic Health Evaluation; ARS, Anticholinergic Risk Scale; CAM-ICU, Confusion Assessment Method – ICU; ICU, Intensive Care Unit; IQR, InterQuartile Range; SD, Standard Deviation; CSHR, Cause-Specific Hazard Ratio; SHR, Subdistribution Hazard Rratio; SOFA, Sequential Organ Failure Assessment

* Corresponding author at: Department of Geriatric Medicine, Diakonessenhuis Utrecht, Bosboomstraat 1 3582 KE, Utrecht, the Netherlands.
E-mail addresses: ondeling@diakhuis.nl (A.M. Vondeling), w.knol@umcutrecht.nl (W. Knol), a.c.g.egberts@umctutrecht.nl (T.C.G. Egberts), a.slooter-3@umcutrecht.nl (A.J.C. Slooter).

https://doi.org/10.1016/j.ejim.2020.04.062
Received 31 January 2020; Received in revised form 9 April 2020; Accepted 29 April 2020
Available online 30 May 2020

delirium is supported by observations that the use of anticholinergic drugs may increase the risk of delirium in non-ICU patients [10]. In addition, acetylcholine is involved in processes such as attention and arousal, and these are particularly affected in delirium [2,9,11]. However, there are very few studies on anticholinergic drugs and the risk of delirium in ICU patients [12,13,28].

It has been hypothesized that severe sepsis and/or septic shock may interact with anticholinergic drugs in increasing the risk of delirium [9]. Both anticholinergic drugs and sepsis may lead to activation of microglial cells, the macrophages of the brain. When microglia is already in an activated state for example due to aging, new stimuli may lead to overactivation, which may lead to long-term cognitive impairment. Furthermore, anticholinergic effects might be more pronounced in older people due to aging-related changes in metabolism, reductions in the number of cholinergic receptors and changes in binding affinity of these receptors, as well as comorbid conditions [7,10,14,15].

The aim of the present study was to investigate whether anticholinergic drug exposure at ICU admission is a risk factor for the development of delirium, and secondly to test the hypothesis that this association is influenced by age and severe sepsis and/or septic shock.

2. Methods

2.1. Setting, study design and population

From January 2011 to June 2013, all adults consecutively admitted to the 32-bed mixed ICU of University Medical Center (UMC) Utrecht, the Netherlands, for at least 24 h, were prospectively evaluated for the occurrence of delirium. Patients for whom a delirium assessment was not possible because of an acute neurological illness that required ICU admission and those with another disorder reducing the ability to determine delirious state, such as mental retardation or inability to speak Dutch or English or patients with cardiac arrest with protocolled sedation, were excluded. Additionally, patients with delirium upon ICU admission as diagnosed by the admitting ICU physician and patients who received haloperidol at ICU admission were excluded. The local ethics review board (METC, University Medical Center Utrecht) gave approval for a waiver to obtain informed consent (IRB number 010/056/c and 12/421/c) given the anonymity of data collection and the noninterventional nature of the study.

2.2. Anticholinergic drug exposure

Medication use at ICU admission was retrieved from the medical records combined with information provided by the patient or his family, and referring letters so combining both medication prescribed at home and new prescribed drugs in the hospital. Each drug was assigned an anticholinergic score based on the Anticholinergic Drug Scale (ADS) (supplementary material 1). This scale is widely used and well validated, using multiple methods to asses anticholinergic burden. [17]. In this scale, the anticholinergic potential of drugs is rated in an ordinal fashion from 0 to 3: signifying no known anticholinergic activity (0), anticholinergic association by a serum assay study (1), some clinical evidence and anticholinergic association by a serum assay study (2), and marked anticholinergic activity (3). The individual scores of all the drugs taken by a patient at ICU admission were then summed to determine a total score for a particular patient.

2.3. Delirium assessment

Each day, in the morning, up until death or ICU discharge, patients were assessed for delirium in the preceding 24 h by a dedicated research team following a 5-step algorithm for daily mental status classification [16]. This algorithm has been developed and validated in the mixed ICU of UMC Utrecht, with interrater observer agreement ranging from 0.94–0.97, 0.75 sensitivity and 0.85 specificity [16]. With this flowchart, each patient was daily assigned a classification per 24 h as: 1) coma, 2) delirium or 3) awake without delirium.

