Time-effect relations of medical interventions in a clinical information system

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Abstract. For the implementation of time-critical decision support algorithms in a clinical information system (CIS) a precise relation between medical interventions and effects needs to be established. We evaluated for selected drugs and infusions the relation in time between charted dose and effect on on-line hemodynamic variables. The time of the intervention was compared with the onset of the change of the hemodynamic variables as determined by new time series methods. The average time difference between intervention and calculated hemodynamic effect was 13.23 min (0 - 29) which did not differ significantly between different interventions. The marked lag between intervention and effect and the great variance of this lag pose an important problem for time-critical decision support. Even after optimizing data acquisition important factors will remain unaccounted for. Therefore, decision support systems may need extensive testing with real-world data before they are released into clinical practice.
(supported by the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 475 "Complexity Reduction in Multivariate Data Structures")

1 Introduction

Clinical Information Systems (CIS) can today provide the health care professional with the complete Electronic Patient Record (EPR) at the point of care. This data may include vital signs (e.g. heart rate, blood pressure), fluid intake and output, medications as well as entire clinical pathways. These CIS are complex database systems with sometimes more than 2,000 variables for each patient [3, 4, 5]. Over the last couple of years knowledge-based systems have been developed that use CIS data to support medical decision making [9]. Especially in operation-critical decision support such as in intensive care medicine a strong influence of the timing of interventions can be assumed. Therefore, in the implementation of time-critical decision support algorithms in a CIS a precise relation between medical intervention (time, dose) and effect needs to be established. For selected drugs and infusions we evaluated the relation in time between charted dose and effect on hemodynamic variables.

2 Methods

On a 16-bed surgical ICU all medication data was charted with a CIS, allowing the user 1 minute time resolution for all data. The system configuration was comprised of the CIS (Emtek Continuum 2000, Version 4.1M3), a Decision Support System (Sybase SQL server 4.9.2), and Statistical Software (SPSS version 6.1, SAS version 6.12) runnung on Sun Sparc under Sun Solaris 1.1.2 and 2.5.
On-line monitoring data was acquired from 148 consecutive critically ill patients (53 female, 95 male, mean age 64.1 years) with extended hemodynamic monitoring requiring pulmonary artery catheters in one minute intervals from the CIS. At total of 11,339 hours of monitoring of heart rate (HR), arterial mean pressure (MAP), and pulmonary artery mean pressure (MPAP) were analyzed.
Effects of interventions were defined as certain patterns of change in the time series of HR, MAP, and MPAP. Those were identified based on second order autoregressive (AR) time series models [6]. Each univariate time series was split into 90 minutes intervals starting with the first observation. The first 60 minutes of each interval were used as the estimation period of the respective AR-model, while the last 30 minutes of each interval served as the prediction period. This 90 minute window was moved over the entire time series in 30 minute increments. For each estimation period a second order autoregressive model was fitted and applied to the prediction period. The actual measurements were compared to the 95% confidence intervals (CI) for the prediction period. Values outside the CI were classified as an outlier, if less than 5 consecutive observations (= minutes) were outside the CI, and as a level change by 5 or more consecutive observations outside the CI. Only prediction periods that showed just one pattern were included. Only level changes of more than 5% were included in the analysis, because even with the 95% CI the pattern recognition discovered also some clinically non-relevant level changes. The time of the onset of a level change was defined by the first observation of this level change outside the CI. Level changes following this definition constituted what we call an effect here on the hemodynamic variables.
The time of the intervention was compared with the onset of the identified effect on the hemodynamic variables as determined by the time series analysis described above. Only time differences of less than 30 minutes were included, because of the 30 minute overlap between the time series window.
An intervention was defined by a change in the dose rate of dobutamine, adrenaline, noradrenaline, nitroglycerin, or by a change of the fluid balance by more than 500 cc in less than 10 minutes. Only effects that could be pharmacologically attributed to the respective intervention were included in the final analysis. The time of the intervention as it was charted in the CIS was compared with the onset of the identified change of the hemodynamic variables.

3 Results

From a total of 80,752 time series analyses, 12,599 included catecholamine or fluid interventions, of which 2.608 intervention-effect pairs met the inclusion cri-

teria for further analysis. The average time difference between intervention as charted and detected hemodynamic effect was 13.23 minutes (0 - 29 min). This time lag did not differ significantly between catecholamines, vasodilators, and rapid infusions. The 90% percentiles for most intervention-effect combinations ranged from 0 to over 25 minutes. Only the median time lag between increase of vasopressors and increase of blood pressure was lower. Changes of fluid balance showed an especially wide variation in their time lag to the associated effect.
The largest number of observations involved rapid fluid changes. As expected, a wide variation of time lags can be found here. Interestingly, the time lags for fluid interventions did not differ markedly from those of most drug interventions. As the half-lifes of the investigated drugs are longer than their action times and removal of fluids takes more time than administration, it could be expected that a decrease of an intervention would show a longer time lag than the respective increase. Except for adrenaline and noradrenaline this could not be confirmed.
In summary, the time lags between medical interventions as charted and hemodynamic effects showed a wide variation. Although there was a tendency that the time lag between catecholamine dosage changes and pressure changes was shorter on the average, there were no relevant differences between any intervention-effect pair. These observations cannot be sufficiently explained by the pharmacological and physiologic properties of the drugs and infusions studied.

4 Discussion

CIS have improved precision and volume of bedside documentation in high acuity areas as shown in several studies [2, 4]. Investigations in dose documentation with CIS show a 99% accuracy in drug documentation [8]. Therefore, documentation with a CIS can be considered highly accurate for non time-critical items. No study known to the authors addresses the issue of time-critical documentation in the ICU. This may be surprising as recent publications emphasize the significance of time-oriented data for clinical decision support [10]. It is pointed out that correct documentation of temporal patterns is essential for decision support in critical care [7].
Our study investigates strong temporal relationships in hemodynamic therapy of the critically ill. It can be expected that changes of catecholamine drips and rapid fluid challenges have an immediate effect within a few minutes on hemodynamic variables, such as heart rate or blood pressure [1].
Surprisingly, our study finds an average latency between the documented change of a drug and the hemodynamic effect of about 13 minutes. Although the average time between increase of vasopressors (adrenaline, noradrenaline) and changes in arterial pressure was shorter at 7.5 minutes, the most striking finding remains the wide variation with a range of over 20 minutes for all interventions. This wide variation may be attributable to several factors: (a) Inaccurate time entries for dose changes or IV fluids by the user. (b) Gradual response of the patient, or rather his/her cardiovascular system, to the intervention which may take time to be recognized by a pattern recognition algorithm that is based on

thresholds. (c) Interindividual differences in the reactivity of patients towards a certain drug. (d) Technical issues of drug and fluid application.

Thus several factors that introduce significant variance in the documentation of temporal patterns may be beyond the user's influence. This time variance can significantly affect the performance of time-oriented decision support algorithms [7, 10]. Some of the time variation may be reduced by improvements in data acquisition and processing: (a) Automatic data transfer from bedside devices wherever possible. (b) Training of users and standardization of charting procedures. (c) Optimization of algorithms for the detection of patterns and change points in time series data. (d) Adaptation of decision support algorithms to account for the variance in temporal patterns.

In summary, the relation in time between interventions and effects shows a large variance which poses a major problem for the implementation of time-critical decision support algorithms. While some of the variation may be reduced by interfacing IV devices with CIS and educating users in more precise documentation, important technical, physiological and pharmacological factors remain unaccounted for. This emphasizes the necessity to test decision support systems extensively with real-world data before they are released into clinical practice. Here further research is needed in time-oriented clinical decision support.

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