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Brief Reports

Plasma Levels of Fluphenazine Decanoate
Effects of site of injection, massage and muscle activity

Depot neuroleptics are now commonly used for maintenance therapy of schizophrenia. Their physicochemical composition makes them ideal for such use because they are long-acting and show stable blood levels for prolonged periods. Their absorption from the site of injection may, however, be affected by local muscle factors. This paper describes three such factors in relation to fluphenazine decanoate: varying the site of injection; massage of the injection site; and effects of muscular exercise. Our results suggest that fluphenazine pharmacokinetics are not significantly affected by any of these factors.

Oral neuroleptics have many practical disadvantages in clinical practice. These include a high rate of non-compliance by patients, an erratic absorption from the gastrointestinal tract, and a high first-pass metabolism in the liver. Depot neuroleptics eliminate or reduce these factors because they are administered directly into skeletal muscles and their absorption into circulation depends on local muscle factors and the physicochemical nature of the preparation.

Three obvious factors do not previously appear to have been investigated. Firstly, the site of injection may be important, since injections given in the buttock region may, in a majority of patients, be deposited, not in muscle, but in subcutaneous adipose tissue (Cockshott *et al*, 1982). Secondly, nurses may or may not apply massage to the site of injection and this could alter the amount of drug entering systemic circulation. Thirdly, anecdotal reports have described occasional stable schizophrenic patients who developed, after a sudden burst of exercise, acute extrapyramidal symptoms, which have been presumed to be due to sudden release of the drug into general circulation from the site of injection. The effects of these factors on the blood levels of fluphenazine decanoate are described here.

Method

Patient characteristics

The patients selected for each of these studies had stable chronic schizophrenia, as diagnosed by Research Diagnostic Critera, and were of either sex and in the age range 18–60 years. All patients had been receiving fluphenazine decanoate injections for more than 12 months, and their dose and interinjection interval had been constant in the previous 6 months.

Designs

Site of injection

Patients who participated in this study ($n=6$), had venous blood samples drawn just before (time 0) and at 0.5, 1, 2, 4, and 8 h after each of two of their normal scheduled injections of fluphenazine decanoate. The first was given in the upper outer quadrant of the buttock, the second in the lateral surface of the thigh, one-third of the distance from the greater trochanter to the lateral epicondyle, using a standard technique on each occasion.

Massage of injection site

The patients who participated in this study ($n=4$) had venous blood samples collected at 0, 0.5, 1, 2, 3, 6, and 24 h after each of two routine injections of fluphenazine decanoate given into the buttock. On the first of these occasions, vigorous massage was applied locally for 15 s after withdrawal of the needle; on the second occasion, no massage was given.

Muscle activity

Four hours after their usual depot injection, (given into the thigh as above), the patients who participated in the study ($n=5$) bicycled for 10 min on a static machine set at ⅓ maximum resistance at a speed equivalent to 12 mph. Venous blood samples were drawn at 1 h, 0.5 h, and just before the exercise, and then soon after, 0.5 h, and 1 h after the exercise had been completed. Blood samples (for control) were also drawn at the same times in relation to the next scheduled depot injection, but with each patient remaining on the bicycle at rest throughout. This study was replicated in another 12 patients on the 7th day post-injection, but without the control session, which was considered unnecessary in view of the short-term stability of plasma fluphenazine levels after the first few days of each injection.