2.4. Other data collection

Demographics, co-morbidities, chronic medication use, ICU admission characteristics, physiological measurements and vital signs, were collected daily by trained physicians dedicated to this patient cohort. When patients were readmitted to the ICU within 24 h after ICU discharge, the two ICU admissions were merged into one admission. Patient comorbidities were defined present when noted in the medical record or when patients used medication to treat the comorbidity, for example insulin or oral anti-diabetics in diabetes mellitus. Whether patients had a history of psychopathology prior to hospital admission was determined using medical records of the hospital information system. Alcohol abuse was considered present when patients used more than three standard units of alcohol per day, as documented in the medical records or mentioned in (proxy) history. The presence of severe sepsis and/or septic shock was classified using the definitions of the American College of Chest Physicians and Society of Critical Care Medicine [18,19,20]. Cardiac failure was defined as a history of heart failure NYHA class II-IV, or an ejection fraction of $<45\%$, or orthopnoea.

2.5. Data analysis

All values were presented as mean with standard deviation (SD), median with the interquartile range (IQR), or number with percentage (%). Differences between groups were assessed using the Student's T-test, Mann-Whitney U test, or Chi Square test, where appropriate. To evaluate the risk of developing delirium during ICU admission dependent on the anticholinergic drug exposure at ICU admission, we performed multivariable competing risk Cox proportional hazard analysis. As both ICU discharge and death compete with the duration of delirium, these act as competing events. Patients discharged from the ICU with palliative care were classified as deceased during ICU admission. The competing risks analysis provides two measures of association: the cause-specific hazard ratio (CSHR), which estimates in this case the direct effects of the anticholinergic drug exposure load on the different outcomes (delirium, ICU discharge and death), and the subdistribution hazard ratio (SHR) which describes in this study the instantaneous risk of developing delirium dependent on the anticholinergic load [21].

In all multivariable models, we adjusted for time-fixed covariables that were chosen a priori based on their expected associations with anticholinergic burden and delirium in the ICU [8]. Only variables with prevalence $>10\%$ were considered for inclusion in the multivariable analyses. The Acute Physiology and Chronic Health Evaluation (APACHE) IV Score was included, as a measure of the severity of illness at ICU admission, and the maximum Sequential Organ Failure Assessment (SOFA) during ICU admission up until death, discharge or delirium (whichever occurred first), as a measure of the evolution of disease severity after ICU admission [22,23]. To avoid overcorrection, a modified SOFA score without the central nervous system component was used to assess daily severity of illness during ICU admission [22].

We assumed that the effect of the anticholinergic load of medication used at ICU admission would be largest in the first days of admission in the ICU, as we assumed that anticholinergic agents would prime the brain for delirium and later during admission other factors would be more relevant. We therefore performed a time-varying cause-specific Cox regression analysis to test for this effect adjusted for the same variables as in the other analyses.

As we hypothesized effect modification by age and severe sepsis and/or septic shock, we performed stratified analyses in four subgroups of patients: aged $<$ 65 years or $\geq$ 65 years, both with and without severe sepsis and/or septic shock at ICU admission.

All statistical tests were performed (mean with standard deviation

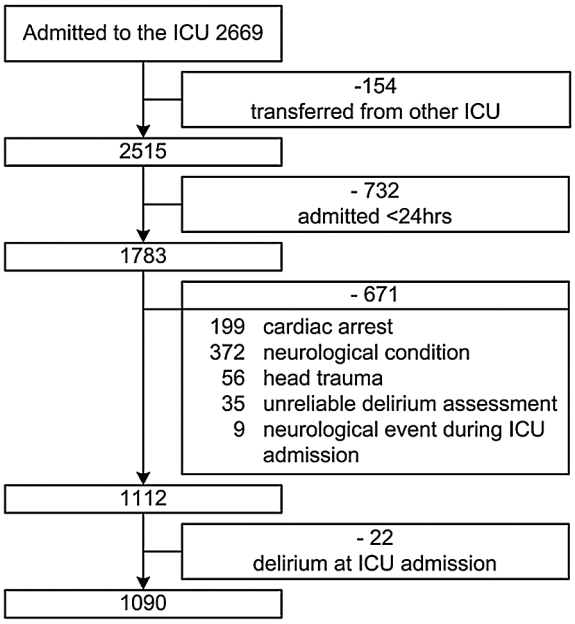

Fig. 1. Flowchart of patient enrollment. Legend: hrs = hours, ICU = Intensive Care Unit.

