Evaluations of echogenicity in gluteal muscle in patients with schizophrenia treated with second generation long-acting injectable antipsychotics: risperidone or aripiprazole

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Second generation long-acting injectable antipsychotics (SG-LAIs) injected muscle region show high-echogenicity with acoustic shadowing on B-mode scan. This study aimed to distinguish two specific types of SG-LAIs at the gluteal muscle. Forty-seven patients [risperidone (RLAI): 28 patients, aripiprazole (ALAI): 19 patients] were examined using grayscale histogram analysis of echo-intensities. Pre- and immediately after (post)-injected SG-LAI region of interest (ROI) was placed on the same sites of gluteal muscle, and the grayscale histograms were recorded. Pre- and post-injected echogenicity values were analyzed using paired t-test, and Pearson’s moment correlation coefficient. Mixed effects model regression analysis was performed on variations in average echogenicity from age and medication type. Statistical significance was at 5%. There was no significant correlation between age and average echogenicity of ROI pre-intramuscular (IM) injection \( r = 0.26, \ p = 0.078 \). In both RLAI and ALAI, the mean echogenicity post-IM injection was significantly higher than pre-IM injection \( \ p < 0.001 \). With increasing age, the values of echogenicity of post-injection was decreased significantly \( \ p = 0.002 \). The increasing values of the echo-intensities post-injections of RLAI showed significantly higher than ALAI \( \ p = 0.002 \). It was considered that administered type of LAI could be identified because each LAI exhibits specific echographically findings, it also will be able to applied clinically.

Keywords: second generation long-acting injectable antipsychotics (SG-LAI), intramuscular injection, water soluble suspension, echogenicity

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Introduction

Second generation long-acting injectable antipsychotics (SG-LAIs) are water-soluble suspensions. It is one of the optimal treatment strategies for patients with schizophrenia through intramuscular (IM) administration. SG-LAIs such as risperidone long-acting injectable (RLAI)\(^1\),\(^2\), paliperidone LAI (PLAI)\(^3\), and aripiprazole LAI (ALAI)\(^4\) have been available for clinical use in Japan. Regardless, side effects/adverse events in patients who were administrated the RLAI\(^5\),\(^6\) and PLAI\(^7\) were reported. When unacceptable side effects occurred, there was no effective treatment for the patients who were injected with IM SG-LAIs. Therefore, it is important to detect local side effects as soon as possible. Ultrasonography become one of the major diagnostic techniques for finding these unusual reactions.

In previous studies using ultrasonography, the “distance from the epidermis to the under-fascia” and “distance from the epidermis to the iliac bone” of the buttocks at the dorsogluteal and ventrogluteal sites in healthy Japanese volunteer subjects\(^8\) and patients with schizophrenia were measured\(^9\),\(^10\) in order to evaluate the optimal IM injection needle length\(^11\) and the optimal gluteal muscular injection needle should be 40–50mm in length. The IM administrated LAIs showed high-echogenicity masses with acoustic shadowing\(^12\),\(^13\).

In addition, Yasuhara et al.\(^14\) suggested that the ultrasonographic findings could be distinguish among RLAI, PLAI and ALAI. The IM LAIs on B-mode scan showed its specific echogenicity in the muscle depending on its physical structures and chemical properties. Each LAI has specific particle size for each LAI, for example, RLAI is encapsulated in the microspheres of 25 to 150\(\mu\)m diameter\(^5\), and the ALAI with nanoparticles of 1 to 10\(\mu\)m in diameter\(^16\).

However, high-echogenicity in the muscle with administration of SG-LAI have not been elucidated. It is important to investigate the detailed examinations of SG-LAI findings in the gluteal muscle on ultrasonography.

The aim of this study was to evaluate the ultrasonographic findings to demonstrate the drug-specific differentiation in two specific types of SG-LAIs administrated in the gluteal muscle.

Methods

1. Subjects

The subjects were patients conforming to the inclusion criteria. Subjects were 47 adult patients with schizophrenia diagnosed according to the International Classification of Diseases 10th revision (ICD-10). Patients were all prescribed to receive the RLAI (28 patients) or ALAI (19 patients). The exclusion criteria were subjects with apparent redness or ulceration at the injection site; with muscular dystrophy, inflammatory muscle disorders, and metabolic muscle diseases which produces high-intensity findings at the starting point of this study. On B-mode scan, the patients who were diagnosed as any type of muscular dystrophy, inflammatory muscle diseases, and metabolic dystrophy were also excluded.

2. Ultrasonographic measurements

Before administration of LAI, dorsogluteal IM injection sites (double-cross injection point) were measured and marked with the subjects at prone position to identify IM site with an imaginary cross then dividing the upper outer quadrant again by another imaginary cross\(^7\),\(^18\).

Prior to the IM injection maneuver, the linear B-mode transducer was placed on the buttocks and scanned manually to detect the area of IM injection. Under continuous B-mode monitoring, the injection maneuver was performed: 1) the injection needle was inserted into the gluteus muscle, and 2) observation of the diffusion state of injection solution was done. All ultrasonographic measurements were performed without using a probe-mounted injection needle insertion guide by an experienced ultrasonic measurement technician, using a 7.5MHz linear and convex array transducer and the Digital Diagnostic Ultrasound Scanner (Hitachi Medical Corporation, Japan). It took about 15 minutes per subject to conduct IM injection while conducting an ultrasonic examination.

