PharmaNote®

Volume 25, Issue 6 March 2010

CYCLOSET®: A UNIQUE APPROACH TO TREATING DIABETES

Michael Meldrum, Pharm.D. Candidate

Diabetes Mellitus (DM) has become more prevalent in the United States. The CDC estimates that 23.6 million people had a diagnosis of DM in 2007, including 1.6 million incident cases. The estimated cost of DM in 2007 was $174 billion.[1]

Current therapy for DM relies on medications that either supplement the bodies ability to produce insulin or improve the bodies response to insulin. Cycloset® is an immediate-release formulation of bromocriptine mesylate (IR-Brom) intended to release the dose quickly at a certain time of day. The new drug application was submitted by Veroscience, a small drug development and research company, which has subsequently partnered with S2 Therapeutics to market and manufacture the drug.[2]

Cycloset® was approved by the FDA on May 5, 2009 after more than ten years of study. The initial application was filed on August 22, 1997, but required multiple supplemental submissions to satisfy the FDA.[3] As part of the approval process, IR-Brom was subject to the new higher standards for DM medications to prove cardiovascular safety.

IR-Brom has been approved for use as an adjunct to diet and exercise for the treatment of adults with Type II DM. Combination therapy with thiazoladinediones and/or insulin has not been adequately studied.[4] The labels of DM medications have been changed recently to reflect a more generic statement of use of addition to diet and exercise. This article will review the unique mechanism of IR-Brom, its pharmacokinetics, adverse effects, and results of the most recent clinical studies.

PHARMACOLOGY

The exact mechanism of IR-Brom in the treatment of DM is unknown; however, bromocriptine decreases A_{1c} and fasting plasma glucose. Bromocriptine may work by resetting the neuroendocrine rhythms in the hypothalamus of DM patients.[5] Research with bromocriptine for the treatment of DM began after the discovery that neuroendocrine levels are altered seasonally in migrating vertebrates, affecting fat stores and glucose utilization. This seasonal variation creates an obese, insulin-resistant and hyperinsulinemic state in these animals.[6] Circadian rhythm alteration is related to the activity of dopaminergic (DA) and serotonergic neurons. Bromocriptine may cause the neuroendocrine activity to be reset by adjusting DA and serotonin activity resulting in increased insulin sensitivity.[7]

The circadian rhythm alteration occurs via a change in the activity of the suprachiasmatic nucleus (SCN). Regulation of the SCN then alters the activity of the ventromedial hypothalamus (VMH) which is responsible for the seasonal insulin resistant state in

INSIDE THIS ISSUE:

CYCLOSET®: A UNIQUE APPROACH TO TREATING DIABETES

ONCE DAILY AMINOGLYCOSIDES: A REVIEW AND UPDATE

Table 1. Pharmacokinetic properties of immediate-release bromocriptine.[4]

CHARACTERISTIC	EFFECT
Absorption/Bioavailability	7% bioavailable; peak concentration 53 min
Food	55-65% increase in bioavailability; peak concentration 90-120 min
Distribution	61 L; 90-96% protein binding
Metabolism	CYP 450 3A4
Excretion	Mostly biliary; 2-6% in urine
Renal/Hepatic Adjustment	None/caution in impairment
Age	Not indicated for pediatric use; no studies in geriatric population
Gender	18-30% increased plasma exposure in females

mammals. The dopamine activity of bromocriptine reduces the activity of noradrenaline and serotonin at the VMH.[6]

PHARMACOKINETICS

IR-Brom is 65-95% absorbed and reaches peak concentration in 53 minutes following oral dosing.[4] The rapid absorption creates the proper peak activity on DA receptors which then resets the circadian rhythm. Bromocriptine is metabolized by the CYP 450 system, specifically 3A4. A high first pass metabolism results in only 7% of absorbed drug reaching circulation. Approximately 2-6% of bromocriptine is excreted in the urine, while the remainder undergoes biliary excretion.

