Pharmacist Performance of the DIE Test to Assess Aminoglycoside Vestibulotoxicity

Denise Carr, Karen Shalansky, Fawziah Marra, and Art Mallinson

ABSTRACT

Background: Aminoglycoside antibiotics can cause irreversible vestibulotoxicity, leading to debilitating effects on balance and vision. The dynamic illegible E (DIE) test was developed at the authors' institution to screen for signs of vestibulotoxicity and hence to prevent permanent vestibular damage; the test is currently conducted by a neurophysiologist.

Objective: The primary goal of this study was to determine whether a pharmacist can perform the DIE test for vestibulotoxicity with accuracy equivalent to that of the neurophysiologist. The secondary goals were to determine the workload associated with conducting the DIE test and to correlate patient characteristics with occurrence of vestibulotoxicity.

Methods: All patients starting aminoglycoside therapy over a 12-week period were screened. All patients older than 18 years of age and receiving a prescription for aminoglycoside therapy for more than 7 days were evaluated for suitability to undergo a DIE test. Patients were excluded if they were unable to sit up for the test, were unable to read at least the top 4 rows of the test chart (because of either visual impairment or mental incompetence), had a language barrier without a translator available, or had a medical contraindication to neck manipulation. Eligible patients were tested first by 1 of 2 pharmacists and were then retested, within 72 h, by the neurophysiologist.

Results: A total of 213 patients were screened, of whom 38 were to receive aminoglycosides for more than 7 days. Fifteen of these patients were excluded because of a medical condition or discharge from the hospital before testing, and the remaining 23 were tested by a pharmacist. The neurophysiologist was unable to retest 7 of these patients, and 1 patient was tested twice; therefore, 16 patients and 17 DIE test results were included in the final analysis. The correlation between the results of the pharmacist and those of the neurophysiologist was 100%. There were no positive test results (score of 3 or more); therefore, no patients with vestibulotoxicity were identified. No aminoglycoside concentrations were considered supratherapeutic, and there were no changes in baseline patient characteristics such as serum creatinine or urea (as blood urea nitrogen). The DIE test took less than 3 min per patient. On average, only 2 or 3 patients would require this test each week, and hence the increase in pharmacist workload would be minimal.

RéSUMÉ

Historique : Les aminosides peuvent causer une vestibulotoxicité permanente, qui entraîne des effets débilitants sur l'équilibre et la vision. Le test du « E illisible dynamique » (EID) a été mis au point par l'établissement auquel sont associés les auteurs, pour dépister les signes de vestibulotoxicité et ainsi prévenir toute atteinte permanente du vestibule; ce test est actuellement administré par un neurophysiologiste.

Objectif : Le principal objectif de cette étude était de déterminer si un pharmacien pouvait administrer le test EID et obtenir des résultats aussi précis que ceux du neurophysiologiste. Les objectifs secondaires étaient de déterminer la charge de travail associée à ladministration de ce test et d'établir une corrélation entre les caractéristiques du patient et l’apparition de vestibulotoxicité.

Méthodes : Tous les patients qui amorçaient un traitement aux aminosides sur une période de 12 semaines ont été évalués. On a ensuite déterminé si les patients de plus de 18 ans qui recevaien une ordonnance pour un traitement de plus de sept jours aux aminosides étaient aptes à subir le test EID. Les patients étaient exclus s’ils étaient incapables de s’asseoir, de lire les quatre premières lignes du tableau d’optotypes (à cause d’un trouble visuel ou d’incapacité mentale), de s’exprimer sans l’aide d’un interprète ou si une manipulation cervicale était médicalement contre-indiquée. Le test a été administré une première fois aux patients admissibles par l’un de deux pharmaciens, puis à nouveau 72 heures plus tard par le neurophysiologiste.

