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### ► To cite this version:

Thilo Bertsche, Martina Fleischer, Johannes Pfaff, Jens Encke, David Czock, et al.. Pro-active provision of drug information as a technique to address overdosing in intensive-care patients with renal insufficiency. *European Journal of Clinical Pharmacology*, 2009, 65 (8), pp.823-829. 10.1007/s00228-009-0643-6 . hal-00534954

**HAL Id: hal-00534954**

**<https://hal.science/hal-00534954>**

Submitted on 11 Nov 2010

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# Pro-active provision of drug information as a technique to address overdosing in intensive-care patients with renal insufficiency

Thilo Bertsche · Martina Fleischer · Johannes Pfaff · Jens Encke · David Czock · Walter E. Haefeli

Received: 11 November 2008 / Accepted: 4 March 2009 / Published online: 25 March 2009  
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## Abstract

**Purpose** To correct overdosing of drugs requiring adjustment based on renal function in intensive-care patients.

**Methods** In a prospective intervention study, we estimated individual glomerular filtration rate and assessed whether medication required dose adjustment based on renal function. Senior clinicians received a structured report containing recommendations as to whether and how to adjust dosage in the individual patient (intervention). Prevalence of overdosed drugs (primary outcome), extent of overdoses, and reasons for nonacceptance of recommendations (secondary outcomes) were assessed.

**Results** Of 138 screened intensive-care patients, 68 (49%) had renal impairment, and 110 (14%) of the 805 prescribed drugs required consideration of renal function. A potential overdose was found in 53/110 drugs (48%) and this rate decreased to 26/110 (24%,  $P < 0.001$ ) after the intervention. The average extent of overdose was reduced from 54% before to 31% after the intervention ( $P < 0.001$ ). The main reasons expressed by the physicians for nonacceptance of recommendations were a large therapeutic index or minor overdoses of the involved drugs.

**Conclusions** In intensive-care patients, overdosing of drugs requiring adjustment based on renal function is still very common. Drug information counselling significantly decreased the prevalence and extent of overdose.

**Keywords** Renal insufficiency · Intensive care · Medication errors · Clinical competence · Drug information services

## Introduction

Inappropriate dosing of drugs in patients with renal impairment is a common drug-related problem leading to adverse events, excessive length of hospital stay, and avoidable cost [1, 2]. Because of the high prevalence of renal insufficiency in critically ill patients and the fact that elimination of roughly one out of seven drugs is mainly determined by the kidneys, modification of dose, dosing interval, or both is often required. For physicians, various sources of drug information are available. The drug label (e.g., summary of product characteristics) contains dosing information as approved by the regulatory authorities. It constitutes the legal basis of drug utilization and is the information source most frequently used by general practitioners [3]. However, for over half of the drugs that presumably do not accumulate in cases of renal failure or do not have renal side effects (e.g., nephrotoxicity), specific recommendations are missing from the drug label [4]. Therefore, it is often unclear whether dose adjustment is necessary or not. Moreover, dose adjustment on the drug label is sometimes based on serum creatinine instead of more reliable markers of glomerular filtration rate such as creatinine clearance ( $Cl_{crea}$ ) [4]. In particular, elderly patients may suffer from renal insufficiency despite apparently normal serum creatinine due to a parallel decline

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in renal function and muscle mass [5, 6]. Thus, it is recommended that renal function should be estimated using equations considering age, gender [5, 6], and body weight [7–9].  $Cl_{crea}$  estimates according to the equations proposed by Cockcroft and Gault [7] or Dettli [8] are widely used. In previous studies, drug information counselling, in which dose adjustments based on calculation methods were recommended, reduced adverse drug event rates [10], the length of hospital stay [2], and direct costs [1, 11]. Recently a new equation—the Modification of Diet in Renal Disease (MDRD-2) equation—has been developed [5, 12] to estimate glomerular filtration rate (eGFR).

However, little is known about the suitability of such methods in routine practice in an intensive-care setting [13] and the acceptance of recommendations based on these methods. Therefore, in the present study, we assessed the prevalence of overdosing in drugs requiring dose adjustment in intensive-care patients with renal insufficiency, studied the effect of drug information counselling for clinicians on the prevalence and extent of overdose, and evaluated the reasons if recommendations were rejected.

