PHARMACY PRACTICE

Implementation of an Aminoglycoside Order Review Process in a Central Dispensary

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INTRODUCTION

An investigation of the methods used to review and process adult aminoglycoside (AG) orders received in our central dispensary was prompted by feedback from triage pharmacists in the department. There was significant variability in practice and a concern regarding this lack of standardization. Since the current system did not contain mechanisms for maintaining minimum standards of practice, the provision of optimal patient care could not be ensured. The pharmacy utilizes a traditional centralized drug distribution system to service an 800-bed tertiary care teaching hospital. In the dispensary, triage pharmacists review all drug orders and have computerized access to patient demographics and laboratory information. Clinical pharmacy services are provided to areas including internal medicine, intensive care, and nephrology; however, no formal pharmacokinetics program exists.

A Pharmacy Committee with administrative, clinical, and dispensary representation was formed to examine adult AG order review procedures and provide recommendations to optimize the process with the existing resources. After reviewing operations in the dispensary and obtaining information from pharmacists, the committee concluded that:

(a) there was significant variability in the methods used to triage adult AG orders in the central dispensary;
(b) the minimum standard of performance and departmental expectations for processing AG orders were unclear; and,
(c) there was significant interest in educational programs and support for the implementation of AG order review guidelines.

The committee recommended that an AG order review project be initiated to:

(a) develop practical guidelines for checking and recommending initial individualized dosing regimens of gentamicin, tobramycin and netilmicin for adult patients;
(b) standardize the triaging of adult AG orders by pharmacists in the central dispensary and introduce a minimum standard of practice; and,
(c) improve the documentation of pharmacist interventions on AG orders.

A baseline audit was conducted of all adult AG order processed during a seven-day period approximately two months before the project was implemented. Forty-one AG prescriptions were assessed for documentation and interventions by triage pharmacists. (Table I) Only ten orders (24%) had documentation of an estimated creatinine clearance (Cl_{cr}) required to assess renal function and check the AG dose. Pharmacist interventions were identified on two orders (5%), and included a recommendation to extend the dosing interval and a non-specific request for the physician to reassess the dose. The audit revealed that triage pharmacists commonly accepted dosing regimens of 80 mg every eight hours for gentamicin, tobramycin, and netilmicin, irrespective of patient demographics. It was evident from the results of the baseline audit that the overall standard of practice for reviewing AG orders was inadequate.

Achieving therapeutic concentrations of AGs has been associated with improved clinical outcomes. [1,2] For gentamicin, tobramycin, and netilmicin, general guidelines for peak concentrations in the range of 6-10 mg/L and troughs less than 2 mg/L have been proposed in an at-

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tempt to optimize efficacy and minimize toxicity.[3] Population pharmacokinetics are used to individualize initial AG dosing regimens and obtain therapeutic concentrations early in therapy. Dosing nomograms, developed from population pharmacokinetic data, provide methods of selecting initial doses based on specific patient demographics. The potential impact of individualized AG dosing on patient care emphasizes the importance of pharmacists ensuring that orders are appropriate before the drug is dispensed.

The initial phase of the AG order review project involved developing complete guidelines for triaging AG orders and implementing the use of a nomogram to check AG doses. Because of the limitations of dosing nomograms, it was important to develop separate order review processes for new AG prescriptions and repeat orders. AG therapy may be reordered every five days based on an automatic stop policy for antibiotics in our institution. In order to adequately assess extended courses of AG therapy, procedures for reviewing repeat orders included additional steps such as interpreting available AG levels and monitoring renal function.

The project was introduced by providing extensive written material and conducting educational sessions for all pharmacists. After implementation, two audits were performed to monitor compliance with the guidelines and to assess the appropriateness of pharmacist interventions. Ongoing feedback was provided for the duration of the project.

