# A Prospective Evaluation And Cost Assessment Of Pharmacist Monitoring Of Patients With Renal Dysfunction Receiving Selected Drugs

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## ABSTRACT

*A pharmacist prospectively monitored 24 frequently prescribed drugs in 120 patients with renal dysfunction to determine appropriateness of dosing and cost assessment of recommendations. Drug dosage criteria and a "Drug Data Sheet" outlining adverse effects and cautions for each drug were developed. A sample intervention letter was also developed to communicate patient specific drug related problems to the physician, with recommendations for change. All adult patients (>18 years old) admitted to the services of General Medicine, Urology, and Respirology who had a measured serum creatinine concentration greater than 95 µmol/L; were not undergoing peritoneal dialysis or hemodialysis, and were receiving one or more of the selected drugs were targeted. A total of 146 medication orders were screened during a six-week period. Fifty-one (35%) of these orders were inappropriate and required intervention. The acceptance rate of the pharmacist's interventions was 98%. A direct drug acquisition cost savings of $435.15 was realized for the six-week study period. Other populations and other drugs requiring dosage adjustment due to decreased renal function need to be examined. Monitoring of patients with renal dysfunction by a pharmacist improved the dosing of drugs and allowed a cost savings.*

**Key Words:** *renal dysfunction, cost assessment, clinical pharmacy*

## RÉSUMÉ

*Un pharmacien a effectué un contrôle prospectif de 24 médicaments couramment prescrits chez 120 patients atteints d'insuffisance rénale, afin d'évaluer la justesse de la posologie et les coûts relatifs aux recommandations. Des critères posologiques et une «Feuille de données sur les médicaments» décrivant les effets indésirables et les mises en garde pour chaque médicament ont été élaborés. Une lettre d'intervention a aussi été mise au point pour communiquer au médecin tout problème pharmacothérapeutique particulier à un patient et les recommandations afférentes. Tous les patients adultes (> 18 ans) admis au département de médecine générale, d'urologie ou de pneumologie et dont les concentrations sériques de créatinine étaient supérieures à 95 µmol/L, qui ne subissaient pas d'hémodialyse ou de dialyse péritonéale, et qui recevaient un des médicaments choisis ou plus, étaient ciblés. En tout, 146 demandes d'exécution d'ordonnance ont été contrôlées sur une période de six semaines et 51 (35 %) de ces demandes n'étaient pas adéquates et nécessitaient l'intervention du pharmacien. Le taux d'acceptation des interventions du pharmacien, était de 98 %. Des économies de coûts d'acquisition directes totalisant 435,15 dollars ont été réalisées au cours de cette période de six semaines. En conclusion, d'autres populations de patients et d'autres médicaments qui nécessitent un ajustement posologique en raison d'une insuffisance rénale, doivent faire l'objet d'études. La surveillance des insuffisants rénaux par un pharmacien a permis d'optimiser la posologie et de réaliser des économies.*

**Mots clés :** *insuffisance rénale, évaluation des coûts, pharmacie clinique*


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## INTRODUCTION

Adverse drug reactions (ADRs) contribute significantly to patient morbidity with an incidence ranging from 2.6% to 50.6% in the general population and 10% to 20% for patients in hospital.[1,2] Patients with impaired renal function are at risk for ADRs because many drugs which are excreted unchanged or as active

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metabolites in the urine may have impaired elimination and accumulate.[2,3] These patients may also exhibit pharmacodynamic alterations due to renal impairment. The development of ADRs in these patients may often be prevented by altering the dosing regimen based on renal function. The objective of this concurrent cost assessment study was to improve patient care by promoting the appropriate dosing of specific renally eliminated drugs for patients with impaired renal function. In addition, the impact of changes in drug dosage on patient outcome and drug cost were evaluated.

## METHODS

The study was conducted at the Victoria General Hospital, a 700-bed, acute care facility in Halifax, Nova Scotia which serves as a referral centre for most of Atlantic Canada. All patients admitted to the Respirology, General Medicine, or Urology services from March 16 to April 28, 1992 with an initial serum creatinine ($S_{Cr}$)> 95 µmol/L who were no less than 18 years of age and did not require any form of dialysis were included in the study .

Renal function was assessed by the glomerular filtration rate (GFR) as approximated by the estimated creatinine clearance (CrCl).[4-15] When the $S_{Cr}$ was found to be stable, the Cockroft-Gault method for estimation of creatinine clearance was employed.[6,7,13-15] If the $S_{Cr}$ was fluctuating more than 17.7 µmol/L (0.2 mg/dl) between measurements, the Jeliffe method was used.[11,12] The lean body weight (LBW) was used to calculate CrCl for all patients unless their total body weight (TBW) was less than LBW. TBW was then used. If their TBW was greater than 150% LBW, a correction factor was applied.[16,17] Each patient's CrCl was revaluated during their hospital stay to ensure the continued appropriateness of the drug dosage.