Résultats : Au total, 213 patients ont été évalués, dont 38 devaient recevoir un traitement de plus de sept jours aux aminosides. De ces 38 patients, 15 ont été exclus à cause de leur état de santé ou parce qu’ils avaient reçu leur congé avant l’administration du test; les 23 autres ont été examinés par un pharmacien. Le neurophysiologiste n’a pu faire subir le test à 7 de ces 23 patients et a fait subir le test deux fois à un patient; c’est pourquoi l’analyse finale compte 16 patients et 17 résultats de test. On a pu établir une corrélation entre les résultats du pharmacien et ceux du neurophysiologiste dans 100 % des cas. Il n’y a eu aucun résultat positif au test (score de trois ou plus); par conséquent, aucun patient n’était atteint de vestibulotoxicité. Aucune concentration sérique d’aminosides n’a été considérée comme supratherapeutique et on n’a noté aucune modification des paramètres initiaux, comme la créatininémie ou l’azotémie. Il a fallu moins de trois minutes par patient pour administrer le test.
INTRODUCTION

Vestibulotoxicity is a potentially debilitating complication of aminoglycoside therapy. It is generally irreversible, occurs in 2% to 25% of patients receiving this drug, and does not usually manifest until at least 7 to 14 days after initiation of therapy. Patients with vestibular dysfunction typically exhibit significant gait disturbances and complain of a bobbing oscillospa in which objects in the line of vision seem to bounce around while the patient is in motion. Aminoglycosides cause the loss of type I and type II hair cells in the cochlea and vestibular apparatus of the inner ear. Gentamicin tends to be more toxic to the vestibule than to the cochlea, although the reasons for this difference are unclear. Tobramycin is associated with the same level of cochlear toxicity as gentamicin but a somewhat lower incidence of vestibulotoxicity. Risk factors that have been proposed but not definitely proven for the development of vestibulotoxicity are greater age, longer duration of therapy, renal dysfunction, previous exposure to aminoglycosides, concurrent administration of other ototoxic medications, and elevated plasma aminoglycoside levels. Although some authors have found a significant association of total aminoglycoside dose and duration of therapy with development of vestibulotoxicity, others have not found a significant correlation. Monitoring of drug levels is common practice, but serum aminoglycoside levels have not yet been shown to be good predictors of potential vestibular damage. The standard gold for evaluating vestibular function is caloric testing, which involves the application of warm and cold water (or air) to the tympanic membranes. Nystagmic response is measured by electronystagmography, and a decrease in response indicates vestibular dysfunction. However, this test is invasive, time-consuming, difficult to perform on very sick patients, and invalidated by the use of any central nervous system depressant medications. The test can take up to 30 min to perform and may cause nausea or vomiting in many patients because of the extreme dizziness that can occur. Responses to caloric screening can also become habituated, resulting in a decline of up to 30% in the caloric response, thus rendering the test unreliable for monitoring.

The dynamic illegible E (DIE) test was developed at the authors’ institution in response to the need for a simpler, yet accurate, screening tool that could be used on most patients. Accuracy is important, as early detection of vestibulotoxicity leads to a greater chance of recovery of function. The DIE test has been validated against caloric testing and is a more sensitive screening tool. The test, which takes less than 3 min to administer, involves a chart containing 7 rows of 10 configurations of the capital letter E (Figure 1). The patient must identify the configuration (up, down, left, or right) starting at the top of a column and reading down, first with the head still and then while the head is moved from side to side by the tester. The test is based on the fact that the vestibulo-ocular reflex (VOR) is able to stabilize an image on the retina at velocities of up to 300°/s. Patients with normal vestibular function should retain their visual acuity as indicated by their ability to read the chart. The change in visual acuity with head movement is quantified and used to predict vestibulotoxicity.

The DIE test is used in facilities across North America because of its sensitivity in measuring VOR. At the authors’ institution, this test is the screening tool currently used for assessing vestibular function in patients receiving aminoglycosides. A neurophysiologist administers the test to patients identified as requiring testing. Typically, these are patients who physicians feel may have an increased risk of vestibulotoxicity or who are already showing some signs of toxicity. Because the neurophysiologist screens only those patients who are referred to him by health care professionals, some patients may be overlooked.

Clinical pharmacists in the institution’s pharmacy department are currently responsible for daily monitoring...
of all patients receiving aminoglycoside therapy for the duration of their hospital stay. These patients are identified by means of a daily computer-generated report. Serum aminoglycoside levels are monitored regularly, and dosages are adjusted in consultation with the physician so as to maintain therapeutic serum levels and minimize toxic effects. Pharmacists do not currently perform the DIE test; however, if this test were added to their regular monitoring, it would augment the level of care that pharmacists provide by consolidating all of the current monitoring techniques under one discipline. In addition, fewer patients would be overlooked, as pharmacists are aware of all courses of aminoglycoside being administered in the hospital. The primary goal of this study was to determine whether a pharmacist could perform the DIE test as accurately as the neurophysiologist. The secondary goals were to determine the effect on the pharmacist workload and to characterize patient characteristics in relation to vestibulotoxicity.

