Effect of Patient Age, Dose, and Chronic Kidney Disease on the Risk of Adverse Reactions to Distigmine

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Although distigmine is known to sometimes cause severe adverse drug reactions (ADRs), such as cholinergic crisis, there are limited data on the risk factors for these ADRs. In this study, we defined a serum cholinesterase (sChE) cutoff level for early detection of ADRs to distigmine and sought to identify risk factors for these ADRs based on this value. This retrospective cohort study included all patients who were prescribed distigmine and underwent measurement of sChE over a period of 8 years at Kaetsu Hospital. Ninety-three patients were included. The sChE cutoff level below which there was an increase in risk of ADRs was defined as 129 U/L based on the levels in patients who had ADRs by receiver operating characteristic analysis. The percentage of ADRs tended to increase with advancing chronic kidney disease (CKD) stage. Multivariate logistic regression analyses showed that a distigmine dose >0.1 mg/kg/d (odds ratio 3.19, 95% confidence interval 1.24–8.19) and age >85 years (odds ratio 3.04, 95% confidence interval 1.18–7.82) were positively associated with an sChE level ≤129 U/L. An sChE cutoff level of 129 U/L is a useful predictor of the risk of an ADR to distigmine, and dose per body weight, age, and CKD progression may pose potential risk of an ADR to distigmine. Therefore, for patients taking distigmine who have these risk factors, the risk of a severe ADR to distigmine can be reduced by decreasing the dose of distigmine and close monitoring of the sChE level.

Key words distigmine; adverse drug reaction; chronic kidney disease; patient age; dose

INTRODUCTION

Distigmine is a reversible cholinesterase inhibitor that is used in the treatment of myasthenia gravis and underactive bladder.1,2) However, its use is associated with gastrointestinal adverse drug reactions (ADRs), such as nausea and diarrhea, via inhibition of cholinesterase. Cholinergic crisis is a particularly severe ADR to distigmine, which requires mechanical ventilation in 20% of patients and is potentially life-threatening in 6% of cases.3,4) Chronic kidney disease (CKD) may be one of the risk factors for ADRs to distigmine because 85% of the drug is eliminated via the kidney, and renal impairment would lead to an increase in serum distigmine level.5) However, there is limited information on the risk factors for ADRs to distigmine, including CKD. Therefore, it is important to clarify these risk factors in the clinical setting.

Early detection of an ADR to distigmine is important to prevent worsening of its severity. A defined cutoff serum cholinesterase (sChE) level could be a useful biomarker for early detection of patients at risk of ADRs to distigmine and will help to avoid the need for measuring serum distigmine level. sChE level is usually measured to assess liver function in the clinical setting and is reduced by cholinesterase inhibitors, including distigmine.6) However, the sChE level at which there is an increased risk of an ADR to distigmine is unknown and remains to be clarified.

In this study, we defined the sChE cutoff level that allows early detection of ADRs to distigmine and identified the risk factors for these ADRs accordingly.

Materials and Methods

This retrospective cohort study included all patients who were prescribed distigmine and who underwent measurement of sChE levels between 2011 and 2018 at Kaetsu Hospital. Prescription data, patient characteristics, sChE levels, and reasons for discontinuation of distigmine were collected from electronic medical records. Patients who were prescribed an alternative cholinesterase inhibitor (e.g., donepezil, pyridostigmine, or ambenonium) and those with comorbid liver disease (Child–Pugh B or C) were excluded. If more than one sChE measurement was available, the most recent result was used. In cases where distigmine was discontinued, the reason for discontinuation and the sChE level at the time of discontinuation were extracted. CKD stage was defined according to the Kidney Disease Outcome Quality Initiative criteria. The estimated glomerular filtration rate (eGFR) was calculated using the equation for the Japanese population.7) The study was approved by the institutional review board of Kaetsu Hospital (approval number 2019-012).