with chi squared for nominal data and student's t-test for continuous data) against 2-sided alternatives and p-values <0.05 were defined as statistical significant. SPSS 20 (IBM, New York, USA) and R version 3.0.1 and SAS/STAT version 14.1 were used to perform the statistical analysis. The R-package "cmprsk" was used to plot the cumulative incidence of delirium in the presence of competing risks [22,25].

3. Results

A total of 2669 patients were screened of whom 1579 were excluded, leaving 1090 included patients (Fig. 1). In 513 (47%) of the included patients, delirium occurred during admission in the ICU. The characteristics of the included patients are presented in Table 1. Of 1090 patients, 481 were admitted for a medical reason, 535 were surgical patients and 74 had a major trauma. Surgical reason were general surgery (abdominal, organ transplant or vascular) in 32% of all patients and 22% of all patients had cardiothoracic surgery or cardiogenic shock. Among medical reasons were 31% of all patients with a sepsis (pneumonia or other), and 15% with another reason. Patients who developed delirium during ICU admission were on average older, more often male, had more often a history of alcohol abuse or heart failure, used more medication classes and had higher maximum SOFA and APACHE IV scores. They also had more often severe sepsis and/or septic shock at ICU admission compared with patients who were never delirious. Further, patients who developed delirium were less likely to be admitted electively, had a longer length of stay in the ICU and higher ICU mortality, with more frequent use of mechanical ventilation, than those who never had delirium.

With a prescription proportion of 17% in the whole study population, furosemide was the most commonly used anticholinergic drug at ICU admission, followed by prednisone (12%), temazepam (7%) and oxazepam (7%). Table 2 shows the exposure to anticholinergic drugs at ICU admission by delirium status during stay in the ICU. Furosemide was the only drug with a significantly different prescription proportion (21% in patients who developed delirium versus 14% in those who did not, $p = 0.008$).

Table 3 shows the risk of delirium according to the ADS score of medication use at ICU admission. Relative to an ADS score of 0, and after adjusting for competing events and covariables, an ADS score of 1 point was not associated with an increased risk of delirium (SHR = 1.13, 95% CI: 0.91–1.40), in contrast to an ADS score ≥ 2 points (SHR = 1.32, 95% CI: 1.06–1.64) (Table 3, Fig. 2).

Table 1
Patient demographics and clinical characteristics.

Characteristic	Delirium[b] (n = 513)		No delirium[b] (n = 577)		p-value
Age in years, mean (SD)	63	(15)	58	(16)	<0.001
Male, n (%)	328	(64%)	328	(57%)	0.02
Comorbidity[a] at hospital admission					
Assisted Living, n (%)	6	(1%)	14	(2%)	0.17
Cerebrovascular disease, n (%)	63	(12%)	52	(9%)	0.10
Alcohol abuses, n (%)	31	(6%)	14	(2%)	0.004
Hypertension, n (%)	184	(36%)	191	(33%)	0.37
Diabetes Mellitus, n (%)	104	(20%)	112	(19%)	0.78
Cardiac Failure, n (%)	77	(15%)	48	(8%)	<0.0001
Psychopathology (all)					0.07
Possible, n (%)	77	(15%)	69	(12%)	
Probable, n (%)	61	(12%)	48	(8%)	
Definite, n (%)	34	(7%)	45	(8%)	
Parkinson's disease, n (%)	1	(0.2%)	0		0.47
No. of medication classes[a], median (IQR)	4	(2–5)	3	(1–5)	<0.001
Elective ICU admission, n (%)	129	(25%)	191	(33%)	0.005
ICU Admission Type					0.70
Medical admission, n (%)	222	(43%)	259	(45%)	
Surgical admission, n (%)	253	(49%)	282	(49%)	
Trauma admission, n (%)	38	(7%)	36	(6%)	
APACHE IV score, mean (SD)	80	(26)	68	(28)	<0.001
Severe Sepsis at ICU admission, n (%)	201	(39%)	106	(18%)	<0.001
Use of mechanical ventilation, n (%)	496	(97%)	519	(90%)	<0.001
Maximum mSOFA score, median (IQR)	8	(6–10)	5	(3–8)	<0.001
Length of ICU stay, median (IQR)	9	(5–19)	3	(2–5)	<0.001
Death at ICU, n (%)	77	(15%)	62	(11%)	0.04

