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Short Communication

A comparison of plasma levels of hyoscine after oral and transdermal administration

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Introduction

Hyoscine (Scopolamine) has a long history of use as an effective drug in the treatment of motion illness [1, 2]. Its side effects are fairly well documented [3], and have generally been considered preferable to motion illness [4]. However, a reduction in the side effects of hyoscine while retaining its efficacy would be desirable. A system has been developed (Alza Corporation, Palo Alto, California) which allows hyoscine to be absorbed across the skin and is designed to produce low, sustained circulating hyoscine levels. This preparation, known as the transdermal therapeutic system, utilizes a small adhesive film attached behind the ear, where favourable skin permeation properties ensure that the rate of drug release determines the rate of entry into the circulation. The rate of release is controlled by a microporous membrane interposed between the reservoir and the adhesive. This route of administration should ensure absorption of hyoscine even when the patient is vomiting. The time course of the concentration in the blood, however, is clearly important.

Variations in absorption, distribution and metabolism make it impossible to predict blood concentrations from the amount of drug administered. Before any significant comparison can be made of the efficacy of the oral and transdermal routes for hyoscine, there is clearly a need for an adequately sensitive and reliable method for determining plasma levels of the drug. This is particularly important in view of a recent report [5] which showed that for a given oral dose of benztropine a wide variation of blood levels was produced. The only alternative, the use of some physiological response to provide a built-in assay, is unlikely to be sufficiently sensitive.

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A gas–liquid chromatographic method [6], and an acid-dye technique [7] are not sufficiently sensitive to measure blood hyoscine concentrations. An HPLC-UV technique [8], developed to measure hyoscine in tablets, was not sensitive enough to measure plasma levels after a normal dose (0.6 mg). Gas–liquid chromatography linked to mass spectrometry [9] provides higher sensitivity but is still not sensitive enough to detect plasma levels after transdermal administration [10]. In this study, plasma levels of hyoscine after oral and transdermal administration have been determined using an adaptation of a radioreceptor assay originally developed for atropine.

Experimental

Twenty-two subjects were divided into two groups and were given one of the following two treatments at 0900 h, one hour after a light breakfast: (1) hyoscine hydrobromide tablet (415 μg hyoscine base) followed one week later by the placebo tablet; (2) transdermal therapeutic system (200 μg priming dose of hyoscine followed by 10 μg/h sustained release) or placebo patch. The system was removed after 12 h. Subjects were crossed over on the following week.

The volunteers first had the nature of the experiment explained to them and their informed consent was received before they were included in the study. Ten subjects (7 male, 3 female, average age 19.9 years (SEM ±4.9), average weight 70.7 kg (SEM ±7.4)) formed group 1 and 12 subjects (male naval ratings; average age 19.8 years (SEM ±0.9), average weight 74.1 kg (SEM ±9.5)) formed group 2. All the subjects were monitored for side effects by a simple questionnaire given every half hour in Group 1 and every hour in Group 2. Blood samples (10 ml) were taken from the ante-cubital vein into EDTA tubes at the following times after drug administration; Group 1: 0, 0.5, 1.0, 2.0, 5.0 h and Group 2: 0, 2.0, 4.0, 6.0, 8.0, 12.0 h. The blood samples were centrifuged at 2000 *g* for 15 min and the plasma was then stored at −20°C.

The previously reported [11] radioreceptor assay for atropine was modified for use with [^{3}H] methylhyoscine, thus permitting the direct estimation of plasma hyoscine levels without precipitation of plasma proteins. Duplicate incubations contained 200 μl plasma, muscarinic receptor preparation equivalent to 200 μg protein and 0.5 nM [^{3}H] methylhyoscine (53.5 Ci/mmol), and were made up to a final volume of 1 ml with 50 mM sodium phosphate buffer, pH 7.4. Samples were incubated, filtered, washed and counted as described previously [11]. A standard curve (Fig. 1) was prepared by adding known amounts of hyoscine to control plasma samples. Concentrations of hyoscine in plasma samples were calculated using the standard curve. The assay was sensitive down to a concentration of 0.25 nmol hyoscine l^{-1} plasma corresponding to 10% inhibition of radioligand binding.

Results

Hyoscine could be detected in the plasma of all 10 subjects receiving the oral dose of 415 μg (1.37 μmol) hyoscine base. As Fig. 2 shows, the time interval before peak plasma levels were reached varied between subjects. The individual plasma profiles suggest that the subjects fall into two groups who show different rates of absorption. A mean peak plasma level of 1.2 nmol l^{-1} (SEM ±0.28) (360 ng l^{-1}) was attained after 0.5 h in five subjects and of 0.76 nmol l^{-1} (SEM ±0.17) (230 ng l^{-1}) in the other five after 1 h. Plasma levels of hyoscine fell to 50% of the peak levels after 2–4 h. The presence of subjective

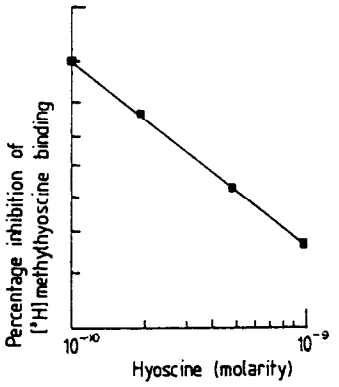

Figure 1
Sensitivity and linearity of the radioreceptor assay.