The doses of 24 drugs which are largely excreted unchanged or as active metabolites in the urine or which should not be used in patients with severe renal dysfunction were evaluated for appropriateness against guidelines for dosing specified by the manufacturer or in the medical literature.

Each time a patient with an order for one of the 24 specified drugs was identified, the pharmacy resident assessed the dose and dosing interval in accordance with the patient's clinical status and renal function, and consulted with other pharmacy staff as appropriate. When inappropriate orders were identified, a recommendation to change the daily dose was made verbally and in writing to the attending physician (including recommended dosing guidelines, and a drug data sheet (Appendix A)).

Patient outcome was assessed by interviewing the patient, the health care provider, and/or reading the medical record. Cost analysis was performed on accepted recommendations. The cost of all the accepted recommendations for daily dosage changes (following dosage or interval adjustment) was subtracted from the cost of the originally prescribed dose. It was assumed the length of therapy was unchanged and that no other changes would have been made without pharmacy intervention. Cost was assessed based on the actual acquisition cost of the drug only and did not include the cost of ancillary supplies (i.e., minibags, etc.), nursing time, potential adverse patient outcomes (side effects or lack of efficacy), or time to make the interventions.

Reviewed medication orders are divided into two groups for analysis: the intervention group (orders requiring modification of the daily dose) and the non-intervention group (orders not requiring modification of the daily dose as the daily dose was appropriate for degree of renal function). A Student's T-test was completed and proportions were compared using the normal distribution for all variables to detect differences between the two patient groups. In addition, Chi Square analysis was applied to detect differences in prescribing or intervention patterns between senior staff (defined as attending physicians and/or residents) and junior staff (interns). P values were considered to be statistically significant if ≤ 0.05.

## RESULTS

Three hundred and seventy-five patients were admitted to the specified patient care units during the study period. One hundred and twenty of these patients

**Table I: Patient Characteristics. Mean data are presented as mean ± SD**

| Demographics | | Intervention Group[a] N=41 | Non-Intervention Group[b] N=79 | Significance |
|---|---|---|---|---|
| Gender (% male) | | 71% | 77% | NS |
| Age (y) | | 75 ± 13 | 71 ± 10 | NS |
| Height (cm) | | 165 ± 11 | 166 ± 20 | NS |
| Weight (kg) | | 73.5 ± 17.5 | 79.1 ± 15.8 | NS |
| Lean Body Wt (kg) | | 61.5 ± 11.1 | 65.0 ± 11.2 | NS |
| Renal Function on Admission | | | | |
| $S_{cr}$ (µmol/L) | Range | 81 - 504 | 96 - 399 | |
| | Mean | 163 ± 88 | 143 ± 56 | NS |
| CrCl (mL/min) | Range | 6.6 - 93 | 8.9 - 97.6 | |
| | Mean | 34 ± 16 | 42 ± 17 | p = 0.03 |
| Concurrent Diseases Which May Affect Renal Function | | | | |
| Prior Renal Impairment | | 14.6% | 10.1% | NS |
| Hypertension | | 19.5% | 22.7% | NS |
| Diabetes | | 19.5% | 15.1% | NS |
| Congestive Heart Failure | | 21.9% | 11.3% | NS |
| Scleroderma | | 2.4% | 0% | NS |

[a] Patients with medication orders requiring a pharmacist initiated decrease in daily drug dosage due to renal dysfunction
[b] Patients with medication orders not requiring a pharmacist initiated decrease in daily drug dosage due to renal dysfunction
NS = Not significant

met the inclusion criteria (Table I). A total of 146 medication orders for 120 patients with varying degrees of renal insufficiency were identified. Of these, 51 medication orders (35%) required modification of the daily dose based on renal function (Table II). The patient characteristics of the intervention and non-intervention groups were similar with respect to demographics and documented concurrent diseases.

Eighteen of the 24 targeted study drugs were prescribed during the study period. No medication orders for acyclovir, cefotaxime, cefoxitin, ganciclovir, piperacillin, or vancomycin were received.