APACHE = Acute Physiology and Chronic Health Evaluation, ICU = Intensive Care Unit, IQR = Interquartile range, n = number, SD = standard deviation, mSOFA = modified Sequential Organ Failure Assessment.

[a] at hospital admission.

[b] during ICU admission; [c]percentages do not count up to 100% due to rounding.

The association of an ADS score ≥ 2 points and delirium declined over time, with a SHR = 1.66 (95% CI 1.24–2.24) in the first 24 h of ICU admission, SHR = 1.59 (95% CI 1.21–2.01) after 48 h, SHR = 1.46 (95% CI 1.14–1.86) after 72 h and SHR = 1.42 (95% CI 1.12–1.80) after 96 h.

With delirium developing in 254/485 (52%) of the patients aged ≥ 65 years, delirium was more common compared with 43% (259/605) in those aged < 65 years ($p = 0.002$). In addition, patients with severe sepsis and/or septic shock developed delirium more often (65%, 201/307) than other patients (40%, 312/783, $p = <0.001$). Within the four subgroups, the frequency of delirium was highest ($p < 0.001$) in the oldest patients with severe sepsis and/or septic shock (73%, 106/146), followed by younger patients with severe sepsis and/or septic shock (59%, 95/161), older patients without severe sepsis and/or septic shock (44%, 148/339) and younger patients without severe sepsis and/or septic shock (37%, 164/444). However, the highest SHR associated with an ADS score ≥ 2 was observed in patients aged ≥ 65 years without severe sepsis and/or septic shock (SHR = 2.14, 95% CI: 1.42–3.21), Table 3.

4. Discussion

In summary, we found that anticholinergic drug use at ICU admission increases the risk of delirium in critically ill patients. This effect

Table 2
Top 10 of most frequently used medication at ICU admission with anticholinergic properties[a].

		All (n = 1090)		Delirium[b] (n = 513)		No delirium[b] (n = 577)	p-value
Furosemide, Rank, n (%)	1.	189 (17%)	1.	106 (21%)	1.	83 (14%)	0.008
Prednisolone, Rank, n (%)	2.	127 (12%)	2.	55 (11%)	2.	72 (12%)	0.42
Temazepam, Rank, n (%)	3.	73 (7%)	3.	34 (7%)	3.	39 (7%)	1.00
Oxazepam, Rank, n (%)	4.	71 (7%)	4.	34 (7%)	4.	37 (6%)	0.98
Digoxine, Rank, n (%)	5.	46 (4%)	5.	26 (5%)	7.	20 (3%)	0.25
Oxycodon, Rank, n (%)	6.	43 (4%)	9	16 (3%)	5.	27 (5%)	0.24
Amitriptyline, Rank, n (%)	7.	38 (3%)	7.	16 (3%)	6.	22 (4%)	0.65
Dipyridamol, Rank, n (%)	8.	35 (3%)	8.	16 (3%)	8.	19 (3%)	1.00
Nifedipine, Rank, n (%)	9.	30 (3%)	6.	17 (3%)	12.	13 (2%)	0.38
Isosorbidedinitrate, Rank, n(%)	10.	28 (3%)	11.	15 (3%)	11.	13 (2%)	0.61
Tramadol, Rank, n(%)	11.	27 (2%)	10.	16 (3%)	14.	11 (2%)	0.28
Codeïne, Rank, n(%)	12.	25 (2%)	15.	11 (2%)	9.	14 (2%)	0.91
Paroxetine, Rank, n(%)	13.	23 (2%)	17.	9 (2%)	10.	14 (2%)	0.58

[a] According to the Anticholinergic Drug Scale.
[b] During ICU admission.

was most pronounced in the first days of ICU admission and declined over time. We confirmed that advanced age as well as sepsis and/or septic shock increased the risk of delirium. However, when we studied these factors together in four strata, the highest delirium risk associated with an ADS score ≥ 2 was observed in patients aged ≥ 65 years without severe sepsis and/or septic shock.

