

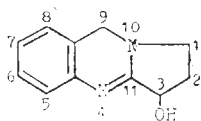
Pharmacokinetics of vasicine in healthy Indian volunteers

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ABSTRACT The pharmacokinetic study of vasicine was conducted on 6 human volunteers after a bolus iv dose of 1.5 mg/kg. The peak plasma concentration of $65 \pm 5 \mu\text{mol/L}$ was obtained at 15 min, and by 4 h only one third of the peak concentration was detected in plasma. These findings correlate well with the clinical studies conducted earlier with vasicine on patients of bronchial asthma.

KEY WORDS vasicine (1,2,3,9-tetrahydropyrrolo-(2,1-b)-quinazoline-3-ol); bronchodilator agent; human experimentation; intravenous injections; pharmacokinetics

Vasicine is one of the major alkaloids of *Adhatoda vasica* Nees. Chemically it is 1,2,3,9-tetrahydropyrrolo (2, 1-b)-3-ol. Intravenous injections of 2.5-10 mg/kg to dogs and rabbits caused respiratory stimulation bronchodilator effect, comparable with that of theophylline⁽¹⁾. Pharmacokinetic studies on mice and rats showed that vasicine followed a biphasic kinetic pattern. In the present investigation kinetic study was made on human volunteers.



Vasicine

1,2,3,9-tetrahydropyrrolo-(2,1-b)-quinazoline-3-ol

METHODS

This study was conducted on six healthy Indian volunteers (4 M and 2 F), aged

19-35 yr ($24 \pm \text{SD } 3$ yr) and weighing 55-71 kg (64 ± 3 kg). Informed consent was obtained from all the subjects before the study. There was no evidence of illness suggested by history, clinical and laboratory examinations. All subjects were non-smokers and instructed to refrain from any medication for at least 7 d prior to the study.

They received a bolus iv dose of vasicine 1.5 mg/kg. Venous blood samples were collected before and at 0.25, 0.5, 1, 2, 4, 8, 16 and 24 h after medication in heparinized tubes. Samples were centrifuged to obtain plasma and stored at -20°C until analysis by spectrophotometric method⁽²⁾.

Vasicine concentrations in plasma were plotted on a semilog paper. The curves were biexponential and kinetics was described by two-compartment open model system⁽³⁾. The linear regression calculation of the terminal 4 points was done by the method of least squares⁽⁴⁾. From the slope of B line and the intercept of the line with y-axis, B was calculated. Using stripping technique α phase and A were computed⁽⁵⁾.

The values of the individual rate constants K_{21} , K_{12} and K_2 were followed as by Notari⁽⁶⁾. Apparent volume of distribution (V_d), volume of central compartment (V_c) and plasma clearance (Cl_p) were calculated according to Niazi⁽⁷⁾. Area under plasma concentration versus time (AUC) was calculated as described by Niazi *et al*⁽⁸⁾.

RESULTS

After a single iv dose of vasicine in

normal persons the peak plasma concentration obtained at 15 min was $65 \pm 5 \mu\text{mol/L}$. The decline was steep during the first hour, thereafter the decline was relatively slow. At the end of 24 h, plasma concentration was $6.5 \pm 1.3 \mu\text{mol/L}$ (Fig 1).

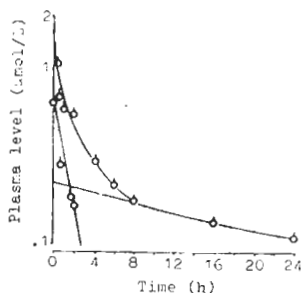


Fig 1. Feathered semilog plot showing time course of plasma vasicine concentration in 6 normal volunteers after iv bolus.

The pharmacokinetic parameters revealed that the fast disposition rate constant was $0.76 \pm 0.16 \text{ h}^{-1}$ which corresponded to distribution $t_{\frac{1}{2}}$ of $0.91 \pm 0.24 \text{ h}$. The slow disposition constant (B) was $0.068 \pm 0.003 \text{ h}^{-1}$ with elimination $t_{\frac{1}{2}}$ of $10.1 \pm 0.7 \text{ h}$.

The individual rate constants K_{12} and K_{21} were $0.18 \pm 0.03 \text{ h}^{-1}$ and $0.59 \pm 0.04 \text{ h}^{-1}$, respectively. The apparent volume of distribution (V_d) was $14.3 \pm 1.1 \text{ L}$. The volumes of central (V_c) and tissue (V_t) compartments were 4.6 ± 0.3 and $0.7 \pm 0.6 \text{ L}$, respectively.

The AUC was calculated to be $508 \pm 26 \mu\text{mol/L}$ per hour and the Cl_p was $0.77 \pm 0.09 \text{ L/h}$.

DISCUSSION

Since the plasma level curve was found to be biexponential, pharmacokinetic evaluation was based on a two-compartment open system model⁽³⁾. A detailed calculation of the data supported the selection of two-

compartment model. The criteria proposed by Notari⁽⁶⁾ were fulfilled in the present study.

Although vasicine was being distributed to the tissues, its return to the central compartment was faster (as the rate constant K_{21} was 3.53 times greater than K_{12}), indicating that more vasicine was available for elimination from the central compartment.

In the clinical studies conducted earlier with vasicine on patients of bronchial asthma, on iv medication the effect started within 10–15 min and lasted 4–5 h. Our findings correlate well with them. The peak plasma concentration reached at 15 min. By 4 h only 1/3 of the peak concentration was present in the plasma, which may be the minimal effective concentration for bronchodilator effect.

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鸭嘴花碱在健康印度志愿者身上的药物动力学

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提要 用分光光度测定法在6名印度健康志愿者身上测定了支气管扩张剂鸭嘴花碱(vasicine)的血药浓度及药物动力学参数。人iv vasicine 1.5 mg/kg后15 min血药浓度达峰值 $65 \pm 5 \mu\text{mol/L}$, 4 h后为峰值的1/3, 24 h为 $6.5 \pm 1.3 \mu\text{mol/L}$ 。此结果与早期临床试用治疗支气管哮喘病人的结果一致。

其血药-时曲线呈二项指数函数关系, 按二室开放模型计算动力学参数为: $K_{\alpha} = 0.76 \pm 0.16 \text{h}^{-1}$, $t_{\frac{1}{2}\alpha} = 0.91 \pm 0.24 \text{h}$, $K_{\beta} = 0.068 \pm 0.003 \text{h}^{-1}$, $t_{\frac{1}{2}\beta} = 10.1 \pm$

0.7h , $K_{12} = 0.18 \pm 0.03 \text{h}^{-1}$, $K_{21} = 0.59 \pm 0.04 \text{h}^{-1}$, $V_d = 14.3 \pm 1.1 \text{L}$, $V_c = 4.6 \pm 0.3 \text{L}$, $V_t = 0.7 \pm 0.6 \text{L}$, $\text{AUC} = 508 \pm 26 \mu\text{mol}/(\text{L}\cdot\text{h})$, and $\text{Cl}_P = 0.77 \pm 0.09 \text{L/h}$ 。

关键词 鸭嘴花碱; 1,2,3,9-四氢吡咯-(2,1-b)-喹唑啉-3-醇; 支气管扩张剂; 人类试验; 静脉注射; 药物动力学