3. Grayscale histogram analysis

Quantitative diagnostic ultrasound imaging has been proposed as a method for estimating muscle quality using measures of echogenicity. Grayscale median (GSM) analysis was performed of the B-mode images and the results were stored in a computer. A number that ranges from 0 for black to 255 for white was used to represent the brightness of each pixel. The same software was used to select an area of interest in an image and count its pixel brightness or intensity\(^19\).

The GSM analysis of the muscle tissue echogenicity was evaluated with Photoshop Premiere Elements 14.0\(^20\). The corresponding grayscale histogram analysis data for each
sonographic image was compared with the same regions of the pre- and post-injected gluteus muscle.

The LAI injected gluteal muscle showed echogenic mass (upwardly convex) with artifacts (acoustic shadowing). The region of interest (ROI) was placed on the high intensity region excluding the contour of the echogenic masses and acoustic shadowing. ROI, as a pre-injected control value in grayscale analysis was placed at the same region with the injected site. Immediately after (post)-injected LAI, remodeling of the muscle may occur to align the position of the pre-injected ROI. This estimated the positional relationship with the fascia, iliac bone, the size of pre- and post-injected ROI set to the same size. This ROI was used as the baseline grayscale value.

4. Statistical analysis

Pearson’s moment correlation coefficient was calculated for the correlation between average echogenicity of ROI pre-IM injection and age. Test for homogeneity of variance (F-test) and Welch’s t-test was used to compare between mean age of patients group treated with RLAI and ALAI. Paired t-test was used to compare between pre- and post-injected SG-LAIs echogenicity of B-mode ultrasound images.

Regression analysis using a mixed effects model was performed on variations in average echogenicity from age and type of medications. Fixed effects included type of SG-LAI, time (pre- and post-injection) and mean centering age; interaction of mean centering age and time (pre- and post-injection); interaction of type of SG-LAI and time (pre- and post-injection). Also, it was set patient as random effect.

All data were analyzed using IBM SPSS ver. 24.0. Statistical significance level was at 5%.

5. Ethical consideration

This study was conducted after approval was received from Tokushima University Hospital Ethics Committee (approval number 2948).

Results

Satisfactory B-mode images were obtained of all 47 patients in this study. The IM LAIs were depicted as increased echogenicity in the muscles.

On the grayscale median analysis, these values in the muscles injected with LAIs were significantly elevated from 108.68 ± 30.85 to 193.61 ± 21.47 in this study (p < 0.001). In both RLAI (pre-IM injection vs. post-IM injection: 104.68 ± 32.06 vs. 198.07 ± 20.83, t = 20.64, p < 0.001) and ALAI (114.58 ± 28.80 vs. 187.05 ± 21.22, t = 15.79, p < 0.001), the average echogenicity of the muscle tissues immediately after IM injection were significantly higher than pre-IM injection (Table 1).

There was no significant correlation between age and averaged echogenicity of ROI of pre-IM injection in all of the subjects as shown in Fig.1. However, the scatterplot showed a weak positive correlation tendency between age and average echogenicity r = 0.26, p = 0.078 (Fig.1).

The mean age of RLAI (n = 28) patients was 50.43 ± 12.64 years old, ALAI (n = 19) patients was 51.58 ± 8.21 years old, there was no significant differences in age of both group (Welch’s t = 0.38, p = 0.707) (Table 1).

The ΔGSM ([post-injected LAIs GSM] − [pre-injected GSM]) showed significantly reduced effect with increasing patients’ age, (p = 0.002). The AGSM of RLAI were significantly higher than those of ALAI (p = 0.002) (Table 2, Fig. 2).

Discussion

In this study, B-mode findings of LAIs administrated through muscles were evaluated immediately after IM injection. Just after administration, the LAI-injected muscles showed marked high echogenicity lesions with acous-
tic shadowing. In this study subjects, at the time of pre-injected (that is normal) echogenicity of the muscles showed higher with increasing age. However, changes of intensity of echogenicity after LAIs injection were dependent on age of subjects. The rate of changes of echo-intensities were gradually reduced with increasing age. Muscle echogenicity increased with age, which may indicate the age-related increase of IM fat content fibrous tissues in the healthy subjects\(^{21,22}\). The results of this study indicated that the increasing of IM fat content may reflect to the increased echogenicity of the muscles. Large fatty tissues, such as subcutaneous fat tissues, are observed as hypoechoic regions on B-mode scan\(^{23}\).

The changes of echogenicity depend on the acoustic impedance on the surface of the fat cells\(^{24}\). Reimers et al.\(^{24}\) mentioned that fat replacement constitutes the main cause of increased muscle echogenicity, whereas IM fibrosis did not significantly affect the muscles’ echogenicity. Nevertheless, Pillen et al.\(^{25}\) concluded that fibrous tissue causes increased muscle echogenicity. From these findings, the echogenicity of fibrotic tissue in the muscular body remains controversial.

