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COMMENTARY

Acetaminophen hepatotoxicity: NO to the rescue

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Severe liver injury as a result of overdose or chronic use of acetaminophen (paracetamol) remains a significant clinical problem, accounting for as much as 40% of cases of acute liver failure. The mechanisms underlying the liver injury caused by acetaminophen have become much better understood in recent years. In this issue, Fiorucci *et al*. report that delivery of nitric oxide (NO) in small amounts to the liver, *via* a novel derivative of the bile acid ursodeoxycholic acid, results in significant protection of the liver from acetaminophen-induced damage. NO appears to produce these beneficial actions through several mechanisms, including the suppression of synthesis of several proinflammatory cytokines. There is also substantial evidence that a NO-releasing derivative of acetaminophen offers several advantages over acetaminophen itself, including enhanced analgesic potency and reduced liver toxicity.
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Acetaminophen (paracetamol) is among the most commonly used analgesics. It effectively reduces fever and mild-to-moderate pain, and is regarded, in general, as a very safe drug. Nevertheless, overdose (often deliberate) of acetaminophen is a common cause of hepatic injury, accounting for ~40% of cases of acute liver failure in the USA (Lee, 2003). This is in part related to the fact that this drug is available over-the-counter. Hepatic injury with acetaminophen is not only associated with overdose or use of high doses; rather, it can be encountered with chronic use at lower doses (<4 g/day), particularly in the presence of other predisposing factors, such as chronic alcohol consumption (McClain *et al*., 1999).

Damage to the liver following acetaminophen ingestion is not due to the drug itself, but to a toxic metabolite (*N*-acetyl-*p*-benzoquinine imine; NAPI) that is generated through the cytochrome P450 group of enzymes in the liver. This metabolite is usually rendered harmless through an interaction with the endogenous antioxidant, glutathione. However, when there is overproduction of the acetaminophen metabolite, glutathione stores in the liver become depleted, and the metabolite begins to accumulate and cause tissue injury. Hepatic injury can be limited through administration of *N*-acetylcysteine, which replenishes liver levels of glutathione.

Acetminophen-induced liver injury may not be attributable solely to direct cytotoxic effects of NAPI. Recent studies have provided evidence for a role of various cytokines and of nitric oxide (NO) in the production of tissue injury following acetaminophen administration at high doses. This leads to induction of apoptosis of hepatocytes. The production of high levels of nitric oxide within the liver, *via* inducible NO synthase (iNOS), may also promote damage *via* interference with mitochondrial respiration (Moncada & Erusalimsky, 2002). However, low (i.e., physiological) amounts of NO in the liver has the opposite effect, protecting the liver against damage induced by tumour necrosis factor-α or Fas-dependent apoptosis (Fiorucci *et al*., 2001b).

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Ursodeoxycholic acid is a bile acid that is used clinically for dissolution of cholesterol gallstones. In this issue of Br J Pharmacol, Fiorucci *et al*. describe a derivative of ursodeoxycholic acid (NCX-1000) that selectively releases low amounts of NO in the liver. This compound dose-dependently reduced acetaminophen-induced mortality and liver injury. It did not interfere with metabolism of acetaminophen, as hepatic glutathione levels were still depleted. However, treatment with NCX-1000 resulted in inhibition of the activation of caspase 3, 8 and 9, and prevention of the induction of apoptosis. Treatment with NCX-1000 also resulted in significant reductions in acetaminophen-induced increases in expression of mRNA for interferon-γ, tumour necrosis factor-α and iNOS in the liver. These actions appear to be attributable to the NO released from this compound, since ursodeoxycholic acid itself did not exhibit beneficial effects in this model. Also, NCX-1000, but not ursodeoxycholic acid, increased liver levels of cyclic GMP.

Over the past decade, NO-releasing derivatives of a number of classes of drugs have been developed. NO-releasing NSAIDs have been shown to exhibit markedly reduced gastrointestinal toxicity, and increased anti-inflammatory potency (Burgaud *et al*., 2002). A significant increase in anti-inflammatory potency has also been observed for NO-releasing derivatives of glucocorticoids and mesalamine (Wallace *et al*., 1999; Paul-Clark *et al*., 2002). As in the study of Fiorucci *et al*. (2004), NO-releasing mesalamine, the parent drug being one of the most widely used medications for inflammatory bowel disease, exhibited an ability to suppress proinflammatory cytokine production that was not seen with the parent drug (Wallace *et al*., 1999). The slow release of low amounts NO from these compounds appears to be responsible for both the increased gastrointestinal safety and the enhanced anti-inflammatory properties that have been observed.

