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Hepatology Highlights

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Pharmacokinetics of acemetacin and its active metabolite indomethacin in rats during acute hepatic damage and liver regeneration by *Chávez-Piña, et al.*

The aim of this study was to examine the pharmacokinetics of acemetacin and of its active metabolite, indomethacin, during the necrotic and regenerative processes occurring after the induction of acute hepatitis by CCl4 in the rat, a widely accepted experimental model of liver damage. They found that one day after CCl_4 administration, liver necrosis was apparent and there was an increase in the circulating levels of indicators of liver damage and regeneration with regard to control conditions. By day 3, histological analysis revealed liver recovery, although not complete, while biochemical indicators of hepatic damage had reverted either totally or partially. Markers of liver regeneration were still increased. Bioavailability acemetacin and indomethacin was comparable to control values. The authors concluded that indomethacin bioavailability after oral administration of its precursor, acemetacin, is significantly reduced by acute hepatitis produced by CCl4. Pharmacokinetic alterations, as liver damage, are reversible, but do not require complete liver regeneration to return to basal conditions.

It is well assumed that hepatic damage results in alterations in drug disposition. Since the liver is the main site of drug biotransformation, it is anticipated that hepatic injury results in a reduction in metabolic clearance. Thus, the effect of liver damage should be particularly important for prodrugs being biotransformed to active metabolites by first-pass effect. It is anticipated that the bioavailability of the active metabolite should be significantly reduced. Notwithstanding, this view is an oversimplification. The effect of hepatic damage on drug disposition depends on the biopharmaceutical properties of each drug, the type of liver injury and the evolution of hepatic damage.

It should be considered that, in the case of acute damage, liver status is dynamic, as injury is followed by a regeneration phase. In this work we show that acute liver damage by CCl_4 produces a significant alteration in the biotransformation of the prodrug acemetacin to its active metabolite, indomethacin, as expected. Changes in indomethacin bioavailability, however, reverted before the liver was completely regenerated. Hence, the biotransformation of acemetacin to indomethacin does not require an intact liver function. Moreover, biochemical and histological indicators of liver damage are not adequate predictors of pharmacokinetic alterations for drugs submitted to an extensive first-pass effect.

Subzero nonfreezing storage of rat hepatocytes using UW solution and 1,4-butanediol. II- functional testing on rewarming and gene expression of urea cycle enzymes by *Guibert EE. et al.*

In the present study the authors analyzed the viability and metabolic competence of isolated rat hepatocytes subjected first, to subzero nonfreezing storage (up to 120 h at -4 ºC) in modified University of Wisconsin (UW) solution with 8 % 1,4-butanediol, and then to a normothermic rewarming step (KHR media, 37 ºC, up to 120 min, carbogen atmosphere). The authors concluded that hepatocytes preserved under cold or subzero conditions up to 120 h followed by 60 min of rewarming, maintain UC enzymes at levels similar to freshly isolated hepatocytes, allowing their use in bioartificial liver devices.

It has been hypothesized that cold preservation at subzero nonfreezing storage of hepatocytes maintain the hepatocytes viability and metabolic functions during the rewarming period, and/or and if it is able to maintain the gene expression of the urea enzymes Carbamyl phosphate synthetase I and Ornithine transcarbamylase during this step. The results presented in the current study propose that the cold subzero stored rat hepatocytes during 120 h are able to maintain the viability and metabolic functions after 120 min of rewarming. Also, these data indicates that the hepatocytes cold subzero stored and rewarmed, maintain Urea cycle enzymes at levels similar to freshly isolated hepatocytes. Rat hepatocytes, stored in these conditions have the capacity to maintain liver specific functions even after 120 h of cold storage.

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