In this study, patients with higher-age, tended to have higher echogenicity of the muscle before injection. In addition, on the grayscale histogram analysis, the rate of changes of the echo intensities were significantly reduced with increasing age. Therefore, it was necessary to take into account the age of the subjects, especially among the elder population, to evaluate the echogenicity changes.

Both RLAI and ALAI were defined as high-echogenicity masses in the gluteal muscles on B-mode scan. The GSM analysis of the echogenicity of the injected LAIs can clarify the changes of intensity, and \(\Delta\)GSM of RLAI were higher than ALAI. The RLAI were larger grayscale ranges showing a much larger spread than those of ALAI on the GSM analysis\(^{14}\). The GSM analysis allows a quantitative evaluation of muscle echogenicity in patients treated with LAIs. Muscle echogenicity was qualitatively expressed as the degree of acoustic brightness of a muscle with LAIs by GSM analysis. The RLAI injected muscles showed more clearly demarcated and strong acoustic shadows as compared with those of ALAI on B-mode findings.

\[ y = 0.73x + 71.51 \]
\[ R^2 = 0.97, r = 0.26 \]
\[ p = 0.078 \]

**Fig.1** Correlation between average echogenicity of the muscle tissues and age at the pre-intramuscular injection

**Table 2** Mixed-model analysis results for response variable of RLAI and ALAI

| Variables | Estimated coefficients (95% CI)* | t | p |
|-----------|---------------------------------|---|---|
| Time (Pre: 0, Post: 1) | 92.97 (85.22, 100.71) | 24.18 | < 0.001 |
| LAI (RLAI: 0, ALAI: 1) | 9.08 ( -6.41, 24.57) | 1.17 | 0.246 |
| Age | 0.71 (0.01, 1.41) | 2.03 | 0.047 |
| Time \(\times\) LAI | -19.88 ( -32.07, -7.68) | -3.28 | 0.002 |
| Time \(\times\) Age | -0.90 ( -1.45, -0.35) | -3.30 | 0.002 |
| Intercept | 105.01 (95.17, 114.85) | 21.35 | < 0.001 |

\(n = 47\) (RLAI : \(n = 28\), ALAI : \(n = 19\)).

*Unstandardized fixed effect coefficients. Pre: 0, pre-intramuscular injection; Post: 1, during intramuscular injection.

LAI, long-acting injectable abtupsychotics; RLAI, risperidone LAI; ALAI, aripiprazole LAI. Age was centered with mean of age (50.9)
Many factors other than patients’ age may influence muscle echogenicity, such as the thickness of the muscles and subcutaneous fatty tissues, the post-injected hemorrhages in the muscles, and the toxicity to the muscle tissues of specific LAIs\(^\text{14}\). The specific molecular structure (microsphere or nanoparticle) of each SG-LAI, physicochemical properties of the drug such as size and density of contained bubbles can also be considered. With many factors affecting IM drug infiltration, such as the size of the muscles, regional blood flow, and LAIs’ lipid solubility of the drug which have specific chemical structures and physiological properties. For example, the size of RLAI particles are larger than ALAI. RLAI is covered with micrometer-sized biodegradable poly(\(d,l\)-lactide-co-glycolide) microspheres which are loaded with risperidone and suspended in sterile saline\(^\text{26}\).

Since data in this study were post-injection, these were not affected by drug release of RLAI. ALAI is a lyophilized powder that needs to be reconstituted with sterile water. Aripiprazole is characterized by particles a mean size about 1 to 10\(\mu\)m as described above which are smaller than risperidone.

The structure predisposes acoustically active encapsulated particles susceptible to rupture by pressure reduction and hence also by ultrasound irradiation. The size and shape of the particles encapsulated LAIs would resemble as acoustically active enhancers. The echogenicity may be reflected by the size and chemical constructions of the particles. If the LAI particle would act as the echo-enhancers, the particles may collapse with the echo irradiation. Excessive irradiation of ultrasound may cause the unexpected early elevation of the concentration of LAIs.

Also, in the patient who received repeated IM injections over months, muscular degeneration such as increased muscle fibrosis, increased fat content, calcification and others might be involved. Therefore, it is very important to reduce the appearance of the muscular degeneration, and injection under B-mode monitoring may be improved by the clinical outcomes. In future studies, it is necessary to determine the relationship between the number of injections and the muscle echogenicity before injection.

**Conclusion**

In both RLAI and ALAI, the average echogenicity of IM injected gluteal muscles increased significantly as compared with pre-IM injection. Just after administration, the LAI-injected muscles showed marked high echogenicity lesions with acoustic shadowing. In this study subjects, echo-
genicity at the time of pre-injected (that is normal) muscles showed higher with increasing age and the LAI-induced high echogenicity gradually illuminated negative linear correlations at echogenicity of immediately post-IM injection. Quantitatively, from the results of this study, the changes of the echo-intensities in pre- and post-injections RLAI had significantly higher echogenicity than ALAI. It was considered that administered type of LAI could be identified because each LAI exhibits specific echographically findings, it also will be able to applied clinically.

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Disclosure statement

The authors report no conflicts of interest in this work.

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