Food increases the percent absorbed and delays the time to peak concentration of IR-Brom, thus administration with food is recommended. IR-Brom is bound by plasma proteins (90-96%) with a half life of approximately 6 hours. Currently, no studies have been performed in patients with renal or hepatic failure. Based on the route of elimination, renal impairment should have little effect on the concentration of bromocriptine, but hepatic impairment may lead to increased concentrations. Therefore, caution should be used in patients with hepatic impairment when taking this medication. A summary of the pharmacokinetic properties of IR-Brom can be found in Table 1.[4]

CLINICAL TRIALS

Six phase II efficacy trials have evaluated quick release bromocriptine formulations (Table 2). These trials demonstrated that IR-Brom was effective in reducing glucose levels in obese Type II DM patients.[6] Multiple phase III trials have also demonstrated that IR-Brom is safe and effective for reducing A_{1c} in DM patients (Table 3). Two larger studies were used to obtain final approval of IR-Brom. Gaziano, et al. evaluated IR-Brom in a double-blind, placebo-controlled, non-inferiority trial designed to determine safety, defined as time to first major adverse event, and efficacy, defined as the change in A_{1c} after 24 weeks of therapy, as the primary outcomes. Enrolled patients were on usual DM therapy (defined as diet alone, 2 oral agents, or insulin plus 1 oral agent) and were randomly assigned to IR-Brom or placebo. Treatment lasted for 52 weeks and patients were assigned in a 2:1 ratio to IR-Brom or placebo (N=3095). A lower risk of the cardiovascular endpoint was found in the IR-Brom treatment group compared to the placebo arm. In addition, no significant difference occurred between groups for the composite of serious adverse events. The authors observed a 0.69 difference in A_{1c} between groups (P= 0.0002) with 52.9% of IR-Brom patients achieving a 0.7 drop in A_{1c} versus 23.5% in the placebo arm (P= 0.0004).[8]

Scranton, et al., in a double blind, placebo-controlled, 52 week trial, evaluated the cardiovascular safety of IR-Brom. Three thousand and seventy participants were randomly assigned in a 2:1 ratio to IR-Brom or placebo in this non-inferiority trial. The primary outcomes of the trial were overall safety and cardiovascular safety. Secondary analysis was planned to look at subgroups in regards to A_{1c} control. Patients were allowed to be on other DM medications but had to be on a stable dose for the first 3 months and then adjustments could be made to the drug regimen as needed. IR-Brom was titrated weekly to the maximum tolerated dose of 4.8 mg/d. IR-Brom was non-inferior to placebo for the adverse effects profile, and showed a 42% macrovascular risk reduction. A_{1c} was reduced to a greater extent with IR-Brom than placebo in all subsets analyzed.[9]

Table 2: Summary of Phase II trials of immediate-release bromocriptine.

Design	Population	Treatment	Findings
Open label	Obese nondiabetic with hyperinsulinemia (n=12)	1.6 mg/day for 2 weeks	• Decreased elevated fasting and post-prandial insulin • Decreased post-prandial glucose
Open label	Obese nondiabetic postmenopausal with hyperinsulinemia (n=13)	1.6 mg/d for 8 weeks	• Decreased post-prandial glucose
Double blind, placebo-controlled	Obese DM II	1.6 mg/d for 16 weeks	• Reduced A_{1c} by 1.8%
Dose response study	Obese DM II	1.6 mg/d to 15 mg/d for 35 days	• Linear relation between increasing IR-Brom dose and 24-hour glucose AUC • Increased side effects above 7.2 mg/d • Optimal dose = 4.8 mg/d
Double blind placebo-controlled	Obese DM II (n=22)	4.8 mg/d for 16 weeks	• Decreased A_{1c} by 1.2% compared to placebo • Decreased FPG by 54 mg/dl compared to placebo
Placebo-controlled	DM II currently using insulin (n=11 placebo; 21 treatment)	4.8 mg/d for 12 weeks	• Decreased A_{1c} by 0.7% compared to placebo • Decreased insulin requirement by 8% over placebo

Adverse effects from clinical trials are summarized in Table 4

Dosing & Administration

The approved dose of IR-Brom is 0.8 mg daily and is intended to be titrated up weekly. The target dose is between 2 and 6 tablets daily (1.6-4.8 mg daily). Since IR-Brom is designed to affect circadian rhythms, it should be taken within the first two hours of waking. Furthermore, IR-Brom should be administered with food to increase the absorption of the drug. Titration is stopped either when 6 tablets per day are reached or side effects limit any further increase in dose.[4]

Cost

Cycloset® is currently not available as Veroscience is in the process of finding a distributor. The company has not released any timeline for when the drug will actually make it to the market.[11]

Table 3. Summary of Phase III trials of immediate-release bromocriptine.

