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ORIGINAL REPORT

Correlated measures in longitudinal analysis of daily drug use patterns in a general intensive care unit†

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SUMMARY

Purpose The objective of the present study is to compare two different study designs (with and without corrections for correlated measures) to identify possible determinants of psychotropic drug use in an intensive care unit (ICU).
Methods In a logistic regression analysis, odds ratios (OR) were calculated for days in which patients were exposed to psychotropics compared with non-exposed days. In order to adjust for correlated measures, logistic regression with a logistic binomial model was applied.
Results We found that adjustment for correlated measures did not result in major changes in the OR. However, with more observations per patient parameter, adjustment for correlation has greater effect.
Conclusions Adjustment for correlated measures may be useful in longitudinal drug analyses. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — hospitals; university; intensive care units; psychotropic drugs; pharmaco-epidemiology; case-control studies; drug utilisation

INTRODUCTION

In a study published earlier, we sought to identify determinants of psychotropic drug prescription in a case-control design and found clear patterns of determinants of psychotropic drug use in intensive care unit (ICU) patients.[1] In order to cope with varying lengths of stay, we used bed-days as unit of analysis. Patients who used psychotropic drugs (cases) acted as their own controls because days exposed to psychotropics were compared with non-exposed days. However, in this analysis no corrections were made for the fact that the observations were correlated.

The objective of the present study is to compare two different study designs, with and without corrections for correlated measures, both taking possible confounding into account, in order to identify possible determinants of psychotropic drug use in an ICU. We will discuss the methodological considerations and pitfalls concerned with these methods.

MATERIALS AND METHODS

Study population and data

Population and data have extensively been described before.[1] We retrospectively collected data over the first 3 months of 1995 from a consecutive sample of 137 patients of 18 years or over admitted to two general ICUs (17 beds in total) in The Netherlands with post-surgical and non-surgical severely ill patients. Patient data (gender, age, length of stay, disease severity, drug use during previous day and reason for admission) and data on type of psychotropics used (antidepressants, benzodiazepines, antipsychotics)

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Table 1. Days of psychotropic use compared to days with no use of psychotropics (presented as odds ratios, OR with 95% confidence interval, CI) adjusted for possible confounding

	Benzodiazepines only		Antipsychotics only		Benzodiazepines & antipsychotics	
Gender						
Female	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	**1.7 (1.0–3.0)**	1.5 (0.8–2.9)	**5.2 (2.2–12.4)**	**4.7 (1.6–14.0)**	0.8 (0.3–2.5)	1.7 (0.2–12.6)
Age						
18–44	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
45–64	0.9 (0.4–2.0)	0.8 (0.3–2.1)	1.1 (0.3–3.9)	1.0 (0.2–4.6)	0.3 (0.1–1.2)	0.2 (0.0–2.8)
>65	0.7 (0.4–1.4)	0.8 (0.3–1.7)	1.0 (0.3–3.1)	0.9 (0.2–3.5)	0.4 (0.1–1.5)	0.3 (0.0–2.9)
Apache-II score						
0–10	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
11–20	**2.6 (1.0–6.8)**	2.4 (0.8–6.8)	0.9 (0.3–3.1)	0.9 (0.2–3.6)	1.8 (0.3–8.7)	2.0 (0.1–29.2)
>21	**2.7 (1.0–7.5)**	3.5 (1.1–11.0)	0.5 (0.1–2.1)	0.5 (0.1–2.6)	1.8 (0.3–11.4)	1.0 (0.0–19.9)
Length of stay						
0–6	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
7–13	0.7 (0.4–1.4)	0.6 (0.3–1.2)	1.7 (0.7–4.3)	1.7 (0.6–4.5)	1.2 (0.3–4.5)	1.5 (0.3–8.4)
14–20	0.8 (0.3–2.1)	0.6 (0.2–1.9)	4.5 (1.2–17.4)	5.8 (1.0–34.5)	4.4 (0.8–23.5)	5.6 (0.5–58.5)
21–27	0.4 (0.1–1.5)	0.2 (0.0–1.2)	0.8 (0.2–4.0)	0.8 (0.1–4.8)	1.8 (0.3–11.1)	4.9 (0.2–109.8)
>28	0.8 (0.4–1.5)	0.5 (0.2–1.2)	1.2 (0.4–3.1)	1.8 (0.4–7.8)	1.1 (0.3–4.0)	1.0 (0.2–7.2)
Drug use during previous day						
Benzodiazepine	**11.8 (7.3–19.2)**	**9.9 (5.8–16.8)**	2.2 (0.9–5.8)	2.5 (0.9–7.0)	**21.0 (8.1–54.4)**	**23.1 (5.2–102.7)**
Antipsychotic	0.5 (0.1–1.4)	0.5 (0.1–1.5)	**23.2 (11.6–46.4)**	**18.5 (7.6–45.0)**	**29.7 (11.6–76.3)**	**9.3 (1.8–48.9)**
Reason for admission						
Surgical	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-surgical	1.4 (0.8–2.6)	1.3 (0.6–2.5)	**6.6 (2.1–20.1)**	**53 (1.4–20.0)**	1.7 (0.4–7.0)	2.2 (0.3–17.5)