PROJECT DESCRIPTION

Loading doses were checked according to the recommended 1.5-2.0 mg/kg of total body weight (TBW) or dosing weight (DW). For obese patients, a dosing weight was calculated by using the equation[4]:

DW = 0.4 (TBW - IBW) + IBW

where ideal body weight (IBW) was obtained from the equations[5]:

IBW (♂) = 50 kg + 2.3 kg/inch over 5 feet

IBW (♀) = 45.5 kg + 2.3 kg/inch over 5 feet

Nomograms including the methods by Sarubbi-Hull,[6,7] Chan,[8] and Dettli[9] were reviewed to assess their predictive performance[10] and practicality in assessing AG maintenance doses. Operations of the central dispensary were also considered when the AG order review process was being developed. The Sarubbi-Hull nomogram, which recommends a dose calculated as a percentage of the loading dose administered at an interval that is adjusted for renal function, was selected (Figure 1). Using pharmacokinetic-based calculations, the original nomogram was modified to provide the most reliable and practical method for assessing the appropriateness of doses on AG orders. Equations described by Sawchuk-Zaske were used to calculate the predicted peak and trough concentrations for each dose and corresponding interval on the original nomogram.[11,12] Parameters used in the calculations included a standard volume of distribution of 0.25 L/kg and elimination rates (k_{el}) based on Cl_{cr}s. ranging from 15 to >90 mL/min. Elimination rates were calculated according to the equation[7]:

$$\mathbf{k_{el}(hr^{-1}) = 0.0024 \times Cl_{cr}(mL/min) + 0.01}$$

Dosing regimens with predicted peaks between 6 and 10 mg/L and troughs less than 2 mg/L were selected and the appropriate interval was "bolded" on the nomogram. A forty-eight hour interval was added to accommodate patients with moderate to severe renal dysfunction. Some of the original doses were modified to include acceptable ranges rather than a single recommended dose. Because of the potential for significant error in the predictions for patients with a Cl_{cr} less than 15 mL/min, values below this limit were not included on the nomogram. It was recommended that peak and trough levels be used to determine appropriate dosing in this patient population.

For the triage pharmacists, the first step in using the dosing nomogram was to obtain the patient's Cl_{cr}. If a measured Cl_{cr} was not available, an estimated value was calculated by using the Cockcroft and Gault equation:[13]

$$\mathbf{Cl_{cr}(mL/min) = \frac{(140\text{-age})\ (TBW\ or\ DW)}{sCr(umole/L)} \times 1.2}$$

where sCr was the serum creatinine and the calculation was multiplied by 0.85 for females. The pharmacists had computerized access to the information required to estimate Cl_{cr} including age, body weight,

Cl_{cr} (mL/min)	t1/2(h)	q8h	q12h	q24h	q48h
≥90	3.1	**84%**			
80	3.4	**70-80**	91%		
70	3.9	**65-76**	88		
60	4.5	71	**84**		
50	5.3	65	**79**		
40	6.5		**60-72**	**92%**	
30	8.4		63	**86**	
25	9.9		57	**81**	
20	11.9			**70-75**	
15	15.1			**50-67**	**70-80%**

Figure 1: Modified Sarubbi-Hull Nomogram ("bolded" areas indicate preferred interval for measured or calculated Cl_{cr}; dose is calculated as % of loading dose which is 1.5-2.0 mg/kg of TBW or DW; for Cl_{cr} <15 mL/min, select q48h interval and use level-assisted dosing; for dialysis patients, use level-assisted dosing)

height, and sCr. If available, serial sCr concentrations and blood urea nitrogen values were reviewed to assess the stability of renal function and hydration status.

As demonstrated in Figure 2, new AG prescriptions were reviewed and the process was documented on each order. If the dose appeared inappropriate, the physician was contacted and an alternate regimen, based on the nomogram, was recommended. Because of the limitations of nomogram-derived predictions, all interventions included a recommendation for a peak and trough level to be obtained on the third dose. Ideally, all interventions would have included follow-up by a pharmacist, however, resource limitations within our department did not allow for this. It was expected that the attending physician would monitor AG concentrations and, if necessary, request assistance for level interpretation. Since the pharmacists were unable to document their interventions in patient charts, documentation on the original orders was emphasized and monitored. The minimum requirement for documentation included the most recent sCr, body weight, calculated Cl_{cr}, and verification of the dose check.

