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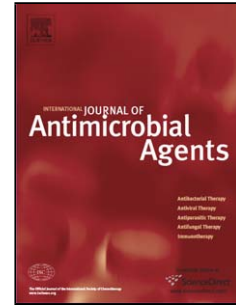


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Intravesical gentamicin for recurrent urinary tract infection in patients with intermittent bladder catheterisation

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ABSTRACT

Clean intermittent catheterisation (CIC) of the bladder is used to imitate normal bladder emptying in patients with bladder dysfunction. CIC is associated with urinary tract infection (UTI) that may be difficult to treat in the case of antimicrobial resistance. The aim of this study was to establish the effect and safety of intravesical gentamicin treatment in such settings. In 2009, intravesical gentamicin treatment was started in selected patients. Here we describe our experience with two patients treated until March 2010. Two patients using CIC suffering recurrent UTI with multiresistant *Escherichia coli* were treated with daily administration of 80 mg intravesical gentamicin. On treatment they appeared asymptomatic. During 8- and 9-month follow-up they were free of UTI, urine cultures were negative and there were no side effects. A systematic review was conducted through searches of PubMed and other databases. Clinical trials that met the eligibility criteria and displayed the efficacy or safety of intravesical aminoglycoside treatment in patients using CIC were studied. Study selection was performed by two independent reviewers. Eight studies were included for review. Owing to study heterogeneity, a meta-analysis could not be performed. Of four controlled studies using neomycin or kanamycin, two demonstrated a significant reduction in bacteriuria, whilst two other trials did not. One case series on neomycin/polymyxin showed that the majority of patients still developed bacteriuria. Three case series using gentamicin all pointed towards a significant reduction in bacteriuria and UTIs. There were no clinically relevant side effects reported but follow-up in all studies was limited. Although data are limited, intravesical treatment with gentamicin might be a reasonable treatment option in selected patients practicing CIC who suffer recurrent UTIs with highly resistant microorganisms.

1. Introduction

Clean intermittent catheterisation (CIC) of the bladder was introduced by Lapides in 1971 to manage children with neurogenic bladder dysfunction [1]. To date, this technique has become an important tool for the management of patients with bladder dysfunction. CIC will ideally be performed every 4–6 h, with the aim of mimicking normal emptying of the bladder and thus preventing overflow incontinence and dilatation of the upper urinary tract with potential loss of renal function. For patients requiring long-term or chronic catheterisation, CIC is considered the preferable method of urinary catheterisation since it is associated with less complications, in particular urinary tract infections (UTIs), compared with chronic indwelling bladder catheterisation [2]. However, even with CIC, colonisation of the bladder frequently develops as has been shown by the presence of significant bacteriuria in 61% of urine samples from patients practicing CIC [3]. Asymptomatic bacteriuria itself does not require antimicrobial treatment, but once symptoms occur it is considered to represent UTI, which is the major complication of CIC [4,5]. Not surprisingly, recurrent UTI frequently occurs, requiring antimicrobial treatment that, in addition to the use of prophylactic antibiotics to prevent new episodes, supports the emergence of resistant organisms and further limits antimicrobial treatment options. In this respect, administration of intravesical gentamicin following CIC has the advantage of treating the site of infection with high local antibiotic concentrations [6].

Here we report two patients practicing CIC suffering recurrent UTI due to multiresistant *Escherichia coli*. When other treatments had failed, these patients were eventually successfully treated with intravesical instillation of gentamicin. In addition, a systematic review was performed to evaluate the effectiveness and potential

complications of this unusual regimen to suppress recurrent UTI in patients undergoing intermittent catheterisation.