Previous literature on acetylcholine activity, anticholinergic drugs and delirium is sparse. Serum acetylcholine activity has been associated with delirium in postoperative [26,27] and medical patients [10,29], providing support for the hypothesis that anticholinergic drug use could increase the risk of delirium. Indeed, in respectively critically ill elderly, postoperative-, palliative care- and acute stroke patients, it was reported that a higher anticholinergic drug load increased the risk of delirium [13,30,31,32,33]. However, more recently, exposure to anticholinergic drugs during ICU admission did not increase the risk of transitioning towards a delirious state [28]. Possible explanations for the discrepancy in findings of the present study and this previous investigation[28] may be that our study measures anticholinergic load prior to ICU admission and found a pronounced effect in the first days of admission. The other investigation looks into anticholinergic load during ICU admission and transition towards delirious state.

Assessment of anticholinergic drug exposure with anticholinergic scales has limitations. Firstly, using these scales the exposure is based on the use or nonuse of drugs with allotted anticholinergic properties.

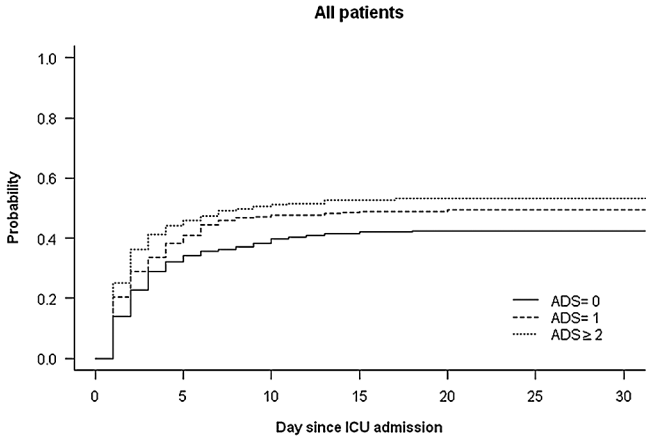

Fig. 2. Cumulative Incidence of delirium in relation to anticholinergic drug exposure. Legend: ADS = Anticholinergic Drug Scale, ICU = Intensive Care Unit.

However, the ultimate anticholinergic effects may also depend on individual pharmacokinetic or pharmacodynamic characteristics such as the plasma concentration at a given dose (because of altered

Table 3
Anticholinergic drug exposure[a] at ICU admission and incidence of delirium[b] stratified for sepsis and age.

	ADS = 0 (n = 512)		**ADS = 1 (n = 284)**		**ADS ≥ 2 (n = 294)**	
Adjusted Subdistributional Hazard Ratios[d] for developing delirium						
All Patients (n = 1090, delirium n = 513)	1	(ref)	1.13	(0.91–1.40)	1.32	(1.06–1.64)
Subgroups						
Age <65 years, no severe sepsis and/or septic shock (n = 444, delirium n = 164)	1	(ref)	1.14	(0.78–1.67)	1.24	(0.84–1.84)
Age <65 years, severe sepsis and/or septic shock (n = 161, delirium n = 95)	1	(ref)	1.12	(0.63–2.01)	1.18	(0.69–2.00)
Age ≥65 years, no severe sepsis and/or septic shock (n = 339, delirium n = 148)	1	(ref)	1.52	(0.99–2.33)	2.15	(1.43–3.25)[c]
Age ≥65 years, severe sepsis and/or septic shock (n = 146, delirium n = 106)	1	(ref)	0.75	(0.47–1.20)	0.84	(0.51–1.39)