First, the cutoff sChE level at which there was an increase in ADRs to distigmine was defined by receiver operating characteristic (ROC) analysis. Second, patient characteristics were analyzed according to the cutoff sChE level, and frequency of ADRs were compared by CKD stage. Finally, multivariate modeling was performed to identify risk factors of patient characteristics that were independently associated with the cutoff sChE level.

Assay for sChE Level sChE level was measured using a commercial kit (Quick Auto Neo Ch-E; Shino-Test Corp., Tokyo, Japan) and an automatic analyzer (BioMajesty JCA-
BM6050; JEOL, Tokyo, Japan). This assay is a routine component of liver function tests at our hospital. Normal range is set at 185–431 U/L.

Statistical Analysis Continuous variables are reported as the median (range) and categorical variables as the frequency (percentage). Univariate analysis was performed using the Mann–Whitney U and Fisher exact tests. In ROC analysis, the cutoff level of sChE for distigmine ADRs was decided by the maximum sum of sensitivity and specificity, and the area under the curve (AUC) and 95% confidence intervals (CIs) were calculated. Multivariate modeling was performed using logistic regression analysis to identify the risk factors that were independently associated with an sChE ≤ 129 U/L, which was defined using ROC analysis. A distigmine dose > 0.1 mg/kg/d, age > 85 years, and CKD stage, which were decided as significant factors from among the patient characteristics, were included in the analysis. Odds ratios (ORs) and 95% CIs were calculated in multivariate analyses. All analyses were performed with R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

RESULTS

Ninety-seven patients were enrolled in the study. All were treated with cholinesterase inhibitor and another two patients were excluded because of concomitant liver disease (Child–Pugh B). Finally, data for 93 patients were included for analysis. Fifty patients (54%) were men and the median patient age and body weight were 84 (range, 50–98) years and 46 (range, 24–77) kg, respectively. Twenty-six patients discontinued distigmine during the study period. However, four patients discontinued distigmine due to low sChE level without ADRs. Thus, it can be considered that 22 patients (24%) had ADRs (Table 1).

From the ROC analysis, the cutoff levels of sChE for ADRs to distigmine and the AUC were calculated as 129 U/L and 0.8 (95% CI 0.7–0.9), respectively (sensitivity 0.86 and specificity 0.68). Patient characteristics were compared by dividing the cutoff level of sChE (Table 2). There was a significantly higher median age (87 vs. 82 years) and a significantly lower median body weight (41 vs. 50 kg). The percentage of ADRs by CKD stage (number of patients with ADR/total number of patients) was as follows: 18% (2/11) in CKD stage 1, 18% (6/33) in CKD stage 2, 25% (9/36) in CKD stage 3, 40% (4/10) in CKD stage 4, and 33% (1/3) in CKD stage 5. Although there was no significant difference among CKD stages (p = 0.66), the percentage of ADRs tended to increase with progressing CKD stage. Figures 1–3 show the associations between patient age and sChE level, between eGFR and sChE, and between distigmine dose according to body weight and sChE. Significant negative correlations were found between patient age and distigmine dose according to body weight and sChE level.

The results of multivariate logistic regression analyses of factors associated with an sChE level ≤ 129 U/L are shown in Table 3. Distigmine dose > 0.1 mg/kg/d (OR 3.19, 95% CI 1.18–7.82) and age > 85 years (OR 3.04, 95% CI 1.18–7.82) were positively associated with an sChE level ≤ 129 U/L.

DISCUSSION

ADRs to distigmine are potentially life-threatening1,3,4 and should be avoided. The findings of this study show that patients with an sChE level ≤ 129 U/L are likely to develop ADRs to distigmine. Furthermore, we found that a distigmine dose > 0.1 mg/kg/d and age > 85 years were risk factors for an sChE ≤ 129 U/L. Although CKD stage was not associated with a low sChE level in multivariate analysis, the percentage of

Table 1. Adverse Reactions to Distigmine and Corresponding Serum Cholinesterase Level

| Event          | n = 22 | sChE, U/L, median (range) |
|----------------|--------|--------------------------|
| Diarrhea       | 16     | 76 (18–325)              |
| Impaired       | 2      | 148 (101–194)            |
| Respiratory    | 2      | 76 (63–88)               |
| Miosis         | 1      | 112                      |
| Bradycardia    | 1      | 11                       |

sChE, serum cholinesterase.

