Improvement of drug prescribing in acute kidney injury with a nephrotoxic drug alert system

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ABSTRACT

Objective Electronic alert systems have shown their capacity for improving the detection of acute kidney injury (AKI). The aim of this study was to design and implement a clinical decision support system (CDSS) for improving drug selection and reducing nephrotoxic drug use in patients with AKI.

Methods The study was designed as an intervention study comparing a pre and post cohort of patients admitted during April 2014 and April 2015, respectively (phase I and phase II). The intervention was a CDSS which provided kidney function and nephrotoxic drug information. Furthermore, an interruptive alert was designed to detect patients suffering an AKI event while taking a nephrotoxic drug and to see if the dose was then reduced or the drug was discontinued by the physicians.

Results One-third of the inpatients were included in the analysis because they met the inclusion criteria (1004 and 1002 patients in phases I and II, respectively). 735 and 761 of them received at least one nephrotoxic alert (73% vs 76%; $p=0.763$). 65 and 88 patients suffered AKI during admission (6.5% vs 8.8%; $p=0.051$). In phase I, patients received 384 nephrotoxic alerts (55%) with 78 (20%) of them provoking a change or discontinuation of the nephrotoxic drug. In phase II this value increased to 154 out of 526 (29%) after implementation of the CDSS ($p<0.01$).

Conclusions A CDSS with interruptive alerts that inform of the development of AKI in real time in patients with nephrotoxic drug prescription has a positive impact on the judicious use of these drugs.

INTRODUCTION

Acute kidney injury (AKI) is associated with significantly increased mortality, length of hospital stay and costs across a broad spectrum of conditions.^{1–5} The overall incidence of AKI in the developed world is estimated to be 2–3 new cases per 1000 people, similar to the incidence of acute myocardial infarction.⁶ Epidemiological data of this pathology varies depending on how this entity is defined.^{2,7,8} It occurs in up to 5–10% of hospitalised patients.⁵ It has been documented that as many as two-thirds of patients in intensive care units have AKI.⁹ In fact, AKI is considered a disorder primarily acquired in hospitals.¹⁰

Drugs are one of the main causes of AKI.^{1,2} The negative outcomes of drug-induced AKI are worthy of attention because up to 70% of patients have residual kidney damage following an episode.⁶ Just over 80% of patients requiring anticancer drugs received a drug that was potentially nephrotoxic,

and dose adjustments for renal insufficiency were required in 53.4% of the prescriptions.¹¹

AKI is more prevalent in patients with chronic kidney disease (CKD). These patients are especially susceptible to AKI which, in turn, may promote the progression of CKD.⁸

Any effort to intervene in the course of AKI prior to severe (and often irreversible) stages will require techniques that can be deployed by front-line clinicians, including attention to nephrotoxic drugs and drug dosing.⁶ Patients who receive drugs that are nephrotoxic or eliminated by the kidneys are reported to experience a high rate of confirmed and potential adverse drug events (ADEs) (10 events/100 and 55 events/100 hospital admissions, respectively).¹²

Recognition of patients with kidney disease by doctors and pharmacists is low, contributing to the increased incidence of AKI in hospitalised patients.¹³ Wilson *et al* found that only 43% of patients who had suffered severe AKI had this diagnosis sufficiently documented in their medical records.⁵ Colpaert *et al* evaluated the impact of real-time AKI alerts on therapeutic intervention by the physicians and the effect on AKI progression.⁴ They found satisfactory results regarding the timelines and number of therapeutic interventions performed on these patients for avoiding further deterioration of kidney function.

Clinical decision support systems (CDSS) have been developed to fully and/or partially automate the detection of AKI in the hospital setting. Studies using these systems have consistently shown that they have the capacity to improve the detection of AKI.⁶ Wilson *et al* holds that the provision of an early electronic alert for AKI could also improve outcomes in hospitalised patients.⁵ Roberts *et al* implemented a CDSS that improved dosing conformity and management of key renally cleared drugs.¹⁴ Boussadi *et al* concluded that CDSS are complementary to the pharmaceutical activity and clinical review, and that they contribute to safety in drug prescribing.¹⁵

