# Pharmacokinetic Properties and Safety Profile of Histamine Dihydrochloride Injection in Chinese Healthy Volunteers: A Phase I, Single-center, Open-label, Randomized Study

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## ABSTRACT

**Purpose:** Histamine dihydrochloride (HDC) injection has been approved in Europe for the treatment of adults with acute myeloid leukemia, used in combination therapy with the T-cell–derived cytokine interleukin-2. Despite years of clinical applications of HDC in Europe, no data are available on its tolerability and pharmacokinetic properties in Chinese patients. The objective of this study was to determine the safety profile and pharmacokinetic properties of HDC in Chinese healthy volunteers (HVs).

**Methods:** In this Phase I, single-center, open-label, randomized study, 20 Chinese HVs were randomized to receive a single dose of 0.5 or 1.0 mg HDC via a 10-minute subcutaneous injection. Whole-blood and urine samples were collected at designated time points after dosing. Plasma and urine concentrations of histamine and metabolite N-methyl histamine were measured using a validated HPLC-MS/MS method. Pharmacokinetic parameters were estimated through noncompartmental procedures based on concentration-time data. Adverse events and evaluation of clinical laboratory tests were used to assess the safety profile. The pharmacokinetic profile for a single-dose of 1.0 mg HDC in Chinese HVs was compared with that in Western HVs.

**Findings:** No severe adverse events occurred in this study, and the severity of all adverse events was grade I according to the Common Terminology Criteria for Adverse Events, version 4.0. For the pharmacokinetic parameters of histamine at the 0.5-mg and 1.0-mg dose levels, $t_{½}$ was 0.50 and 1.02 hours; $T_{max}$ was 0.15 and 0.14 hours; mean $C_{max}$ was 26.59 and 71.01 nmol/L; $AUC_{0-t}$ was 8.35 and 20.43 nmol/h/L; $AUC_{0-\infty}$ was 9.61 and 22.69 nmol/h/L; accumulated amount excreted in urine within 24 hours was 125.93 and 145.52 nmol; and maximum urine excretion rates were 21.85 and 38.94 nmol/h, respectively. For N-methyl histamine at the 0.5-mg and 1.0-mg dose levels, $t_{½}$ was 0.58 and 0.66 hours; $T_{max}$ was 0.28 and 0.26 hours; mean $C_{max}$ was 17.01 and 23.54 nmol/L; $AUC_{0-t}$ was 7.72 and 17.08 nmol/h/L; $AUC_{0-\infty}$ was 9.01 and 19.62 nmol/h/L; accumulated amount excreted in urine within 24 hours was 331.7 and 583.21 nmol; and maximum urine excretion rates were 53.29 and 133.53 nmol/h, respectively.

**Implications:** Both single-dose 0.5 mg and 1.0 mg HDC were well tolerated in Chinese HVs, and the pharmacokinetic profile of HDC in Chinese HVs was characterized in this study. A single dose of 1.0 mg HDC had a more rapid but similar extent of absorption, a wider distribution, and a little more rapid elimination in Chinese HVs compared with Western HVs. Findings from this study support additional clinical trials for HDC using in Chinese patients. Chinese Clinical Trial Registry identifier: ChiCTR-ONC-13003954. (*Clin Ther.* 2015;37:2352–2364)


**Key words:** Chinese, healthy volunteers, histamine dihydrochloride, pharmacokinetics, safety.

*Accepted for publication July 21, 2015.*
http://dx.doi.org/10.1016/j.clinthera.2015.07.017
0149-2918/$ - see front matter

