Human studies on the bioavailability of a quaternary ammonium compound, tiemonium iodide and tiemonium methosulphate

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Summary

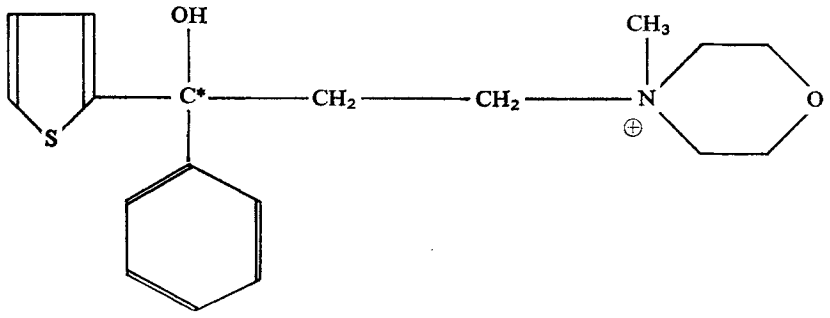
Five volunteers were administered capsules containing ^{14}C-labelled tiemonium iodide and 4 volunteers received capsules of ^{14}C-labelled tiemonium methosulphate. Serum, urine and faecal levels of tiemonium were measured. The percentage of the dose absorbed was determined after a further labelled intravenous injection into 3 of the volunteers. The drug appeared to be poorly absorbed, as expected for quaternary ammonium compounds, but there was no difference in the bioavailability of these two tiemonium salts.

Key words: Tiemonium – quaternary ammonium compounds – radioisotope scanning – biopharmaceutics – pharmacokinetics

Introduction

Previous work on the pharmacokinetics of quaternary ammonium compounds in animals and man has been limited by the lack of serum level data. Early work was carried out on benzomethamine,[5] atropine, and l-hyoscyamine. More recently, hyoscine butylbromide (butylscopolamine) has been studied.[2-4,7,9] All these

Figure 1. Structural formula of tiemonium



*indicates position of ^{14}C

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compounds were found to be poorly absorbed, hence recovery in the urine was low, the majority of the dose being eliminated directly in the faeces.

In an investigation on the bioavailability of two salts of tiemonium ('Viscer-algine'†), the iodide and methosulphate, the use of radioactively labelled compounds has made it possible to follow the time-course of the drug in the plasma of volunteers for up to 8 hours and, therefore, to correlate serum levels of a quaternary ammonium compound with its absorption and excretion pattern in man.

Chemically, tiemonium is 4-[3-hydroxy-3-phenyl-3-(2-thienyl)-propyl-4-methyl-morpholinium. Its structural formula is shown in Figure 1.

Methods and materials

The oral dose of tiemonium used in the trial was decided after an initial tolerance study in 2 healthy male volunteers. Nine healthy male volunteers, aged 30 to 58 years, then took 3 unlabelled 50 mg capsules of either salt in a blind fashion at 09.00, 13.00, and 18.00 hours on the day preceding the trial. A fourth ^{14}C-labelled capsule (30μCi) was administered at 08.30 hours on the day of the trial, the subject having fasted for 12 hours before this dose. A fifth non-labelled capsule was administered at 13.00 hours on the day of the trial, after a light lunch. Fluids were permitted up to 1 hour before oral administration of the product at 08.30 hours. Blood samples were taken at 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48 and 72 hours after administration of the radioactive dose, and were then centrifuged to obtain serum. Urine and faecal samples were collected at 24-hour intervals, up to 72 hours. Following a similar regimen, 3 further volunteers received an injection of 5 mg tiemonium (5μCi) which replaced the fourth oral capsule. Blood sampling in these volunteers was at 0.1, 0.2, 0.3, 0.75, 1, 1.5, 2, 3, 4, 7 and 11 hours.

Radioactivity in the biological samples was measured by liquid scintillation counting in a Packard Tri-Carb Spectrometer Model 2425. Correction for quenching was made by the use of an automatic external standard. Serum (1 ml) was pipetted into a counting vial containing 10 ml Instagel. Urine was treated similarly. Faecal samples were weighed and homogenized in 500 ml distilled water, then 400 mg faecal homogenate was placed in a quartz boat and burnt in a Beckman Biological Material Oxidiser. The carbon - 14 dioxide produced was trapped in 15 ml of a basic scintillation cocktail (Harvey Corporation). The cocktail was then counted and corrected for quenching. All samples were analyzed in duplicate. Urine and faeces radioactivity was expressed as a percentage of the dose administered.