2. Methods

2.1. Search strategy

A comprehensive literature search was performed to identify all clinical trials reporting intravesical UTI treatment with aminoglycosides in patients using intermittent catheterisation and assessing the efficacy or safety of this intervention. The search was performed on 3 March 2010. In co-operation with a trained librarian, the following databases were searched: PubMed (1949 to February 2010); EMBASE (OVID version, 1980 to March 2010); Web of Science (1945 to March 2010); Cochrane Library (1990 to March 2010); CINAHL (EBSCOhost version, 1982 to January 2010); Academic Search Premier (EBSCOhost version, 1865 to March 2010); and ScienceDirect (1823 to March 2010). The search strategy consisted of the AND combination of three main subjects, 'aminoglycosides', 'intravesical administration' and 'intermittent catheterization'. For these three subjects, all relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases but also the free-text word variations of these concepts. In general, the search consisted of the combination of the following terms: aminoglycosides, gentamicin, neomycin, kanamycin, butirosin sulfate, sisomicin, hygromycin, amikacin, dibekacin, nebramycin, metrizamide, framycetin, paromomycin, ribostamycin, puromycin, spectinomycin, streptomycin, dihydrostreptomycin sulfate, streptothricins, streptozocin, netilmicin, tobramycin, AND intravesical administration, instillation, irrigation AND intermittent catheterization or

urinary catheterization. This search strategy was optimised for all consulted databases, taking into account the differences in the various controlled vocabularies as well as differences in database-specific technical variations (e.g. the use of quotation marks).

2.2. Study selection

Two reviewers (PLdE and CvN) independently determined study eligibility on the basis of the published abstracts; if eligible or indeterminate, the full article was retrieved for further review. Studies were excluded if they were reviews, editorials, guidelines, non-human studies or written in non-English language. All retrieved articles were discussed by the two reviewers and based on their consensus final selection for inclusion in the systematic review was made.

2.3. Data extraction

The following data were extracted from each study: (i) year of publication; (ii) study design; (iii) patient population; (iv) details of intervention; (v) number of participants; (vi) detection of aminoglycoside serum levels; and (vii) clinical and microbiological outcomes. The two reviewers independently extracted the data and discussed the final outcome.

The quality of each individual study was determined using the level of evidence classification of the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net>).

2.4. Statistical and microbiological methods

Although the aim was to perform a meta-analysis, the interventions evaluated in the selected studies were too heterogeneous, thus this was not feasible.

Interobserver agreement between the two reviewers with regard to study selection was assessed using the Cohen κ test, in which a κ value of 0.41–0.60 corresponds to fair agreement, 0.61–0.80 to good agreement, 0.81–0.92 to very good agreement and 0.93–1.00 to excellent agreement [7].

Urine cultures were performed using standard microbiological methods, and resistance to antimicrobials was defined using European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [8].

3. Results

In 2009, intravesical treatment with gentamicin was started in selected patients practicing CIC who developed recurrent UTIs with a gentamicin-susceptible uropathogen but who otherwise had very limited treatment options. Here we describe our experience with two patients treated until March 2010.

3.1. Case 1

An otherwise healthy 68-year-old male had a history of neurogenic bladder of unknown aetiology requiring CIC for almost 10 years. Urodynamic evaluation demonstrated a neurogenic acontractile detrusor function as defined by the International Continence Society [9]. Over the years he frequently suffered from UTIs,

with predominant complains of dysuria and lower abdominal pain. Urinary cultures almost constantly grew *E. coli*. He was usually treated with oral courses of nitrofurantoin, ciprofloxacin and trimethoprim/sulfamethoxazole (SXT). However, in the past few years the frequency of UTI increased to once every month.

To evaluate the therapeutic options for these recurrent UTIs, he was referred to the infectious diseases outpatient department of Leiden University Medical Center (Leiden, The Netherlands). At that time, urine and semen cultures simultaneously grew a multiresistant *E. coli* [extended-spectrum β -lactamase (ESBL)-negative, resistant to ampicillin, cefuroxime, ciprofloxacin, nitrofurantoin, SXT and tetracycline, and sensitive to ceftriaxone, gentamicin and fosfomycin] and *Enterococcus faecalis*. Computed tomography (CT) and ultrasonography of the urinary tract were normal. By exclusion, chronic bacterial prostatitis was diagnosed. Because he clinically responded well to self-treatment with SXT (960 mg twice a day), it was decided to continue this for 6 weeks as the urine culture turned negative; repeated semen culture still grew *E. faecalis* in the absence of bacteriuria. However, 2 weeks after a new episode of UTI developed with the same *E. coli* strain. For the next few months he was treated with prostatic massage combined with ceftriaxone, but this strategy appeared to be unsuccessful both clinically and microbiologically.

