

Intramuscular Diffusion Status of Risperidone and Aripiprazole Long Acting Injectable (LAI) by Ultrasonography

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Abstract

The aim of this study was to consider the characteristics of intramuscular diffusion status of risperidone and aripiprazole long acting injectable (LAI) by ultrasonography. Subjects were 40 adult subjects diagnosed with schizophrenia and treated with LAI [32 patients were risperidone LAI (RLAI) and 8 patients were aripiprazole LAI (ALAI)]. However, in this paper, only three cases (one RLAI case and 2 ALAI cases) were selected to illustrate the diffusion effects of both LAI. Dorsogluteal intramuscular (IM) injection sites were measured at prone position using the “double cross” method. Before LAI injection, the distance from the epidermis to the under-fascia (DEUF), and distance from the epidermis to the iliac bone (DEI) at the IM injection site were assessed by using ultrasonography: 1) the injection needle was inserted to the gluteus medius, and 2) observed the diffusion status within the muscle injected RLAI and ALAI were confirmed using the B-mode ultrasonography. Both RLAI and ALAI were depicted as high echogenicity with acoustic shadowing. It was considered that the diffusion states of LAIs by ultrasonography were important time course evaluations providing objective evidence.

Keywords

Diffusion Status, Risperidone, Aripiprazole, Long Acting Injectable (LAI), Ultrasonography

1. Introduction

Long-acting injectable (LAI) is an approach to administering typical and atypical anti-psychotic medications for patients with schizophrenia [1]. Since the introduction of risperidone LAI (RLAI) in 2009 in Japan [2], two additional atypical antipsychotics have become available in LAI formulation: paliperidone [3] (2013) and aripiprazole [4] (2015).

RLAI is the first atypical antipsychotic available in an injectable formulation, and its efficacy and tolerability have been demonstrated in clinical trials [5]-[7]. Recently, a second generation antipsychotic is developed as a long-acting injection, in the form of a suspension of lyophilized aripiprazole reconstituted with an aqueous diluent, for intramuscular administration [8]. Aripiprazole LAI (ALAI), an extended-release injectable suspension for intramuscular use, is the first dopamine partial agonist available as an LAI and is approved for the treatment of schizophrenia [9] [10]. ALAI has a lower metabolic risk [11] and a lower risk for QT prolongation [12]. Although these different depot options help with medication adherence and encourage better treatment outcomes, these options differ in terms of specific indications, approved injection sites, needle gauge and length, injection interval, availability of prefilled syringes, and potential for drug-drug interactions [13].

In many countries, these LAIs are approved for the treatment of schizophrenia and administered intramuscularly using the deltoid or gluteal muscles [14]. The suggested site for RLAI is the gluteal muscle with a needle length of 2 inches (50 mm) [15], while with ALAI [16] the suggested site is the gluteal muscle with a needle length of 1.5 inches (38 mm) [17].

LAIs are administered using different types of needle gauges and for intramuscular (IM) injection. Nurses and physicians need to assess the injection sites and how to insert the needles. Previous study [18] reports injection needle lengths for optimal IM injection for adult subjects. Previous research using ultrasonographic data is used to detect insertion sites [19], depth of needle insertion into specific muscles [20], and visualization of medication dispersions [21].

Some disadvantages of LAIs include: retention of medications in the muscles for a long period of time. It is also known that IM injections have injection site side-effects [22]. To prevent these, it is critical to evaluate the anatomical and morphological changes before and after LAIs are injected by using a non-invasive ultrasonography. However, little is known about how LAIs are diffused in the gluteal muscle tissue.

The aim of this study is to consider the characteristics of intramuscular diffusion status of RLAI and ALAI by the ultrasonography.

2. Materials and Methods

2.1. Subjects

Subjects were 40 adult subjects diagnosed with schizophrenia and treated with LAI (32 RLAI and 8 ALAI). These patients were recruited from hospitals within the Kumamoto and Aomori prefectures in Japan. Criteria for participant selection included, being diagnosed with schizophrenia based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) F2 criteria. Inclusion criteria were a diagnosis of schizophrenia; treated with RLAI or ALAI; and aged between 20 - 70 years. Exclusion criteria were diagnosis of systemic or neurologic diseases, including disturbances of hematopoiesis; pregnant; dependent on any substances other than nicotine during the 5 years before enrollment; and communication difficulty.