Study	Design	Treatment	Findings
Cincotta et al.[6] (1999)	• Placebo-controlled • Obese DM II • N=494	• Sulfonylurea plus placebo or IR-Brom • IR-Brom titrated weekly to 4.8 mg/d for 24 week	• IR-Brom decreased A_{1c} 0.21% (P<0.0001) • A_{1c} difference 0.55% IR-Brom vs placebo (P<0.0001) • Reduced FPG 23 mg/dl vs placebo (P<0.0001)
Cincotta et al.[6] (1999)	• Placebo-controlled • Obese DM II • N=159	• IR-Brom monotherapy • IR-Brom titrated weekly to 4.8 mg/d for 24 week	• IR-Brom reduced A_{1c} by 0.17% and A_{1c} between group difference 0.56% (P<0.02) • IR-Brom reduced FPG by 31 mg/dl (P<0.001)
Pijl et al.[5] (2000)	• Double blind, placebo-controlled • Obese DM II • N = 22	• IR-Brom titrated weekly to 4.8 mg/d for 16 weeks	• Reduced FPG by 22 mg/dl (P=0.02) • Reduced A_{1c} by 0.6% compared with 0.6% increase for placebo (P=0.009)
Aminorroaya et al.[10] (2004)	• Double blind, placebo-controlled • Obese DM II • N = 40	• IR-Brom 2.5 mg/d for 12 weeks	• Reduced FPG by 27.54 mg/dL (P<0.01) • IR-Brom reduced A1c by 0.4% (P=0.06) • A_{1c} difference of 1.5% between groups with -0.4% in IR-Brom and 1.1% in placebo (P<0.01)

Table 4. Adverse events in trials with immediate-release bromocriptine.[4]

ADVERSE EFFECT	IR-BROM (%)	PLACEBO (%)
Monotherapy	*n = 80*	*n = 79*
Nausea	26 (32.5)	6 (7.6)
Rhinitis	11 (13.8)	3 (3.8)
Headache	10 (12.5)	7 (8.9)
Asthenia	10 (12.5)	5 (6.3)
Dizziness	10 (12.5)	6 (7.6)
Constipation	9 (11.3)	3 (3.8)
Sinusitis	8 (10.0)	2 (2.5)
Diarrhea	7 (8.8)	4 (5.1)
Amblyopia	6 (7.5)	1 (1.3)
Dyspepsia	6 (7.5)	2 (2.5)
Vomiting	5 (6.3)	1 (1.3)
Infection	5 (6.3)	4 (5.1)
Anorexia	4 (5.0)	1 (1.3)
Adjunct to Sulfonylurea	*n = 244*	*n = 250*
Nausea	62 (25.4)	12 (4.8)
Asthenia	46 (18.9)	20 (8.0)
Headache	41 (16.8)	40 (16.0)
Flu syndrome	23 (9.4)	19 (7.6)
Constipation	24 (9.8)	11 (4.4)
Cold	20 (8.2)	20 (8.0)
Dizziness	29 (11.9)	14 (5.6)
Rhinitis	26 (10.7)	12 (4.8)
Sinusitis	18 (7.4)	16 (6.4)
Somnolence	16 (6.6)	5 (2.0)
Vomiting	13 (5.3)	8 (3.2)
Amblyopia	13 (5.3)	6 (2.4)
52-Week Safety Trial	*n = 2054*	*n = 1016*
Nausea	661 (32.2)	77 (7.6)
Dizziness	303 (14.8)	93 (9.2)
Fatigue	285 (13.9)	68 (6.7)
Vomiting	167 (8.1)	32 (3.1)
Diarrhea	167 (8.1)	81 (8.0)
Constipation	119 (5.8)	52 (5.1)

SUMMARY

Cycloset® was approved on May 5, 2009 for the treatment of Type II DM. The addition of IR-Brom to current therapy is expected to provide a minor additional reduction in A_{1c}. However, this option is currently unavailable in the United States.