In an attempt to suppress the recurrent UTIs, it was decided to start treatment with intravesical gentamicin after sterilisation of the urine with fosfomycin (one dose of 3 g). Informed consent was obtained. A solution of 80 mg gentamicin in 20 mL of normal saline was instilled once daily after catheterisation. The solution was left overnight in the bladder until the next catheterisation. Thus, high-dose gentamicin

was locally in the bladder for ca. 8 h per day. This treatment was well tolerated. During 9 months of follow-up he has been free of UTI while he continued the daily intravesical gentamicin treatment. Urine cultures performed every 3 months and one semen culture performed after 3 months were all sterile. Repetitive urinalysis ruled out leukocyturia. Serum levels of gentamicin remained undetectable (<0.3 mg/L) and renal function was stable. The urine gentamicin trough level measured just before the next catheterisation was 0.6 mg/L. Cystoscopic evaluation after 9 months of gentamicin bladder instillation revealed a normal uroepithelium bladder.

3.2. Case 2

A 70-year-old female visited the outpatient clinic because of recurrent UTIs. Her medical history revealed type 2 diabetes mellitus, diabetic neuropathy and osteoarthritis leading to wheelchair-limited mobility. She had suffered from recurrent UTIs for more than 20 years, occasionally complicated by pyelonephritis. She was allergic to nitrofurantoin.

Ultrasonography revealed a post-void residual volume of 500 mL. Urodynamic evaluation demonstrated a neurogenic acontractile detrusor function that was ascribed to diabetic neuropathy [9]. She started to perform CIC four to six times daily. During the next year she had frequent episodes of symptomatic UTI. Finally, she required antibiotic UTI treatment (fosfomicin) every month to suppress symptoms of dysuria and lower abdominal pain. Repetitive urine cultures revealed that her bladder was invaded with a multiresistant *E. coli* (ESBL-positive, resistant to β -lactams, ciprofloxacin and SXT, and sensitive to nitrofurantoin, fosfomicin and gentamicin). Because treatment options were limited, twice-daily gentamicin (80 mg in 20 mL of

normal saline) intravesically was then started after sterilising the urine with one dose of fosfomicin (3 g) and obtainment of informed consent. Intravesical gentamicin was left in the bladder until the next catheterisation; thus, high-dose gentamicin was locally in the bladder twice daily for ca. 4–6 h. During 8 months of follow-up she was free of UTI while she continued the intravesical gentamicin treatment. Urine cultures performed every 2 months were all sterile. Repetitive urinalysis ruled out leukocyturia. Serum levels of gentamicin were undetectable and renal function was stable. The urine gentamicin level measured in a morning urine sample after the last gentamicin had been instilled the evening before was >100 mg/L. On one occasion she temporarily stopped instilling the gentamicin solution owing to motor disabilities. Within 2 weeks she developed a symptomatic UTI that was successfully empirically treated with fosfomicin by her primary care physicians; a urine culture was not done. After 8 months of treatment she fractured her forearm and thus was not able to perform CIC. A chronic indwelling bladder catheter was placed and the intravesical gentamicin treatment was stopped. Soon after the bladder became colonised with another non-resistant *E. coli* strain (ESBL-negative and sensitive to β -lactams, ciprofloxacin, SXT, nitrofurantoin, fosfomicin and gentamicin).