METHODS

Patients

All hospital inpatients at Vancouver General Hospital, a 500-bed tertiary care hospital, and home IV patients who were receiving aminoglycoside antibiotics (gentamicin, tobramycin, or amikacin) were identified by means of computer-generated daily reports, which identify all new antibiotic prescriptions initiated in the previous 24-h period. All patients older than 18 years of age who were given an aminoglycoside prescription for more than 7 days were evaluated for suitability to undergo the DIE test. Patients were excluded if they were unable to sit up to perform the test, were unable to read at least the top 4 rows of the chart because of visual impairment or mental incompetence, had a language barrier with no translator available, or had a medical contraindication to neck manipulation.

Study Design

The study was approved by the Clinical Research Ethics Board, and written informed consent was obtained from all patients tested. Physicians in the high-use aminoglycoside wards were informed of the study. Two pharmacists (D.C. and K.S.) were trained by the neurophysiologist to administer and interpret the DIE test. The training session took approximately 30 min, with the neurophysiologist acting as a control patient to familiarize the pharmacists with the technique. One of the pharmacists (D.C.) was also familiarized with an abnormal result by observing the neurophysiologist performing the test on a patient with known vestibulotoxicity. For each patient participating in the study, 1 of the 2 trained pharmacists performed the test within 72 h after the patient had been identified for inclusion. The neurophysiologist administered the test again within 72 h of the initial test. Three patients were tested independently by the 2 pharmacists and the neurophysiologist to assess inter-rater reliability. Any abnormal results obtained by the neurophysiologist were to be recorded in the patient’s chart and the physician notified to allow discussion of alternative antibiotic treatment, according to standard procedure. Follow-up DIE tests were performed at 7-day intervals for the duration of aminoglycoside therapy.

DIE Test Description

The patient is seated in either a chair or the hospital bed approximately 6 to 12 ft (1.8 to 3.7 m) away from a chart that consists of 7 rows of 10 configurations of the capital letter “E” (Figure 1). The rows of E’s differ in size, ranging from a size corresponding to 20/100 vision at 12 ft for the largest (top) row through 20/80, 20/60, 20/40, 20/30, 20/25, and 20/20 vision for the bottom row. The patient is asked to read a given column, indicating the direction of each E (up, down, right, left). The size of the E’s decreases as the patient reads down. The smallest row that the patient can read correctly with the head held still is defined as his or her visual acuity. The head is then grasped by the tester and constantly turned, in an arc of about 60°, from right to left and back to the right, once per second. The patient reads a different specified column on the chart while undergoing this head movement. The patient’s DIE test score is determined by subtracting the number of rows read correctly with the head moving from the number of rows read correctly with the head held still. A score of 2 or less is considered to represent a normal change in visual acuity with the head movement. If the score is
3 or more, some vestibular deficit may be present, and further testing is recommended.

Data Collection
The following data were collected for all patients: baseline characteristics, daily dose of aminoglycoside, total dose, duration of therapy, daily dose at test time, concurrent ototoxic agents, serum creatinine and urea (as blood urea nitrogen or BUN) at baseline and at the end of therapy, DIE test results, and any reported side effects. To assess pharmacist workload, the total number of new aminoglycoside courses was recorded daily.

Statistical Analysis
The primary outcome measure was the ability of the pharmacist to perform the DIE test. A kappa analysis was used to assess the correlation between the pharmacists’ and the neurophysiologist’s results. Descriptive statistics were used to analyze workload and the proportion of courses requiring the DIE test.