In the grey columns the presented results are also adjusted for correlated measures. Significant associations are printed in bold.

were extracted from the medical records by means of a standardised data collection form. Medication was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Medication termed 'as needed' was not included in the analysis.

The acute physiologic and chronic health evaluation (APACHE)-II classification system was used to classify patients according to severity of disease on admission.[2] This system uses a score (range 0–71) based on worst values during 24 hours of 12 routine physiologic measurements combined with age and previous health status to provide a standardised measure of severity of disease. This score has been validated and is correlated with subsequent risk on hospital death.[2] Patients were stratified according to APACHE-II scores into three categories: low (0–10), middle (11–20) and high (>21) severity of disease. Furthermore, patients were stratified according to reason for admission into surgical ICU admission and other reasons, mostly severe internal diseases.

Study designs

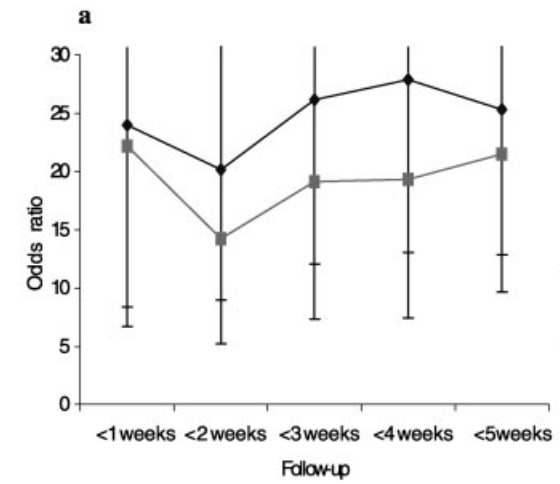
Bed-days were taken as unit of analysis in order to cope with varying lengths of stay in the ICU. Non-24 hour admission days were excluded, effectively omitting the day of admission and discharge.

1) We compared days exposed to psychotropics with days not exposed to psychotropics and calculated odds ratios (OR) for various possible factors associated with exposed days. In this way, a single patient could contribute to both exposed and unexposed days. Adjustment for possible confounding was performed by an unconditional logistic regression analysis with exposed days as dependent variables and all possible factors associated with exposed days as independent variables.
2) In addition to adjustment for possible confounding, adjustment for correlated measures in individual patients was performed by logistic regression with a logistic-binomial model for distinguishable data with random effects. Again, exposed days were compared to non-exposed days, but in addition the patient-identifier was included as a random effect term.

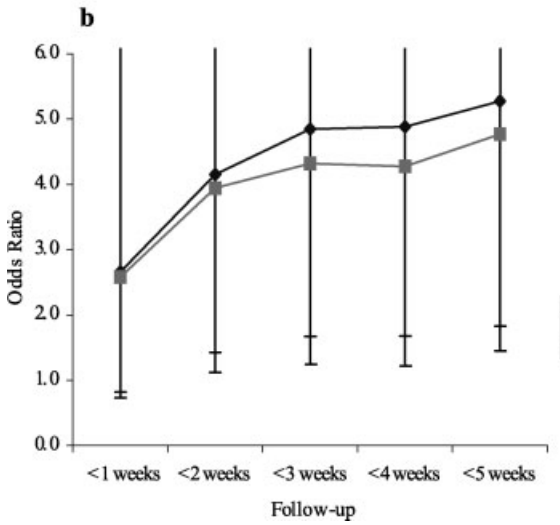
Data were analysed using EGRET and SPSS package.

