Evidence for the Lack of a Human Metabolic Isotope Effect of a Deuterium Analog of Fluphenazine

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INTRODUCTION

The antipsychotic agent fluphenazine is available for oral administration as the hydrochloride salt, or for intramuscular depot injection as the decanoate or enanthate ester. Despite widespread use of the drug over many years, however, there are few data on the single dose pharmacokinetics of fluphenazine in patients. The problem is that newly admitted acute schizophrenic patients are usually too ill to be able to take part in a study designed to establish the single dose pharmacokinetics of fluphenazine after having taken the first dose at the commencement of drug therapy. By the time fluphenazine plasma concentrations have been brought to steady state and the patient's clinical condition has stabilized, it would be unethical to withdraw the drug in order to provide a washout period in preparation for a single dose pharmacokinetic study, and Eichelbaum and coworkers (1) have outlined some of the difficulties involved in the determination of the kinetics of a drug while at steady state. Plasma levels taken during a dosing interval at steady state do not provide reliable data on the elimination $t_{1/2}$ or volume of distribution when the dosing interval (τ) is shorter than the $t_{1/2}$ of the drug, and variation in τ will also lead to inaccuracies in estimates of clearance (1). In consequence, there are few reliable data on the pharmacokinetics of neuroleptic drugs at steady state (2).

An alternative approach to the study of the kinetics of a drug at steady state is to substitute one dose of the unlabeled drug with a single pulse dose of a stable isotope labeled drug (isotopomer). We hypothesize that this approach may be applicable to fluphenazine which has a large apparent volume of distribution (398 ± 202 l, unpublished human intravenous data) and a relatively short half-life (13.1±4.1 h, unpublished human intravenous data). These data imply that there may be a late phase of elimination that has not been detected hitherto because of inadequate assay sensitivity. In clinical practice, however, the daily intake of oral fluphenazine in schizophrenic patients is often administered in divided doses at 6 or 8 hourly (often uneven) intervals that are less than the reported half-life. In this situation, data obtained during a dosing interval at steady state are unlikely to provide reliable information on half life or volume of distribution. The emergence of a putative plasma level range to optimize therapeutic effects and minimize disabling side effects of fluphenazine (3) has given added impetus to the development of techniques to permit targeted dosage adjustments based on the pharmacokinetic characteristics of individual patients.

A series of deuterium labeled analogs of fluphenazine was synthesized in our laboratories (4). Studies in dogs showed that the single dose kinetic profile of $[^2H_4]$fluphenazine (Figure 1) was virtually identical to that of fluphenazine, indicating the absence of any metabolic isotope effect (5). The present study was carried out to investigate whether a metabolic isotope effect was detectable in humans.

MATERIALS AND METHODS

The study was carried out (in accordance with a protocol approved by the local ethics Committee) in five DSM-III-R schizophrenic patients, who had been free from oral fluphenazine for one month and intramuscular fluphenazine for at least three months before the study. After an overnight fast, each patient received a single capsule containing 5 mg fluphenazine dihydrochloride and 5 mg $[^2H_4]$fluphenazine dihydrochloride (4). Venous blood samples (10 ml) were collected in evacuated tubes, without allowing the blood to contact the rubber stoppers (6), immediately predose (0 h) and at, 1, 2, 3, 4, 6, 8, 9, and 24 hours after drug administration. The plasma was immediately separated by centrifugation (3000 × g) for 10 min and stored at −20°C until analysis. Plasma concentrations of fluphenazine and $[^2H_4]$fluphenazine were measured by a new MS-MS method (7) for the simultaneous quantification of fluphenazine and $[^2H_4]$fluphenazine (Figure 1) in plasma.

RESULTS AND DISCUSSION

Plasma concentrations of fluphenazine and $[^2H_4]$fluphenazine were very low after the simultaneous oral administration of 5 mg doses of each isotopomer, the mean maximum concentration being only 232 pg/ml. Nevertheless, the MS-MS analytical method was of adequate sensitivity to allow simultaneous determination of plasma concentrations of both analytes in each patient for 24 h post dose. No drug was detectable in predose plasma samples harvested from any volunteer. Figure 1 shows the individual plasma concentration versus time profiles of fluphenazine and $[^2H_4]$fluphenazine which were almost superimposable for each of the five patients.