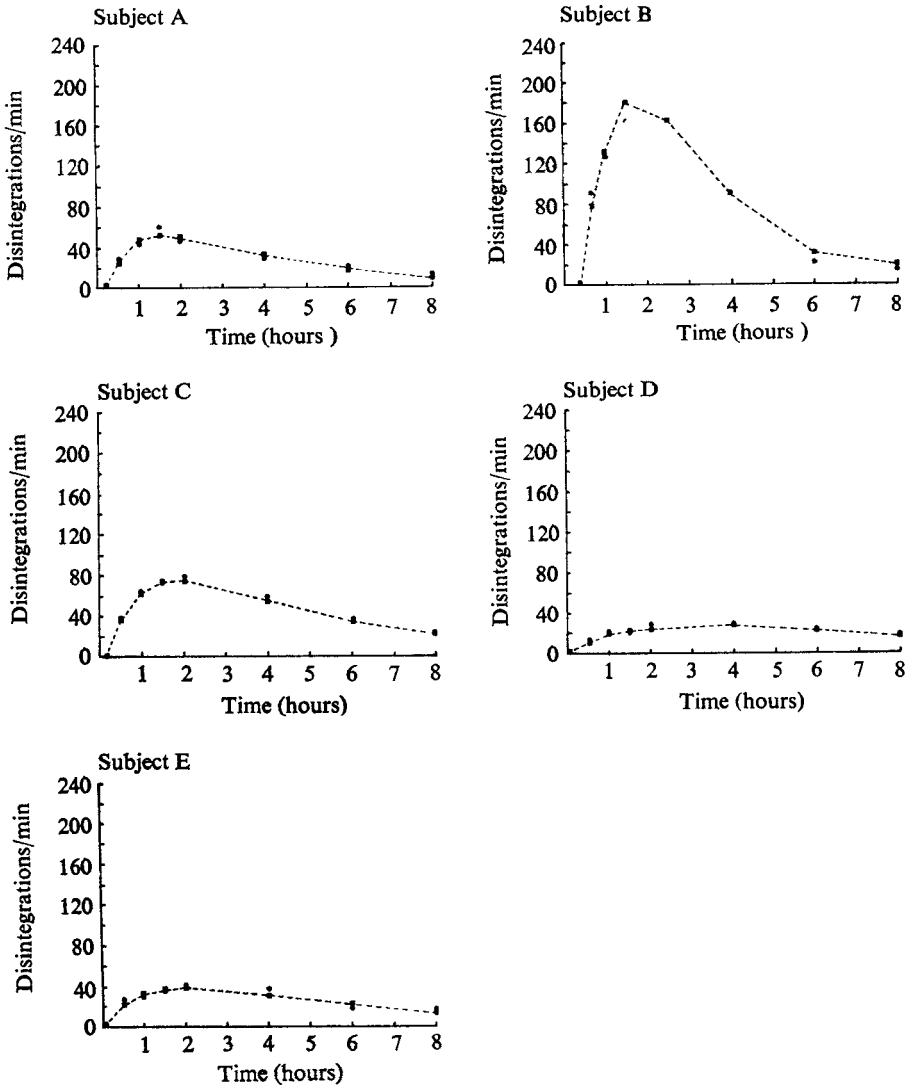
Results

Serum levels

The serum levels of tiemonium iodide after the 50 mg labelled capsule are shown for the 5 subjects in Figure 2. Similarly, the serum levels for the 4 subjects taking tiemonium methosulphate are shown in Figure 3.

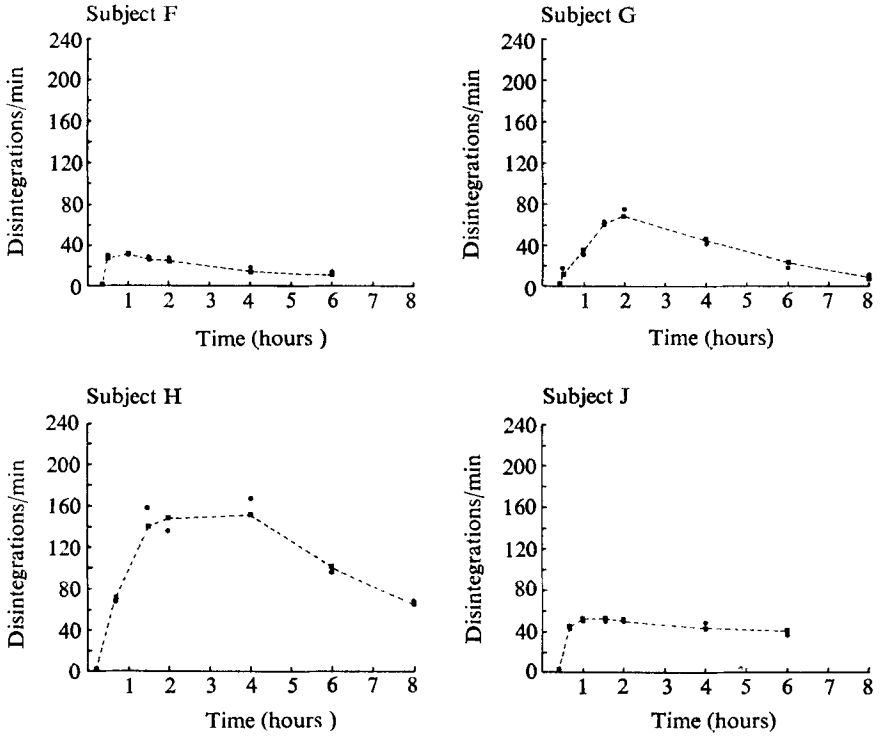
†trade mark, CERM

Figure 2. Serum levels of ^{14}C tiemonium iodide in 5 normal volunteers after oral administration