## Methods

### Patients and setting

Patients from the gastroenterological intensive care unit (ICU) of the University Hospital of Heidelberg were prospectively enrolled into the study. The unit consists of 24 beds, 10 of which are equipped for mechanical ventilation. This ICU is primarily concerned with the treatment of patients with upper and lower gastrointestinal bleeding, infectious diseases including sepsis, kidney, and liver diseases including post-transplantation care, and intoxications. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg.

### Study design

Between January 1 and March 31, 2008, consecutive patients with renal insufficiency [estimated glomerular filtration rate (eGFR) < 50 mL min<sup>-1</sup> per 1.73 m<sup>2</sup> or creatinine clearance ( $Cl_{crea}$ ) < 50 mL min<sup>-1</sup>] were enrolled in the study on day 2 after admission to the ICU. Day 2, or the following work day after weekends and public holidays, was selected because by then the medication has generally been adjusted to the brands available in the local hospital formulary and all information that is needed for the estimation of renal function is available.

During the ward round on this day, all drugs and dosage regimens were documented. Then dosing recommendations

for drugs with active ingredients requiring dose adjustment to renal function were calculated by a clinical pharmacist. Within 2 h after the ward rounds, senior clinicians in charge of the patients were informed in writing whenever prescribed doses exceeded the calculated dosing recommendations. The clinicians were then asked to decide whether and how the doses should be modified. Additionally, and if available for the concerned drug, the clinicians were asked whether they would request therapeutic drug monitoring. The physicians' actual changes in the dosage regimen immediately after counselling or their reasons for rejecting the recommendations were documented. The reasons were classified into five different categories: (1) minor overdose ( $\leq 20\%$ ) without clinical relevance, (2) moderate to large overdose ( $>20\%$ ) without clinical relevance because of the large therapeutic index of the respective drug, (3) expected benefit from higher dose, (4) dose adjustment not done due to expected or observed improvement in renal function, and (5) therapeutic drug monitoring was advised prior to deciding about dose modification.

### Outcomes

The prevalence of overdosed drugs before and after the intervention was assessed as the primary outcome. The extent of overdose before and after the intervention and the reasons for nonacceptance of the respective recommendations were assessed as secondary outcomes.

### Estimation of renal function

Renal function was estimated using Dettli's equation for creatinine clearance ( $Cl_{crea}$ , Eq. 1, [7, 8]) and MDRD-2 equation (Eq. 2, [5]) to estimate glomerular filtration rate (eGFR) while assuming that renal function  $\approx Cl_{crea} \approx eGFR$ .

$$Cl_{crea} (\text{mL} \times \text{min}^{-1}) = [150 - \text{age}(\text{years})] \times \text{weight}(\text{kg}) \times [\text{creatinine}(\mu\text{mol} \times \text{L}^{-1})]^{-1} \times k \quad (1)$$

where  $k$  is 0.9 for females and 1.1 for males.

$$eGFR (\text{mL} \times \text{min}^{-1} \text{ per } 1.73\text{m}^2) = 186 \times \text{creatinine}(\text{mg} \times \text{dL}^{-1})^{-1.154} \times \text{age}(\text{years})^{-0.203} \times 1.212(\text{if black}) \times 0.742(\text{if female}) \quad (2)$$

### Dose adjustment methods

For all prescribed active ingredients, the fraction of the bioavailable amount of a drug that is eliminated extrarenally ( $Q_0$ ) was extracted from a web-based clinical decision support system [14]. Dose adjustment based on renal

function was considered mandatory if at least 70% of the drug was eliminated by the kidneys in unchanged form (i.e.,  $Q_0 < 0.3$ ).

For these drugs, relative individual elimination capacity  $Q$  was calculated as follows [8]:

$$Q = \left[ (1 - Q_0) \times \left( \text{eGFR} \times \{100 \text{ mL} \times \text{min}^{-1}\}^{-1} \right) \right] + Q_0 \quad (3)$$

Then individual dose reductions ( $\text{dose}_{\text{individual}}$ ) were calculated assuming that the dosing interval would be kept unchanged [8].

$$\text{dose}_{\text{calculated}} = Q \times \text{dose}_{\text{standard}} \quad (4)$$

where  $\text{dose}_{\text{standard}}$  is the regular dose approved for treatment of the respective disease in patients with normal renal function as published on the drug label. Additionally and if available, dosing recommendations mentioned on the drug label for the observed renal function (according to Dettli and MDRD-2 estimations) were also mentioned in the report.

