Pharmacodynamic and Pharmacokinetics of BW 825C:
A New Antihistamine


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Summary. The new H1-receptor antagonist BW 825C and triprolidine (2.5 and 5 mg) were administered to 12 healthy male volunteers in a double blind placebo controlled, balanced, crossover design. Histamine antagonism was measured by assessment of flare and weal areas after intradermal injection of histamine. The 2 compounds were approximately equipotent in blocking the flare and weal response to intradermal histamine and had a similar duration of action. Triprolidine impaired performance of vigilance and reaction time (p < 0.05) compared with placebo while BW 825C did not. Drowsiness measured using visual analogue scales followed both triprolidine treatments, but not BW 825C. BW 825C had a plasma half-life (t1/2) of 1.7 ± 0.2 h and triprolidine of 4.6 ± 4.3 h. The peak plasma level of BW 825C was approximately 6 times that of triprolidine. It was concluded that BW 825C might be a clinically active H1-antagonist with reduced sedative side-effects.

Keywords: triprolidine, BW 825C; pharmacokinetics, pharmacodynamics, sedation, intradermal histamine, human performance

Until recently, when two new drugs, terfenadine and astemizole [10] were introduced, all H1-histamine receptor antagonists caused sedation. These drugs are commonly used for symptomatic relief of allergic rhinitis in a relatively healthy group of patients who generally will continue their normal daily activities. H1-antagonists lacking CNS activity are therefore desirable.

BW 825C \[\text{[(E)-3-(6-[3-pyrrolidino-1-(4-tolyl) prop-1E-enyl]-2-pyridyl] acrylic acid, is a derivative of triprolidine (Fig.1). It is an H1-antagonist with a potency similar to triprolidine in the guinea pig ileum and the histamine aerosol test. In the rat, however, the compound does not readily enter the nervous system as demonstrated by plasma: brain ratios of 5-30 [4]. This contrasts with triprolidine, which has plasma: brain ratios of 0.17–0.40 [8]. It is therefore possible that the new compound may produce less sedation than triprolidine.}

This study was designed to compare the intensity and duration of the effects of BW 825C and triprolidine on histamine antagonism, subjective effects, performance tests and autonomic measures, and to assess any relationship between these effects and the pharmacokinetic properties of the drugs.

Methods

Subjects
Twelve healthy male volunteers were recruited. Their ages ranged from 20–42 years and their weights from 56–83 kg. They gave their consent after a full explanation of the nature of the study. On the experimen-
tal day they were allowed a light, standardised breakfast before 07.30 a.m., but were not allowed to smoke or drink alcohol or caffeine-containing drinks from 22.00 p.m. the previous day until the tests had been completed. The subjects were transported to and from the laboratory and were paid.

Design and Treatments
This study was a randomised double-blind, placebo-controlled crossover trial. All 12 subjects received each of the following 6 treatments, prepared in identical gelatin capsules: (a) lactose placebo; (b) BW825C 1 mg; (c) BW825C 2 mg; (d) BW825C 4 mg; (e) triprolidine hydrochloride 2.5 mg; (f) triprolidine hydrochloride 5 mg. The subjects were studied in 3 groups of four at intervals of not less than five days, and received treatments in order according to a 6 x 6 Latin squares that were balanced for occasion and the preceding treatment.

Histamine Antagonism
The central area of the back was divided symmetrically into 16 squares and the siting of the different doses of intradermal histamine injections at different times was determined by a Graeco-Latin Square to reduce possible variation in the histamine flare and weal response due to different locations on the back. Histamine acid phosphate was injected in 4 concentrations (0.1, 0.4, 1.6 and 6.4 µg histamine base in 0.1 ml of saline) \[5\]. The injections were performed with a Panjet automatic injector (Schuco International).

Twenty minutes after the histamine injections the flare and weal areas were measured. The area was calculated assuming an elliptical shape. All injections were made by the same physician and all measurements were made by the same observer.

Autonomic Measures
The following groups of tests were used.

Heart Rate (radial pulse).

Blood Pressure (mercury sphygmomanometer).

Pupil Diameter \[1\]. This was recorded photographically with a fixed focus camera and subsequently measured after projection. The average of right and left measurements was used for analysis.

Visual Nearpoint \[7\]. This was measured using a test type affixed to a carpenter's tape measure. The subject held the end of the measure adjacent to the eye, moving the main bulk of tape away from and towards the eye, and stopping when the type could be read clearly. Two recordings were made with the type receding and two with the type approaching the eye. The value used is the mean of the four readings.

Salivary Secretion. The dental roll technique was used. Dental rolls are placed in stoppered tubes and weighed. The rolls are then placed between gum and cheek on left and right and beneath the tongue in the buccal cavity, i.e. 3 rolls for each measurement. The rolls are left in situ for exactly 2 min and gently removed with forceps and placed in their respective tubes, stoppered and reweighed.

CNS Performance Tests

Auditory Vigilance Test \[13\]
The subject listens via headphones to a tape recording 1 h in duration with 0.5 s tones occurring every 2 s in white noise. Tones of 0.4 s duration occur randomly and are the signals to be reported by pressing a button.

Auditory Reaction Time Test \[6\]
The subject has to press a microswitch as rapidly as possible on hearing randomly occurring short tones for 15 min.

Tapping Test
The subject taps a microswitch as rapidly as possible for 1 min. The total number of taps is recorded.

Subjective Effects
Subjective effects were analysed by means of visual analogue scales \[11\]. An additional line "no itching/severe itching" was completed after each session of intradermal histamine injections, and at the same time subjects were asked to estimate the duration of itching. The individual scales were classified into three factors, alertness, contentedness and claspyness \[11\]. Equal weightings were used and no transformations were performed on the raw data.

Pharmacokinetics
After completion of the double blind pharmacodynamic study the subjects came back on two occasions one week apart. On one occasion they received