2.2. Methods of Collection of Typical Examples, and the Study Period

The study was conducted from June 2013 to November 2015. During this period, all subjects were examined by ultrasonography. However, in this paper, only three cases (one RLAI and 2 ALAI cases) were selected to illustrate the diffusion effects of both LAI.

2.3. Measurement

Dorsogluteal IM injection sites were measured with the subjects at prone position to identify the injection site using the "Double Cross" method [23]. This method divides the buttocks with an imaginary cross then dividing the upper outer quadrant again by another imaginary cross.

Before LAI injection, the distance from the epidermis to the under-fascia (DEUF), and distance from the epi-

dermis to the iliac bone (DEI) at IM injection site was assessed using ultrasonography. Then, 1) the injection needle was inserted to the gluteus medius, and 2) observation of the diffusion state of injection solution under the B-mode ultrasonography. All ultrasonographic measurements were performed by an experienced sonographer using a 7.5 MHz linear and convex array transducer and the Digital Diagnostic Ultrasound Scanner (Hitachi Medical Corporation, Japan).

2.4. Ethical Consideration

This study was conducted after approval was received from Tokushima University Hospital Ethics Committee (approval number 2948). Both verbal and written consents were obtained from the prospective subjects of the study. Patient consent for ultrasonography images was also obtained. The consent also included a statement of understanding that images may be used for educational purposes, lectures, and publications.

3. Results

Figures 1-3 exhibit the diffusion of RLAI and ALAI in the corresponding muscles of each case. In all subjects, injected LAIs in the muscle were clearly confirmed on B-mode images. Both RLAI and ALAI in all of the 40 cases showed the high echogenicity with acoustic shadowing. Immediately after the injection of RLAI and ALAI into the muscles the medications could be monitored by ultrasonography in all cases. However, the degree of acoustic shadowing of ALAI was stronger than RLAI.

Case 1: Typical Example of RLAI Ultrasound Data

Figure 1 is a typical example of RLAI. Gender: male. Age: 50 years old. Height: 158.0 cm. Weight: 45.0 kg. BMI: 18.1 kg/m². Left side DEUF of gluteus medius was 9.4 mm, and DEI was 50.1 mm.

Case 2: Typical Example of ALAI Ultrasound Data

Figure 2 is atypical example of the diffusion of the ALAI. Gender: male. Age: 57 years old. Height: 148 cm. Weight: 61.5 kg. BMI: 28.08 kg/m². ALAI dosage: 400 mg. Right side DEUF of gluteus maximus was 16.2 mm, gluteus medius was 21.4 mm, and DEI was 63.4 mm.