Given the high prevalence of decreased glomerular filtration rate (GFR) in hospitalised patients and their vulnerability to suffer harmful ADEs, it is necessary to continue improving CDSS. The morbidity and mortality associated with hospital-acquired renal insufficiency dictate that we need to find ways to prevent it.² CDSS have the potential to increase AKI recognition, reduce the time to therapeutic interventions in order to prevent progression of AKI and improve outcomes.¹⁶ Identification and avoidance of nephrotoxic medicines should be

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Figure 1 Identification of patients with prescribed nephrotoxic drug.

a high priority in research and practice.¹⁷ CDSS advancement requires alerts which focus on the appropriate use of potentially nephrotoxic medications.¹⁸

Objectives

The hypothesis for this research was that CDSS providing patient-specific recommendations in real time would improve drug selection and the quality of drug prescribing.

The goals of this study were to characterise inpatients in terms of kidney function in order to determine the prescription habits for nephrotoxic drugs and to assess the impact of a CDSS on nephrotoxic drug prescribing in patients with kidney disease.

METHODS

Study site and setting

This study was carried out in a general teaching hospital in Spain with more than 300 adult beds. Since 2000, care providers use a locally developed and maintained information system (SI-XXX) with electronic medical record and computerised prescriber order entry (CPOE). Two out of every three drug prescriptions are made by resident doctors. Over the past 10 years, several CDSS have been integrated into this SI-XXX, including drug interactions and drug allergies.

Computerised detection of patients with nephrotoxic drugs and AKI

The Pharmacy department, in collaboration with the Nephrology and Information departments, developed and implemented a CDSS that identified patients with nephrotoxic drugs and those with prescribed nephrotoxic drugs who suffered AKI. Patients prescribed with a nephrotoxic drug were identified by a kidney icon with a blue 'N' on their drug prescription screen. A kidney icon with a red 'N' highlighted patients with any prescribed nephrotoxic drug who suffered an AKI event during hospital admission (figure 1).

AKI was defined as an increase in serum creatinine (SCr) by 0.3 mg/dL within 48 hours or an increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within

the prior 7 days, in accordance with the definition provided by the Kidney Disease Improving Global Outcomes (KDIGO).⁸ One nephrologist and two clinical pharmacists classified 66 drugs available in the hospital formulary as nephrotoxic (table 1).

Intervention description

By selecting the kidney icon the user could see the 'kidney function report', which includes the drugs to be monitored in renal insufficiency. This report shows the analytical values of SCr, automatically estimated glomerular filtration rate (eGFR) with Cockcroft–Gault (CG) and Salazar–Corcoran in patients with a body mass index $>30 \text{ kg/m}^2$, and drugs prescribed to the patient that needed to be reviewed, including nephrotoxic ones (figure 2).^{19 20}

When a new nephrotoxic drug was added to a patient's prescription, a 'nephrotoxic alert' appeared; this alert provided a new window in which the clinician could see information regarding the patient's kidney function as well as other nephrotoxic drugs that had been prescribed, as shown in figure 3.

In addition to these two passive interventions, which did not interrupt clinician prescribing, an interruptive alert was designed—namely, a nephrotoxic drug prescribed in a patient suffering AKI ('n+AKI alert'). When accessing the prescription of a patient suffering an AKI event while taking a nephrotoxic drug, a pop-up window would appear (figure 4).

Study design

The CDSS (intervention) was designed and, after its performance among its potential users, it was implemented in March 2015 in the hospital CPOE system. The study was designed as an intervention study comparing a pre and post cohort of patients. Inclusion criteria consisted of inpatients >18 years with at least two SCr values during the study period. The pre-intervention period (phase I) included patients admitted from 14 April 2014 to 29 April 2014 and the post-intervention period (phase II) included patients admitted from 14 April 2015 to 29 April 2015.

