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Prevention of excessive doses in electronic prescribing systems

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Medication errors within the treatment process substantially contribute to the risk of harmful therapy outcomes. Even though medication errors may occur at all stages of drug treatment, more than 50% take place during the prescription itself. Most of those errors concern the selection of inappropriate and often excessive doses, thus promoting dose-dependent adverse drug reactions. Detailed data regarding the incidence of prescription of excessive doses is, however, still missing, especially for the large population of outpatients.
Although the prescription of excessive doses may be due to unintentional lapses, e.g. writing or calculation errors, about two of three errors are caused by a lack of knowledge of the responsible physician. Clinical decision support systems (CDS) are designed to provide crucial information about the patient's individual condition, specific drug properties and/or their mutual dependencies during the prescription process. Once implemented in electronic prescribing platforms and hence offering immediate feedback, such systems can improve both prescribing quality and patient outcome. Despite their enormous potential, CDS systems face a low acceptance rate in every-day use, primarily because physicians perceive the displayed feedback as insignificant in clinical practice. A successful implementation therefore requires the restriction to relevant recommendations. For drug dosage, such specificity can only be achieved if the individual status of each patient is considered. Thus, all parameters modulating intra- and interindividual variability in drug exposure (e.g. co-morbidity, age-associated pharmacodynamic changes, impaired elimination organ function, interacting co-medication) have to be incorporated and matched with the individual patient's characteristics to personalise the recommendation.

The aim of this study was to (i) determine the incidence of prescription of excessive doses, (ii) to develop a CDS system for individual upper dose limits, and (iii) to prospectively evaluate its effect on prescribing quality. The study was conducted at the University Hospital Heidelberg.

The incidence of prescription of excessive doses was assessed in a retrospective analysis of electronic prescriptions. Electronic prescriptions were included which (i) were generated using the electronic prescribing platform at outpatient clinics of the University Hospital Heidelberg and (ii) contained a drug with known significant dose-dependent toxicity. During the 32-week study period, 16 of 633 electronically prescribed drugs (2.5%) exceeded defined standard upper dose limits as provided in the summary of product characteristics (SPC). The prescription of excessive dosages is therefore frequent even in high-risk drug classes, which demonstrates the need for efficient strategies to prevent potentially fatal medication errors.

The retrospective analysis did not consider the individual condition of each patient. For the prospective study, upper dose limits individualised for (i) age, (ii) renal function, (iii) liver disease, (iv) co-medication, (v) indication of the drug, and (vi) administration of loading doses were extracted from the SPC. A comprehensive software algorithm was developed to match these upper dose limits with patient information taken from the electronic chart, to thereby select the appropriate value, and to subsequently personalise the upper dose limit to the patient's renal function. The CDS system was integrated into the local electronic prescribing platform which enabled an immediate comparison of prescribed dose with the individual limit for each patient and hence immediate feedback. The impact of this system was evaluated in a two-phase, prospective study (phase 1: baseline; phase 2: intervention) over 90 days. The main outcome measure was the frequency of excessive doses before and after the intervention. Secondary endpoints included the potential induction of medication errors, reasons for alert adherence, and physicians' acceptance of the system.
In phase 1, 552 of 12197 prescriptions (4.5%) exceeded upper dose limits. In phase 2, 559 excessive doses warnings were initially triggered (4.8%, p=0.37). Physicians were responsive to one in four warnings (134/559), namely by appropriately modifying the dosage regimen (N=119) or switching to an alternative drug (N=15) with an appropriate dosage. Thus, the implementation of the CDS system decreased the number of finally prescribed excessive doses to 425 (3.6%) which represents a 20% decrease compared to baseline ($p<0.001$). The system did not induce any new medication errors, assessed as underdosage or underuse of drugs. Physicians' alert adherence correlated significantly with patient's age and the prescribed drug class. In addition, physicians responded to alerts more often when an active ingredient was prescribed twice within the same medication regimen and were more likely to override alerts caused by elevated plasma concentrations Moreover, their alert adherence decreased with the number of concurrently prescribed drugs.

For ongoing maintenance of the system, approaches to enhance straightforward updating and to optimise the knowledge base are required. Therefore, two online dosage databases were assessed as alternative data sources for the laborious extraction of standard upper dose limits from the drug label. Both databases showed limited usefulness because of insufficient concordance with the SPC information. In order to complement the SPC's poor dosage information in drug interactions, a literature-based approach for deduction of dosage information from pharmacokinetic trials was developed and tested for appropriateness in the frequently prescribed substance group of statins. For 14 statin-drug combinations defined upper dose limits were available in both SPC and the literature and correlated significantly (Spearman R=0.77, p=0.006), confirming the theoretical approach to deduce upper dose limits from pharmacokinetic studies.

In conclusion, this research project demonstrated that the prescription of excessive doses in outpatients as well as at the interface of tertiary and primary care is frequent with one in twenty prescriptions exceeding individual upper dose limits. Implementation of a highly specific, algorithm-based CDS system reduced the number of prescriptions of excessive doses by 20% which represents a substantial improvement in prescribing quality. In addition, detailed knowledge from the SPC can be personalised even further when using standardised dosage calculations for pharmacokinetic drug interactions.