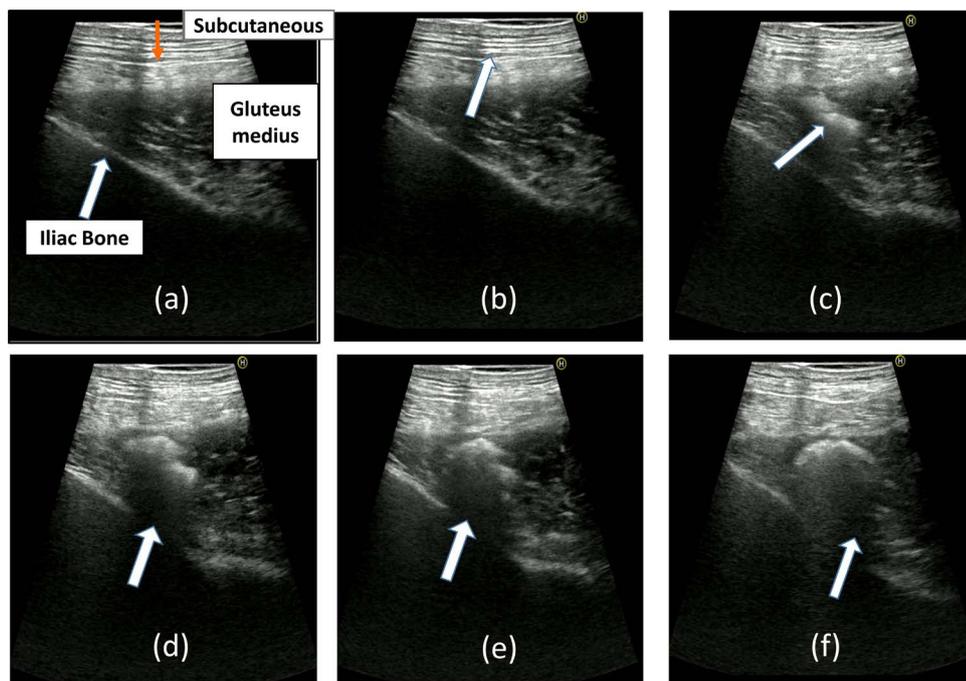


Figure 1. Typical example of ultrasound images in RLAI (case 1) from before injection to after injection. (a) Iliac bone appears as a distinct bright echogenic line with no visible structures beneath. (b) View of gluteal muscle and fascia using a convex transducer. (c) This is the image of RLAI at the time of start injection. (d) This was the image in RLAI diffusion. In the deep area, attenuation by acoustic shadow was observed by RLAI injection, a state where the iliac became unclear. (e) This situation was internal flow of RLAI in the muscle. (f) This is an image after RLAI injection.

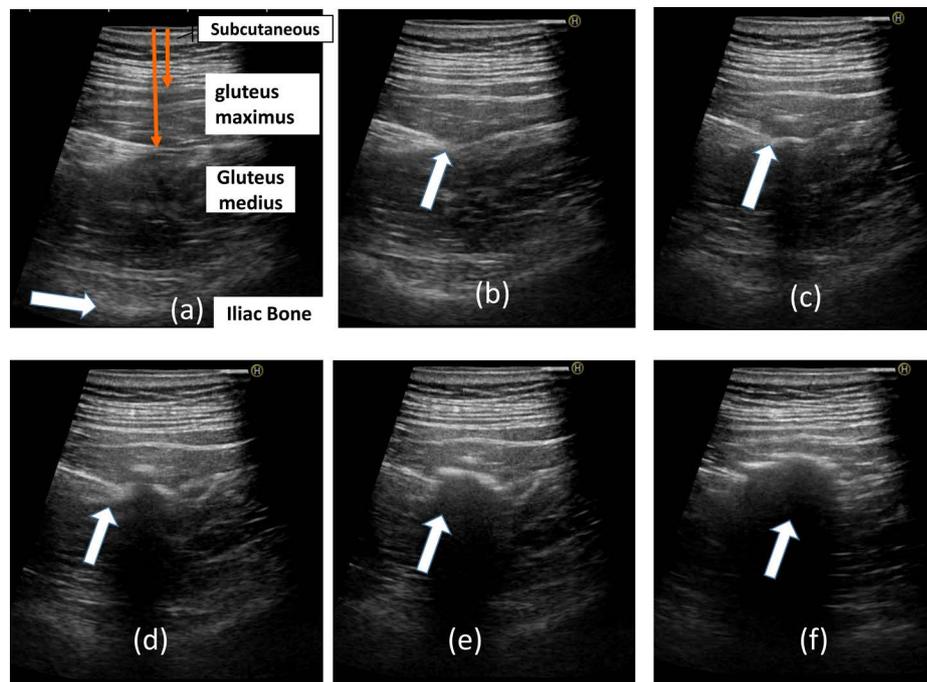


Figure 2. A patient with schizophrenia, Gender: man, Aged: 57. Height: 148 cm. Weight: 61.5 kg. BMI: 28.08 kg/m². ALAI dosage: 400 mg. Right side DEUF of gluteus maximus was 16.2 mm and gluteus medius was 21.4 mm Left side DEI was 63.4 mm. (a) Iliac Bone appears as a distinct bright echogenic line with no visible structures beneath. (b) View of gluteal muscle: By the insertion of the needle to the gluteus medius muscle membrane, distortion of the fascia is observed. (c) this is the image of RLAI at the time of start injection. (d) In the deep area, attenuation by acoustic shadow is observed by ALAI injection. This image is an injection of ALAI into the gluteus medius; diffusion of ALAI is also observed in the gluteus maximus muscle. (e) Acoustic shadow is maximized by the injection of ALAI, the iliac cannot verify in this image. (f) This is an image after ALAI injection.

Case 3: Typical Example of ALAI Ultrasound Data

Figure 3 is a typical example of the diffusion of the ALAI. Gender: female. Age: 56 years old. Height: 148 cm. Weight: 63.9 kg. BMI: 29.17 kg/m². ALAI dosage: 400 mg. Left side DEUF of gluteus medius was 17.4 mm, and DEI was 54.0 mm.

