*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.*

## Breakthrough symptoms after switching long-acting injectable paliperidone palmitate from the gluteal to the deltoid site of administration

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A 34-year-old white man in whom schizophrenia was diagnosed at the age of 24 years was trialed over the course of illness on risperidone, olanzapine and aripiprazole. Although he responded well to these medications, he experienced relapses secondary to nonadherence. After discussing options to improve compliance and prevent relapse, he agreed to try long-acting injectable paliperidone palmitate. The initiation regimen consisted of 150 and 100 mg administered into the deltoid muscle on days 1 and 8, respectively, followed by 150 mg every 28 days into the gluteal muscle. On this regimen, the patient was free of positive symptoms. After 14 months, his maintenance dose was changed to the deltoid muscle (150 mg every 28 d). Four months later, the week before his next scheduled injection, he had breakthrough auditory hallucinations. As a consequence, the maintenance regimen was changed to 150 mg administered into the deltoid muscle every 3 weeks. The patient has been on this regimen for 9 months without any breakthrough symptoms.

The breakthrough symptoms may have been due to differences in the rate and extent of drug absorption between the sites of injection. The rate of absorption from a depot into the vasculature is influenced by many factors. For example, formulations using different vehicles and salts of the active drug are used to control the rate of drug absorption. Injection technique also impacts bioavailability of drugs administered intramuscularly. Although intended to penetrate the striated muscle fibres, poor technique can result in the drug being deposited into the subcutaneous adipose tissue, resulting in a slower and more erratic rate of absorption. Physiologic factors also impact absorption and bioavailability of drugs administered intramuscularly. Compared with the gluteal muscle, the deltoid muscle has greater blood flow, allowing for a faster rate of drug absorption. Exercise that increases blood flow will also result in a faster rate of drug absorption. Finally, obesity to the point where the injection technique is compromised will reduce overall bioavailability. Taken together, all of these factors can lead to variability in the rate and extent of drug absorption.

Site-dependent differences in the pharmacokinetics of paliperidone palmitate have been documented:

- In a randomized, single-dose, open-label, dose proportionality study of paliperidone palmitate ($n$ = 201), the median maximum plasma concentration (dose normalized to 50 mg) was found to be higher (range 9%–65%) after deltoid injection than gluteal injection.[1] Time to maximum (tmax) plasma concentration and half-life of paliperidone palmitate 150 mg were both shorter when administered into the deltoid muscle than the gluteal muscle (tmax: 14 v. 17 d, respectively; half-life: 40.6 v. 49.1 d, respectively).
- U.S. Food and Drug Administration drug submission review of a population pharmacokinetic study (using simulation scenarios with significant covariates)[2] revealed that compared with deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady state (about 4 wk longer).[3]

By definition, bioequivalence depends on rate and extent of drug absorption.[4] If good injection technique is followed, then the site of administration will not affect the extent to which paliperidone palmitate reaches the systemic circulation. However, the rate of absorption of paliperidone is quicker when administered via the deltoid muscle. As such, administering paliperidone palmitate via the deltoid muscle versus the gluteal muscle may not be bioequivalent.[5]

Clinicians need to be vigilant when switching between administration sites using long-acting injectable paliperidone. Since the rate of absorption via deltoid administration is faster, it is possible that a therapeutic plasma concentration may not be maintained for the duration of the manufacturer's recommended dosage interval of 4 weeks. In such cases, reducing the dosage interval to every 21 days may be appropriate; not every patient receiving paliperidone palmitate via the deltoid muscle needs to be on a 3-week regimen. The rate of absorption from the deltoid muscle is patient-specific and thus the dosing interval will reflect this.

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