ICU = Intensive Care Unit, SHR = subdistributional hazard ratio.
[a] measured with the anticholinergic drug scale (ADS).
[b] Using competing risk cox proportional hazard analysis.
[c] statistical significant with p-value <0.05.
[d] Adjusted for age, gender, depression, hypertension, diabetes mellitus, cerebrovascular disease, current drinking status, cardiac failure, Acute Physiology and Chronic Health Evaluation IV Score, elective ICU admission (vs emergency), surgery before ICU admission, severe sepsis and/or septic shock at ICU admission (not in stratified analysis) and modified maximum Sequential Organ Failure Assessment Score.

bioavailability), an altered brain access (because of age and disease-related changes in the blood-brain barrier), and/or modified sensitivity at the receptor level (because of a change in the binding affinity to the muscarinic receptor or displacement from the receptor by other drugs) [39]. All these issues could be an explanation for the larger effect of anticholinergic burden in older patients in our study population.

Further, there is no consensus which scale represents anticholinergic load best [34]. Several scales have been developed, but these define anticholinergic activity differently; some use anticholinergic serum activity in combination with expert opinion [17], others also include clinical information [24,35] and mix with other drug types [34]. Consequently, the scales differ in the number of included drugs. Different scales are also used for different side-effects of anticholinergic agents, such as the risk of dementia, falls, death and hospitalization [34]. We used the ADS to quantify anticholinergic load, as it may be superior to other scales because it is based on a serum radio receptor assay to quantify drug-induced muscarinic blockade as a measure of an individual's level of anticholinergic activity [27,36,37]. It is thought that the ADS reflects the cumulative anti-muscarinic burden of all substances present in a person's serum, including medication, drug metabolites and possibly endogenous substances.

We found that furosemide was the most commonly used drug at ICU admission that contributed to the ADS score. This drug was therefore, in part, responsible for the association of an ADS score ≥ 2 and delirium in our study. However, experts doubt the anticholinergic properties of furosemide [34,38]. It could therefore be hypothesized that the association of the ADS score with delirium might be due to confounding by indication, i.e. the ADS score could be associated with delirium because cardiac failure, the main indication for furosemide, increases delirium risk. score and delirium. With additional adjustments for cardiac failure we corrected for the main indication for prescribing furosemide. As this did not change our results [data not shown], the main indication for prescribing furosemide (e.g. cardiac failure) seems not to be a confounding factor for risk of delirium in our study. We further found an equal distribution in use of benzodiazepines and codeine in the delirium and the non-delirium groups. However, our study was not designed to evaluate the risk of individual drugs on delirium.

Psychotropic drugs particularly contribute to the ADS score, and it could therefore be hypothesized that the observed association of the ADS score with delirium might be due to the fact that psychotropic drugs are more often used by patients with pre-existing psychopathology, which increases the risk of delirium [40]. We could not adjust for pre-existing psychopathology as the classification that we used previously was based, in part, on psychotropic drugs use [40]. However, when we studied the association of an ADS score ≥ 2 points with delirium, we found that the strength of this relationship declined over time. This argues for a true association between the ADS score and delirium as the administration of certain psychotropic drugs that are used before ICU admission might be discontinued during ICU stay. As expected, the incidence of delirium in our cohort was highest in older patients with severe sepsis and/or septic shock [9]. The underlying mechanism for this association may be that during sepsis, peripherally produced pro-inflammatory cytokines enter the brain, leading to a neuro-inflammatory state with neurotoxic effects [9,41], and that neuro-inflammation is most pronounced in elderly patients in whom microglia is already primed, leading to overactivation in sepsis. It is presumed that the cholinergic neurotransmitter system inhibits this neuro-inflammatory state [9]. The finding that the risk of delirium associated with the highest anticholinergic drug load was highest in the stratum of older patients without severe sepsis and/or septic shock, was therefore unexpected. Is should however be noted that patients without the classification “severe sepsis and/or septic shock” were also in a neuro-inflammatory state as inflammation is also associated with reasons for ICU admission, such as major surgery or polytrauma.

Strengths of our investigation include the large sample size, the prospective data collection, the extensive adjustment for important confounders and incorporation of competing events in our statistical analysis. Further, we used a reliable and thorough ascertainment of delirium based on a validated algorithm for daily classification of mental status including at least two delirium assessments per day.