4. Discussion

The LAIs were noted as high echogenic masses with an acoustic shadowing. Also, B-mode finding can provide the minute information of the locations, sizes, shapes of injected LAIs.

Acoustic shadowing is an artifact seen in ultrasound imaging in which an intensely echogenic line appears at the surface of structures which block the passage of sound waves [24]. In RLAI, part of the ilium was not visualized by an acoustic shadow from midway through injection. However, the attenuation by the acoustic shadow in the deep part near the center of the tip around the injection needle immediately after ALAI was injected. Therefore, the ilium was not visualized.

It was confirmed that the difference between the diffusion images of the drug particles after dissolution of RLAI and ALAI was evident. The particle size of the microsphere of RLAI formulation has been reported to be between 25 and 150 micrometers [6]. It might be the differences of the composition of the suspension that contributed to the cause of the difference of the acoustic shadow on post-injection. Also, RLAI has attached microspheres with the drug, and is uneven in the shape of the surface. The reports from clinical site, the aqueous solution after dissolution indicates that there is a clotting potential of microsphere by its dosage form in an injection syringe.

On the one hand, ALAI is a lyophilized powder that needs to be reconstituted with sterile water to form an injectable suspension without affecting the original molecule. Aripiprazole having a mean particle size of about 1 to 10 microns [10] as described above is characterized by particles which are smaller than risperidone.

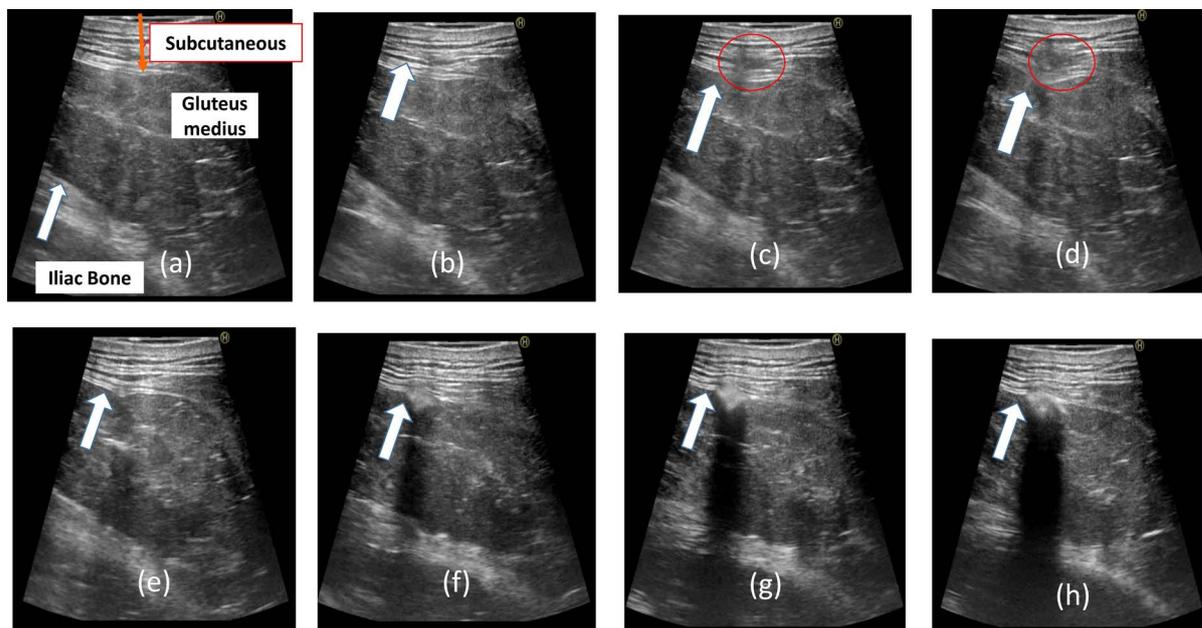


Figure 3. A patient with schizophrenia, Gender: woman. Aged: 56. Height: 148 cm. Weight: 63.9 kg. BMI: 29.17 kg/m². ALAI dosage: 400 mg. Left side DEUF of gluteus medius was 17.4 mm Left side DEI was 54.0 mm. (a) Before needle puncture, iliac can be confirmed. (b) Insertion position of the injection needle. (c) The tip of the needle has been confirmed in the gluteus maximus. (d) The needle has been confirmed in the gluteus maximus muscle, the fascia of the gluteus maximus is distorted at the bottom by pressure on the fascia of the injection needle. (e) By the penetration of the injection needle, the gluteus maximus is returned to the original position. (f) ALAI injection at the start of the image. By injection of ALAI, attenuation by acoustic shadow was observed in the deep part. (g) By acoustic shadow due to the injection of ALAI, iliac is unclear.

