Evaluations of muscle echogenicities in patients treated with second generation long acting injectable antipsychotics

Yuko YASUHARA¹⁾, Tetsuya TANIOKA¹⁾, Kensaku TAKASE²⁾, Yueren ZHAO³⁾, Kazushi MOTOKI⁴⁾, Takaharu AZEKAWA⁵⁾

¹⁾ Department of Nursing, Institute of Biomedical Sciences, Tokushima University Graduate School

²⁾ Tokushima Prefectural Central Hospital

³⁾ Department of Psychiatry, Fujita Health University

⁴⁾ Tokushima Prefectural Kaifu Hospital

⁵⁾ Shioiri Mental Clinic

非定型抗精神病薬持効性注射の筋肉内輝度の評価

安原 由子¹⁾, 谷岡 哲也¹⁾, 高瀬 憲作²⁾, 趙 岳人³⁾, 元木 一志⁴⁾, 阿瀬川 孝治⁵⁾

¹⁾ 徳島大学大学院医歯薬学研究部保健科学部門看護学系

²⁾ 徳島県立中央病院

³⁾ 藤田保健衛生大学医学部精神神経科学講座

⁴⁾ 徳島県立海部病院

⁵⁾ 汐入メンタルクリニック

Our previous study evaluated the B-mode findings of the muscle infiltrated with second generation long acting injectable antipsychotics (SG-LAIs). SG-LAIs were seen as a high-echogenicity mass with marked acoustic shadowing in the gluteus medius muscle. The aim of this study was to examine the echogenicities of the muscle with SG-LAI. This study demonstrated 3 patients with schizophrenia under treatment with risperidone (RLAI), paliperidone (PLAI) and aripiprazole (ALAI) (one case each). Quantitative diagnostic ultrasound imaging has been proposed as a method of estimating muscle quality using echogenicities. Grayscale histogram analysis of Photoshop Premiere Elements 14.0 was used to determine the muscle tissue echogenicity in a region of interest (ROI). The pre- and post-injected SG-LAI echogenicities were analyzed using a paired *t*-test with a significance level of 5%. Each SG-LAIs could be illustrated as high echogenic masses with acoustic shadowing. The corresponding grayscale histogram values of selected ROI in the injected muscles were significantly increased in all cases. It was considered that the diffusion states of SG-LAIs by ultrasonography were important time course evaluations providing objective evidence.

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

(Received February 28, 2017; Accepted April 20, 2017)

Introduction

Antipsychotic depots or long-acting injections were introduced in the 1960s as a means of improving medication adherence and thereby enhancing desired clinical outcomes¹⁾. Several first-generation (FG)-long-acting inject-

able antipsychotics (LAIs) and three second-generation LAIs (SG-LAIs) are currently available for administration into either the gluteal or deltoid muscle. These LAIs are administered by intramuscular (IM) injection. A single injection effect lasts within the range of 1 week to 3 months, depending on the compound and formulation^{2,3)}.

Reprint request

安原由子：〒770-8509 徳島県徳島市蔵本町 3-18-15 徳島大学大学院医歯薬学研究部保健科学部門看護学系看護管理学分野
Yuko YASUHARA: Department of Nursing Outcome Management, Institute of Biomedical Sciences, Tokushima University Graduate School, 18-15, Kuramoto-cho 3, Tokushima 770-8509, Japan
E-mail: yasuhara@medsci.tokushima-u.ac.jp, Tel and Fax: +81-88-633-7629

Risperidone long-acting injection (RLAI)^{4,5)} was the first SG-LAI. Since then, two other SG-LAIs, paliperidone LAI (PLAI⁶⁾), and aripiprazole LAI (ALAI)⁷⁾ have become available in Japan. These new formulations provide patients and physicians a choice of administration site for LAI.

Meanwhile, side effects/adverse events with these drugs may occur. It was reported that in the case of a malignant syndrome in patients who received RLAI^{8,9)}, 19.9% was discontinued due to adverse events in the case of PLAI during the trial in Japan¹⁰⁾. Also, there are no specific antidotes to SG-LAIs. These LAIs require medical supervision, and monitoring should continue until the patient recovers¹¹⁻¹³⁾. If serious adverse events occur, it is desirable to be able to remove an injected LAI from muscle. Therefore, it is considered important that ultrasonic diagnostic apparatus is useful for identifying injected LAI into the muscle.

Previous study has confirmed cases in which LAI diffused in the gluteus muscle and diffuses along the fascia. This was evidenced by using an ultrasonic diagnostic apparatus¹⁴⁾. Also, it was observed that both RLAI and ALAI were depicted as having high echogenicity with acoustic shadowing and high echogenic mass in the gluteus medius¹⁵⁾. Quantitative diagnostic ultrasound imaging has been proposed as a method for estimating muscle quality using measures of echogenicity¹⁶⁾.