NCX-1000 may represent an important tool for preventing or reversing the liver damage caused by acetaminophen. Previous studies have shown that this compound can also protect the liver from immune-mediated injury, raising the

possibility that it could be useful in various types of hepatitis, as well as being of value for treatment of portal hypertension (Fiorucci *et al*., 2001a,b). In the long term, the solution to the acetaminophen hepatotoxicity issue may be one of the sister molecules of NCX-1000, the NO-releasing derivative of acetaminophen itself. This drug (NCX-701) exhibits significant anti-inflammatory activity and has been shown to be much more potent as an analgesic, and much less toxic to the liver than the parent drug (al-Swayeh *et al*., 2000; Futter *et al*., 2001; Fiorucci *et al*., 2002).

References

AL-SWAYEH, O.A, FUTTER, L.E., CLIFFORD, R.H. & MOORE, P.K. (2000). Nitroparacetamol exhibits anti-inflammatory and anti-nociceptive activity. *Br. J. Pharmacol.,* **130,** 1453–1456.

BURGAUD, J.L., RIFFAUD, J.P. & DEL SOLDATO, P. (2002). Nitric-oxide releasing molecules: a new class of drugs with several major indications. *Curr. Pharm. Des.,* **8,** 201–213.

FIORUCCI, S., ANTONELLI, E., DISTRUTTI, E., MENCARELLI, A., FARNETI, S., DEL SOLDATO, P. & MORELLI, A. (2004). Liver delivery of NO by NCX-1000 protects against acute liver failure and mitochondrial dysfunction induced by APAP in mice. *Br. J. Pharmacol.,* **143,** 33–42.

FIORUCCI, S., ANTONELLI, E., MENCARELLI, A., PALAZZETTI, B., ALVAREZ-MILLER, L., MUSCARA, M., DEL SOLDATO, P., SANPAOLO, L., WALLACE, J.L. & MORELLI, A. (2002). A NO-releasing derivative of acetaminophen spares the liver by acting at several checkpoints in the Fas pathway. *Br. J. Pharmacol.,* **135,** 589–599.

FIORUCCI, S., ANTONELLI, E., MORELLI, O., MENCARELLI, A., CASINI, A., MELLO, T., PALAZZETI, B., TALLET, D., DEL SOLDATO, P. & MORELLI, A. (2001a). NCX-1000, a NO-releasing derivative of ursodeoxycholic acid, selectively delivers NO to the liver and protects against development of portal hypertension. *Proc. Natl. Acad. Sci. USA,* **98,** 8897–8902.

FIORUCCI, S., MENCARELLI, A., PALAZZETI, B., DEL SOLDATO, P., MORELLI, A. & IGNARRO, L.J. (2001b). An NO-derivative of ursodeoxycholic acid protects against Fas-mediated liver injury by inhibiting caspase activity. *Proc. Natl. Acad. Sci. USA,* **98,** 2652–2657.

FUTTER, L.E., AL-SWAYEH, O.A. & MOORE, P.K. (2001). A comparison of the effect of nitroparacetamol and paracetamol on liver injury. *Br. J. Pharmacol.,* **132,** 10–12.

LEE, W.M. (2003). Acute liver failure in the United States. *Semin. Liver Dis.,* **23,** 217–226.

MCCLAIN, C.J., PRICE, S., BARVE, S., DEVALARJA, R. & SHEDOFSKY, S. (1999). Acetaminophen hepatotoxicity: an update. *Curr. Gastroenterol. Rep.,* **1,** 42–49.

MONCADA, S. & ERUSALIMSKY, J.D. (2002). Does nitric oxide modulate mitochrondrial energy generation and apoptosis? *Nat. Rev. Mol. Cell Biol.,* **3,** 214–220.

PAUL-CLARK, M.J., MANCINI, L., DEL SOLDATO, P., FLOWER, R.J. & PERRETTI, M. (2002). Potent antiarthritic properties of a glucocorticoid derivative, NCX-1015, in an experimental model of arthritis. *Proc. Natl. Acad. Sci. USA,* **99,** 1677–1682.

WALLACE, J.L., VERGNOLLE, N., MUSCARA, M.N., ASFAHA, S., CHAPMAN, K., MCKNIGHT, W., DEL SOLDATO, P., MORELLI, A. & FIORUCCI, S. (1999). Enhanced anti-inflammatory effects of a nitric oxide-releasing derivative of mesalamine in rats. *Gastroenterology,* **117,** 557–566.

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