♦ ♦ ♦

REFERENCES

1. National Diabetes Fact Sheet, 2007. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf
2. Cycloset®. http://www.Cycloset.com Accessed Oct 12, 2009.
3. FDA Approval Letter. Available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/020866s000ltr.pdf
4. Cycloset® Package Insert. Last Revised April 2009.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020866lbl.pdf
5. Pijl H, Pipek R, Ohashi S, Iozzo P, Matsuda M, Lancaster JL, et al. Bromocriptine: A novel approach to the treatment of type 2 diabetes. Diabetes Care 2000;23(8):1154-1161.
6. Cincotta AH, Meier AH, Cincotta Jr, M. Bromocriptine improves glycaemic control and serum lipid profile in obese Type 2 diabetic subjects: a new approach in the treatment of diabetes. Exp Opin Invest Drugs 1999; 8 (10):1683-1707.
7. Cincotta AH, Meier AH. Bromocriptine Inhibits In Vivo Free Fatty Acid Oxidation and Hepatic Glucose Output in Seasonally Obese hamsters (*Mesocricetus auratus*). Metabolism 1995;44(10):1349-1355.
8. Gaziano JM, Ezrokhi M, Cincotta AH, Scranton RE. Effects of Timed Cycloset®™ (a Quick Release Formulation of Bromocriptine Mesylate) Administration on Safety, Cardiovascular Event Rate, and Glycemic Control in Subjects with Type 2 Diabetes Receiving Diet, Oral Hypoglycemic, and/or Insulin Treatment Regimens [poster]. 67th Scientific Sessions of the American Diabetes Association; 2007 Jun 22-26; Chicago (IL).
9. Scranton RE, Cincotta AH, Ezrokhi M, Gaziano JM. Cycloset® (Quick-Release Bromocriptine Mesylate), a Novel Centrally Acting Treatment for Type 2 Diabetes [abstract no. 80 plus poster]. Canadian Diabetes Association; 2008 Oct 15-18; Montreal (QU).
10. Aminorroaya A, Janghorbani M, Ramezani M, Haghighi S, Animi M. Does Bromocriptine Improve Glycemic Control of Obese Type-2 Diabetics? Horm Res 2004;62:55-59.
11. Johnson CY. A drug's journey from idea to reality. May 7, 2009. www.boston.com/business/healthcare/articles/2009/05/07/a_drugs_journey_from_idea_to_reality/

♦ ♦ ♦

ONCE DAILY AMINOGLYCOSIDES: A REVIEW AND UPDATE

David Joeckel, Pharm.D. Candidate

Aminoglycosides (AGs) were first introduced in 1944 with the discovery of streptomycin. Over the next 15 years, neomycin, kanamycin and paromycin were developed. Although these AGs are still available today, they are rarely used due to their increased risk of toxicity. Currently the most commonly used AGs are gentamicin, approved by the FDA in 1966, and tobramycin, and amikacin, which were introduced in 1975 and 1976, respectively.[1,2]

AGs are an effective treatment option in patients with susceptible gram negative bacterial infections and cover many serious organisms including *Acinetobacter*, *Citrobacter, Enterobacter, Pseudomonas*, and *Serratia* spp. AGs are used for treatment of septicemia, osteomyelitis, meningitis, respiratory tract infections, and febrile neutropenia. AGs also treat gram positive organisms including staphylococcus and streptococcus species when used synergistically with beta-lactams.[2]

This article will discuss the properties of AGs that allow them to be effective when dosed once daily (ODD), as well as compare the use of multiple daily dosing with ODD, and summarize relevant studies suggesting ODD is superior to multiple daily dose regimens.

TOXICITY

Although effective bactericidal agents, caution is required with AGs due to nephrotoxicity and ototoxicity. Nephrotoxicity typically occurs several days after administration when drug begins to accumulate in the renal tubules. AG accumulation occurs when trough concentrations remain elevated for an extended duration, generally above 2 mcg/ml. AGs are renally eliminated and accumulate in the tubules following glomerular filtration.[3,4] Although nephrotoxicity is a concern, it is reversible upon drug discontinuation as trough levels fall.

Ototoxicity is the other major adverse effect associated with AGs. This process is irreversible and presents with permanent hearing loss and vestibular damage. Ototoxicity is a result of drug accumulation and consistently elevated peak concentrations, generally greater than 12 to 15 mcg/ml for gentamicin and tobramycin.[3,5] Despite the possibility of toxicity, and the development of new antibiotics, AGs remain important agents in the treatment of many infectious diseases.

MULTIPLE DAILY DOSING

Traditional recommendations suggest AGs be administered in multiple daily infusions, usually every 8 to 12 hours. Multiple daily dosing assumes drug concentrations remain above the minimum inhibitory concentration (MIC) for the entire duration of therapy. Early data suggested that when concentrations fell below the MIC, AGs were not effectively killing the infecting organisms, and the risk of resistance increased.

However, when concentrations are elevated for extended durations and continually remain above the MIC, the risk of toxicity increases.[6,7]

Other disadvantages of multiple daily dosing include frequent serum creatinine and lab monitoring. Labs must be drawn at the appropriate time or results will be misleading and lead to unnecessary dosage adjustments and further increase the risk of toxicity.[6,7] Overall, this process increases costs and the likelihood of errors. An effective alternative to multiple daily dosing is ODD of AGs. The rationale for ODD is based on two characteristics of these drugs: concentration dependent killing and the post-antibiotic effect (PAE).

