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Short communication

Development of an HPLC method for determination of diphenidol in plasma and its application in an oral multi-dose bioequivalence study in a healthy female mexican population

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Abstract

Diphenidol was determined by an HPLC method developed in our laboratory. It was validated and proved to be linear in the 40–400 ng/ml range. Accuracy for quality-control samples for intra and inter day assays ranged from 96.1–98.9% and 98.8–101.4%, respectively. This method was applied to a multi-dose bioequivalence study. No serious side effects were observed in the multi-dose design. Pharmacokinetic parameters (mean ± standard error [S.E.]) of Cavg (ng/ml) and AUC_{tau} (ng h/ml) for reference and test products were 139.54 ± 12.66 versus 148.60 ± 16.51 and 551.07 ± 53.53 versus 588.78 ± 69.02, respectively. Log-transformed values were compared by analysis of variance (ANOVA) followed by the classical 90% confidence interval (CI 90%) test and Schuirmann's test. Confidence limits ranged from 91.48–116.18% for C_{max} and from 91.24–117.65% for AUC_{tau}. These results suggest that the analytical method was linear, precise, and accurate for our purpose, and that both assayed formulations were bioequivalent.

Keywords: Diphenidol pharmacokinetics; Reversed-phase HPLC; Multi-dose clinical trial

1. Introduction

Diphenidol (DPN) [1,1-diphenyl-4-piperidino-1-butanol hydrochloride] (Fig. 1) [CAS No. 3254-89-5] is an non-phenothiazinic antiemetic agent employed for some time as a treatment for vomiting and vertigo, principally in patients with Meniere's disease and labyrinthopathies. DPN has been also used as a prophylactic against nausea and vomiting during surgery, cancer chemotherapy, and radiotherapy. The mechanism by which diphenidol exerts its antiemetic and antivertigo effects is not precisely known. It is thought to diminish vestibular stimulation and depress labyrinthine function. Action on modulating the chemoreceptive trigger zone may also be involved in the effect. DPN also possesses a weak peripheral antimuscarinic action [1,2]. It has been reported to cause serious adverse effects including hallucination and confusion (usually within the third day of therapy or at elevated doses) and occasionally drowsiness, dry mouth, depression, restlessness, headache, and transitory hypotension [1–3].

Following oral administration of DPN, peak concentrations – usually achieved between 1.5 and 3 h and with elimination half-life of approximately 4 h – have been reported [1]. However, no information with regard to its pharmacokinetic profile has been reported, in part due to the fact that determination of DPN in plasma by any method has always been hampered by the problem of stet selectivity and sensitivity due to poor detectability, in that its molar absorption coefficient in UV region is very low. Moreover, the structure does not present either fluorescence or electrochemical properties that can be used for detection by these conventional techniques.

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