The results of the calculations based on the Dettli and MDRD-2 estimations and the recommendations of the drug label were forwarded to the senior clinicians in writing. In most patients, however, weight had to be estimated by senior clinicians, and for many drugs no dose recommendations were available on the drug label. Therefore, the extent of overdose was assessed by calculating individual dosage adjustment with the MDRD-2 equation, which is independent of weight.

#### Quantification of the extent of overdoses

To relate the suggested daily dose to actually administered daily doses, an overdose factor  $f$  was defined (Eq. 5):

$$f = 1 + \left[ (\text{dose}_{\text{admin}} - \text{dose}_{\text{calculated}}) \times (\text{dose}_{\text{calculated}})^{-1} \right] \quad (5)$$

where  $\text{dose}_{\text{admin}}$  is the administered total daily dose for the individual patient on day 2 and  $\text{dose}_{\text{calculated}}$  is the reduced total daily dose as calculated using the MDRD-2 equation.

#### Power calculation and data analysis

According to the findings of a pilot study ( $n=20$  patients), we presumed that 50% of the drugs requiring dose adjustment based on renal function would be affected by an overdose (primary outcome). A reduction in overdosed drugs of about 40% due to the intervention was considered clinically relevant (i.e., a reduction to 30% after the intervention). Assuming rates in this range in a pairwise analysis, a single-sided McNemar's test (only an overdose

was assessed) at a significance level of  $\alpha=0.05$  and with a sample size of 123 drugs requiring dose adjustment for renal function would provide a power of  $1-\beta=0.80$ . Presuming that one in seven drugs will require adjustment for renal function and co-administration of 13 drugs per patient (as in the pilot study), about 860 drugs or 66 patients were required for this survey.

Data are reported as follows: frequencies as number and percentage, continuous data as mean value with standard deviation or 95% confidence interval (95% CI), as appropriate. The two groups were compared by McNemar's test or Wilcoxon signed-rank test, as appropriate. A  $P$ -value  $\leq 0.05$  was considered significant. Calculations were conducted by KyPlot 2.0 (KyensLab, Tokyo, Japan), SigmaStat for Windows 3.0 (SPSS, Chicago, IL, USA), SPSS for Windows (SPSS, Chicago, IL, USA), or nQuery Advisor 7.0 (Statistical Solutions, Saugus, MA, USA).

## Results

### Patient and drug characteristics

From 138 consecutively screened patients, 68 (49.3%) had renal impairment and were included in the study (Table 1). The patients with renal impairment were treated with 805 drugs ( $11.9 \pm 3.8$  per patient) of which 254 (31.6%) were administered by mouth, 513 (63.7%) parenterally, and 38 (4.7%) by other routes of administration (e.g., transdermal therapeutic systems). For 110 (13.7%) of the 805 prescribed drugs,  $Q_0$  was  $< 0.3$  indicating that a dose adjustment should be considered. Antibiotics (imipenem/cilastatin, meropenem), antimycotics (fluconazole), and antivirals (ganciclovir) were the most common substances with a  $Q_0$  value  $< 0.3$  (Fig. 1).

### Prevalence of overdosed drugs and overdose rates

A potential overdose was found for 53 (48.2%) of the 110 drugs. The prevalence (primary outcome) decreased to 26 (23.6%) after the intervention ( $P < 0.001$ ) and the overdose extent  $f$  was reduced from 1.54 (95% CI: 1.41–1.65) to 1.31 (1.19–1.43) ( $P < 0.001$ ) indicating a reduction in average overdoses to 31 from 54%.