Concentration-Dependent Killing

AGs exhibit concentration dependent killing, meaning the extent of killing is increased when the bacteria are exposed to increasing drug concentrations. They are most effective when peak concentrations are at least ten times greater than the MIC. Traditional dosing usually does not produce peak concentrations at this level. Although ODD results in increased peaks, these peaks do not result in increased toxicity because concentrations do not remain elevated long enough for accumulation to occur. This method results in decreased toxicity and increased efficacy.[8,27,28]

Post-Antibiotic Effect

The PAE means AGs will continue to be bactericidal despite drug concentrations falling below the MIC. This effect may last up to 8 hours after serum concentrations fall below the MIC and decreases exposure to AGs and potentially toxic levels, making drug accumulation less likely. This characteristic allows for continued killing at low levels and significantly decreases the occurrence of nephrotoxicity.[9,10,26,28]

Clinical Studies

Several meta-analyses have compared once daily dosing with traditional dosing. AGs used in these trials included netilmicin, amikacin, gentamicin, sisomicin, and tobramycin. A majority of patients had severe infections including pneumonia, bacteremia, urinary tract infections, and intra-abdominal infections.

Barza M, et al. evaluated 21 clinical trials performed between 1966 and 1995 involving a total of 3091 adult and pediatric patients.[11] ODD of AGs was compared with either two or three times daily dosing. No significant decrease in antibiotic failures was observed with ODD (RR 0.83, 95% CI: 0.57-1.21, p=0.32) although significance was reached with the fixed effect model (p=0.02). A nonsignificant reduction was also observed in favor of a single daily dose in patients with febrile neutropenia (RR 0.52, 95% CI: 0.11-2.46). Nephrotoxicity was significantly decreased with ODD (RR 0.74, 95% CI: 0.54-1, p=0.05), although there was no difference in observed ototoxicity (RR 1.09, 95% CI 0.68-1.75). The authors concluded that ODD is at least as effective as MDD, has a trend toward decreased failures, and significantly decreases nephrotoxicity.

Ferriols-Lisart, et al. compared ODD with MDD regimens in 18 clinical trials involving 2317 immunocompetent adult patients performed between 1988 and 1995.[12] ODD was significantly more effective than the MDD (odds ratio 1.47, 95% CI: 1.13-1.94), defined as the resolution of signs and symptoms of infection. ODD showed a significant reduction in nephrotoxicity (odds ratio 0.60, 95% CI: 0.04-0.86), although ototoxicity was not significantly reduced (odds ratio 0.56, CI: 0.26-1.16). The authors concluded that ODD is an effective alternative to multiple daily dosing.

Hatala, et al. performed a meta-analysis of 17 randomized, controlled trials performed between 1966 and 1995 including immunocompetent adults.[13] Trials

Table 1. Comparison of once-daily versus multiple-daily dosing of aminoglycosides.

Study	Studies	N	Efficacy	Nephrotoxicity	Ototoxicity
Barza, et al.[11] (1996)	21	3091	Trend favored ODD RR 0.83 (95% CI: 0.57-1.21)	ODD < MDD RR 0.74 (95% CI: 0.54-1)	No difference RR 1.09 (95% CI 0.68-1.75)
Hatala, et al.[13] (1996)	17	811	Trend favored ODD RR 0.91 (95% CI: 0.63-1.31)	Trend favored ODD RR 0.87 (95% CI: 0.60-1.26)	Trend favored ODD RR 0.67 (95% CI: 0.35-1.28)
Ferriols-Lisart, et al.[12] (1996)	18	2317	ODD > MDD OR 1.47 (95% CI: 1.13-1.94)	ODD < MDD OR 0.60 (95% CI: 0.04-0.86)	ODD < MDD OR 0.56 (95% CI:0.26-1.16)

ODD = once-daily dosing; MDD = multiple daily dosing; RR = relative risk (risk ratio); OR = odds ratio; 95% CI = 95% confidence interval.

Table 2. Once daily dosing in specific patient populations.

