Title: Effect of repeated administration of 4-methylpyrazole on renal function and lipid peroxidation products in rat kidney after ethylene glycol poisoning

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<AT>Effect of repeated administration of 4-methylpyrazole on renal function and lipid peroxidation products in rat kidney after ethylene glycol poisoning
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<ABS-HEAD>Highlights► A model of repeated 4-methylpyrazole in the treatment of ethylene glycol poisoning ► Monitoring by ethylene glycol and glycolic acid concentrations with renal function ► Predisposition of renal dysfunction and lipid peroxidation after 4-methylpyrazole ► Increasing data about the use of 4-methylpyrazole in the poisoning treatment

<ABS-HEAD>Abstract
<ABS-P>Toxic effects of ethylene glycol (EG) and its metabolites are mainly related to metabolic acidosis and kidney damage. EG biotransformation involving CYP2E1 affects the oxidant-antioxidant balance. The study assessed the effect of repeated administration of 4-methylpyrazole (4MP, 15 mg/kg b.w. after 2 hours, followed by 10 mg/kg b.w. every 12 hours) on renal function (creatinine, urea and urinary protein levels) as well as products of kidney's lipid peroxidation (MDA and TBARS levels) in rats poisoned with EG (5745 mg/kg b.w.). Serum EG and glycolic acid (GA) concentrations were measured throughout the experiment. Repeated administration of 4MP reduced the rate of EG elimination, extended the period of EG persistence in serum and significantly limited formation of GA. The study showed the temporary intensification of kidney oxidative processes that correlated with changes in kidney function. It was found that the use of 4MP in EG poisoning inhibited its biotransformation to toxic metabolites, but simultaneously intensified oxidative damages in kidneys.

<H1>1. Introduction

Ethylene glycol (EG) is a type of dihydric alcohol commonly used in many branches of industry, e.g., as a component of antifreeze fluid for vehicle radiators, in the production of paints and varnishes, plant protection products, cosmetics and cleaning agents (Brent, 2001; Caravati et al., 2005). Acute EG poisoning occurs mostly accidentally. Poisoning is characterized by a relatively high mortality rate. The rate ranges between 1 and 22% depending on the amount of ingested alcohol and the time span between alcohol ingestion and initiation of therapy. Ethylene glycol is miscible with water and more or less soluble in alcohols, aldehydes and ketones. It is rapidly distributed in total body water with a volume of distribution of 0.7 to 0.8 L/kg (Gomes et al., 2002; HazDat 2007; Bronstein et al., 2011, Latus et al., 2012). EG is biotransformed into glycolaldehyde and glycolic acid (GA), principally by dehydrogenases: alcohol (ADH) and aldehyde (ALDH). Further biotransformation leads to the formation of metabolites responsible for symptoms of severe metabolic acidosis (glycolic, glyoxylic and oxalic acids) and renal toxicity (mainly oxalic acid and its salts) (Brent, 2001; McQuade et al., 2014; Eder et al., 1998). In addition, biotransformation of EG involves cytochrome P450, especially isoform CYP2E1, leading to the formation of formaldehyde and a subsequent release of hydrogen peroxide, which is a hydroxyl radical precursor (Barceloux et al., 1999; Porter, 2012; Kukiełka and Cederbaum, 1991). The activity of free radicals is responsible for lipid peroxidation, damage of proteins, nucleic acids and carbohydrates, as well as for oxidant-antioxidant imbalance (Halliwell, 1990; Kukiełka and Cederbaum, 1995). EG poisoning is characterized by a variety of clinical symptoms, that are manifested at a particular time after exposure. In the initial period of intoxication, disorders of the nervous system and gastrointestinal tract are dominant, and subsequently metabolic acidosis develops. Oxalic acid is accumulated in renal tubules in the form of calcium oxalate crystals, which results in necrotic changes of tubular epithelium and renal failure (Brent, 2001; Porter, 2012; Caravati, 2005; McMartin and Wallace, 2005).