Various pharmacokinetic parameters were calculated for each salt of tiemonium, using a two compartment model: $C(t) = \frac{FD}{V}\left\{\frac{Ka}{Ka\text{-}Ke}\right\}$ [exp. (-ke(t-l)-exp. (-ka(t-l)], where C(t) is the concentration at time t, in hours, Ka is the absorption rate constant, Ke is the elimination rate constant, and l is the lag time. The computer programme provided values for the lag time, the time from swallowing the capsule until some of the drug was absorbed into the systemic circulation, the absorption half-life, and the

Figure 3. Serum levels of ^{14}C tiemonium methosulphate in 4 normal volunteers after oral administration



elimination half-life. In 2 subjects, a negative lag time was calculated. For these subjects, a lag time of zero was assumed and the computer recalculated using the model: $C(t) = \frac{FD}{V}\left\{\frac{Ka}{Ka\text{-}Ke}\right\}$ (exp. (-ket)-exp (-kat)].

Computer drawn decay curves showing the rate of elimination of the tiemonium iodide following intravenous injection are shown in Figure 4.

The results for both routes of administration are summarized in Table I. By using the method of Shand *et al.*,[8] the percentage of tiemonium absorbed was calculated as 6%.

Urinary levels

The percentage of the dose excreted in the 24-hour collection periods was calculated, enabling an approximate value for the urinary excretion half-life to be calculated by a linear regression analysis (Table II).

Faecal excretion

Table III gives the percentage of the dose of either salt of tiemonium, given by the oral and intravenous route, excreted over a total of 72 hours.

Figure 4. Serum levels of ^{14}C tiemonium iodide in 3 normal volunteers after intravenous administration

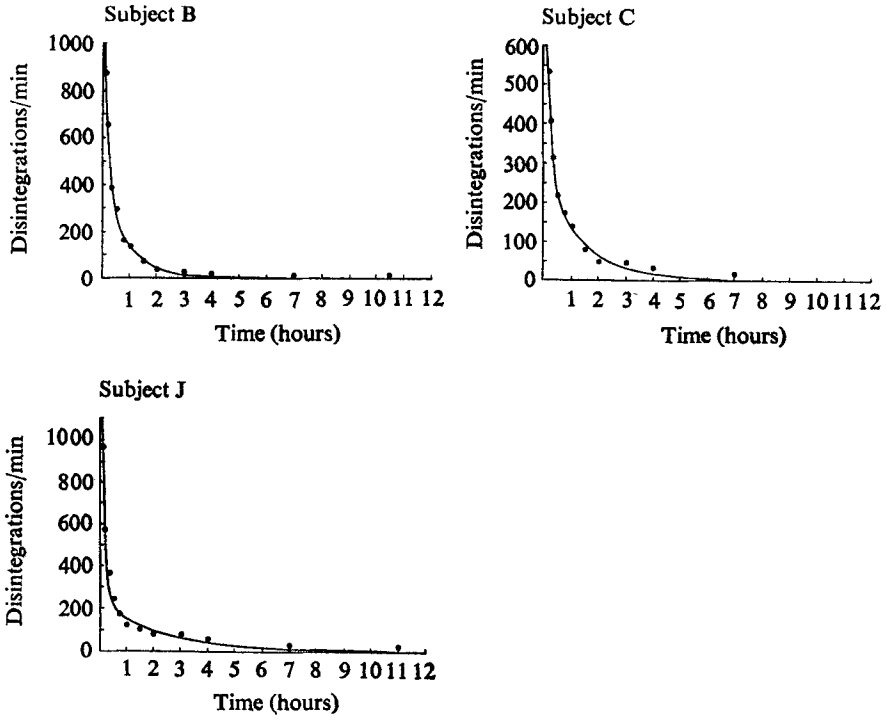


Table I. Serum pharmacokinetic data for 2 salts of tiemonium

Subject	Lag time (h^{-1})	Absorption half-life (h^{-1})	Elimination half-life (h^{-1})
Oral – tiemonium iodide			
A	0.3	0.4	2.6
B	0.4	0.9	1.0
C	0.1	0.7	2.6
D	0	1.4	3.5
E	0	0.8	2.9
Oral – tiemonium methosulphate			
F	0.4	0.1	3.7
G	0.4	1.1	1.3
H	0.2	1.6	2.0
J	0.4	0.1	10.6
Intravenous – tiemonium iodide			
B	0	0.1	0.6
C	0	0.1	1.0
J	0	0.1	1.6

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