**Table II: Medication Orders of Patients with Renal Dysfunction Requiring Dosage Adjustment by a Pharmacist[a]**

| Drug Category | Drug Name | Total # of Orders Received | # of Orders Requiring Interventions(%) |
|---|---|---|---|
| 1. Antimicrobials | ceftazidime | 1 | 1 ( 2.0%) |
| | cefuroxime | 22 | 5 ( 9.8%) |
| | ciprofloxacin | 4 | 1 ( 2.0%) |
| | cotrimoxazole | 25 | 6 (11.8%) |
| | gentamicin | 8 | 4 ( 7.8%) |
| | nitrofurantoin | 1 | 1 ( 2.0%) |
| | norfloxacin | 20 | 1 ( 2.0%) |
| | penicillin G | 1 | 1 ( 2.0%) |
| 2. $H_2$ Histamine Antagonists | ranitidine IV | 33[b] | 3 ( 5.9%) |
| | ranitidine oral | | 20 (39.2%) |
| 3. Other | allopurinol | 9 | 7 (13.7%) |
| | hydrochlorothiazide | 1 | 1 ( 2.0%) |

[a] no interventions were required for ampicillin (3), cefazolin (1), cephalexin (4), cimetidine (1), digoxin (9), metoclopramide (1)
[b] combined IV and po

**Table III: Cost Savings Associated With Dosage Adjustment for Individual Medication Orders**

| Drug | | # of Orders | # of Doses | Average Cost Per Dose ($) | Total |
|---|---|---|---|---|---|
| ALLOPURINOL | PO | 7 | 42 | 0.016 | $0.067 |
| CEFTAZIDIME | IV | 1 | 3 | 21.08 | $63.24 |
| CEFUROXIME | IV | 5 | 25 | 7.65 | $191.25 |
| CIPROFLOXACIN | PO | 1 | 6 | 2.36 | $14.16 |
| COTRIMOXAZOLE | PO | 4 | 12 | 0.08 | $0.96 |
| GENTAMICIN | IV | 4 | 8 | 3.49 | $27.96 |
| HYDROCHLOROTHIAZIDE | PO | 1 | 19 | 0.19 | N/A [a] |
| NITROFURANTOIN | PO | 1 | 24 | 0.48 | N/A [a] |
| NORFLOXACIN | PO | 1 | 5 | 2.06 | $10.30 |
| PENICILLIN G SODIUM | IV | 1 | 28 | 2.02 | $56.56 |
| RANITIDINE | IV | 3 | 24 | 1.74 | $41.76 |
| RANITIDINE | PO | 20 | 123 | 0.23 | $28.29 |

[a] Other medications substituted **TOTAL:** $435.15

The intervention rate differed according to medical service. The medication orders requiring intervention were 53% from medicine, 37% from urology, and 10% from respirology; the medication orders not requiring intervention were 22% from medicine, 58% from urology, and 20% from respirology ($p = 0.001$).

Thirty-one of the 51 interventions were evaluated for outcome, although formal outcome criteria for each drug were not established. In 17 cases, the patients were discharged too soon to evaluate efficacy and in three cases, the patients died with multiple medical problems. Of the evaluable interventions, 30 (97.7%) were considered therapeutically effective according to the categories described by Hepler and Strand.[18] These included, cure of a disease, stopping or slowing a disease process, reduction or elimination of symptoms, or prevention of a disease or symptoms. Therapeutic efficacy was similar in the non-intervention group (96%). The occurrence of adverse effects was similar between study groups (4% in the intervention group and 0% in the non-intervention group), but the study was not designed to confidently detect a difference.

Of the 146 medication orders screened, 48 were written by interns and 98 were written by either residents or staff physicians. Medication orders written by interns were more likely to require intervention than those written by residents or staff physicians (48% vs 29%) ($p = 0.025$).

Cost was assessed based on the actual acquisition cost of the drug only and did not include the cost of ancillary supplies (i.e., minibags, etc.), nursing time, potential adverse patient outcomes (side effects or lack of efficacy), or time to administer the program.

An average of $8.53 was saved with each intervention for a total of $435.15 over a six-week time period on three patient care units (Table III). If this is extrapolated to include all patients admitted

to the Victoria General Hospital over one year (assuming a constant intervention rate of 28% and an equal utilization of the specified drugs for all units in the hospital), the annual cost savings would be $28,139.70.

The initial dosing of ranitidine and allopurinol did not meet the guidelines in the majority of cases. Although alterations in cefuroxime and ceftazidime dosing accounted for only a few of the pharmacy-initiated interventions, the associated cost savings were substantial ($254.49).

The acceptance rate of the pharmacist initiated interventions was 98%.