Table 1 Classified nephrotoxic drugs

Aciclovir	Hydrochlorothiazide
Adefovir	Ibuprofen
Amikacin	Indapamide
Amiloride	Indinavir
Amphotericin B	Indomethacin
Amphotericin B lipid complex	Immunoglobulin
Amphotericin B liposomae	Interferon
Atenolol	Iobitridol
Canrenoate	Iodixanol
Captopril	Iohexol
Carboplatin	Iomeprol
Celecoxib	Ioversol
Ciclosporin	Irbesartan
Cidofovir	Ketorolac
Cisplatin	Lisinopril
Chlorthalidone	Lithium
Colistimethate	Losartan
Dextran	Mannitol
Diazoxide	Meloxicam
Diclofenac	Methyldopa
Dihydroergotamine	Methotrexate
Diltiazem	Minoxidil
Enalapril	Mitomycin
Spironolactone	Naproxen
Foscarnet	Nicardipine
Furosemide	Nifedipine
Gadobutrol	Parecoxib
Gadobenate, meglumine	Pentamidine
Gadodiamide	Sulindac
Gadopentetate, meglumine	Tacrolimus
Gadoxetate disodium	Tobramycin
Ganciclovir	Torsemide
Gentamicin	Verapamil

Patients undergoing renal replacement therapy techniques were excluded.

The nephrotoxic drug was considered to be a probable contributor to the development of an AKI event when nephrotoxic exposure preceded a diagnosis of AKI. The impact of the interruptive alerts, 'n+AKI alerts', was evaluated during 48 hours after the first appearance of the alert. The patient's prescription was reviewed to determine if the nephrotoxic drug dose had been reduced or if the drug had been discontinued.

In the pre-intervention cohort, neither passive nor interruptive alerts were activated or visualised by clinicians. They were evaluated as if the alert system was already implemented and activated, as potential alerts. In the post-intervention cohort, all alerts were activated so clinicians could see them and their impact could be evaluated.

Statistical analysis

Statistical analysis of the data obtained was performed using Stata program Version 12. The value of 0.05 was established for the error α and 0.1 for the error β (power 95%). A ratio of 1:1 between the pre- and post-intervention cohorts was used and a bilateral analysis was performed. Data from both cohorts that follow a normal distribution were compared using the Student t-test and those that did not follow this distribution were analysed with the Mann–Whitney U test. Qualitative and categorical

dichotomous variables were analysed in contingency tables NxM in which the value of χ^2 was determined. The results were expressed as mean values with 95% CI, proportions or median as appropriate. Statistical significance was established at $p < 0.05$.

RESULTS

There were 2995 admitted patients in phase I and 3015 in phase II. One-third of the patients were included in the analysis because they met the inclusion criteria (1004 vs 1002 patients; $\chi^2 = 0.09$; $p = 0.763$). The pre- and post-intervention periods were not statistically different with regard to baseline characteristics and patient renal function, as shown in table 2. The number of patients who developed AKI was 65 (6.5%) in the pre-intervention period and 88 (8.8%) in the post-intervention period ($\chi^2 = 3.79$; $p = 0.051$).

There were 1963 nephrotoxic alerts in phase I and 2087 in phase II ($\chi^2 = 0.27$; $p = 0.602$). Diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) were responsible for 70% of the alerts in both phases, followed by angiotensin receptor blocker (ARB) and angiotensin-converting enzyme (ACE) inhibitors. The most commonly prescribed nephrotoxic drugs were furosemide, hydrochlorothiazide, torasemide, spironolactone, enalapril, losartan, metamizole and tacrolimus; 73% of patients included in phase I ($n = 735$) and 76% in phase II ($n = 761$) received at least one nephrotoxic alert ($\chi^2 = 0.55$; $p = 0.459$).

Of the patients receiving nephrotoxic alerts, 10% ($n = 72$) of those in phase I and 13% ($n = 99$) of patients in phase II suffered an AKI event during admission ($\chi^2 = 0.05$; $p = 0.044$).

'n+AKI alerts' ($n = 384$ in phase I and $n = 526$ alerts in phase II) were studied in detail to assess whether the AKI event could have been caused by the nephrotoxic administration and also to determine if the 'n+AKI alert' had an impact on modifying drug prescriptions. The detailed analysis of these alerts showed that, in 55% and 67% of these cases in phase I and phase II, respectively, the development of the AKI event followed the administration of the nephrotoxic drug ($\chi^2 = 13.49$; $p < 0.05$).