The processing of repeat orders, depicted in Figure 3, involved a review of the patient's laboratory data to identify potential AG-induced nephrotoxicity and to obtain and document level results. If a repeat order was received and levels were not available, the appropriateness of the dose was re-assessed utilizing the nomogram as described for new orders. A repeat order with a dose which still appeared appropriate was processed with a recommendation to the physician that peak and trough levels be obtained. If the dose check indicated that the regimen was no longer appropriate for the patient, a recommendation for dosage adjustment, based on the nomogram, was made with the suggestion that levels be obtained on the third dose.

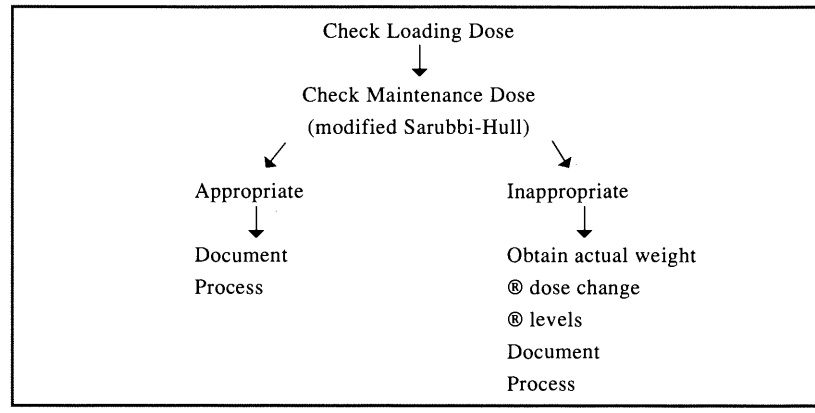

Figure 2: Aminoglycoside Order Review Algorithm for New Prescriptions (® = recommend)

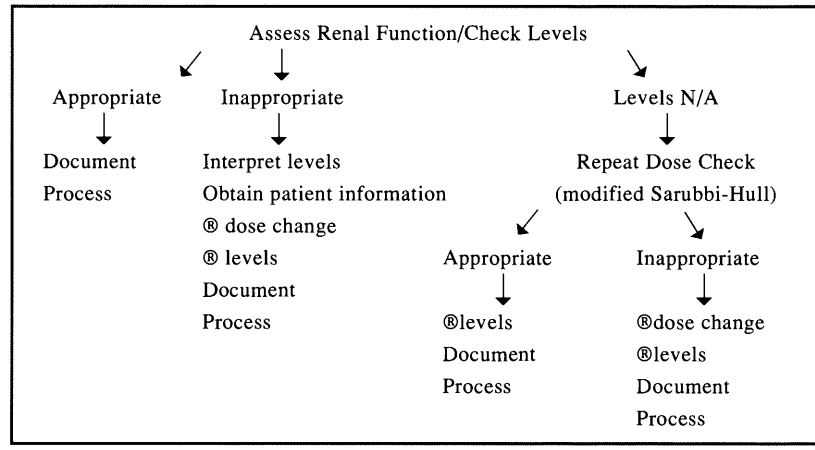

Figure 3: Aminoglycoside Order Review Algorithm for Repeat Prescriptions (N/A = not available, ® = recommend)

A repeat order was processed, if peak and trough concentrations on the same regimen were available and appropriate. Therapeutic AG troughs were defined as concentrations between 0.5 and 2.0 mg/L or 0.5 and 1.5 mg/L in patients at increased risk for renal toxicity. Peak AG levels between 6 and 10 mg/L were considered therapeutic except when used for the treatment of lower urinary tract infections where concentrations between 4 and 6 mg/L were accepted. If the levels obtained were inappropriate, an alternate dosing regimen was selected based on level interpretation and other pertinent patient information. It was emphasized that when levels were available, it was not appropriate to use the nomogram to assist in subsequent dosing. Such cases were generally referred to the clinical pharmacy section since the project did not include sufficient training in clinical pharmacokinetics and level interpretation. The AG order review process was developed to assist pharmacists in triaging AG orders and was not intended to provide a pharmacokinetic service from the central dispensary. Ideally, a pharmacokinetic service would included the additional resources to decentralize pharmacists allowing them to review charts, make recommendations and monitor patient progress.