Author	Study Design	Condition	Once Daily Dose	Control Arm	Results
Del Priore et al.[15] (1996)	Randomized	Postpartum endometriosis	Gentamicin 5mg/kg + clindamycin	1.75mg/kg 3x/day + clindamycin	• No efficacy difference. • Dose adj to reach desired peak: 0% ODD vs 37% MDD • Cost analysis (per pt) ODD = $16.12 vs MDD = $41.75 (P=<0.001)
Livingston et al.[16] (2003)	Randomized	Postpartum endometriosis	Gentamicin 5mg/kg + clindamycin 2700 mg x 1	Gentamicin 120 mg Q8H + clindamycin 900 mg Q8H	• Success rate: 82% ODD vs 69% MDD (P=0.12) • Decreased administration cost (no values given)
Locksmith et al.[17] (2005)	Ranomized	Chorioamnionitis	Gentamicin 5.1mg/kg	Gentamicin 120mg LD, 80mg Q8H	• No difference in outcomes or toxicity. Maternal vs cord peak conc.: 18.2mcg/ml vs 7.1mcg/ml (P <0.001).
Contopoulos-Ioannidis, et al.[18] (2004)	Meta-analysis	Nonspecific infections	Gentamicin 4-5mg/kg	Gentamicin BID or TID	• Efficacy trends favored ODD: RR 0.71 (95% CI 0.45 to 1.11). • Nephrotoxicity: ODD<MDD RR 0.33 (95% CI 0.12-0.89).
Riethmueller et al.[19] (2001)	Randomized cross-over	Cystic fibrosis (*Pseudomonas aeruginosa*)	Tobramycin 10mg/kg/day	Tobramycin 10mg/kg/day (3 divided doses)	• No efficacy difference between groups (14 days of tx).
Smyth et al.[20] (2005)	Ranomized	Cystic fibrosis	Tobramycin 10mg/kg/day	Tobramycin 10mg/kg/day (3 divided doses)	• ODD as effective as MDD. Nephrotoxicity: Favored ODD (95% CI -15.7 to -0)
Vic et al.[21] (1998)	Ranomized	Cystic fibrosis	Tobramycin 15/mg/kg/day	Tobramycin 15mg/kd/day (3 divided doses)	• ODD: Significant improvements in FEV and FVC (P<0.05)
Whitehead et al.[22](2002)	Ranomized	Cystic fibrosis	Tobramycin 10mg/kg/day	Tobramycin 10mg/kg/day (3 divided doses)	• ODD: significant improvements in FVC (P=0.013) • Renal function: No change
Conil et al.[24] (2006)	Pharmacokinetic	Burn patients	Amikacin 20mg/kg/day	N/A	• Burns > 15% of the body: 15-20 mg/kg dose not sufficient to reach desired peak.

were excluded if more than 50% of patients had a lower UTI as AGs concentrate in the urine regardless of dosing regimen. Results demonstrated no significant difference in bacteriologic cure between dosing regimens (RR 1.02, 95% CI: 0.99-1.05). However, a nonsignificant reduction was observed in mortality (RR 0.91 95% CI: 0.63-1.31), nephrotoxicity, RR 0.87 (95% CI: 0.60-1.26) and ototoxicity, RR 0.67 (95% CI: 0.35-1.28) with ODD. Based on these relative risks, the authors concluded that ODD is at least as effective as MDD and has a trend toward reduced toxicity and mortality.

Overall, these meta-analyses demonstrate that ODD is at least as effective as traditional dosing and has significantly fewer cases of toxicity. This regimen provides a simplified dosing schedule, decreases the need for monitoring, and decreases drug exposure for patients.

ONCE-DAILY DOSING IN SPECIFIC POPULATIONS

ODD of AGs has been widely accepted as the preferred dosing regimen. The multiple benefits of ODD have lead to studies conducted on patient populations that have been historically excluded from ODD recommendations.

Several studies have found ODD effective in both pregnant and postpartum women for infections including postpartum endometriosis, choriamnionitis, and pelvic inflammatory disease.[15,16,17] Gentamicin 5 mg/kg once daily, based on actual body weight, was the most common dose in these studies (Table 2).

Contopoulos-Ioannidis, et al. performed a meta-analysis of 24 randomized, controlled trials between 1991 and 2003 including children and neonates.[18] No significant difference was observed with microbiological failures, but trends favored ODD with a risk ratio of 0.71 (95% CI 0.45 to 1.11, p=0.13). ODD was significantly superior with a risk ratio of 0.33 (95% CI 0.12-0.89, p=0.03) in nephrotoxicity outcomes. No significant difference in ototoxicity was observed (RR 1.06 (95% CI 0.51-2.19, p=0.92). The authors concluded that ODD has the potential for increased safety and efficacy compared to MDD when used for children and neonates.

ODD has also been evaluated in patients with cystic fibrosis (Table 2).[19-23] Four clinical trials have compared ODD to TID dosing and found it an effective alternative with decreased nephrotoxicity. Although cystic fibrosis remains an exclusion criteria for ODD, these trials suggest ODD may be an effective treatment option following further studies (Table 2).

Lam, et al. used pharmacokinetic modeling to determine an effective dose for tobramycin when given once daily for cystic fibrosis.[23] These authors concluded that female patients < 14 years old would require a dose of 7 mg/kg/day, with all other patients requiring a dose of 9 mg/kg/day. Although these doses may be effective, they are solely based on pharmacokinetic modeling and still require safety and efficacy evaluation.