Effect of intervention on drug modification and discontinuation during AKI

More than half of the 'n+AKI alerts' had a temporal relationship between the nephrotoxic administration and the development of the AKI event: 210 alerts in phase I and 351 in phase II. A positive impact of the 'n+AKI alert' was found. There was a 45% increase in changes in nephrotoxic prescription, reductions or drug discontinuation in the post-intervention period with respect to the pre-intervention period: 154 nephrotoxic prescriptions from the existing 526 were changed in phase II (29%) compared with 78 nephrotoxic prescriptions from the initial 384 changed in phase I (20%) ($\chi^2 = 0.39$; $p < 0.001$). A positive and significant impact of the 'n+AKI alerts' was observed in the prescription of nephrotoxic drugs with an increase in the reduction or discontinuation of the drug dosing. Drugs more commonly discontinued were diuretics and NSAIDs in phase I and diuretics and immunosuppressors in phase II.

DISCUSSION

AKI is a common complication suffered by hospitalised patients. Nephrotoxic drugs are a probable cause of more than half of these cases. A CDSS with interruptive alerts that informs of the development of AKI in real time in patients who have been prescribed nephrotoxic drugs has a positive impact on the reduction of the use of these drugs.

Figure 2 Kidney function report. Translations/abbreviations: 'Función renal y medicamentos', kidney function and drugs; Crs, serum creatinine; CG, Cockcroft–Gault; NKF, National Kidney Foundation; 'Fecha', date; 'Contraindicaciones', contraindications; 'Ajustes', adjustments; 'Precauciones', precautions; 'Nefrotóxicos', nephrotoxic.

AKI occurred in 6.5% and 8.8% of the studied patients, respectively. Other studies have reported different rates of AKI: 7.2% in the study by Nash *et al*, 13% in the study by McCoy *et al* and 1.4% in the study by Kohli *et al*.^{1 2 21} Colpaert *et al* found that one out of every two patients had AKI, according to the RIFLE classification.⁴ This difference may be due to the use of urinary output data because more than 90% of the AKI detections were achieved with this criterion.⁴

Our study showed that up to 70% of the patients had at least one nephrotoxic drug prescribed. The nephrotoxic potential of these drugs, diuretics, NSAIDs, ARBs and ACE inhibitors, is well known. Drawz *et al* developed a predictive score for hospital-acquired AKI, classifying the use of these drugs as a risk factor with an OR of 2.²² Different authors have recommended that the use of NSAIDs should be avoided in patients with kidney disease stages 4 or 5.²³ They consider

Figure 3 Nephrotoxic drug information. Translations/abbreviations: 'Nefrotóxico, vigilar FR', nephrotoxic, follow-up of renal function; FR, renal function; Crs, serum creatinine; CG, Cockcroft–Gault; PD, adjusted body weight.

Figure 4 N+AKI alert. Translations: 'Elevación de Crs, posible insuficiencia renal aguda. Revisar el uso de nefrotóxicos', increase in serum creatinine, possible acute renal injury. Check nephrotoxic drug use.

the implementation of a programme for identifying nephrotoxic drugs to be helpful in avoiding the use of these drugs.

The information provided by the CDSS was shown in different ways depending on the severity of the potential adverse event, as recommended.^{17 24 25} An interruptive alert appeared when a nephrotoxic drug was given to a patient with AKI whereas a passive alert (non-interruptive) was used for purely preventive information. The prescriber must actively select the kidney icon to visualise available data, as in the study by McCoy *et al.*²⁶ Also coinciding with the study by McCoy *et al.*, our study designed an alert display to show the prescriber data for the kidney function along with a list of drugs and the corresponding specific recommendations based on the patient's renal status. Other studies, such as the one designed by Sellier *et al.*, have been designed in a similar way.²⁷ Physicians and pharmacists could visualise the tool that had been designed.²⁶ This type of design also helps pharmaceutical validation, showing kidney function evolution and drugs that should be closely monitored on the same screen.¹⁵

In 55% and 67% of all patients suffering AKI during admission it was not possible to rule out whether nephrotoxic drugs were involved in these events. Kohli *et al* studied elderly patients (>60 years) and found that nephrotoxic drugs contributed to the development of acute renal failure in 66% of patients who developed it in the hospital.¹ Nash *et al* found that 16% of episodes of AKI were attributed to medications.² This study differs from ours in terms of the criteria for assigning the possible cause of AKI.