### Reasons for nonacceptance and involved drugs

One key reason (11 cases, 42.3%) for nonacceptance of a dose adjustment in the remaining 26 drugs (Fig. 2) was that a moderate to large overdose ( $>20\%$ ) was considered irrelevant because of the large therapeutic index of the respective drug. These cases most often concerned fluconazole ( $n=8$ ). In 8/26 instances (30.8%), senior clinicians

**Table 1** Patient characteristics ( $n=68$  consecutive ICU patients with renal impairment<sup>a</sup>)

Parameter	Value
Female (%)	31 (45.6%)
Age (years)	65.3±13.8
Weight (kg)	76.4±14.1
Active ingredients per patient ( $n$ )	11.9±3.8
Serum creatinine (mg 100 mL <sup>-1</sup> )	2.26±1.56
eGFR (mL min <sup>-1</sup> per 1.73 m <sup>2</sup> )	27.0±11.9
Cl <sub>crea</sub> (mL min <sup>-1</sup> )	35.8±16.6
Renal function category based on Dettli's equation <sup>a</sup>	
Cl <sub>crea</sub> >50 mL min <sup>-1</sup>	11 (16.2%)
30<Cl <sub>crea</sub> ≤ 50 mL min <sup>-1</sup>	30 (44.1%)
15<Cl <sub>crea</sub> ≤ 30 mL min <sup>-1</sup>	18 (26.5%)
Cl <sub>crea</sub> ≤ 15 mL min <sup>-1</sup>	9 (13.2%)
Renal function category based on the MDRD-2 equation <sup>a</sup>	
eGFR>50 mL min <sup>-1</sup> per 1.73 m <sup>2</sup>	1 (1.5%)
30<eGFR ≤ 50 mL min <sup>-1</sup> per 1.73 m <sup>2</sup>	30 (44.1%)
15<eGFR ≤ 30 mL min <sup>-1</sup> per 1.73 m <sup>2</sup>	24 (35.3%)
eGFR ≤ 15 mL min <sup>-1</sup> per 1.73 m <sup>2</sup>	13 (19.1%)

Cl<sub>crea</sub> Creatinine clearance, eGFR estimated glomerular filtration rate, MDRD-2 abbreviated MDRD equation

<sup>a</sup>Renal function < 50 mL min<sup>-1</sup> according to at least one calculation method (Eq. 1 or 2)

considered minor overdoses (≤20%) clinically irrelevant. The most frequent drugs in this group were fluconazole ( $n=3$ ), meropenem ( $n=2$ ), and imipenem/cilastatin ( $n=2$ ). In 1/26 prescriptions (3.8%, receiving ramipril), benefit from higher doses was expected. In no case was dose adjustment refused due to expected or observed improvement in renal function, and in 5/26 (19.2%) no reason was given. In 1/26

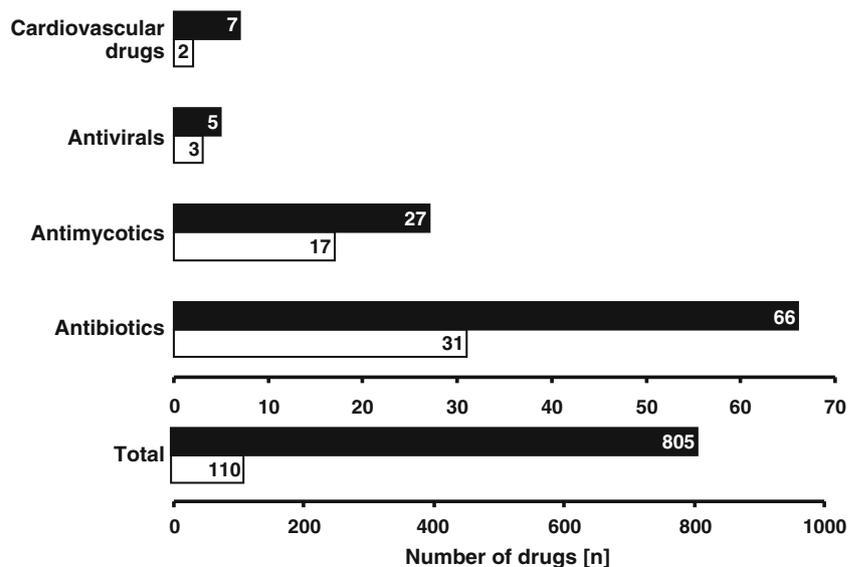
prescriptions (3.8%, concerning vancomycin), the intervention prompted therapeutic drug monitoring to confirm the presumed overdose. At 14.6 mg/L, vancomycin trough concentration exceeded the lab's upper limit (10 mg/L) but was still considered acceptable, and doses were not reduced by the clinicians.