RESULTS

Table 1 shows OR for patient parameters adjusted for confounding. In the grey columns results are presented which are also adjusted for correlated measures. No major differences in the point-estimates of



Follow-up	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
<1 week	24.0 (8.4-68.8)	22.2(6.7-73.4)
<2 weeks	20.1 (9.0-45.1)	14.3 (5.2-39.0)
<3 weeks	26.2 (12.1-56.7)	19.1 (7.3-49.6)
<4 weeks	27.9 (13.1-59.5)	19.3 (7.5-49.9)
<5 weeks	25.3 (12.8-49.9)	21.5 (9.6-47.8)



Follow-up	Unadjusted OR (95% CI)	Adjusted OR 95% (CI)
< 1 week	2.7 (0.8-8.6)	2.6 (0.8-8.9)
<2 weeks	4.2 (1.4-12.1)	3.9 (1.1-13.7)
<3 weeks	4.8 (1.7-14.1)	4.3 (1.3-14.7)
<4 weeks	4.9 (1.7-14.2)	4.3 (1.2-14.8)
<5 weeks	5.3 (1.8-15.2)	4.8 (1.5-15.5)

Figure 1. Effects of increasing number of observations on odds ratios (OR) in two patient parameters (previous antipsychotic use (a) and non-surgical IC-admissions (b)) on antipsychotic prescribing, presented as OR with 95% confidence intervals (CI), using the logistic binomial model to adjust for correlated measures

the OR were found. However, in most cases confidence intervals (CI) were wider and less significant values were found in the analysis with adjustment for correlated measures.

In Figure 1 the effect of increasing number of observations per patient parameter on the logistic binomial model is illustrated with two examples. Figure 1a shows the effect on the odds ratio for use of antipsychotic drugs during the previous day on antipsychotic prescribing, while Figure 1b shows the same effect on the odds ratio for non-surgical admissions. Both graphs show an increased diverging with more measurements per variable indicating a greater effect of adjusting for correlation with more observations.

DISCUSSION

The term 'repeated measures' refers to multiple observations of either exposure or outcome on the same sampling unit, often a patient or subject.[3] Often these observations within the same subject, will be correlated and this has to be taken into account when analysing these data. However in pharmacoepidemiological studies, possible intra-subject correlation is often not taken into account. With more and more

longitudinal databases available for observational research, the progress in measurement of exposure patterns over time, and the availability of outcomes measures on detailed patient level, the number of studies involving repeated measures is increasing.

In the present study, we compared two different study designs (with and without corrections for correlated measures). We found no major differences in the point estimators of the OR between the two methodologies used. However, the CI after adjustment for correlated measures were considerably wider in most cases resulting in a loss of statistical significance. It is to be expected that adjustment for correlated measures has a bigger effect when more observations per patient parameter are present. We simulated this in our data by stratifying for length of follow-up, or in other words number of patient-days contributed to the dataset. We saw an increase in the effect of adjustment for correlation with increasing number of observations per patient included in the model. Adjustment for correlation seems to be especially pertinent with multiple observations per subject. However, CI were for the greater part overlapping probably due to small numbers.

In conclusion, we have shown that adjustment for correlated measures in data with many observations per patient is feasible and relatively simple to perform. Although in this study, adjustment did not result in major changes in the OR found, we did find that with more observations per patient parameter, adjustment for correlation has greater effect. Adjustment for correlated measures is useful in longitudinal drug analyses.

KEY POINTS

- In pharmacoepidemiological studies, possible intra-subject correlation is often not taken into account.
- In this study, we saw an increase in the effect of adjustment for correlation with increasing number of observations per patient.
- Adjustment for correlation seems to be especially pertinent in longitudinal drug analyses with multiple observations per subject.

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