RESULTS
Over a 12-week period from November 2000 to February 2001, aminoglycoside therapy was initiated for 213 patients. Thirty-eight of these patients were receiving the drug for more than 7 days. Twelve patients were excluded because of their medical condition, and 3 were discharged before the pharmacist could test them. Of the 12 excluded for medical reasons, 9 were on ventilator support in the intensive care unit and 3 were burn patients whose injuries prevented proper manipulation of the head for testing. Of the 23 remaining patients, 7 were tested by the pharmacist but were discharged before they could be tested by the neurophysiologist, and 1 patient had 2 sets of DIE tests, 1 week apart. Thus, there were 16 patients and 17 DIE test results available for analysis.

The primary indications for aminoglycoside therapy were febrile neutropenia (7 patients or 44%), infective endocarditis (4 patients or 25%), osteomyelitis (3 patients or 19%) and abdominal infections (2 patients or 12%) (Table 1). Gentamicin was the primary aminoglycoside prescribed (9 patients or 56%), and no patients received amikacin (Table 1). Eight patients received a total of 16 courses of concurrent ototoxic medications: vancomycin, furosemide, and antineoplastic agents such as cyclophosphamide and cisplatin. The DIE test results for these patients did not differ from those of patients not receiving ototoxic medications. Baseline serum creatinine and BUN were within normal limits for all patients and did not change over the course of therapy.

### Table 1. Demographic Characteristics of 16 Patients Who Underwent Dynamic Illegible E Testing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (and SD) or No. (and %) of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men/Women)†</td>
<td>11/5</td>
</tr>
<tr>
<td>Mean age and SD (years)</td>
<td>49.3 (15.1)</td>
</tr>
<tr>
<td>Mean weight and SD (kg)</td>
<td>74.2 (14.4)</td>
</tr>
<tr>
<td>Aminoglycoside prescribed</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Indication for therapy</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Courses of concurrent ototoxic drugs‡</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Mean serum creatinine and SD (µmol/L)</td>
<td>77.4 (14.6)</td>
</tr>
<tr>
<td>Mean BUN and SD (mmol/L)</td>
<td>4.4 (1.3)</td>
</tr>
</tbody>
</table>

* SD = standard deviation, BUN = blood urea nitrogen.  
† One man underwent 2 sets of dynamic illegible E tests, 1 week apart.  
‡ The 16 courses of concurrent ototoxic drugs were given to a total of 8 patients.

Mean daily aminoglycoside doses at the time of DIE testing were within normal limits, as were the peak and trough serum levels determined from serum drug level monitoring (Table 2). The normal limits were based on standard aminoglycoside dosing of 3 to 6 mg kg⁻¹ day⁻¹, therapeutic peak levels of 4 to 10 mg/L, and troughs of less than 2 mg/L. The mean total dose was 56.8 mg/kg (Table 2), and the highest cumulative dose was 99 mg/kg. The mean duration of therapy was 14.9 days (Table 2), with the longest course at the time of the DIE test being 22 days. No adverse effects were reported during treatment with aminoglycoside therapy, as indicated by patient interviews and nursing notes. All patients completed the prescribed course of therapy, with 94% of dosage adjustments being made within 3 to 5 days after initiation of therapy, just after the first serum samples were drawn for drug monitoring. No doses were changed after the first 7 days of treatment.

For all 17 DIE test results obtained by a pharmacist and repeated by the neurophysiologist there was 100% correlation, including complete correlation among the 2 pharmacists and the neurophysiologist for the 3 patients who were tested independently by all 3 testers. There were 15 DIE test scores of 0, which means that these patients experienced no change in visual acuity with head movement relative to when the
head was held still. There were 2 DIE test scores of 1 (i.e., the number of rows that could be read correctly with the head moving was 1 less than could be read with the head held still). All 17 test results were considered normal; therefore, none of the patients exhibited signs of vestibular dysfunction on screening with this test. During the study period, only 1 of the 16 patients was referred to the neurophysiologist by means of a physician request in the chart.

DISCUSSION

The primary objective of this study was to determine whether a pharmacist could perform the DIE test with the same accuracy as the neurophysiologist who usually performs the test. To the authors’ knowledge, no other study of performance of this test by a pharmacist has been undertaken. The 100% correlation for scores obtained by the pharmacists and the neurophysiologist shows that a pharmacist can perform the test with the same accuracy. However, there were no positive test results in this study (i.e., no scores of 3 or more), so it is not possible to conclude that pharmacists could detect patients with vestibulotoxicity with the same accuracy as the neurophysiologist. However, the test is very easy to perform and the results are measured quantitatively; therefore, it is unlikely that correlation for higher (abnormal) scores would be significantly less than that for lower (normal) scores. A larger sample size would help to confirm this assumption by increasing the chance of including patients with vestibulotoxicity.