## Discussion

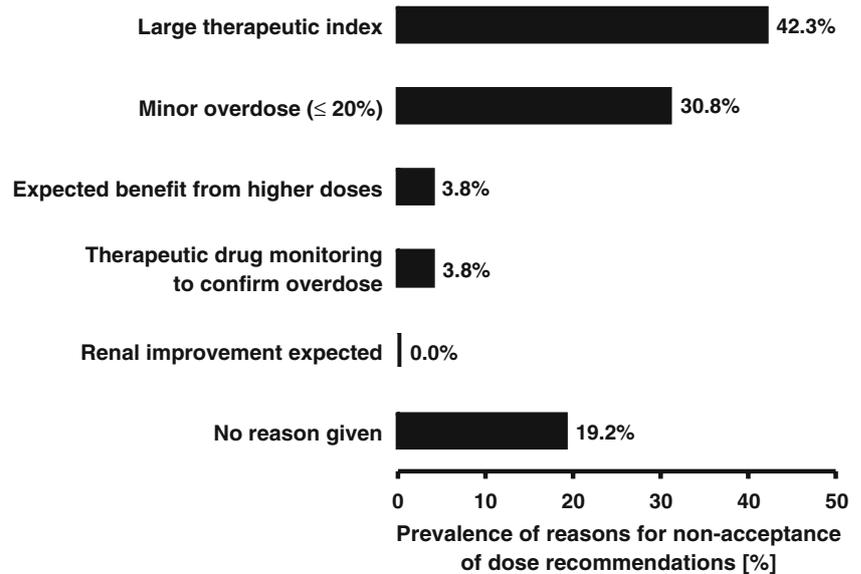
Although overdosing is a well-known problem with drugs requiring dose adjustment in patients with renal impairment, we found a high prevalence of nearly 50% of not adjusted drugs in an intensive care setting. We assessed renal function and calculated appropriate dosages for drugs requiring dose adjustment based on renal function. We then gave written recommendations for all newly admitted patients within a short-time frame of 2 h after the ward rounds as to whether and how to adjust the dosage. Because in earlier studies [1] a significant fraction of dose reductions were not executed, we also assessed the reasons why recommendations were not transferred into practice.

The prevalence of renal insufficiency in hospitalized patients is considerable and depends on the setting. Two earlier studies in university hospitals reported a prevalence of 15% [2] and 17% [1] in general internal medicine patients. In ICU patients with significant co-morbidity, the expected prevalence is higher and indeed almost half of our patients had renal impairment. These patients received on average 12 drugs concurrently and nearly 2 drugs per patient required dose adjustment based on renal function. Hence dose adjustment in these patients is a common necessity.

**Fig. 1** Number of drugs in a given category prescribed to 68 ICU patients with renal impairment (black bars) and number of drugs requiring dose adjustment ( $Q_0 < 0.3$ ) in those categories (white bars). Other drugs whose elimination also largely depends on renal function ( $n=30$  drugs, in particular anticonvulsants and drugs for alcohol withdrawal) were always dosed correctly (data not shown)



**Fig. 2** Reasons for nonacceptance of dosing recommendations in a drug information intervention in 68 ICU patients with renal impairment ( $n=26$  drugs requiring dose adjustment to renal function)



In agreement with earlier studies in other areas, excessive doses were frequent, i.e., about 50% of prescriptions were inappropriate, and acceptance rates of the suggested dose modifications were far from complete [1, 2]. In a former study in internal medicine patients, 19% of the recommendations were rejected [1]. At 24%, the number of drugs not adjusted to the recommended dosage was very similar in our survey, although we enrolled only intensive-care patients and, therefore, the pattern of drugs was likely different. Thus, while our intervention intercepted overdoses in over 50%, a rather large fraction of drugs still required dose adjustment.

