Hepatoprotective Effects of Selected Water-Soluble PARP-1 Inhibitors

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Objectives
We have hypothesized that inhibiting PARP may ameliorate the toxicity of CT by preserving NAD/ATP levels required for apoptosis, or repair and cell survival.

RESULTS
Acute administration of CT caused dose dependent increases of PARP activity in the liver of ICR mice

Effect of different PARP inhibitors on PARP activity in liver of CT intoxicated ICR mice

Positive control represents CT administered at dose of 0.6 mL/kg. PARP inhibitors were injected i.p 1 hr before carbon tetrachloride. ABA, AIQ and PJ-34 were injected at a dose of 30 mg/kg, 3 mg/kg and 3 mg/kg, respectively. Liver tissue was collected at 24 hrs of intoxication. Error bars represent SEM for n=8

Changes of ALT in CT intoxicated ICR mice at various times following administration of PJ-34

• PJ-34 administration protected against CT-induced toxicity up to 1 hour after CT treatment.
• There was a correlation observed between a reduction of lipid peroxidation caused by treatment with PJ-34 and reduced cytotoxicity, which suggests that a free radical mechanism is involved in the protective effects of PARP inhibitors.
• PJ-34 did not affect superoxide dismutase activity in the liver of CT intoxicated ICR mice.

SUMMARY
• Carbon tetrachloride increased PARP activity in liver of ICR mice.
• Different PARP inhibitors ameliorated expression of CT toxicity measured by changes in ALT.
• The protective effect of different PARP inhibitors is correlated with reduction of PARP activity in liver. The most potent effect was produced by PJ-34.
• PJ-34 administration protected against CT-induced toxicity up to 1 hour after CT treatment.
• There was a correlation observed between a reduction of lipid peroxidation caused by treatment with PJ-34 and reduced cytotoxicity, which suggests that a free radical mechanism is involved in the protective effects of PARP inhibitors.
• PJ-34 did not affect superoxide dismutase activity in the liver of CT intoxicated ICR mice.

These results provide support for a protective effect of water-soluble PARP inhibitors that may have efficacy in preventing some chemical-induced hepatotoxicity.

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