Limitations include the lack of confirmation of drugs used at ICU admission, we did not include this as an exclusion criterium. Since adherence is a common problem we cannot be sure whether drugs retrieved from the medical records and referring letters were actually taken, this upholds ass well for PRN medication. PNR medication was scored as actually taken by the patient. Further, we did not have information on time of use, frequency, or dose. There could also be an effect of discontinuing medication after admission to the ICU. It is known that unintentional discontinuation of medication at ICU admission can have a deleterious effect on mortality [42]. Therefore, confounding effect of changes in medication with anticholinergic properties around ICU admission cannot be ruled out. The prevalence of dementia in our cohort was 0.4% which precluded inclusion of this variable in multivariable analysis. Also renal and/or hepatic failure were not prevalent enough to include in the analysis. Further, we could not use the latest criteria for sepsis and septic shock as these were published after data collection [43] We classified patients discharged with palliative care ($n = 6$) as deceased, at least 4 of them were deceased during hospital admission. This was a single-center study, which limits generalizability. Finally, we cannot exclude residual confounding due to unmeasured confounders, although we adjusted extensively.

5. Conclusions

We found that exposure to drugs with anticholinergic effects before ICU admission increases the risk of developing delirium during critical illness. We could not confirm our hypothesis that this risk was particularly high in elderly patients with severe sepsis and/or septic shock. As delirium is difficult to treat and associated with negative outcomes, prevention is of paramount importance. Our results suggest that limiting anticholinergic drug exposure at ICU admission could have efficacy in the prevention of delirium.

Ethical approval and consent to participate

The local ethics review board (METC, University Medical Center Utrecht) gave approval for a waiver to obtain informed consent (IRB number 010/056/c and 12/421/c) and approved the entire research manuscript.

Consent for publication

All authors approved the manuscript for publication.

Authors' contributions

AV, WK, TE and AS were responsible for the study conception and design. AV and AS acquired and analyzed the data. AV drafted the manuscript and WK, TC and AS contributed to refinement. All authors read and approved the final manuscript.

Funding

None

Declaration of Competing Interest

None of the authors has any proprietary interests or conflicts of interest related to this submission. This submission has not been published anywhere previously, and it is not simultaneously being considered for any other publication.

Acknowledgements

The authors thank P.M.C. Klein Klouwenberg, MD. PharmD. PhD., A.E. Wolters, MD, W. Pasma, DVM., and IJ Zaal, MD. PhD. Department of Intensive Care Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands for their support and assistance in data acquisition and analysis. We further thank P.M.J. Welsing, Julius Center UMC Utrecht for help with statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.04.062.