Table 3. Exclusion criteria for ODD of AGs.

• Elderly (Age ³ 70)	• Dialysis
• Endocarditis	• CrCL < 20 ml/min
• Synergy (Gram(+) organisms)	• Cystic Fibrosis
• General surgery prophylaxis	• Ascites
• Liver disease	• Hearing impaired
• Burns	• Fluid retention

Conil, et al. studied once daily amikacin in burn patients.[24] Burns cause altered pharmacokinetics and changes in volume of distribution. ODD has generally been considered inappropriate for this patient population. The authors found patients with significant burns to > 15% of the body did not reach the desired peak concentration with the standard 15-20 mg/kg dose, which was attributed to altered pharmacokinetics and an increase in drug clearance in burn patients. Significant burns remains an exclusion criteria for ODD until further studies are performed (Table 3).

DETERMINING ONCE-DAILY DOSE

Step 1: Determine Dosing Weight (DW)

AGs are distributed into the extracellular fluids, have poor distribution into tissues, and have difficulty crossing cell membranes. Ideal body weight (IBW) is the preferred dosing weight. Actual body weight is used when less than the calculated IBW and in pregnant patients. Adjusted body weight (ABW) is used when total body weight is 30% greater than IBW.

IBW (males): 50 kg + (2.3 x height in inches > 60 in)

IBW (females): 45 kg + (2.3 x height in inches > 60 in)

ABW (obese) = IBW + 0.4 x (total body weight - IBW)

Step 2: Determine AG Dose

The AG dose is calculated by multiplying the appropriate body weight calculation (above) by specified mg/kg doses of AGs (Table 4).

Table 4. Once-daily dosing by weight.

DRUG	DOSE
Gentamicin*	5-7 mg/kg x DW
Tobramycin*	5-7 mg/kg x DW
Amikacin	15-20 mg/kg x DW

*IDSA recommends 7 mg/kg plus an additional antipseudomonal beta lactam when *Pseudomonas* is suspected.

Step 3: Determine Dosing Interval

The dosing interval is based on the patient's calculated creatinine clearance (CrCl) (Table 5). CrCl is tested at baseline, then weekly. ODD is recommended if CrCl ≥ 60 ml/min. The dosing interval is extended beyond 24 hours when CrCl < 60 ml/min.

MONITORING

ODD does not require peak concentration monitoring. Trough concentrations are checked 24 hours after administration or within one hour of the next infusion. The desired trough for gentamicin and tobramycin is < 1 mcg/ml and < 5 mcg/ml for amikacin. If trough is at desired level, no future monitoring is necessary.[29,30]

Nomograms are commonly used to monitor troughs and determine if an interval adjustment is necessary. A random trough level is drawn 6-16 hours after the infusion, and based on concentration results the interval can be expanded to every 36 hours or every 48 hours.

COST COMPARISON

ODD provides an economic benefit with reductions in the cost of drug, supply, preparation, administration, and monitoring. Hitt, et al. retrospectively analyzed the cost of once daily gentamicin and found a 58% decrease in cost of therapy including treatment of nephrotoxicity. With an average of 4.5 days of treatment, total blood samples drawn per patient was reduced from 1.7 to 0.65 with once daily dosing with a 62% reduction in monitoring costs. Nephrotoxicity costs were reduced from $182 to $55 per patient.[25]

SUMMARY

ODD of AGs provides an effective alternative to multiple daily dosing. ODD is at least as effective as traditional dosing, reduces toxicity, decreases monitoring, and results in an overall cost reduction. In the appropriate patient, ODD of AGs has become widely accepted as the preferred dosing regimen.

♦ ♦ ♦

REFERENCES

1. Gilbert DN. Aminoglycosides. In: Mandell GL, Bennett JE, Dolin R, eds. Douglas and Bennett's Principles and practice of infectious diseases. New York: Churchill Livingston, 1995:279-301.
2. Chambers HF, et al. The aminoglycosides. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill, 1996;1103-21.
3. Kahlmeter G, et al. Aminoglycoside toxicity – a review of clinical studies published between 1975 and 1982. J. Antimcrob. Chemother 1984;13 (Suppl. A):9-22.
4. Moore RD, et al. Risk factors for nephrotoxicity in patients treated with aminoglycosides. Ann Intern Med. 1984;100(3):352-7.
5. Tran BH, et al. Aminoglycoside ototoxicity: influence of dosage regimen on drug uptake and correlation between membrane binding and some clinical features. Acta Otolaryngol 1988;105:511-5.
6. Mattie H, et al. Determinants of efficacy and toxicity of aminoglycosides. J Antimicrob Chemother 1989;24:281-93.
7. McCormack JP, et al. A critical reevaluation of the "therapeutic range" of aminoglycosides. Clin Infect Dis 1992; 14:320-339.
8. Moore RD, et al. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155:93-99.