Based on former studies [1, 2], we expected such an acceptance rate and for this reason we also assessed the reasons for nonacceptance. In an earlier study, nonacceptance often involved drugs whose action could easily be monitored (e.g., cardiovascular drugs such as betablockers), and physicians may have preferred relying on clinical responses in some cases [1]. However, most of the rejected recommendations in our study were declined because the therapeutic index was considered large enough or the overdose too small to cause harm to the patient. However, it might still be advisable to lower doses in these cases to reduce avoidable costs [1]. Whether this will justify the personnel expenses arising from such an intervention has to be scrutinized and should also take into consideration the fact that remaining amounts of parenteral drugs will usually be discarded for reasons of stability and hygiene. Irrespective of costs, the correction of even small overdoses will prevent unnecessary exposure to active substances and accumulation of metabolites with unknown effects and safety problems. In addition, in view of patient compliance, it may also be advantageous to administer fewer tablets although this is less important in an ICU setting with most

drugs being administered intravenously. However, once implemented in a computerized physician order entry (CPOE) system, the costs of such an intervention will be considerably less and such systems may also suggest optimum use of available strength and vial sizes and thus further promote the economic use of expensive drugs even, or particularly, in the hectic environment of an ICU.

Antimicrobial agents were the drugs most often involved in dosing errors and the antifungal fluconazole was the drug most often given in relatively high amounts. In these cases, physicians justified dose selection by excellent tolerance of the drug, disregarding costs of potentially unnecessary doses. In the present study, only one intended overdose of an ACE inhibitor was detected; it was made in order to exploit the potential nephroprotective effects of doses exceeding those on the drug label [15–17].

The results of this study may help optimize drug information services particularly when they are computer-based because in different areas [18], including dose adjustment for renal insufficiency [2, 19, 20], computerized clinical decision support systems successfully prevented overdosing. However, such systems are not forcefully used in routine care unless they are integrated into a CPOE [21]. Because in our setting a CPOE was not yet available, we used a computerized system [14] to standardize the intervention. As is done with many other reports generated in a hospital, the recommendation was printed out and forwarded to the clinicians, i.e., it was well integrated into the routine workflow on the ward. The results of this study might also be useful for further development of computerized systems because they reveal the physicians' reasons for disregarding recommendations and will thus help tailor electronic decision support to the needs of ICU physicians. In general, alerts that do not result in an action should be

avoided. Otherwise “alert fatigue” will likely happen, which may lead to rejection of helpful and even truly important alerts. Besides missing implementation in routine practice, alert fatigue was identified as a major cause resulting in the creation of new medication errors by computerized systems [22–24].

Some limitations in the present study should be considered. The study was not designed to assess the impact of dose adjustment on clinical outcome. It is therefore not clear whether previously observed beneficial effects of dose adjustment with a calculation method [2] also apply to ICU patients. Further, in ICU patients renal function may be unstable and therefore using only one creatinine value limits accurate assessment of actual renal function [25]. However, assuming that in the early course of the disease in most ICU patients, creatinine is stable or increasing, creatinine clearance on day 2 might have overestimated renal function, making dose reductions even more essential. In addition, due to the expected high heterogeneity of the population, we compared drug dosing before and after an intervention in the same patients without an independent control group. For our intervention, we chose day 2 after admission when the medication was expected to be adjusted to the needs of the current disease. Hence we assessed the impact of an intervention at a time when doses should be tailored to the needs of the individual patient and treatment of the leading cause of admission should be initiated. Whether this was indeed the optimum timing of the intervention remains open. Obviously such support might already be useful on the day of admission, and errors might also occur later in the course of the disease suggesting that decision support should be provided continuously.

## Conclusion

In intensive-care patients, renal impairment is common and up to half of the drugs requiring dose adjustment are not dosed appropriately. Therefore, interventions are urgently needed to avoid dosing errors in daily practice. Standard calculations to adjust dosage based on renal function were used for an effective intervention consisting of drug information counselling for senior clinicians on the ward. This intervention substantially reduced the prevalence of overdosed drugs. Because this study only used data readily available in routine care, this intervention may easily be transferred to settings with computerized patient charts thus reducing its expense.

**Acknowledgements** We would like to thank all physicians on the ward for their helpful support in data collection. This work was funded by the University of Heidelberg. No conflicts of interest were present.

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