In order to assess the effect of interruptive alerts that detected patients with AKI and nephrotoxic drugs, we evaluated whether changes in prescribed nephrotoxic drugs occurred 48 hours after the AKI event. Another study that also used this time period is that by Such *et al.*²⁸ A larger number of modifications in nephrotoxic prescriptions was observed in the post-intervention phase than in the pre-intervention phase (29% vs 20%).

Therefore, there was a positive impact of AKI alerts on nephrotoxic drug prescription. Nephrotoxic doses were withdrawn or reduced in a significantly greater percentage in phase II than in phase I. Automated AKI alert systems should be viewed as an opportunity to prompt clinical evaluation rather than provide a diagnostic label.¹⁶

This research study has several limitations. It was evaluated in a single hospital with a high frequency of use of CDSS so its results may not be extrapolated to other hospitals. However, the nephrotoxic classification and the design of alerts can be adapted. The number of nephrotoxic alerts and patients suffering AKI was higher after our intervention. As AKI may have multiple causes, partly from the use of nephrotoxic drugs, we cannot rule out whether this finding is relevant to our study. It may be suggested that the 'sole reliance on electronic health record generated alerts without active healthcare team integration and assessment represents a major barrier to

Table 2 Study population

	Phase I	Phase II	p Value
Age (years)	63±16	65±14.8	0.104
Weight (kg)	73.5±15.8	72.9±15.6	0.780
Men (%)	60	60	0.745
GFR category 1 (%)	35	36	0.408
GFR category 2 (%)	35	33	0.361
GFR category 3 (%)	20	21	0.765
GFR category 4 (%)	7	6	0.600
GFR category 5 (%)	4	4	0.804
CKD (%)	31.6	31.1	0.909
AKI (%)	6.5	8.8	0.051

AKI, acute kidney injury; CKD, chronic kidney disease (MDRD-4 <60 mL/min/1.73 m²); GFR, glomerular filtration rate estimated with modification of diet with renal disease (MDRD-4)

the realisation of the potential of CDS to improve healthcare quality and outcomes'.²⁹ As we did not assess AKI severity, it is not possible for us to determine whether or not severe AKI decreased. However, our aim was to exert an influence on the prescription of nephrotoxic drugs in patients with AKI and this goal was achieved. We may conclude that the alerts are efficacious in the avoidance of nephrotoxins.²⁵

CONCLUSIONS

Renal failure is a major health problem in hospitalised patients. An intervention system integrated into the electronic prescribing system was developed, implemented and evaluated. It enables continuous monitoring of patients with kidney disease and the use of nephrotoxic drugs. The tool allows clinicians to identify patients with probable kidney disease and to study the evolution of their kidney function.

The application designed increases drug information and nephrotoxic recommendations at the time of prescription. It is a complementary contribution to the work done by pharmacists in the validation process. This information promotes awareness in doctors during the drug prescribing process, constituting an educational benefit. The tool proved useful in detecting possible AKI episodes related to nephrotoxic drug administration. It had an impact on the suspension and modification of nephrotoxic drug prescription in patients suffering AKI during admission. Given the high prevalence of kidney disease in hospitalised patients and their risk of suffering ADEs, continuous improvement of CDSS for reducing medication errors in this type of patient as well as for identifying and avoiding potential nephrotoxic drugs must be a priority in both research and clinical practice.

Competing interests None declared.

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What this paper adds?

What is already known on this subject?

- ▶ Acute kidney injury (AKI) occurs in up to 5–10% of hospitalised patients, with drugs being one of the principal causes.
- ▶ Clinical decision support systems (CDSS) enable early detection of AKI events, thereby decreasing progression to higher AKI stages.
- ▶ CDSS have the potential to increase AKI recognition, reduce the time to therapeutic interventions which prevents progression of AKI, and improve outcomes.

What this study adds?

- ▶ A CDSS, with automatic AKI detection and interruptive alerts, is effective in reducing the use of nephrotoxic drugs.
- ▶ Easier detection of AKI results in a more prudent use of nephrotoxic drugs, which is an important metric of alert efficacy.

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