Table 5. Dosing intervals for aminoglycosides.

Drug	CrCl ³ 60 ml/min	CrCl 40-59 ml/min	CrCl 20-39 ml/min
Gentamicin	Dose every 24 hrs	Dose every 36 hrs	Dose every 48 hrs
Tobramycin	Dose every 24 hrs	Dose every 36 hrs	Dose every 48 hrs
Amikacin	Dose every 24 hrs	Dose every 36 hrs	Dose every 48 hrs

* Once daily dosing is not recommended if CrCl < 20 ml/min.

9. Vogelman B, et al. Kinetics of antimicrobial activity. J Pediatr 1986;108:835-40.
10. Craig WA, et al. Post-antibiotic effects in experimental infection models: relationship to in vitro phenomena and to treatment of infections in man. J Antimicrob Chemother 1993;31:149-58.
11. Barza M, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ 1996;312:338-45.
12. Ferriols-Lisart et.al. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. Am J Health-Syst Pharm 1996;53:1141-50.
13. Hatala R, et al. Once-daily aminoglycoside dosing in immunocopetent adults: a meta-analysis. Ann Intern Med 1996;124:717-25.
14. Galloe AM, et al. Aminoglycosides: single or multiple daily dosing? A meta-analysis on efficacy and safety. Eur J Clin Pharmacol 1995;48:39-43.
15. Del Priore G, et al. A comparison of once-daily and 8-hour gentamicin dosing in the treatment of postpartum endometritis. Obstet Gynecol 1996;87:994–1000.
16. Livingston J, et al. Gentamicin and clindamycin therapy in postpartum endometritis: the efficacy of daily dosing versus dosing every 8 hours. Am J Obstet Gynecol 2003;188:149–52.
17. Locksmith G, et al. High compared with standard gentamicin dosing for chorioamnionitis: a comparison of maternal and fetal serum drug levels. Obstet Gynecol 2005;105:473–79.
18. Contopoulos-Ioannidis DG, et al. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004;114(1):e111-8.
19. Rietmueller J, et al. Optimized intravenous antibiotic treatment with ceftazidime (thrice-daily vs. continuous) and tobramycin (thrice vs. once-daily) in CF patients [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; Vienna, Austria. 2001:P192.
20. Smyth A, et al. Once vs. three times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis – the TOPIC study: a randomized controlled trial. Lancet 2005;365(9459):573-8.
21. Vic P, et al. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. Archives of Disease in Childhood 1998;78(6):536-9.
22. Whitehead A, et al. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. European Respiratory Journal 2002;19(2):303-9.
23. Lam W, et al. Pharmacokinetic modeling of a once-daily dosing regimen for intravenous tobramycin in paediatric cystic fibrosis patients. J Antimicrob Chemother 2007;59(6):1135-40.
24. Conil JM, et al. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents 2006;28(3):226-30.
25. Hitt CM, et al. Pharmacoeconomic impact of once-daily aminoglycoside administration. Pharmacotherapy 1997;17:810-4.
26. Zhanel GG, et al. Pharmacokinetic contributions to postantibiotic effects. Focus on aminoglycosides. Clin Pharmacokinet 1994;27:377-92.
27. Nordstrom L, et al. Does administration of an aminoglycoside in a single-daily dose affect its efficacy and toxicity? J Antimicrob Chemother 1990;25:159-73.
28. Parker SE, et al. Practicalities of once-daily aminoglycoside dosing. J Antimicrob Chemother 1993;31:4-8.
29. Winston L, et al. Once-daily dosing of Aminoglycosides: How much monitoring is truly required? Am J Med 2003;114:239-40.
30. Nicolau DP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39(3):650-5.

Did you know?

PharmaNote® is also available electronically!

If you'd prefer to receive PharmaNote monthly via...

E-mail: Please send an email with your name and e-mail address to the *Assistant Editor* (ssmithm@ufl.edu) and we would be happy to add you to the distribution list. All e-mail addresses are kept confidential.

Web: PharmaNotes from 2002-present are available free of charge from the UF College of Pharmacy:

http://www.cop.ufl.edu/safezone/doty/pep/pharmanote/index.htm

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida