ARTICLE

The practice of once-daily aminoglycoside dosing in Canada: A national survey

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ABSTRACT

The impetus to adopt the use of once-daily aminoglycoside (ODA) therapy has been growing. Controversy however, regarding the exact role of ODA therapy continues to persist. A survey of Canadian hospitals was undertaken to identify perceptions and practice regarding ODA therapy. Information regarding hospital demographics and the institutional practice of dosing and monitoring traditional intermittent aminoglycoside and ODA therapy was obtained. Of 134 hospitals evaluated, 103 (77%) reported using ODA therapy. Primary applications of ODA therapy included urinary tract infection (84%), intra-abdominal infections (79%), pneumonia (78%), sepsis (75%) and bacteremia (69%). Contraindications for ODA therapy included pregnancy (82.7%), renal impairment (71%), dialysis (56%) and ascites (54%). Wide differences in the daily dosage and monitoring of ODA therapy were noted. Clinical judgement (48.9%) was often used to determine whether aminoglycoside serum concentrations were required for ODA therapy. Extension of the dosing interval was the most common (65%) method of adjusting ODA therapy. The use of ODA therapy in Canada appears widespread. Differences in the daily dosing, monitoring and indications for ODA therapy were noted suggesting that the optimal use of ODA therapy may require further refinement.

Key words: Aminoglycoside, survey.

RÉSUMÉ

L'engouement pour le traitement aux aminoglycosides à dos uniquotidienne (ADU) est de plus en plus grand. Cependant, la controverse entourant le rôle exact du traitement ADU persiste toujours. Un sondage a été mené auprès des hôpitaux canadiens pour connaître les habitudes de prescription et d'administration du traitement ADU. Ainsi, les renseignements sur les données démographiques de la population de patients des hôpitaux et sur les habitudes de chaque établissement en matière de posologie et de suivi du traitement intermittent classique au aminoglycosides et du traitement ADU on été recueillis. Des 134 hôpitaux sondés, 103 (77 %) ont dit recourir au traitement ADU. Le traitement ADU était principalement utilisé dans les cas d'infections des voies urinaires (84 %), d'infections intra-abdominales (79 %), de pneumonie (78 %), de septicémie (75 %) et de bactériémie (69 %). Les contre-indications au traitement ADU comprenaient la grossesse (83 %), l'insuffisance rénale (71 %), la dialyse (56 %) et l'ascite (54 %). D'importantes différences dans la posologie quotidienne et le suivi du traitement ADU ont été observées. L'opinion clinique était souvent utilisée (49 %) pour determiner si oui or non les concentrations sériques d'aminoglycosides étaient nécessaires au cours du traitement ADU. Le prolongement de l'intervalle posologique était la méthode d'ajustement du traitement ADU la plus souvent utilisée (65 %). Le recours au traitement ADU au Canada semble donc largement répandu. Les différences en termes de posologie quotidienne, de suivi et d'indication du traitement ADU ont été relevées et portent à croire que l'utilisation optimale du traitement ADU pourrait nécessiter d'autres mises au point.

Mots clés : aminoglycosides, sondage.

INTRODUCTION

The concept of once-daily aminoglycoside (ODA) therapy has attracted much attention over the past decade. Within the last few years, the impetus for hospitals to adopt ODA dosing has gained considerable momentum. Despite the increasing use of ODA, questions regarding dosing and monitoring remain.[1] Traditionally, in patients with normal renal function, aminoglycosides have been administered intravenously (IV) every 8 hours. The potential advantages of ODA versus traditional dosing, include ease of administration, similar efficacy, similar or less nephrotoxicity, less monitoring as well as cost savings.[2–6] These advantages have encouraged the apparent widespread application of ODA as standard therapy in Canada and the United States.

Several clinical trials to date have shown the efficacy of ODA and the incidence of nephrotoxicity to be similar to traditional intermittent administration.[2–9] These studies have not demonstrated a clear clinical benefit resulting from improved antibacterial efficacy as a consequence of ODA. Recent meta-analyses have also indicated efficacy and toxicity to be similar to traditional dosing.[10–17] However, differences in dosage regimen design, patient populations and definitions of toxicity make general extrapolations difficult. In addition, the application of ODA in certain infections (e.g. endocarditis) or patient populations (e.g. pregnancy, renal dysfunction or burn patients) have not been fully explored.[1, 4, 6, 18]

A recent survey (1993) of ODA use in 336 US hospitals found almost 20% used ODA.[19] Controversy regarding the

Table I — Number of respondents, by province

Province	No. of respondents
British Columbia	16
Alberta	13
Saskatchewan	5
Manitoba	9
Ontario	57
Quebec	14
New Brunswsick	4
Nova Scotia	11
Prince Edward Island	2
Newfoundland	3
Total	134

optimal dose, adjustment in renal impairment, role and timing of serum concentration monitoring were also reflected in this survey. This survey also found differences in the dosing and monitoring of ODA therapy. In Canada, there is a paucity of information describing the use of ODA. An informal survey in 1994 found 9 of 34 hospitals in Canada used ODA therapy.[20] Unfortunately, no further detail was available. We conducted a national survey in 1996 to describe the practice of ODA with gentamicin and tobramycin in Canada.

METHODS

A copy of the survey instrument used by the original investigators in the US was obtained with their permission.[19] The survey was modified and adapted to the Canadian health care system. The survey comprised 31 questions primarily set up as check boxes with a few short answer questions. Depending on the question, respondents were asked to check all applicable options. The survey focused on gentamicin and tobramycin.

A list of hospitals was obtained from the 1995 Canadian Directory of Accredited Health Care Facilities.[21] The directory lists the bed composition and medical and surgical services provided by all Canadian health care institutions. Hospitals with adult or pediatric acute care medical or surgical beds were identified based on the bed composition and services listed in the directory. Candidates were grouped into bed sizes; 100–199 beds, 200–499 beds and 500 beds or more. Emphasis was placed on collecting data from large urban centres in each province. Hospitals were defined as teaching versus nonteaching hospitals based on affiliation with a medical school.[19]

Table II — Affiliations and once-daily aminoglycoside (ODA) use, by hospital size (no. of beds)

	Response by size (and % among respondents)			
Variable	100–199	200–499	≥500	Overall
No. of hospitals	27 (20)	73 (55)	34 (25)	134 (100)
Average no. of beds	145 ± 27	328 ± 87	723 ± 239	391 ± 247
Medical school affiliation	4 (15)	27 (37)	30 (88)	61 (46)
Pharmacy school affiliation	9 (33)	35 (48)	31 91	75 (56)
Use ODA therapy	21 (78)	56 (77)	26 (77)	103 (77)
Frequency of ODA use				
Frequent	2 (10)	22 (39)	11 (42)	35 (34)
Moderate	9 (43)	12 (21)	6 (23)	25 (24)
Infrequent	10 (48)	22 (39)	9 (35)	41 (40)

Primary investigators contacted the subject hospitals by telephone to secure the participation of pharmacists familiar with the pattern of aminoglycoside use within their respective institutions. Participants were subsequently contacted by telephone and appointments for interviews were established. Copies of the survey were faxed to each participant prior to the interview. Each participant had a minimum of 35 days before the interview to complete the survey. Interviews were conducted between June 24, 1996 and August 15, 1996.

DATA ANALYSIS

Results were recorded and entered into a relational database (R:Base® 4.5++ for DOS). Data were verified prior to analysis. Frequencies and descriptive statistics were used to

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Table III — Empiric/treatment indications and contraindications for once-daily aminoglycoside (ODS) therapy. Indications are based on information from 100 respondents; contraindications are based on information from 98 respondents.

Indication	Respondents No.	%
Urinary tract infection	84	84
Intra-abdominal infection	79	79
Pneumonia	78	78
Sepsis	75	75
Bacteremia	69	69
Pelvic inflammatory disease	43	43
Febrile neutropenia	32	32
Cystic fibrosis	6	6
Skin soft tissue	4	4
Other	8	8
Contraindication		
Pregnancy	81	83
Renal impairment	70	71
Dialysis	58	56
Ascites	53	54
Febrile neutropenia	37	38
Endocarditis	31	32
Burns	29	30
Pediatrics	28	29
Cystic fibrosis	25	26
Prophylaxis	19	19
Breast feeding	18	18
Cirrhosis	12	12
Postpartum	11	11

characterize the use of once-daily aminoglycosides among the study participants.

RESULTS

Demographics

Of the 152 institutions contacted, 143 (92%) participated in the study. Of these, 134 of 143 (94%) were considered evaluable based on the bed size inclusion criteria. Nine institutions were excluded from analysis because their bed size was less than 100 beds. Data from hospital corporations or health authorities/board (i.e. hospitals under one administration) were treated as a single institution unless otherwise specified by the respondent(s). The distribution of participating hospitals among the 10 provinces is listed in Table 1.

Of the 134 institutions, 27 (20%) had bed sizes between 100–199, 73 (55%) had bed sizes between 200–499 and 34 (25%) had more than 500 beds (Table II). Among the participants, bed sizes ranged from 100–1460 (average 391±247 beds). Overall a total of 52,449 beds across Canada were represented. Based on affiliation with a medical school, 61 hospitals were categorized as teaching with the remaining 73 as nonteaching. With respect to aminoglycoside formulary status, 99% of the respondents included gentamicin, 87% included tobramycin, 52% included amikacin and 10% included netilmicin.

Once-daily aminoglycoside use

Of the 134 respondents, 103 (77%) indicated that ODA administration was used in their institutions. When compared to overall aminoglycoside use within each institution, 35 (34%) of 103 indicated ODA was used frequently (50–99% of the time), 27 (26%) hospitals used ODA moderately (25–49% of the time), with the remaining 41 (40%) institutions using ODA infrequently (0–24% of the time) (Table II).

The 5 most common empiric/treatment indications for ODA included urinary tract infections (UTI) (84%), intra abdominal infections (79%), pneumonias (78%), sepsis (75%) and bacteremia (69%) (Table III). The 4 most common contraindications for ODA administration included pregnancy (83%), renal impairment (71%), dialysis (56%) and ascites (54%) (Table III). Four (4%) respondents indicated they had no contraindications for ODA therapy. For nonurinary tract infections, 85 (83%) indicated they would always use ODA with a concomitant agent such as a betalactam. Only 33 of 101 (33%) hospitals used ODA for prophylaxis. Prophylactic use of ODA included urologic procedures (29, 88%) and colorectal procedures (20, 61%). Other reported prophylactic indications of ODA included orthopedic surgery (6%), endoscopy (5%), vascular surgery (2%), endocarditis prophylaxis (2%) and abdominal surgery (1%).

When the respondents were asked about the administration of ODA according to age, 101 (98%) respondents used ODA in patients between 18–65 years of age. Eleven (11%) hospitals used ODA in patients between 12–18 years old. Seventy-eight (76%) respondents used ODA in patients older than 65 years. Nine (9%) respondents indicated they would use ODA in pediatric patients (1–18 years of age) while 2 (2%) respondents used ODA in patients less than 1 year old.

Dosing with ODA was variable, with 41 (41%) respondents using a range of dosing and 59 (59%) used fixed mg/kg/day dosing initially. In institutions using a range of doses for ODA, the range of dosing was found to be extremely variable from as low as 1.5–2.0 mg/kg/day to 3–7 mg/kg/day. Fifty-seven (97%) of the 59 hospitals which used fixed mg/kg/day dosing, the average dose was 5.6±0.8 mg/kg/day. Two (3%) other institutions reported using a daily dose of 240 and 425 mg/day respectively.

With respect to initiation of ODA, 11 (11%) respondents indicated pharmacists were always involved, sometimes involved in 82 hospitals (82%) and never involved in 10 (10%). Of the 69 respondents with infectious diseases (id) consultants, 5 (7%) were always involved in initiating ODA therapy, sometimes in 45 (65%) and never in 19 (28%) hospitals.

Once-daily aminoglycoside monitoring practice

Overall, 86% of the respondents reported monitoring serum aminoglycoside concentrations. Twenty-five (28%) institutions reported monitoring both peak and trough aminoglycoside serum concentrations, 54 (61%) respondents monitored trough concentrations only, 6 (7%) monitored the peak only and 30 (34%) obtained a single serum concentration 4–18 hours post dose. Seven institutions obtained serum concentrations based on clinical judgement or individualized pharmacokinetic dosing. The frequency of monitoring aminoglycoside concentrations were varied and are summarized in Table IV. Clinical judgement was frequently (49%) used to determine whether aminoglycoside serum concentration was required compared to scheduled monitoring of aminoglycoside concentrations (Table IV). In terms of pharmacists actively monitoring ODA therapy, 57 (55%) institutions indicated always involved, 37 (36%) as sometimes involved and 9 (9%) hospitals indicated never involved.

