

Effect of Oral Charcoal on Plasma Levels of Intravenous Methyl Proscillaridin

G. G. Belz and H. Bader

Abteilung Pharmakologie der Universität Ulm und Bundeswehrkrankenhaus Ulm, Germany

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Summary. Six healthy volunteers received 1.0 mg of methyl proscillaridin intravenously two times at a 21 day interval. During one of the periods they received 2 g t.i.d. of activated charcoal.

Glycoside plasma levels were determined over 48 hours using a ^{86}Rb -erythrocyte assay. During the period with charcoal, the plasma levels 10 to 48 hours after application were about 60% of the controls. The differences in plasma levels with and without charcoal were statistically significant at $2\alpha < 0.05$.

The results show that methyl proscillaridin undergoes enterohepatic circulation. In the case of glycoside intoxication with methyl proscillaridin it seems promising to attempt treatment with activated charcoal.

Key words: Cardiac glycosides, methyl proscillaridin, enterohepatic circulation, activated charcoal, glycoside intoxication.

Plasmaspiegel nach Methylproscillaridin intravenös. — Der Einfluß oraler Aktivkohlegaben.

Zusammenfassung. In einem Zeitintervall von 21 Tagen erhielt jeder einzelne von sechs gesunden Probanden zweimal je eine Dosis von 1,0 mg Methylproscillaridin intravenös injiziert. In randomisierter Reihenfolge erhielten sie nach einer der Glykosidinjektionen 3×2 g Aktivkohle täglich oral. Die Glykosid-Plasma-Spiegel wurden mit dem ^{86}Rb -Erythrocyten-Assay über 48 Std gemessen. Während der Periode mit Aktivkohle erreichten die Glykosid-Plasma-Spiegel 10—48 Std nach Applikation nur etwa 60% der Kontrollwerte ($2\alpha < 0,05$). Das Ergebnis läßt auf einen enterohepatischen Kreislauf des Methylproscillaridin schließen. Im Falle einer Glykosidintoxikation erscheint bei diesem Glykosid ein Behandlungsversuch mit Aktivkohle erfolgversprechend.

Schlüsselwörter: Herzglykoside, Methylproscillaridin, enterohepatischer Kreislauf, Adsorbentien, Aktivkohle, Glykosidintoxikation.

In previous studies the authors had established data on the pharmacokinetics of proscillaridin and methyl proscillaridin [2-4]. It was shown in 1960 that in rats, the scilla glycoside scillaren is excreted mainly in the bile [7]. Data on bile excretion and enterohepatic circulation of scilla glycosides in man however are not available until now.

The present study was undertaken to establish the following thesis: If methyl proscillaridin (M.P.) undergoes enterohepatic circulation in man, it should be possible to influence pharmacokinetics of intravenously administered glycoside by oral administration of charcoal, which is known to bind to a high degree cardiac glycosides and their metabolites in vitro [5, 6].

Methods

Six healthy males (aged 21 to 34 years) volunteered for the study which was carried out in a randomized cross-over design. The first group of 3 volunteers received a dose of 1.0 mg of methyl proscillaridin (Knoll AG., Ludwigshafen, Germany) intravenously over a period of 30 min using a constant-rate infusion pump. 21 days later they were given the same medication of methyl proscillaridin together with

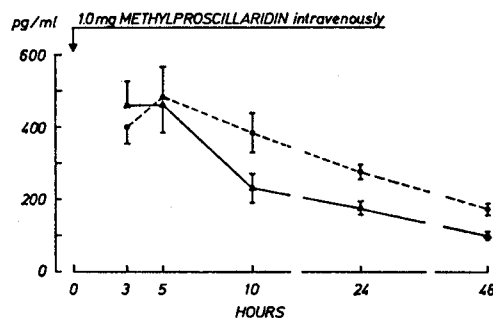


Fig. 1. Mean ($\bar{x} \pm s_x$, $n=6$) plasma glycoside concentrations 3 to 48 hours following intravenous application of a single dose of 1.0 mg of methyl proscillaridin in normal volunteers with ($\triangle-\triangle$) and without ($\circ-\circ$) oral charcoal treatment. The high initial plasma concentrations 1 hour after application are not shown for reasons of the measurement. With all six volunteers the values with charcoal were lower than without charcoal

2 g t.i.d. of activated charcoal suspended in a glass of water. The second group received the first glycoside dose plus the charcoal, and 21 days later the glycoside alone.

The first charcoal doses were given 10 min before the start of the infusion.

Plasma glycoside concentrations were measured using a modified ^{86}Rb -erythrocyte assay [1, 3].

Statistical significance was analyzed using a sign test. The mean M.P. plasma concentrations 3 to 48 hours after intravenous administration are presented in the figure. One hour after the administration no significant difference is observed in the mean plasma levels between the groups treated with and without charcoal (with charcoal: $\bar{x} = 1685$, $s_x = 317$ pg/ml; without charcoal: $\bar{x} = 1315$, $s_x = 212$ pg/ml, $n = 6$ each). Each individual plasma concentration measured during charcoal treatment after 10 hours after glycoside administration is below the corresponding one without charcoal. Plasma levels after 10 hours are only about 60% of the control when charcoal is given. For the course of the individual values from 10 to 48 hours, the difference of the two periods is significant at a level of $2\alpha < 0.05$ (sign test).

Our results show that the pharmacokinetics of intravenously administered M.P. are distinctly influenced by oral charcoal treatment. This result can be explained by bile excretion and intensive enterohepatic circulation of M.P. The bile excretion would also explain the observation that the elimination of proscillaridin glycosides is independent of the kidney function [2].

In the case of glycoside intoxication with M.P. it seems promising to make an attempt of treatment with charcoal.

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Dr. G. G. Belz
Abt. Pharmakologie der Univ.
D-7900 Ulm
Oberer Eselsberg
Federal Republic of Germany