EVALUATION

With the AG order review project

there was the opportunity to provide advanced education on the AGs and their pharmacokinetics. The audits not only identified individual needs of the staff, but provided significant information and valuable feedback. Supplemental material was also supplied during sessions which were conducted to review interesting or unusual cases.

Audits I and II were designed to monitor the overall process and ensure compliance with the AG order review guidelines by pharmacists in the central dispensary. Although available levels were interpreted to assess the results of pharmacist interventions, the audits were not designed to evaluate clinical outcomes of patients. In future audits, the incorporation of a clinical outcome assessment would provide important information relating to the impacts of pharmacy practice on patient care.

Audit I, which was performed one month after implementation of the program, was not blinded to the triage pharmacists. Fifty-two adult AG prescription including 39 initial and 13 repeat orders were identified over a seven-day period. (Table I) A comprehensive review of each order was performed to:

(a) assess documentation on AG orders by triage pharmacists;
(b) assess pharmacist interventions based on the AG order review process;
(c) identify potential interventions which were not addressed during the order review; and,
(d) provide feedback to pharmacists and assess the need for additional educational sessions.

The results of Audit I demonstrated that only 27 orders (52%) met the minimum requirement for documentation. Pharmacist interventions were identified on 10 orders (19%) and included recommendations for changing dose, changing interval, and obtaining levels. All interventions were appropriate based on the dosing nomogram and AG order review guidelines, and the physician acceptance rate was 80%. Four additional orders were identified on which dosing changes may have been indicated. During educational sessions, these cases were presented and the potential interventions were discussed.

In response to the insufficient documentation observed during the first audit, a stamp was developed to improve documentation and facilitate the AG order review process (Figure 4). Audit II, which was conducted one month after introduction of the documentation stamp, was blinded to the triage pharmacists. The results, presented in Table I, indicated an improvement with 37 (82%) of the 45 prescriptions having adequate documentation. Pharmacist interventions were identified on 12 orders (27%) and all

Table I: Results of Adult Aminoglycoside Order Audits

	Baseline Audit[1]	Audit I[2]	Audit II[3]
Total AG orders	41	52	45
New orders	N/A	39	31
Repeat Orders	N/A	13	14
Documentation[4]	10 (24%)	27 (52%)	37 (82%)
Interventions	2 (5%)	10 (19%)	12 (27%)
Change dose	0	2	1
Change interval	1	2	1
Change dose, interval	0	3	6
Obtain levels	0	3	6
Potential interventions	N/A	4	3

[1] 7 day audit conducted 2 months prior to project
[2] 7 day audit conducted 1 month after project initiation
[3] 7 day audit conducted 1 month after documentation stamp
[4] for the baseline audit, included measured or estimated Cl_{cr}; for Audits I and II, included sCr, body weight, Cl_{cr}, and verification of dose check
N/A not assessed

Age: _____ $_{s}$Cr/date: _____

Wt $_{estimate}$: _____ kg Cl_{cr}: _____ mL/min

Wt $_{actual/DW}$: _____ kg Cl_{cr}: _____ mL/min

Diagnosis: _____

Peak (mg/L)	Trough	Date	Regimen

Dose Check: Appropriate: [ ]
Recommendations:
Dose: _____
Levels: [ ]

Initials: _____ Discussed with: _____

Figure 4: Documentation Stamp for Aminoglycoside and Vancomycin Orders

recommendations were appropriate. The physician acceptance rate of 75% was comparable to that of the first audit. Three additional orders had the potential for pharmacist intervention.

The impact of the AG order review project on pharmacy practice was assessed by comparing the documentation and interventions during the baseline audit to those of Audits I and II. Even though the minimum requirement was relatively lenient, the documentation on orders reviewed during the baseline audit was deficient with only one quarter of the orders documenting a Cl_{cr}. A measured or estimated Cl_{cr} was the only requirement for documentation as it was assumed that sCr and body weight were obtained for the calculation. In addition, the documentation of levels was not included since the retrospective design made it difficult to determine whether the triage pharmacists had access to the information at the time the order was processed. Subsequent audits demonstrated continued improvement in documentation with greater than 80% of the Audit II orders meeting the minimum requirements. Prior to the project, the number of interventions was also limited with the baseline audit only identifying two cases (5%) in which a pharmacist intervened on an AG order. Subsequent audits demonstrated an increase in the number of recommendations with 27% of Audit II orders involving pharmacist interventions.

A strategy for regular assessment of the AG order review process was required to maintain current standards of practice and identify opportunities for further improvement. Annual audits will be performed to maintain an ongoing evaluation, provide feedback to pharmacists, monitor changes in practice over time, and identify the impacts on patient care.

In conclusion, an AG order review process was successfully implemented to standardize the triaging of adult AG prescriptions. Feedback from pharmacists indicated that the program provided significant educational benefits and facilitated the processing of AG orders in the central dispensary. The processing guidelines standardized the approach to triaging AG orders and the dosing nomogram provided a method of assessing and selecting individualized dosing regimens.

AMINOGLYCOSIDE DOSING GUIDELINES
(Gentamicin/Tobramycin/Netilmicin)

LOADING DOSE (LD): 1.5 - 2.0 mg/kg [total body wt (TBW) or dosing wt (DW)]
* for obese patients (TBW > 30% above ideal body wt), calculate dosing weight: DW = 0.4 (TBW - IBW) + IBW

MAINTENANCE DOSE:
ESTIMATED CREATININE CLEARANCE: (Cockcroft, Gault. Nephron 1976;16:31)

$$Cl_{cr}\ (mL/min) = \frac{(140 - age)(TBW \text{ or } DW)}{sCr\ (umoles/L)} \times 1.2\ (\times 0.85 \text{ for } ♀)$$

MODIFIED SARUBBI-HULL NOMOGRAM - Percentage of Loading Dose Required for Dosage Interval Selected: (Sarubbi-Hull. Ann Intern Med 1976;85:183)

Cl_{cr} (mL/min)	t1/2(h)	q8h	q12h	q24h	q48h
≥90	3.1	**84%**			
80	3.4	**70-80**	91%		
70	3.9	**65-76**	88		
60	4.5	71	**84**		
50	5.3	65	**79**		
40	6.5		**60-72**	**92%**	
30	8.4		63	**86**	
25	9.9		57	**81**	
20	11.9			**70-75**	
15	15.1			**50-67**	**70-80%**

* bolded areas indicate preferred interval
* dose calculated as % of loading dose (1.5-2.0 mg/kg of TBW or DW)
* round off dose to nearest 10 mg
* Cl_{cr}<15 mL/min: select q48h interval, use levels to assist dosing
* dialysis patients: use levels to assist dosing

PEAK AND TROUGH LEVELS: (available daily)
* obtain pre and post levels around 3rd dose (after 4-5 half-lives)
* trough: 0.5 - 2 mg/L (within 45 min of dose)
  0.5 - 1.5 mg/L if risk factors for nephrotoxicity
* peak: 6 - 10 mg/L (20-30 min after infusion completed)
  4 - 6 mg/L adequate for UTI
  7 mg/L necessary for pneumonia/serious infections

RENAL FUNCTION:
* monitor daily in unstable and 3X/week in stable patients

The above dosage guidelines are derived from pharmacokinetic principles, and are intended to provide estimates for an initial dose. The nomogram is not a substitute for therapeutic drug monitoring and interpretation of patient specific concentrations.

Figure 5: Laminated Pocket Ruler for Hospital-Wide Distribution

The emphasis on complete documentation supports current strategies in the profession to improve the documentation of pharmacist activities. Considering the limited interventions identified during the baseline audit, the program had a substantial impact on the number of pharmacists's interventions.

The success of the AG project resulted in the development of similar procedures for vancomycin order review. In an attempt to promote hospital-wide consistency, the dosing guidelines for AGs and vancomycin were compiled onto a laminated pocket ruler for distribution to prescribers (Figure 5). The program is a practical approach to centralized drug order review which could be adapted to meet the needs of a variety of hospital pharmacy departments.

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