Serum creatinine was routinely monitored in patients receiving ODA in 71 of 87 (82%) hospitals. The frequency of monitoring varied from daily to weekly (Table iv). Serum creatinine was monitored every 3 days in 51% of the respondents. In response to declining renal function or increasing aminoglycoside concentrations, clinicians would most commonly maintain the dose and extend the interval (65%), change to traditional intermittent dosing (32%) or follow a nomogram (32%) (Table v).

ODA support and rationale

The respondents indicated that the most common reason ODA was initiated or promoted over traditional intermittent dosing was the perception of equal effectiveness (87%) and less toxicity (86%). Other reasons included cost savings of ODA compared to traditional dosing (61%), ODA perceived to be innovative or a progressive method of administration (48%), convenience (10%) and physician awareness (5%). With respect to cost savings, only 13 respondents provided estimated cost savings for ODA ranging from $600–$60,000 (Cdn.) per year (median $5,000). Exclusion of the $60,000 estimate reduces the median to $3,700 (range $600–$10,000) in terms of cost savings per year. The 13 respondents indicated these savings were based on reduction in laboratory and drug monitoring (78%), pharmacy and nursing time (44%), supply or admixture costs (22%) and drug/wastage (22%).

DISCUSSION

Within the last 5 years, many hospitals have implemented ODA therapy over traditional intermittent aminoglycoside dosing. This move has been supported by several clinical trials and many review articles. The attractive features of ODA therapy are similar efficacy and similar or lower toxicity, decreased costs associated with decreased monitoring and preparation and finally the potential for outpatient treatment. Although concerns with ODA therapy continue to exist, the move to ODA appears to be rapid. Our study found 76% of hospitals surveyed in Canada use ODA therapy. This figure is considerably higher than the 20% reported by Schumock and colleagues and the 27% previously reported in Canada[19, 20] This is not unexpected since the original US survey was conducted in September of 1993, almost 3 years before our study.

The high percentage of hospitals in Canada using ODA therapy at the time our study is perhaps misleading; only 35% of the 95 hospitals indicated that ODA was used frequently (i.e. less than 50% of overall aminoglycoside use within their institutions). The remaining institutions appear to use ODA far less frequently. This was probably reflective of the practice of ODA in Canada at the time of our study. With respect to initiation of ODA therapy, our respondents indicated pharmacists were always or sometimes involved in initiating ODA 91% of the time

Table IV — Frequency of aminoglycoside serum concentration and serum creatinine measurements for once-daily aminoglycoside (ODA) therapy. Responses relating to serum aminoglycoside levels are based on answers from 88 respondents; responses relating to serum creatinine levels are based on answers from 95 respondents, who may have chosen more than one answer.

Frequency	Respondents No.	%
Serum aminoglycoside		
Every 3 days	19	22
Weekly	12	14
Not routinely	14	16
Clinical judgement	43	49
Serum creatinine		
Every day	8	8
Every 2 days (e.g. 3 times/wk)	17	18
Every 3 days (e.g. q2–4h)	48	51
Weekly	3	3
Not routinely	4	4
Prior to ODA therapy	2	2
Clinical judgement	21	22

Table v — Method of once-daily aminoglycoside dose adjustment in patients with renal impairment or high serum aminoglycoside concentration, based on responses from 101 respondents who may have chosen more than one answer.

Response	Respondents No.	%
Maintain dose, extend interval	66	65
Change to traditional dosing	32	32
Use dosing nomogram	26	26
Lower dose, maintain interval	13	13
Switch to alternative drug	6	7
Clinical judgement	6	6
Not adjusted	2	2

followed by id consultants who initiated ODA 64% of the time.

Our response rate of 92% provides a good cross-section of hospitals in Canada. This response rate is higher than previously reported by Schumock and colleagues (68%) as a result of directly contacting the institutions and obtaining their responses.[19] Our survey documented the indications (uti, intra abdominal infections, pneumonia, sepsis and bacteremia) and contraindications (pregnancy, renal impairment, dialysis and ascites) for ODA use by respondents in Canada. For the most part the indications and contraindications were similar to those found in the US survey. Some institutions reported using ODA administration for surgical antibiotic prophylaxis. We are not aware of literature support for the prophylactic use of ODA. Many institutions indicated that ODA therapy would not be used in patients with renal dysfunction. This is not surprising since the vast majority of clinical trials have focused on patients with normal renal function. To date little has been published in the literature to guide clinicians on adjusting ODA dose in patients with renal impairment. Of interest, 4 respondents indicated their institutions had no contraindications for ODA therapy.