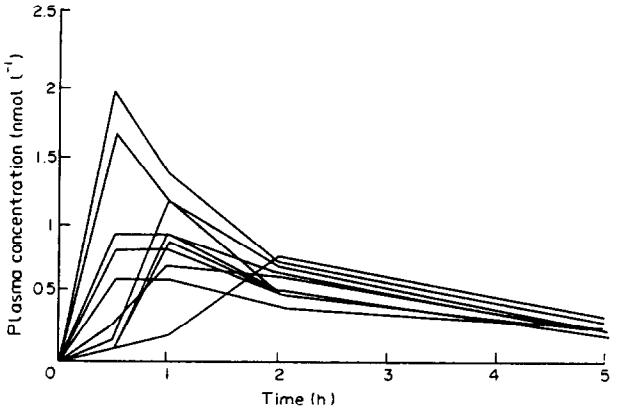

Figure 2
Individual plasma drug levels after 415 μg oral hyoscine base.

side effects was noted in seven of the individuals (Table 1). No side effects were reported in the placebo group.

In the group of subjects given the transdermal hyoscine only four subjects had detectable levels of hyoscine (Fig. 3). There was little or no absorption observed in the first 2 h after application of the patch. Peak levels of 0.42 nmol l^{-1} (SEM ±0.12) (127 ng l^{-1}) were attained at 8 h and remained approximately at this level in the 12 h sample (0.39 nmol l^{-1} (SEM ±0.13)). Hyoscine given by this route did not produce significant side effects except for a slight drowsiness (Table 1) in two of the subjects in whom plasma hyoscine could be detected. The placebo patch produced no side effects and hyoscine-like activity was not detected in the plasma of these subjects.

Discussion

The results indicate that the radioreceptor assay is sensitive enough to detect plasma levels of hyoscine after an oral dose of 415 μg base. The data suggest that the subjects could be split into two groups with peak plasma levels after half an hour and after an hour. More data would be required to confirm this result. The only previous report of plasma levels after oral administration of hyoscine appears to have been performed on a

Table 1
Subjective side effects

Treatment	Time (h) 0.5	1.0	2.0	4.0	5.0	8.0	12.0
Oral 415 μg hyoscine base (n = 10)	Slight drowsiness (2)*	Dry mouth (2) Light head (3)	Dry mouth (4)		Drowsy (1) Dry mouth (1)		
Transdermal hyoscine (n = 12)			Slight drowsiness (1)	Slight drowsiness (1)		Slight drowsiness (1)	

* Number of subjects suffering the side effects.

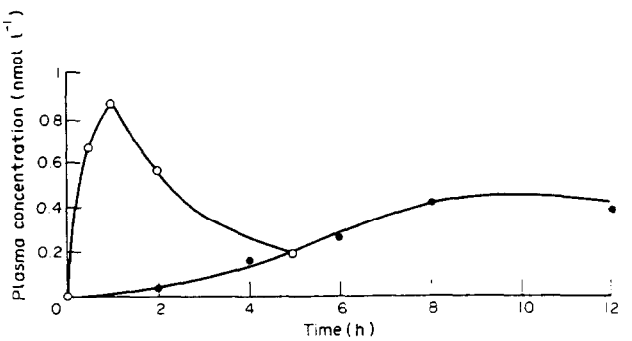

Figure 3
Plasma hyoscine levels. ○ 415 μg hyoscine base (N < 10). ● Transdermal therapeutic system (N = 4).

single subject [10], who attained a peak plasma level of 10.4 nmol l^{-1} (3.15 μg l^{-1}) approximately an hour after receiving 906 μg hyoscine base.

The plasma levels of hyoscine in the subjects given the transdermal therapeutic system were, in most cases, below the detection limits of the radioreceptor assay. This may be because absorption from the patch is unreliable or variable between individuals, or because the elimination rate of the drug from plasma is faster than the absorption rate. It may be possible to distinguish between these two possibilities by increasing the hyoscine dose by applying more than one patch. Alternatively, it may be feasible to increase the sensitivity of the assay by, for example, extraction-concentration of the plasma hyoscine.

Plasma levels of hyoscine produced by the transdermal therapeutic system have not previously been reported. Urinary excretion rates (peak rate approximately 0.6 μg h^{-1}) were much lower in 15 subjects given the transdermal system than in 2 subjects given 906 μg hyoscine base (peak rate approximately 20 μg h^{-1}) [10]. Thus, it would be expected that plasma levels produced by the transdermal hyoscine would indeed be lower than those produced by oral hyoscine (415 μg).

The advantage of the transdermal therapeutic system in motion illness is that a single dose of hyoscine is effective for up to 72 h compared with an oral dose which retains its effectiveness for only 6 h. The transdermal system has been reported to protect

individuals from motion illness in ocean-going yachts [12, 13] and from the motion produced by controlled laboratory motion stimuli in the Slow Rotation Room [14, 15] and in the Motion Generator [16]. Minimal side effects of transdermal hyoscine were noted in these cases.

The results reported here confirm that use of the transdermal system results in lower, sustained circulating plasma levels of hyoscine and diminished side effects when compared with an oral dose of 415 μg hyoscine (base). Whether these levels and the timing of the maximum plasma concentration will be appropriate in the treatment of motion illness remains to be determined.

Hyoscine has, in the past, been administered in doses that are higher than necessary for protection in motion illness [1]. The transdermal system represents a reduction in the dose of hyoscine but is not always suitable as a form of therapy in motion illness. Thus, with a sensitive blood hyoscine assay an effective oral dose could be found which produced the same blood levels as the transdermal system.

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