Given the increasing focus on pharmaceutical care, it is important that pharmacists continue to enhance their role in patient care. Pharmacists at the authors’ institution have a significant presence as part of the health care team in most areas of the hospital. Therapeutic drug monitoring by pharmacists has been common practice for many years; therefore, it seems reasonable that any additional aspect of drug monitoring for potential toxicity would serve to enhance pharmacists’ role on the health care team. Although no patients with vestibulotoxicity were found in this study, the reported incidence of vestibulotoxicity (2% to 25%) is significant because the effects are so devastating for patients, especially if the problem is not detected early.5-7 By definition, the purpose of a screening tool is to identify signs of a potential adverse event before it leads to permanent damage. The DIE test is a simple, accurate screening tool,13 yet it is underutilized for this purpose. If pharmacists were to incorporate the test into their daily monitoring activities, all patients initiating aminoglycoside therapy could be identified through the daily antibiotic report that clinical pharmacists refer to at the beginning of each day and hence all patients with potential for vestibulotoxicity would be screened and identified before irreversible damage occurred. Under the current system, many patients who might benefit from monitoring are being overlooked, because the neurophysiologist has no way of knowing which patients are receiving aminoglycosides at any given time. In fact, the neurophysiologist receives only approximately 20 in-hospital consults per year for DIE monitoring related to aminoglycoside therapy. Giving pharmacists this responsibility would allow the test to be used to its full potential and would enhance the pharmacist’s role in patient care.

Introduction of a new job responsibility always raises the question of increased workload and how this will affect existing daily activities. This test takes less than 3 min to perform, and with a mean duration of aminoglycoside therapy of 15 days, only 2 or 3 tests per patient would be required, on average. A total of 213 patients initiated aminoglycoside therapy over the 12-week study period, or an average of 18 patients per week. Given that only 12% of these patients were eligible for testing (26/213), only 2 or 3 patients per week would require the DIE test. This amounts to less than one test per day, which would not constitute a significant increase in pharmacist workload, especially considering that several clinical pharmacists are working on any given day. Because of the limited number of patients requiring this test, the department has opted to train a select pool of pharmacists, rather than trying to maintain the testing skills of several clinical pharmacists who may not have the opportunity to administer the test.

One limitation of this study was the small sample size. Unfortunately, 7 patients tested by the pharmacist were not tested by the neurophysiologist and had to be excluded from the analysis. This was a loss of 30% of the initial sample size, which is significant in such a
small group. Another limitation was the lack of a positive (abnormal) test result. While this was obviously good news from a patient care perspective, it did not allow correlation of specific patient variables with vestibulotoxicity. Because there have been conflicting reports about the risk factors for vestibulotoxicity, it would be advantageous to determine these factors and thus identify patients at increased risk before therapy is initiated. With this information, therapy could be avoided in high-risk patient groups and DIE testing initiated at an earlier stage in moderate-risk groups. Total duration of therapy, total dose, and serum drug levels were all within normal limits of aminoglycoside therapy in this study. However, with no abnormal DIE test scores, the results cannot confirm or dispute whether these factors may be correlated with the occurrence of vestibulotoxicity. A review of 36 patients with normal baseline renal function who displayed gentamicin vestibulotoxicity concluded that, as far as the vestibular system is concerned, there is no safe gentamicin dose or serum level. A third limitation is the up to 72-h time lapse between pharmacist and neurophysiologist testing, which might have led to discrepancies in test scores. However, all test scores were negative and no adverse symptoms were reported by the patients during this interval, so it is unlikely that this delay affected the results.

CONCLUSIONS

This study showed that a pharmacist can perform the DIE test with the same accuracy as the neurophysiologist in patients who do not exhibit vestibulotoxicity. Currently, a select group of clinical pharmacists at the authors’ institution are administering the DIE test for their own patients and upon request by another pharmacist as part of routine aminoglycoside monitoring; the neurophysiologist continues to respond to chart consults by the physician.

References


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