3.3. Study selection

The search strategy revealed 117 references. Of these, ten articles were selected for further review by one reviewer and nine by the other reviewer. Interobserver agreement between the reviewers was excellent, with a κ value of 0.94 ($P < 0.001$). After reviewing and discussing the ten articles, two articles were excluded: one article appeared to be a review that reported no original data [10] and the other article did

not primarily assess the efficacy or safety of aminoglycoside bladder instillations [11]. Details of the literature search and study selection are outlined in Fig. 1.

3.4. Study characteristics

Characteristics of the included studies are presented in Table 1. Overall, the level of evidence of all studies was limited. Five studies included hospitalised adult patients with newly diagnosed neurogenic bladder dysfunction requiring intermittent catheterisation in order to evaluate the prophylactic value of antibiotic bladder instillations in preventing bacteriuria [12–15,17]. The primary outcome assessed in these studies was the presence of significant bacteriuria. Either neomycin or kanamycin were the aminoglycosides of interest.

Two studies included children with neurogenic bladder and gentamicin bladder instillations [6,18]. Both were case series that indicated a reduction of bacteriuria and UTI with intravesical gentamicin.

Finally, one study described case reports involving outpatient adult females with recurrent UTI [16]. All four patients were diagnosed with haemorrhagic cystitis and had a residual volume on urodynamic evaluation. CIC was started with gentamicin bladder instillations. There were no UTIs reported on treatment.

3.5. Efficacy of intravesical aminoglycoside

Because of the heterogeneous nature of the included studies and the lack of a comparative arm in most studies, performing a meta-analysis or data pooling was

inappropriate. Therefore, the main outcomes of the individual trials are summarised in Table 1.

In two trials with a control group, including a randomised controlled trial (RCT), aminoglycoside instillation of the bladder significantly reduced the incidence of bacteriuria [14,15]. Another RCT and a retrospective case–control study could not demonstrate any difference in outcome [12,17].

In a prospective case series, all 10 children had sterile urine after 1 week of treatment, whereas *E. coli* was yielded in three of the urine cultures at baseline [6]. Breakthrough UTI occurred in 26% of the children examined by Defoor et al. [18]. All those were on low-dose gentamicin (14.4 mg once daily), suggesting that a higher dosage of gentamicin is required to prevent UTI [18].

3.6. Safety of intravesical aminoglycoside

Reports upon safety were scarce and poor. None of trials that investigated neomycin instillation presented details on drug toxicity or adverse effects. Pearman [14] stated that haematuria or other clinical evidence of chemical cystitis did not occur in any of the patients who received kanamycin/colistin instillations. None of the children investigated had detectable gentamicin serum levels [6,18]. Small increases in serum creatinine levels were observed in 3 of 80 children evaluated by Defoor et al. [18], but this was ascribed to underlying renal disease; no side effects, allergic reactions or clinical toxicities were documented.

4. Discussion

In this study, we demonstrated that intravesical gentamicin treatment was successful and safe in two patients practicing CIC who suffered from recurrent UTI. In one case it even suppressed chronic bacterial prostatitis. In addition, the systematic review summarises the available literature on the effectiveness and safety of intravesical aminoglycoside administration in patients practicing CIC.

The concept of intravesical drug delivery lies in the uroepithelium, a transitional epithelium lining the inner surface of the bladder. This layer is known to exhibit a tough barrier function that allows the instillation of potentially toxic drugs to achieve a localised pharmacological effect whilst avoiding systemic effects [19]. Diffusion of aminoglycosides across the uroepithelium is even more limited because of their polar cationic nature. Thus, by administering aminoglycosides intravesically, high antimicrobial concentrations can be achieved with minimal concern of adverse effects such as nephrotoxicity or ototoxicity. Furthermore, it may thus prevent the development of antimicrobial resistance. Because in our patients the bladder was infected with a multiresistant *E. coli*, we opted to treat them intravesically with relatively high dosages of gentamicin to prevent further emergence of resistance. Compared with previous studies, the dosage (80 mg) used was considerably higher [6,16,18]. This may have been overtreatment, but based on the literature review we can conclude that the optimal dosage remains unclear. However, even with the high dose used, no systemic absorption of gentamicin was observed as serum levels were repeatedly undetectable. This supports the hypothesis that systemic side effects are not to be expected.