Repeated measures (univariate) ANOVA on the log transformed plasma concentrations revealed significant subject effects, as would be expected in view of the reported (8) wide between subject variability in the single dose pharmacokinetics of fluphenazine in psychiatric patients. There was, however, no significant isotopomer effect, which is much more important in the present context. Similarly, examination of within subject effects revealed a significant effect of time and a significant subject by time interaction

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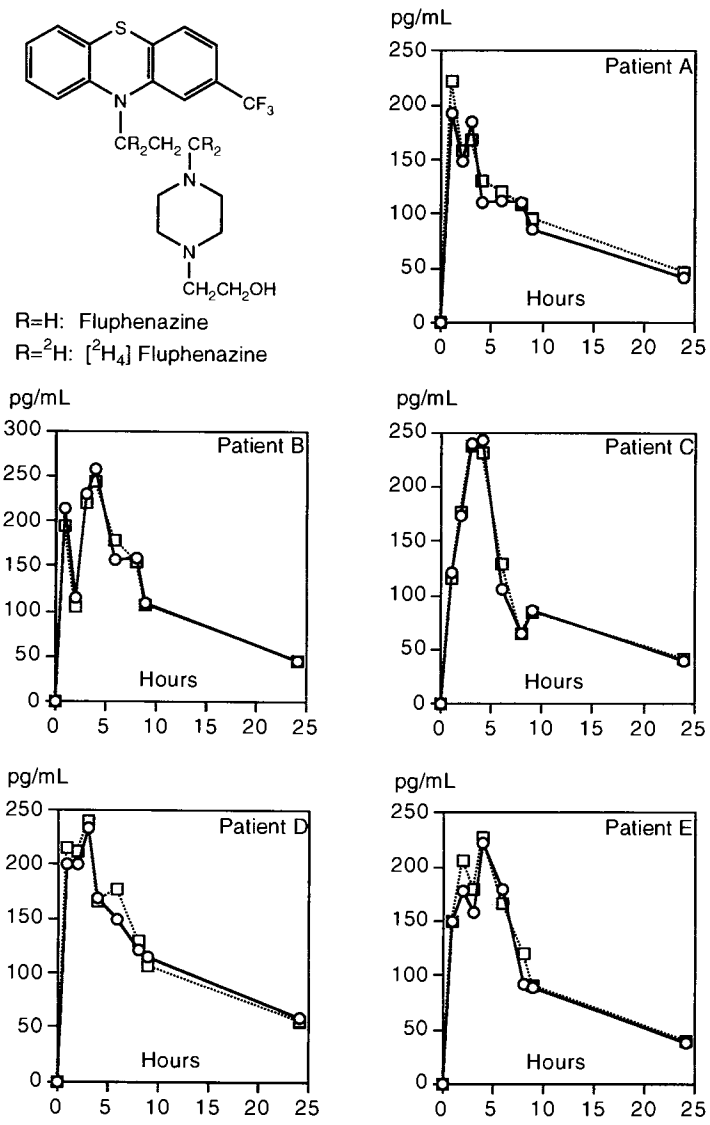

Fig. 1. The structures of fluphenazine and its isotopomer, and the plasma concentration versus time profiles of fluphenazine (circles) and [$^2H_4$]fluphenazine (squares) after oral administration of a capsule containing 5 mg of each isotopomer to each of 5 DSM-III-R schizophrenic patients.

term, which would be expected, but the all important isotopomer v. time interaction term was not significant. It was therefore concluded that there was no significant isotope effect in the human pharmacokinetics of the [$^2H_4$]fluphenazine isotopomer shown in Figure 1. Pharmacokinetic parameters calculated from these data were comparable with those reported previously (8) after a study in which 21 neuroleptic free schizophrenic patients were given 10 mg single oral doses of unlabeled fluphenazine.

The present study showed that the human pharmacokinetics of fluphenazine were not altered by the substitution of four deuterium atoms in place of hydrogens at the positions shown in Figure 1. The most likely reason for the lack of effect is that carbon atoms bearing the isotope labels are not subject to extensive metabolism. These data suggest that [$^2H_4$]fluphenazine is a suitable isotopomer with which to investigate the potential use of the stable isotope in the investigation of the pharmacokinetics of fluphenazine in schizophrenic patients.

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