References

[1] van den Boogaard M, Schoonhoven L, van der Hoeven JG, van AT. Pickkers P Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study. Int J Nurs Stud 2012;49:775–83.
[2] Zaal IJ. Slooter AJ Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. Drugs 2012;72:1457–71.
[3] Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, Truman B, Bernard GR, Dittus RS. Ely EW Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32:955–62.
[4] Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard R. Inouye SK The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892–900.
[5] Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, Ehtisham A, Nold J, Agarwal S, Azocar R. Burke P The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med 2009;37:1898–905.
[6] Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–16.
[7] Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157–65.
[8] Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A systematic review of risk factors for delirium in the intensive care unit. Crit Care Med 2015;43(1):40–7.
[9] van Gool WA, van de Beek D. Eikelenboom P Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 2010;375:773–5.
[10] Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F. Elie M Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161:1099–105.
[11] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edn Arlington, VA: American Psychiatric Publishing; 2013.
[12] Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Ely EW Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21–6.
[13] Tune L, Carr S, Cooper T, Klug B. Golinger RC Association of anticholinergic activity of prescribed medications with postoperative delirium. J Neuropsychiatry Clin Neurosci 1993;5:208–10.
[14] Trzepacz PT. Anticholinergic model for delirium. Semin Clin Neuropsychiatry 1996;1:294–303.
[15] Ray PG, Meador KJ, Loring DW, Zamrini EW, Yang XH. Buccafusco JJ Central anticholinergic hypersensitivity in aging. J Geriatr Psychiatry Neurol 1992;5:72–7.
[16] Zaal IJ, Peelen LM, van Dijk D, Slooter AJ. Development and validation of an eight-step flowchart based on the CAM-ICU: a quick and highly adaptable tool to determine the presence of delirium in ICU patients. Critical Care 2011:15.
[17] Carnahan RM, Lund BC, Perry PJ, Pollock BG. Culp KR The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol 2006;46:1481–6.
[18] Klein Klouwenberg PM, Ong DS, Bos LD, de Beer FM, van Hooijdonk RT, Huson MA, Straat M, van Vught LA, Wieske L, Horn J, Schultz MJ, van der PT, Bonten MJ. Cremer OL interobserver agreement of centers for disease control and prevention criteria for classifying infections in critically ill patients. Crit Care Med 2013;41:2373–8.
[19] Klein Klouwenberg PM, Ong DS, Bonten MJ. Cremer OL Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. Intensive Care Med 2012;38:811–9.
[20] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Sibbald WJ Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
[21] Fine JP. Gray RJ A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999;94:496–509.
[22] Vincent JL, de MA, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F. Blecher S use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793–800.
[23] Zimmerman JE, Kramer AA. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34:1297–310.
[24] Rudolph JL, Salow MJ, Angelini MC. McGlinchey RE the anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168:508–13.
[25] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stats 1988;16:1141–54.
[26] Golinger RC, Peet T. Tune LE Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987;144:1218–20.
[27] Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF. Coyle JT Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2. 651–65345.
[28] Wolters AE, Zaal IJ, Veldhuijzen DS, Cremer OL, Devlin JW, van Dijk D. Slooter AJ Anticholinergic medication use and transition to delirium in critical ill patients: a prospective Cohort study. Crit Care Med 2015;43:1846–52.
[29] Flacker JM, Cummings V, Mach Jr. JR, Bettin K, Kiely DK. Wei J The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6:31–41.
[30] Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62(Suppl 21):11–4.
[31] Zimmerman KM, Salow M, Skarf LM, Kostas T, Paquin A, Simone MJ. Rudolph J Increasing anticholinergic burden and delirium in palliative care inpatients. Palliat Med 2014;28:335–41.
[32] Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R. Figueira ML Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. Eur J Neurol 2004;11:699–704.
[33] Engberts ACG, van der Craats ST, van Wijk MD, Alkilabe S, Van den Bemt PMLA, Mattace-Raso FUS. Anticholinergic drug exposure is associated with delirium and postdischarge institutionalization in acutely ill hospitalized older patients. Parmacol Res Perspect 2017(3). Jun 5.
[34] Welsh TJ, van der Wardt V, Ojo G, Gordon AL, Gladman JRF. Anticholinergic dryg burden Tools/Scales and advers outcomes in different clinical settings: a systematic review of reviews. Drugs Aging 2018;35:523–38.
[35] Summers WK. A clinical method of estimating risk of drug induced delirium. Life Sci 1978;22:1511–6.
[36] Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, Kirshner MA, Sorisio DA, Bies RR. Gharabawi G anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008.
[37] Gerretsen P. Pollock BG Drugs with anticholinergic properties: a current perspective on use and safety. Expert Opin Drug Saf 2011;10:751–65.
[38] Salahudeen MS, Duffull SB. Nishtala PS anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr 2015;15:31. Mar 25.
[39] Mangoni AA, van Munster BC, Woodman RJ. de Rooij SE Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause post-discharge mortality in older hospitalized patients with hip fractures. Am J Geriatr Psychiatry 2013;21:785–93.
[40] Sajjad A, Wolters AE, Veldhuijzen DS, Peelen LM, Welling MC, Zaal IJ, van Dijk D, Slooter AJC. Psychopathology prior to critical illness and the risk of delirium onset during intensive care unit stay. Intensive Care Med 2018;44(8):1355–6. https://doi.org/10.1007/s00134-018-5195-8. Aug.
[41] Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. Biochem Soc Trans 2011;39:945–53.
[42] CM1 Bell, SS Brener, Gunraj N, Huo C, Bierman AS, Scales DC, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA 2011;306(8):840–7. Aug 24.
[43] Levy ML, Philips GS, Shankar HAri M, et al. Developing a new definition and assessing new clinical criteria for septic shock. JAMA 2016:775–87. Aug 315.