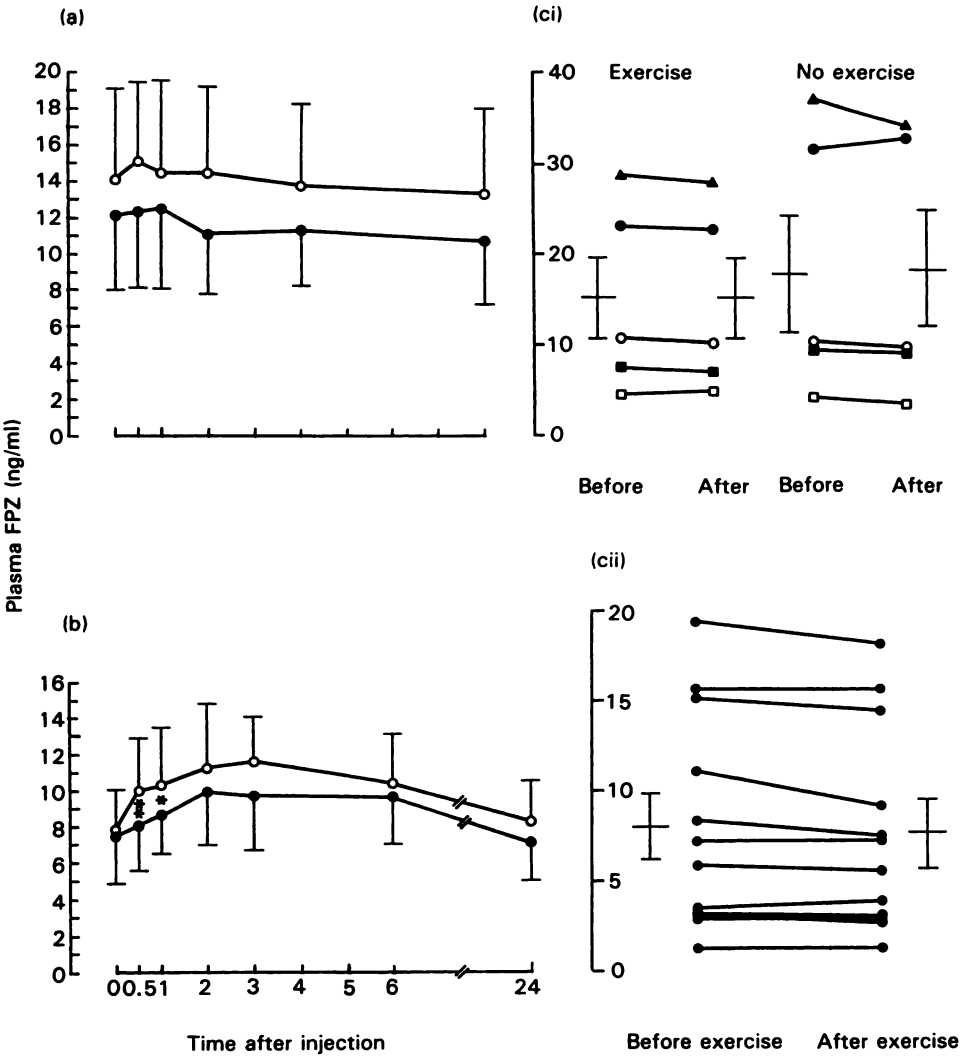

FIG. 1 Plasma concentrations of fluphenazine: (a) effect of changing site of injection ○ = thigh; ● = buttock; $n = 6$; (b) effect of massage of injection site ○ = no massage; ● = massage; $^{**}P = 0.02$, $^{*}P = 0.04$; (c) effect of muscle exercise on the day of injection (i) and on the 7th day post-injection (ii). Vertical bars represent mean ± standard error of the means. Data in (c) is shown for each patient before and after exercise.

Serum neuroleptic assay

This was carried out by the radioimmunoassay technique (Wiles & Franklin, 1978).

Results

The results of these studies are all presented in Fig. 1.

Site of injection

There were no significant differences in the plasma profiles of drug injected in the buttock compared with those from injections into the thigh.

Massage of injection site

At 0.5 and 1 h after injection, plasma fluphenazine concentration after massage was significantly lower than the concentration at the same time-points without massage (comparison of changes from time 0, $P = 0.02$ and 0.04 respectively). None of the subsequent differences in the profiles were statistically significant.

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Muscle activity

After exercise on 7th day post-injection, there was a slight decrease in the mean plasma fluphenazine concentration, which was statistically significant ($P = 0.03$). No differences were observed for exercise on the day of injection. No major clinical events of significance were recorded during the experiments or subsequently.

Discussion

The results of this study suggest that neither active muscular exercise nor the site of injection were pharmacokinetically important factors in the absorption profile of fluphenazine from the standard depot injection of the decanoate dissolved in sesame oil. Previous studies have shown higher and more-rapidly obtained peak blood levels after aqueous injection into the deltoid region as compared with the injection into the buttock (Cohen *et al*, 1972; Schwartz *et al*, 1974), which are not associated with significant differences in blood supply or total drug clearance, and were attributed by Cockshott *et al* (1982) to failure of the buttock injections to reach the muscle layer. The most likely explanation of our results may be related to the mechanism of depot-injection dispersion into oil microglobules that are absorbed, partially via the lymphatic system, into general circulation (Svendson *et al*, 1980). This would tend to minimise differences in absorption rates between different tissues.

The minimal effect of bicycle exercise on the absorption into circulation of fluphenazine decanoate, in contrast to the clear increase in absorption of drugs such as insulin from aqueous solutions, may be explained similarly. What was, in fact, a slight fall in mean plasma level after exercise on the day of injection was less than that of the replication without exercise, and if it represents anything other than random fluctuation, may relate to the declining phase of the post-injection surge of plasma fluphenazine (Wiles & Gelder, 1979). This is unlikely to be the explanation for the small, but statistically significant, decrease 7 days later. However, since the plasma fluphenazine concentration at this time is almost constant within the space of a few hours (Wiles, 1980, unpubl.), it may result from the haemodilution associated with exercise (Diem & Lentner, 1970).

Contrary to what might have been expected, our study of local massage suggests that the manoeuvre causes delay in the absorption of drug, for at least the first hour. The transient vasoconstriction that results from local trauma associated with massage is a possible explanation; Hansen & Kristensen (1973) found a decreased or negative ^{133}Xe clearance value during the 2 min following massage of the calf muscles (triceps surae).

In view of the small number of patients involved in our studies, it would be premature to make broad generalisations. However, our results do confirm, at a pharmacokinetic level, what clinical experience has found to be the case, namely that the majority of schizophrenic patients can be stabilised on a constant dose of fluphenazine decanoate for very considerable periods of time, without significant unpredictable fluctuations in either therapeutic or extrapyramidal effects.

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