However, no studies have revealed the change in brightness before and after administration of LAIs. Also, few cases have revealed the change in brightness of muscle tissue echogenicity in a region of interest (ROI) before and after administration of LAIs. This study provides specific three cases of change in brightness of muscle tissue echogenicity in a ROI of patients with schizophrenia under treatment with RLAI, PLAI and ALAI.

Methods

1. Subjects

Three cases were selected to illustrate the diffusion effects of RLAI, PLAI and ALAI. A case without apparent redness or ulceration at the injection site was selected.

2. Ultrasonographic measurements

Before administration of LAI, double-cross injection site of the buttocks was marked with a felt-tipped pen^{17,18)}. Dorsogluteal IM injection sites were measured with the subjects at prone position to identify with an imaginary cross then dividing the upper outer quadrant again by another imaginary cross.

Prior to the IM injection maneuver, the B-mode scan was used to examine 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 by an experienced sonographer using a 7.5 MHz linear and convex array transducer and the Noblus Digital Diagnostic Ultrasound Scanner (Hitachi Ltd, Japan). And it took approximately 15 min to measure these data.

3. Grayscale histogram analysis

Quantitative diagnostic ultrasound imaging has been proposed as a method for estimating muscle quality using measures of echogenicity.

Digitized grayscale images were stored in a computer as a collection of individual spots or pixels of light. 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 intensity¹⁹⁾.

Grayscale histogram analysis of Photoshop Premiere Elements 14.0 was used to determine the muscle tissue echogenicity in a ROI²⁰⁾. The corresponding grayscale histogram analysis data for each sonographic image showed similar estimates of gluteus muscle echogenicity using both ROI selection methods.

The injection site after the LAI injection has high brightness part (upwardly convex) and the artifact (acoustic shadowing) just below the high brightness part. The ROI were placed in the high brightness region excluding the hair line on the surface and acoustic shadowing. ROI, as a pre-injected control values in grayscale analysis, was placed at the same depth in the injected site. However, there was deformity due to the injected medicine after injection, therefore the same site was estimated from the positional relationship with the fascia, iliac bone, and an ROI of the same size as the post-injection ROI was set. This ROI was used as the baseline grayscale value.

A paired *t*-test with a significance level of 5% was used to analyze the differences in echogenicity expressed as grayscale values (number of pixels) using the selected pre- and post-images of the ROI.

4. Ethical consideration

This study was conducted after approval was received

Table 1 The corresponding grayscale histogram values of ROI in the injected muscles

	The number of pixels of ROI	Grayscale histogram values		<i>t</i>	<i>p</i>
		Before RLAI administration	During administration		
		Mean $\pm$ SD	Mean $\pm$ SD		
RLAI (Case 1)	1,166	81.80 $\pm$ 14.32	205.21 $\pm$ 29.80	127.46	***
PLAI (Case 2)	754	161.69 $\pm$ 22.67	200.25 $\pm$ 25.63	30.94	***
ALAI (Case 3)	675	109.20 $\pm$ 6.46	175.82 $\pm$ 12.79	120.79	***

Paired *t*-test: ****p* < 0.001.

ROI: region of interest; RLAI: risperidone long-acting injectable antipsychotics; PLAI: paliperidone long-acting injectable antipsychotics; ALAI: aripiprazole long-acting injectable antipsychotics.

Fig.1 Pre- and post-typical ultrasonic images of region of interest and the corresponding grayscale histogram values in ALAI (Case 3)

B-mode finding of the gluteal muscle in pre- (upper) and post-injection (lower) of ALAI. After administration of ALAI, the mean grayscale histogram values became higher compared with the pre-injected values. ALAI medications were depicted as a high echogenic mass with acoustic shadowing.

from Tokushima University Hospital Ethics Committee (approval number 2948).

Results

RLAI, PLAI and ALAI medications were depicted as a high echogenic mass with acoustic shadowing. The corresponding grayscale histogram values of selected ROI in the injected muscles were significantly increased in all cases (Table 1). Typical case in ALAI is shown on Fig.1.

Case 1 is an example of RLAI. Gender: male. Age: 30 years old. Height: 168 cm. Body weight: 68.6 kg, BMI:

24.3 kg/m². RLAI dosage was 25 mg. Depth of inserted needle was 50 mm.

Corresponding grayscale histogram values were significantly higher during administration (205.21 $\pm$ 29.80) than before RLAI administration (81.80 $\pm$ 14.32) (*t* = 127.46, *p* < 0.001, the number of pixels of ROI was 1,166).

