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Revealing of pharmacokinetic peculiarities of surface active drug promethazine in its interaction with caffeine in rabbits

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ABSTRACT

The interaction of caffeine and promethazine in rabbits has been investigated. The drugs were administered as single oral doses (200 mg caffeine and 100 mg promethazine) as well as simultaneously with an interval of 15 min. The sequence of administration of the drugs was varied.

The influence of caffeine on the pharmacokinetics of promethazine is expressed by: (a) strong increase of C_{max}, AUC, AUMC and MRT of promethazine; (b) decreasing of k_{el}, CL and V_{ss} of promethazine. Significant changes are also observed in the pharmacokinetics of caffeine under the influence of promethazine. Besides these changes are depending on the sequence of administration of drugs. The values of C_{max}, AUC, AUMC and MRT are reduced, but values of k_{el}, CL and V_{ss} occur when promethazine enters first and then caffeine. In contrast to this, the values of C_{max}, AUC and AUMC increase, CL and V_{ss} decrease, but values of MRT and k_{el} remain practically unchanged in case when caffeine was administered first and then promethazine.

This nontrivial interaction of drugs may be stipulated by formation of sufficiently stable complexes of promethazine and caffeine in small intestine. It is probable that the structure and properties of these complexes are different in various mixtures and are depending on the sequence of administration of drugs. The presystem elimination of caffeine is enhanced, but first-pass effect of promethazine is suppressed in complex when promethazine enters first. The first-pass effect in complex is suppressed for both drugs when caffeine is administered first and then promethazine.

1. Introduction

Caffeine (Caff) is a strong stimulator of central nervous system. Stimulation of metabolic processes in different organs and tissues, as well as secretory action of stomach proceeds under the influence of Caff.

Caff is absorbed well in the gastrointestinal tract, is permeated easy through tissues, undergoes demethylation and hydroxylation in the liver [1]. Metabolism of Caff is realized basically by CYP 1A2 enzyme, however other enzymes also participate in its conversion process [1]. Caff is considered as a validated marker of CYP 1A2 enzymes [1–7]. Some drugs inhibit the biotransformation of Caff, e.g. fluvoxamine [2,3], omeprazole [4,7], ephedra alkaloids [8], verapamil [9,10], but some drugs cause an induction of Caff, e.g. rifampin [5]. Caff influences renal clearance of lithium [11,12], pharmacokinetics of carbamazepine and sodium valproate [13], reduces significantly seizure protective ability of antiepileptic drugs: phenylhydantoin diazepam, phenobarbitone and carbamazepine [14,15].

Promethazine (PMZ) is widely used as antihistamine drug. PMZ possesses sedative and antiemetic effects, local anesthetic properties, it is also used for motion sickness [16]. Molecules of PMZ are characterized by considerable surface activity. Formation of micelles takes place in solution at critical micelle concentration (CMC = 4.4×10^{-2} M) [17,18]. PMZ is characterized by considerable first-pass effect in humans and rabbits [19–22]. These factors introduce a significant contribution in the interaction of drugs [23,24]. The interaction of PMZ with antiepileptic drug carbamazepine (inductor of microsomal liver enzymes) and chlorpromazine (drug with surface active nature and ability to presystem metabolism) was studied by us early [25,26]. It was found that PMZ intensifies the presystem metabolism of both carbamazepine and chlorpromazine, which is conditioned by surface active nature of PMZ. On the other hand, decreasing of first pass effect of PMZ takes place under the influence of chlorpromazine possessing higher surface activity in comparison with PMZ [26,27]. Thus, a strong influence

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