Neomycin was the first aminoglycoside to be administered directly into the bladder, initially to prevent bacteriuria in hospitalised patients with indwelling devices by means of continuous or intermittent irrigation [10]. However, this has not been advocated since Warren et al. [20] could not show any benefit in patients with indwelling catheters.

The review has some limitations that are predominantly related to the quantity, quality, design and heterogeneity of the original literature on this topic. In general, the few included studies had methodological flaws, the studies were heterogeneous and the sample sizes were small. Consequently, the evidence summarised in this review is not sufficient to draw definite conclusions on the effectiveness and safety of aminoglycoside instillations. As a tool to prevent bacteriuria in hospitalised patients, some benefit has been suggested but the results are not consistent [12,14,15]. Furthermore, most studies included in this review did not differentiate between symptomatic and asymptomatic bacteriuria. The clinical relevance of intravesical aminoglycoside treatment therefore remains unclear in most of the studies. An exception might be the intravesical installation of gentamicin, as the three studies all point towards a significant reduction of bacteriuria and UTI in selected patients with recurrent UTI [6,16,18]. Combined with our own experience in two patients, we therefore consider intravesical gentamicin to be a reasonable treatment option in selected patients. This may contradict a recently published international guideline on the management of catheter-associated UTI [21] that recommends not using catheter irrigation with antimicrobials. However, this recommendation is predominantly based on studies in patients with a chronic indwelling urinary catheter in which intravesical installation of antimicrobials is more like a rinsing of the drainage bag and catheter

rather than active treatment of bladder infection. In contrast, in our experience high-dose gentamicin remained in the bladder for over 8 h per day when left following intermittent catheterisation; 80 mg gentamicin in 20 mL of normal saline (=4000 mg/L) was left in the bladder and, assuming a volume of 500 mL will be catheterised at the next catheterisation, the urine gentamicin level will still be 160 mg/L as was confirmed by Case 2. Therefore, we consider the potential development of antimicrobial resistance to be unlikely.

Regarding the safety of intravesical gentamicin, in 90 children reported in the literature there was no systemic absorption [6,18]. Previously, negligible absorption of neomycin during post-operative irrigation through indwelling devices was reported [22]. However, caution is still warranted as two reports have noted neomycin ototoxicity following bladder irrigation through indwelling catheters [23,24]. Nevertheless, it should be emphasised that serum neomycin levels were not monitored whilst all these patients had end-stage renal disease. Moreover, there are no data on long-term follow-up of patients treated with intravesical aminoglycosides and one study suggested that it may disrupt the uroepithelium [25]. The duration of intravesical gentamicin treatment should therefore be determined based on an individual risk–benefit assessment.

In summary, we conclude that intravesical treatment with gentamicin appears to be safe and effective in treating and suppressing UTI in patients practicing CIC. In selected patients with very limited treatment options for UTI, such intravesical gentamicin treatment might therefore be considered as a reasonable alternative to improve patients' quality of life. Potential side effects should be closely monitored as

long-term data are lacking. Although the overall evidence remains limited, these data suggest that further studies on intravesical gentamicin treatment should be performed in patients using CIC who suffer UTIs with highly resistant microorganisms.

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Competing interests

None declared.

Ethical approval

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Fig. 1. Flow diagram of articles searched, excluded, reviewed and included in the systematic review on intravesical treatment with aminoglycosides in patients practicing clean intermittent catheterisation of the bladder.