The dosage for ODA therapy was found to be variable among the respondents. We were surprised to find that roughly half of respondents used a range of ODA dosing (e.g. 3–7 mg/kg/day) while the remaining respondents used fixed daily dosages. This was unexpected because the vast majority of the literature used a fixed mg/kg/day initial dosage.[2, 4–9] This diversity of practice suggests confusion with regard to the optimal dose of an aminoglycoside for ODA. The timing and frequency of aminoglycoside serum concentrations for monitoring also appeared to be highly variable. Sixty-one percent of institutions monitor a trough serum aminoglycoside concentration while another 34% obtain a random level sometime after the ODA dose. Of interest is the finding that 14% of the respondents do not conduct or require serum concentration monitoring for ODA therapy. It is possible that the decision not to obtain serum concentrations may be based on clinical judgement; however, this was not indicated in their response. Although controversial, serum concentration monitoring may be necessary in patients with aminoglycoside concentrations well below the anticipated duration of the PAE.[1, 6, 22, 23]

Although there appears to be consensus on the efficacy of ODA therapy, our results suggest that the implementation of ODA is not consistent. Several different methods of implementing ODA therapy have been reported ranging from a fixed dose (mg/kg/day) to the use of area under the concentration curve or a targeted approach.[9, 24–27] Comparison of the ODA program in Portland, Oregon versus the program in Hartford, Connecticut reveals differences with respect to the initial mg/kg dose, timing of serum aminoglycoside concentrations, pharmacokinetic monitoring and dose individualization.[9, 25]

There are limitations to our survey. We attempted to obtain data from pharmacists familiar with the prescribing of aminoglycosides within their institutions. As with any type of survey study, the information provided may be subjective and could not be validated by our researchers. It is possible that some of our respondents may not have been familiar with the terminology and current application of ODA therapy. Two respondents indicated that ODA therapy was used in neonates. However, the rationale of daily aminoglycoside administration in this population is due to renal immaturity rather than the adoption of ODA therapy as discussed in the literature.[28, 29] In addition, the survey focused initially on hospitals in urban centres and hospitals with 100 or more beds. As a result, our survey results cannot be extrapolated to smaller or rural hospitals in Canada.

In addition, because the survey was conducted, many more hospitals probably have adopted ODA therapy. However, questions and the absence of literature to guide the use of ODA have continued since our survey was conducted. Rodvold and colleagues have recently commented that the use of a given ODA dose in one institutional may not be applicable to another institution.[18] Additionally, the accuracy of the one nomogram has also been questioned.[30] Thus, questions pertaining to monitoring, dosing in patients with renal impairment, indications or certain patient populations have continued. Although we believe ODA is an innovative and useful tool, we believe the issues identified in our survey have continued to exist to present day.

Few pharmacoeconomic studies have been published documenting cost minimization or the savings from decreased monitoring, decreased admixture and administration time.[3, 6, 31] Only 12.6% of respondents were able to provide estimated cost savings data, which ranged from $600–$60,000 per year. The reduction in laboratory and serum concentration monitoring was the most significant component of their estimated savings. The larger figure was attributed to a reduction in service payment to a contracted intravenous admixing service as a result of implementing ODA therapy. Recent studies suggest that the cost of ODA therapy per treatment course is 40–50% less than traditional intermittent aminoglycoside administration.[32, 33] Cost reductions have been attributed to decreased preparation and administration costs (pharmacy and nursing time) as well as decreased monitoring. The potential for cost reduction would vary depending on the infrastructure (drug delivery systems, preparation, etc.) within a given institution. Future well designed pharmacoeconomic studies would be desirable to address the economic benefit of ODA therapy.

It has been suggested that the change from traditional aminoglycoside therapy to ODA has been slow.[34] We feel however, that based on the available data, the use of ODA in Canada is increasing. Considering the vast geographical distances in Canada, smaller institutions may benefit from

the use of ODA with respect to less serum concentration monitoring and ease of administration. The advantages of ODA therapy appears promising. However, differences in the daily dosing, monitoring and indications for ODA therapy noted in our survey suggests that the optimal use of ODA therapy may require further refinement.

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