The B-mode images of ALAI had more sharpened margins and strong acoustic shadowing compared with those of RLAI. This study provided a non-invasive method for distinguishing these LAIs.

The RLAI is administered to the buttocks using a dedicated injection needle size (20 G, 2 inches). Also, ALAI is administered using the 22 G (38 mm) injection needle in Japan. Comparison of the injection needle, ALAI has a small inner diameter of the needle than the RLAI. Therefore, there is a possibility that ALAI injection can be administered faster than RLAI. Internal diameter is proportional to the outside diameter, resulting in difference in time of delivery of medication during injection of the drug solution with RLAI and ALAI. There is a possibility of an image difference considering diffusion state.

Many LAIs are formulated to create a poorly soluble depot from which the active agent is delivered over time. In animal experiments (in both non-human primates and rodents) [25], after LAI injected into intramuscular and subcutaneous tissue was reported to have reaction changes. Therefore, it was thought that these long acting injectables are at risk for developing localized chronic-active inflammation in the tissue.

In human being, RLAI studies [26] [27] reported that drug injection sites for the majority of patients revealed no redness, swelling, tenderness, or induration at either the deltoid muscle or gluteal muscle injection sites. Moreover, for the majority of patients, ALAI study [28] reported absence of any pain, redness, swelling and induration following the first and last injections of aripiprazole 400 mg monthly.

Nevertheless, severe complications from injection site reactions have been reported [29]. Clinically, it is difficult to evaluate and study the precise location of an injected medication into the buttocks. Computed Tomography (CT), can evaluate whether the drug reached the muscle or the subcutaneous tissue [30] [31]. In the clinical practice, CT is difficult to use to evaluate the precise location of an injected medication into the buttocks. Therefore, it is not a standard procedure to use any other monitoring device during hypodermic injections.

An actual visualization method of the site of injection immediately after injection is required to accurately assess the deposition of the medication during IM injections. It was considered a beneficial finding from using the ultrasonographic evaluation to determine the diffusion status of medications injected into the muscle, in patients treated with LAI. Therefore it is important as the future of clinical studies, to clarify the diffusion of LAI in the muscle using the B-mode ultrasonography.

In this paper, we reported the characteristics of the diffusion status of RLAI and ALAI. It was considered that the diffusion state was related to the dose and muscle mass and type of drugs, and the difference in the rate of administration. However, the data exhibited that the extensive shadowing may severely diminish image quality or completely erase the information behind the injected LAIs. This was one of the disadvantages in evaluating the IM injection by ultrasonography.

It is important to note, however, that the procedure for data collection was used in four other successful investigations by Tanioka, Yasuhara, and Sakamaki *et al.* [19]-[21] [32]. This procedure provided credible data on diffusion location, rates, and absorption using RLAI. While prior studies used risperidone, the present study used ultrasound imaging of aripiprazole. However, one of the major limitations of this study is concerning subject selection. While RLAI was administered twice a month, ALAI was administered to patients only once a month. In particular, ALAI was only launched in 2015 in Japan. Therefore, prospective subjects were limited and difficult to recruit to obtain comparable subjects. Nevertheless, the protocol of the data collection was not a problem. Similarly, the ultrasonographic instrument was always available at the appointed time for data collection.

5. Conclusion

This study of the diffusion status and differences in the muscle of RLAI and ALAI was able to confirm the effect of using different needle sizes through diffusion rates shown by the B-mode ultrasonography. Both RLAI and ALAI medications were depicted as a high echogenic mass with acoustic shadowing. B-mode ultrasonography was one of the most useful monitoring tools for obtaining data from patients with schizophrenia who were treated with LAIs. It was considered that B-mode ultrasonography could provide objective evidence in time course evaluations.

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