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# The potential harmful effect of molsidomine on the embryos of wistar rats

**Dr. Fadhil Wasfi**
Jordan

Molsidomine is an established drug for the treatment of coronary heart disease. It acts via the metabolite SIN-1 through liberation of NO. Experiments have proven the identity of NO and EDRF. Investigation of the molecular mechanism of action of molsidomine/SIN-1 indicate that molecular oxygen initiates NO formation through a one-electron abstraction from the intermediate. Ex vivo experiments in rats and in vitro studies in human coronary arteries showed that marked tolerance is induced with glyceryl trinitrate, whereas prolonged exposure to SIN-1 does not cause tolerance. Therfore it was really an unfair practice to treat tge rats as such but to check the effect of it on the pregnant ladies it was really necessary .Responses to SIN-1 is not modified in nitrate-tolerant human arteries. Stimulation of soluble guanylate cyclase underlies the antiaggregatory actions of EDRF. Likewise SIN-1 inhibits platelet aggregation in various models. In dogs and pigs with critical stenosis molsidomine reduced significantly the frequency and the severity of cyclical reductions of coronary blood flow.The objective of this study was to examine the effect of molsidomine on the embryos of Wistar rat. Pregnant rats were treated with 10mg/kg subcutaneously either on the 10th or 9th & 10th or 8th,9th & 10th or 7th,8th,9th & 10th mating day. The largest study of molsidomine evaluated 533 patients. These patients received a placebo run-in phase followed by random assignment to two differing doses of molsidomine in a crossover design. Both doses of molsidomine resulted in significantly longer total exercise duration and fewer episodes of angina than placebo. Weekly angina episodes were reduced significantly in patients given either dose of molsidomine compared to angina frequency during the run-in phase. Molsidomine, a cardiovascular drug, acts in a similar fashion to organic nitrates. The SIN-1A metabolite of molsidomine has a pharmacologically active group of nitric oxide, which increases levels of cyclic GMP, and decreases intracellular calcium ions in smooth muscle cells. This leads to relaxation of smooth muscle in the blood vessels, and inhibits platelet aggregation.Molsidomine hepatically metabolized to linsidomine. Linsidomine releases nitric oxide (NO) from endothelial cells when it decays, and acts as the active vasodilating metabolite responsible for molsidomine's pharmacological effects. Oral absorption of Molsidomine is found to be 95.5% ±4.5. Presystemic metabolism is noted to be 56% and metabolism is reported extensive by Liver. Renal Excretion accounts for 95 % and plasma half-life is 5 hr. Back to top. Though no head-to-head comparison of molsidomine versus nitrates has been performed, molsidomine has a similar hemodynamic profile to long-acting nitrates, with similar positive and negative effects, due to its nearly identical mechanism of action. In another study, molsidomine showed a 40% decline in efficacy after 14 days of use, suggesting the development of tolerance. The result showed that molsidomine produced a significant frequent abortion and hyperemic changes beside its effect on the somite numbers and crown-rump length of embryo. It is concluded that molsidomine (a nitric oxide donor) is potentially harmful to embryos and it can be categorized under category B3 and it effect should be considered if it is prescribed to pregnant women In pregnant rats, chronic NO-synthase inhibition induces the development of a pre-eclamptic syndrome, characterized by an increase in maternal blood pressure, a loss of vascular refractoriness to pressor stimuli, a reduction in litter size and a decrease in pups (and maternal) weight. We investigated whether a NO-donor, molsidomine, administered during NO synthase inhibition, could restore a normal pregnancy. Pregnant rats were given these one very often let's say daily, starting from day 14 of gestation, saline (controls), or L-NAME or molsidomine or the L-NAME + molsidomine combinations. All the components examined such as maternal blood pressure and body weight, litter size, pups weight and vascular reactivity to pressor stimuli were investigated. L-NAME alone, as compared to controls, increased maternal blood pressure, reduced litter size increased foetal reabsorptions and decreased foetal weight . Vascular reactivity to pressor stimuli was enhanced. 4. Molsidomine alone, as compared to controls, dose-dependently decreased maternal blood pressure but had no effect vascular reactivity and, whatever the dose, on foetal outcome. 5. The L-NAME-molsidomine combinations dose (of molsidomine)-dependently limited the rise in the maternal blood pressure and thereby inducing the by L-NAME alone but unexpectedly, dose-dependently and significantly worsene pregnancy evolution, e.g., at 30 mg kg-1 1: litter size, foetal reabsorption a , foetal weight . Vascular reactivity to pressor stimuli was paradoxically further enhanced. 6. Thus, in a chronic NO deprivation-induced model of pre-eclampsia in rats, molsidomine , possibly because of its hypotensive action, worsens the foetal outcome, which questions the usefulness of NO-donors in pre-eclamptic women.

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