Table 2. Patient Characteristics Compared by Dividing the Cutoff Value of sChE

|                      | All (n = 93) | sChE ≤ 129 U/L (n = 42) | sChE > 129 U/L (n = 51) | p*  |
|----------------------|--------------|-------------------------|-------------------------|-----|
| Age, years, median   | 84 (50–98)   | 87 (65–98)              | 82 (50–96)              | 0.03|
| Male sex, %          | 50 (54)      | 21 (50)                 | 29 (57)                 | 0.54|
| BW, kg, median       | 46 (24–77)   | 41 (24–65)              | 50 (33–77)              | <0.01|
| CKD stage, %         |              |                         |                         |     |
| 1                    | 11 (12)      | 8 (19)                  | 3 (6)                   | 0.10|
| 2                    | 33 (35)      | 10 (24)                 | 23 (45)                 |     |
| 3                    | 36 (39)      | 17 (41)                 | 19 (37)                 |     |
| 4                    | 10 (11)      | 6 (14)                  | 4 (8)                   |     |
| 5                    | 3 (3)        | 1 (2)                   | 2 (4)                   |     |
| Distigmine dose, %   |              |                         |                         |     |
| 1.25 mg              | 4 (4)        | 2 (5)                   | 2 (4)                   | 0.94|
| 2.5 mg               | 35 (38)      | 15 (36)                 | 20 (39)                 |     |
| 5 mg                 | 54 (58)      | 25 (60)                 | 29 (57)                 |     |
| Distigmine dose ≤ 0.1 mg/kg/d, % | 36 (39) | 21 (50) | 15 (29) | 0.06 |

* sChE ≤ 129 U/L group vs. sChE > 129 U/L group, Mann–Whitney U test or Fisher’s exact test (p < 0.05). BW, body weight; CKD, chronic kidney disease.
Inhibitors using only butyrylcholinesterase (15) because the quantity of acetylcholinesterase in human serum is low. However, acetylcholine is hydrolyzed by both acetylcholinesterase and butyrylcholinesterase (15), and the inhibitory concentration of distigmine is the same for both esterases (16). In addition, acetylcholinesterase and butyrylcholinesterase are expressed differently according to tissue type (13) and genetic variation (13). Thus, it should be kept in mind that an assessment of sChE levels does not reflect all the effects of cholinesterase.

Our study has some limitations in that it had a retrospective, single-center design and a small sample size. Therefore, a larger study is needed to confirm our findings. In addition, sChE level was measured in our patients only when clinically necessary, single-center design and a small sample size. Therefore, a larger study is needed to confirm our findings. In addition, sChE level was measured in our patients only when clinically necessary.
indicated, such as when liver disease or an ADR to distigmine was suspected. Therefore, the patients in this study may not be representative of the general population. Furthermore, patients with Child-Pugh B or C liver disease were excluded. Also, there were 3 patients with body weight <30 kg in this study, whom we generally consider to be a special population. Finally, our study included only patients who were being treated with distigmine for underactive bladder. Whether or not our findings would be the same in patients with other conditions treated with cholinesterase inhibitors, such as myasthenia gravis and glaucoma, is unknown.

In conclusion, low sChE level may be a useful marker of the risk of an ADR to distigmine in the clinical setting. Patients who are receiving distigmine at a dose >0.1 mg/kg/d and those aged >85 years are at high risk of these ADRs. CKD progression may pose potential risk of an ADR to distigmine. Therefore, when patients taking distigmine have these risk factors, we can reduce the likelihood of a severe ADR such as cholinergic crisis by decreasing the dose of distigmine and closely monitoring their sChE levels.

Conflict of Interest The authors declare no conflict of interest.

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