Case 2 is an example of PLAI. Gender: female. Age: 50 years old. Height: 159 cm. Weight: 60.9 kg, BMI: 24.1 kg/m². PLAI dosage was 100 mg. Depth of inserted needle was 30 mm.

Corresponding grayscale histogram values were signifi-

cantly higher during administration (200.25 ± 25.63) than before PLAI administration (161.69 ± 22.67) ($t = 30.94$, $p < 0.001$, the number of pixels of ROI was 754).

Case 3 is an example of ALAI. Gender: male. Age: 50 years old. Height: 165 cm. Weight: 99.7 kg, BMI: 36.6 kg/m^2 . ALAI dosage was 400 mg. Depth of inserted needle was 38 mm.

Corresponding grayscale histogram values were significantly higher during administration (175.82 ± 12.79) than before LAI administration (109.20 ± 6.46) ($t = 120.79$, $p < 0.001$, the number of pixels of ROI was 675).

Discussion

The brightness on grayscale histogram analysis of LAI injection site was significantly higher during the injection as compared with the before the injection image in all cases. The t value showing the degree of significant change in brightness: $t = 30.94$ in Case 1 (RLAI), $t = 127.46$ in Case 2 (PLAI), and $t = 120.79$ in Case 3 (ALAI), each.

Differences in diffusion state were observed in RLAI, PLAI, and ALAI under visual confirmation by the ultrasonography. It was considered that the influence of the particle size of the water-soluble suspension of LAI, the steric molecular structure, the amount of air contained in the particles, and the concentration of the suspension.

The particle size of each LAI is a dispersed suspension using Microscopic RLAI is 25 to $150 \mu\text{m}^{21)}$, PLAI is nanometer size microcrystals²²⁾. Also, the ALAI of nanoparticles is 1 to $10 \mu\text{m}^{23)}$. The difference in this property and the length of injection needles (RLAI is 50 mm, PLAI and ALAI are 38 mm) might reflect the echogenicity on B-mode scan.

In the future, it is necessary to increase the number of subjects and to clarify the differences including the change rate of brightness by each LAI, age, and administration periods of LAI. In this study, the change in brightness immediately after administration of LAI was examined, but it was considered there was a possibility that adverse events may occur after a lapse of time. Therefore, it is also necessary to observe changes in brightness of the injection site of the drug over time.

Conclusion

This study measured the brightness semi-quantitatively using grayscale histogram analysis. RLAI, PLAI and ALAI medications were depicted as a high echogenic mass with acoustic shadowing. The corresponding grayscale histo-

gram values and echo intensity of selected ROI in the injected muscles were significantly increased in RLAI, PLAI, ALAI cases. It was considered that the diffusion states of SG-LAIs by ultrasonography were important time course evaluation providing objective evidence. Representative examples of three drugs are presented, but each has its own characteristics, suggesting the possibility of being distinguished by ultrasonic diagnostic equipment.

Acknowledgments

The authors would like to thank the patients of the study and all staff members of the hospital who helped in the research.

Disclosure: The authors report no conflicts of interest in this work.

References

- 1) Singh SM, Haddad PM, Husain N, et al.: Cross-sectional comparison of first-generation antipsychotic long-acting injections vs risperidone long-acting injection: patient-rated attitudes, satisfaction and tolerability. *Ther Adv Psychopharmacol* 2016; 6: 162-171. doi: 10.1177/2045125316632458.
- 2) Agid O, Foussias G, Remington G: Long-acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention. *Expert Opin Pharmacother* 2010; 11: 2301-2317; doi: 10.1517/14656566.2010.499125.
- 3) Magnusson MO, Samtani MN, Plan EL, et al.: Population Pharmacokinetics of a Novel Once-Every 3 Months Intramuscular Formulation of Paliperidone Palmitate in Patients with Schizophrenia. *Clin Pharmacokinet* 2016; 56: 421-433. doi: 10.1007/s40262-016-0459-3.
- 4) Janssen Pharmaceutical K.K.: New release RISPERDAL Consta® Intramuscular Injection [internet]. [accessed 2017 Jan 17], <http://www.janssen.com/japan/press-release/20060623> (in Japanese).
- 5) Olivares JM, Rodriguez-Morales A, Diels J, et al.: Long-term outcomes in patients with schizophrenia treated with risperidone Long-acting injection or oral antipsychotics in Spain: Results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiatry* 2009; 24: 287-296; doi: 10.1016/j.eurpsy.2008.12.002.
- 6) Janssen Pharmaceutical K.K.: New release XEPLION® Aqueous Suspension for IM Injection [internet]. [accessed 2017 Jan 17] <http://www.janssen.com/japan/press-release/20130920> (in Japanese).
- 7) Otsuka Pharmaceutical Co.: Otsuka Granted Approval in Japan for a New Formulation of ABILIFY – ABILIFY for Extended-release Injectable Suspension, for Intramuscular Use – Indicated for Schizophrenia [internet]. [accessed 2017 Jan 17] https://www.otsuka.co.jp/en/company/release/2015/0326_03.html
- 8) Mall GD, Hake L, Benjamin AB, et al.: Catatonia and mild neuroleptic malignant syndrome after initiation of long-acting injectable risperidone: case report. *J Clin Psychopharmacol* 2008; 28: 572-573. doi: 10.1097/JCP.0b013e318185a6ee.
- 9) Yamashita T, Fujii Y, Misawa F: Neuroleptic malignant syndrome associated with risperidone long-acting injection: a case report. *J Clin Psychopharmacol* 2013; 33: 127-129. doi: 10.1097/01.jcp.0000426180.89572.51.