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Table 1

Characteristics of studies on intravesical treatment with aminoglycosides in patients using clean intermittent catheterisation (CIC) of the bladder

Study	Design	Population	Intervention (No. of patients)	Follow-up	Serum levels	Outcomes on effectiveness	Level of evidence ^a
Haldorson et al., 1978 [12]	Retrospective case-control study	108 adults with acute neurogenic bladder disease, hospitalised for bladder re-training	Instillation of 0.1% neomycin solution after each catheterisation ($n = 53$) vs. no treatment ($n = 55$)	Until normal bladder function was achieved: mean 6 weeks; median 4 weeks; range 1–19 weeks	NR	No significant difference in incidence of bacteriuria per patient in the neomycin group (28/53) vs. control group (27/55)	4

Rhame and Perkash, 1979 [13]	Retrospective case series	70 hospitalised male adults with SCI and neurogenic bladder	Instillation of neomycin/polymyxin solution after each catheterisation	Mean 72 days; median NR; range NR	NR	38 patients (54%) developed at least one episode of bacteriuria	4
Pearman, 1979 [14]	Retrospective case-control study	47 hospitalised adults with SCI and neurogenic bladder	Instillation of 150 mg kanamycin plus 30 mg colistin after each catheterisation ($n =$ 22) vs. no treatment ($n = 25$)	Until normal bladder function was achieved: mean, NR; median NR; range 9–180 days	NR	Incidence of bacteriuria per catheterisation in the kanamycin group was one-half the incidence in the control group: 11 patients in the kanamycin group developed at least one episode of bacteriuria vs. 23 patients in the control group	4

Anderson, 1980 [15]	RCT	33 hospitalised male adults with SCI and neurogenic bladder performing sterile intermittent catheterisation every 4 h or 8 h	Instillation of 4.8 mg neomycin and 24 000 U polymyxin B after each catheterisation, thus three or six times daily ($n = 17$) vs. no treatment ($n = 16$)	Until discharge or until normal bladder function was achieved: mean NR; median NR; range NR	NR	For patients catheterising six times daily, neomycin instillations significantly reduced the rate of bacteriuria per catheterisation day compared with controls (10/510 vs. 27/568, respectively; $P < 0.05$). The reduction in the rate of bacteriuria was not significant for patients catheterising three times daily	2b
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McGuire and Savastano, 1987 [16]	Case reports	4 outpatient female adults with recurrent and intractable UTI	Instillation of 4.8–7.2 mg gentamicin after every catheterisation (maximum daily dose 28.8 mg)	Mean 46 weeks; median 42 weeks; range 12–88 weeks	NR	Urine cultures were sterile in all patients provided that they were on treatment	4
Pearman et al., 1988 [17]	RCT	15 hospitalised male adults with SCI and neurogenic bladder	Instillation of 150 mg kanamycin plus 30 mg colistin after each catheterisation ($n = 7$) vs. instillation of 25 mL of Trisdine ^b after each catheterisation ($n = 8$)	Until normal bladder function was achieved: mean NR; median NR; range 7–143 days	NR	5 of the 7 males on kanamycin instillation developed at least one episode of bacteriuria at a rate of 0.0053 per catheterisation. There was no significant difference in the mean incidence of bacteriuria between the two groups	2b

Wan et al., 1994 [6]	Prospective case series	10 children with neurogenic bladder who performed CIC	Daily instillation of 28.8–57.6 mg gentamicin	1 week: mean NR; median NR; range NR	ND	After 1 week of treatment, all patients had sterile urine	4
Defoor et al., 2006 [18]	Retrospective case series	80 children, of whom 69 performed CIC and 11 had indwelling or suprapubic catheters	Instillation of 14.4 mg gentamicin once (prophylactic) or twice (therapeutic) daily	Mean NR; median 90 days; range 3– 1095 days	ND	21 patients (26%) had at least one breakthrough infection, all of whom were on the prophylactic dose	4

NR, not reported; SCI, spinal cord injury; RCT, randomised controlled trial; ND, not detectable.

^a The level of evidence is classified according to the Oxford Centre for Evidence-Based Medicine.

^b A solution of chlorhexidine gluconate 0.01% added with ethylene diamine tetra-acetic acid disodium salt and Tris buffer.