## INTRODUCTION

Histamine dihydrochloride (HDC) injection* was approved in Europe on October 7, 2008.[1] HDC is a synthetic derivative of the biogenic amine histamine (Figure 1). HDC in combination with the T-cell-derived cytokine interleukin-2 (IL-2) has been used as maintenance therapy in adults with acute myeloid leukemia (AML) during the first remission, with the aim of preventing relapse.[2–5] T cells and natural killer (NK) cells are 2 major lymphocytes in the immune system, and they are effective for killing tumor cells. IL-2 can activate T cells and NK cells to attack and destroy cancer cells, and is used clinically to eliminate residual blasts and prevent relapse of AML.[6,7] However, activation of T cells and NK cells, including by IL-2, is inhibited by reactive oxygen species in tumor-associated macrophages.[8,9] HDC can inhibit nicotinamide adenine dinucleotide phosphate oxidase, reducing the secretion of reactive oxygen species to maintain the activation of T cells and NK cells by IL-2 and other lymphocyte activators.[8–10] The addition of subcutaneous (SC) HDC to SC IL-2 can protect T cells and NK cells against tumor-induced immunosuppression, and it is a clinically efficacious and tolerable treatment for patients with AML in remission.[2,11]

Histamine is an organic nitrogenous compound involved in local immune responses and is produced in mast cells found in tissues such as skin, bronchial and intestinal mucosa, and in central nervous system. In healthy humans, released histamine rapidly diffuses into the surrounding tissues and bloodstream within minutes. In mammals, released histamine is rapidly inactivated via 2 main enzymatic pathways. In one pathway, histamine is methylated by histamine N-methyltransferase to form N-methyl histamine (NMH); in the other pathway, histamine is deaminated by diamine oxidase to from imidazoleacetic acid.[12,13] Histamine N-methyltransferase plays the dominant role in degradation of histamine in the airway, gut, and brain.[14] The determination of metabolite NMH in plasma and urine can provide a good parameter for measuring histamine release.[13] Histamine is eliminated mainly through metabolism in the liver and other tissues. Half-life for exogenous histamine varied between studies, with a mean of 0.5 to 1 hour. In a study of renal handling of infused

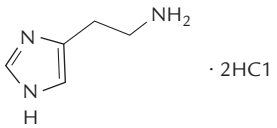


Figure 1. Structure of histamine dihydrochloride.

$^{14}$C-histamine in healthy male subjects, $^{14}$C-histamine and its metabolites in arterial and renal venous blood and in the urine were measured. During the first 6 hours, the radioactivity of exogenous $^{14}$C-histamine is largely excreted in the urine. A large part of the histamine removed from the blood is metabolized in the kidney, with only a small fraction excreted unchanged in the urine, and the major metabolites in urine are NMH and N-methyl imidazole acetic acid.[1]

Preclinical studies show that histamine has an inhibitory effect on NK-cell–sensitive tumors, such as human melanomas in a mouse experimental model,[15] intestinal tumors in rats,[16] and colorectal tumors in mice.[17] Histamine also synergizes with IL-2 to reduce the growth of adenocarcinoma[18] and intracerebral tumors[19] in rat models. In previous clinical studies of HDC summarized in the European Public Assessment Report (EPAR)[1] from the European Medicines Agency, pharmacokinetic parameters were calculated via noncompartmental methods and the only data available came from healthy volunteers (HVs) administrated a single SC dose of 1.0 mg HDC. In one pharmacokinetic study reported in EPAR, which included 21 HVs given a 10-minute SC injection of 1.0 mg HDC, the $t_{½}$ was 0.23 hour, mean $C_{max}$ of histamine was 49.10 nmol/L, and mean $AUC_{0-t}$ was 22.3 nmol/h/L.

In previous pharmacokinetic studies in EPAR, high inter-individual variability was observed, with %CV 40% to 60% for $C_{max}$ and 35% to 55% for $AUC_{0-t}$.[1] Genetic polymorphisms for histamine-metabolizing enzymes are responsible for inter-individual variation in histamine metabolism.[20] For example, genetic variation among individuals can result in up to 5-fold differences in histamine N-methyltransferase activity.[21] No clinically significant differences between groups were observed in a comparison of pharmacokinetic parameters by ethnic origin, but the study was small, with only 5, 33, and 10 Asian, Caucasian, and Hispanic subjects, respectively. In addition, the histamine pharmacogenomics in

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