The effect of repeated intravenous and oral doses of molsidomine (N-carboxy-3-morpholino-sydnonimine-ethylester) on plasma renin activity and plasma catecholamine levels in conscious dogs*)

S. Bacher, O. Kraupp, B. Stanek, and G. Rabberger

Pharmakologisches Institut der Universität Wien

Summary

The responses of plasma renin activity (PRA) and plasma catecholamine levels to molsidomine, administered both intravenously and orally, were investigated in conscious trained dogs.

Intravenous administration of molsidomine at increasing dosage up to 0.4 mg/kg with a constant dose interval of 4 hours did not lead to a sustained increase in PRA. By contrast, a significant increase in PRA was still present after 4 hours on administration of 0.4 mg/kg molsidomine by the oral route. This longer-lasting increase in PRA following oral administration is discussed in relation to the conversion of molsidomine to an active metabolite in the liver. A reduction of dose interval to 3 hours or less led to a marked cumulative increase in PRA.

It appears that substances acting via venous pooling lead to persistent activation of the renin angiotensin aldosterone system (RAA system), which counteracts its primary therapeutic effect. A slight increase in plasma noradrenaline levels was observed in response to repeated oral administration of 0.4 mg/kg molsidomine at a dose interval of 2 hours, indicating participation of the sympathetic nervous system in the counterregulatory process.

Key words: molsidomine, renin angiotensin aldosterone system, plasma catecholamines, counterregulation

Introduction

In a previous study (3) the possibility of attenuation of the therapeutic effect of isosorbide dinitrate (ISDN) by activation of the RAA system was considered, since dose intervals shorter than 3 hours led to a cumulative increase in PRA. It seemed therefore of importance to clarify whether molsidomine, another long-acting vasodilator with a peripheral site of action similar to ISDN (14), would elicit counterregulatory mechanisms. Molsidomine exerts its antianginal effect via lowering of the venous return by dilation of the capacitance vessels, leading to diminished ventricular volume, a decrease in cardiac output and, hence, a decrease in myocardial oxygen consumption (2, 8, 14, 9).

*) A preliminary report of this study has been presented at the 21st Spring Meeting of the Deutsche Pharmakologische Gesellschaft (Naunyn-Schmiedeberg's Arch. Pharmacol. 311, R 43, 1980).
It was the aim of the present study in conscious dogs to examine whether molsidomine evokes increases in PRA. The dose interval was varied in order to investigate cumulation of counterregulatory processes on oral administration of molsidomine, which proved to be more effective than intravenous injection.

Methods

Altogether 14 mongrel dogs of either sex, weighing 17–32.5 kg, were used in the experiments. For investigation of changes in heart rate, arterial blood pressure and PRA after a single oral dose of 0.4 mg/kg molsidomine, 6 dogs were trained over a few weeks to submit to puncture of the femoral artery and to stand quietly in a special frame throughout a period of 4 hours.

After an overnight fast, but unlimited access to water, the femoral artery was punctured and a catheter inserted. Measurements of blood pressure and heart rate via a Statham Transducer were continuously registered on a Beckman RM dynograph over the experimental period of 4 hours.

Control experiments with administration of empty gelatine capsules at time 0 were performed on the same dogs.

Further experiments were carried out on 8 dogs trained to submit to venepuncture in order to avoid stress reaction during the experimental period. The animals were allowed complete freedom of movement and unlimited consumption of water, but they had no access to food during the experiment. Molsidomine was given intravenously in doses of 0.1, 0.2 or 0.4 mg/kg (dissolved in 0.9 % NaCl) at a dose interval of 4 hours and orally in a dosage of 0.4 mg/kg (by means of gelatine capsules) with intervals of 4, 3, or 2 hours between administration. Preceding control experiments were performed on the same 8 dogs. Controls were repeated on 4 dogs after the experiments with molsidomine. Since no difference existed between the effects of intravenous administration of 0.9 % NaCl and the response to oral administration of empty gelatine capsules at time 0, control experiments under the latter conditions were used as reference.

Blood samples of 1 ml and 2.5 ml, respectively, were removed for determination of PRA and plasma catecholamines.

PRA was determined by radioimmunoassay according to Haber et al. (12), and plasma catecholamines were assayed radioenzymatically according to Da Prada et al. (7). The surface areas under the curves were calculated with reference to the initial (8 a.m.) value. The results were statistically evaluated by analysis of variance, Tukey test (22) and Student's t-test.

Results

1. Experiments on restrained dogs

The hemodynamic effects of 0.4 mg/kg molsidomine following a single oral dose of the substance were studied over a period of 4 hours in conscious dogs which were trained to stand in a rack. The changes are presented as mean values ± SEM in figure 1. The predominant effect of molsidomine was a significant reduction in systolic blood pressure. There was also a marked increase in heart rate, which was accompanied by a rise in PRA. Preadministration values were almost reached at the end of observation period of 4 hours.