## DISCUSSION

Patients in this study were elderly with a mean age of 75 years in the intervention group and 71 years in the non-intervention group. Patients in both groups had relatively low creatinine clearances. Renal insufficiency may occur with the normal aging process and with a number of disease states including hypertension, diabetes mellitus, and congestive heart failure.[19-21] Patients who are elderly and/or have these diseases could benefit from monitoring of drug doses based on estimated creatinine clearance by a pharmacist.

Various studies have been reported in the literature in which the dosages of drugs which are renally excreted are monitored by the pharmacy according to estimated creatinine clearance. Cost savings generated by such programs ranged from $838.00 to $14,659.00 per year depending upon the number of drugs included, the size of the institution, and the type of program used. The type of intervention used in these studies included verbal communication and/or a written note to the attending physician and resulted in an acceptance rate of pharmacy-initiated intervention of 74-93%.[22-27] In this study, the acceptance rate was higher, possibly because of the additional educational component provided by the drug data sheet.

There are a number of limitations of this study. Only selected drugs and patients were chosen for study, and it is uncertain whether these results apply to other types of patients or drugs. Drug dosage was based on the patient's clinical need and estimated CrCl. Since CrCl is only an estimate of GFR, doses may have been inappropriately adjusted if the calculated CrCl inaccurately estimated GFR. Patients were not followed after discharge. Therefore, outcome could not be determined in many patients as they were discharged prior to the drug's effect be coming apparent. This is a common criticism of other studies.[28,29] Formal outcome criteria for each drug were not developed. The design and sample size were not sufficient to determine differences in outcome or adverse reactions. A control group was not provided. Therefore, differences in patient outcome with and without pharmacist intervention could not be ascertained. Nevertheless, in the patients who did require dosage reduction, it appeared this could be done safely without apparent detriment to therapeutic efficacy.

The pharmacist in this study did not provide pharmaceutical care to the identified patients. However, since completion of the project and adoption of the pharmaceutical care model for some patients by the hospital, the dosing guidelines and data sheets developed have allowed pharmacists to be comfortable in dealing with the actual or potential drug-related problem of too high a drug dosage for the patient with compromised renal function.

Many of the patients studied received drugs at doses which had the potential to cause ADRs. These potential adverse drug reactions may have been avoided as a result of pharmacist monitoring of dosages of renally eliminated drugs in patients with renal dysfunction. Patient outcome did not appear to be compromised by dose adjustment. The potential direct drug acquisition cost savings of such a program (estimated in excess of $28,000.00 annually at this institution) is great and may be even greater when other more expensive intravenous drugs are included (as are used in intensive care units). The majority of the cost savings in this study was attributed to four drugs (ceftazidime, cefuroxime, penicillin G, and ranitidine). Education programs need to be developed to improve the dosing of drugs in patients with renal dysfunction and those identified as being dosed inappropriately most often can be targeted first.

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**Appendix A**

**DOSING GUIDELINES FOR ALLOPURINOL**

| $CL_{cr}$ (mL/min) | Dose & Frequency |
|---|---|
| 0 - 9 | 100mg q72h |
| 10 - 19 | 100mg q48h |
| 20 - 39 | 100mg q24h |
| 40 - 59 | 150mg q24h |
| 60 - 79 | 200mg q24h |
| 80 - 99 | 250mg q24h |
| ≥100 | usual (300mg) q24h |

**DRUG DATA SHEET**

**Allopurinol** (Zyloprim®)

**Cost:** Oral: 100mg tablet $ 0.01
300mg tablet $ 0.03

**Half Life:**

| Normal renal function | Anuria |
|---|---|
| 2 hours | prolonged |

**Metabolites:** Yes (oxypurinol active; half life normal renal function 18-30 hours)

**Percent Excreted Renally:** Allopurinol 7%
Oxypurinol 70%

**Adverse Reactions/Toxicity:**

Dermatologic: Rash; urticaria; (rarely) exfoliative dermatitis; Steven's Johnson syndrome.

* Hematologic: Aplastic anemia (case report); granulocytopenia; thrombocytopenia; leucopenia.

* Hypersensitivity Syndrome: Epidermolytic necrosis; hepatitis; eosinophilia; leucopenia; vasculitis.

Gastrointestinal: Diarrhea/nausea/vomiting.

CNS: Peripheral neuropathy; paresthesia; headache.

Other:** Malaise; headache; increased BUN; fever; chills; nausea; vomiting; lymphadenopathy.

**Comments:** * There is a higher incidence of adverse reactions (especially hypersensitivity syndrome and hematologic abnormalities) in patients with impaired renal function, therefore, dosage adjustment is necessary.

** Renal toxicity may also occur in patients with renal disease.

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*Other drug data sheets available from authors on request.*