- 10) Takahashi N, Takahashi M, Saito T, et al.: A Long-term, Open-Label Study of Paliperidone Palmitate in Patients with Schizophrenia. *Prog Med* 2013; 33: 2393-2412 (in Japanese).
- 11) Janssen Pharmaceutical K.K.: Risperdal CONSTA® Intramuscular Injection, Interview Form [internet]. [accessed 2017 Jan 17]
<http://database.japic.or.jp/pdf/newPINS/00056941.pdf> (in Japanese)
- 12) Janssen Pharmaceutical K.K.: XEPLION® Intramuscular injection, Interview Form [internet]. [accessed 2017 Jan 17]
<http://database.japic.or.jp/pdf/newPINS/00062041.pdf> (in Japanese).
- 13) Otsuka Pharmaceutical Co.: ABILIFY® prolonged release aqueous suspension for IM injection, Interview Form [internet]. [accessed 2017 Jan 17]
<https://www.otsuka-elibrary.jp/di/prod/product/file/abj/abjbnotk.pdf> (in Japanese).
- 14) Yasuhara Y, Sakamaki S, Tanioka T, et al.: Optimal length of intramuscular injection needle and drug absorption by ultrasound evaluation. *Neurosonology* 2013; 25: 91-94 (in Japanese).
- 15) Yasuhara Y, Tanioka T, Takase K, et al.: Intramuscular diffusion status of risperidone and aripiprazole Long Acting Injectable (LAI) by ultrasonography. *Open J Psychiatr* 2016; 6: 165-172. doi: 10.4236/ojpsych.2016.62020.
- 16) Matsumoto S, Tai K, Ichimaru K, et al.: Examination of echo intensity by comparison with control muscle. *Neurosonology* 2015; 28: 49-53. doi: 10.2301/neurosonology.28.49 (in Japanese)
- 17) Cocoman A, Murray J: Intramuscular Injections: a review of best practice for mental health nurses. *J Psychiatr Ment Health Nurs* 2008; 15: 424-434. doi: 10.1111/j.1365-2850.2007.01236.x.
- 18) Tanioka T, Sakamaki S, Yasuhara Y, et al.: Optimal needle insertion length for intramuscular injection of risperidone long-acting injectable (RLAI). *Health* 2013; 5: 1939-1945. doi: 10.4236/health.2013.512262.
- 19) Lal BK, Hobson RW 2nd, Pappas PJ, et al.: Pixel distribution analysis of B-mode ultrasound scan images predicts histologic features of atherosclerotic carotid plaques. *J Vasc Surg* 2002; 35: 1210-1217. doi: 10.1067/mva.2002.122888.
- 20) Harris-Love MO, Seamon BA, Teixeira C, et al.: Ultrasound estimates of muscle quality in older adults: reliability and comparison of Photoshop and Image J for the grayscale analysis of muscle echogenicity. *PeerJ* 2016; 4 : e1721. doi: 10.7717/peerj.1721.
- 21) D'Souza S, Faraj JA, Giovagnoli S, et al.: Development of risperidone PLGA microspheres. *J Drug Deliv* 2014; 2014: 620464. doi: 10.1155/2014/620464.
- 22) Junghanns J, Muller R: Nanocrystal technology, drug delivery and clinical applications. *Int J Nanomedicine* 2008; 3: 295-309. doi: 10.2147/IJN.S595.
- 23) Kostanski JW, Matsuda T, Nerurkar M, et al.: Controlled release sterile injectable aripiprazole formulation and method. US Patent No.8030313 B2, 2007.
<https://www.google.com/patents/US8030313>