Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

Induction of Heme Oxygenase-1: Reducing Hepatic Ischaemia-Reperfusion Injury in Liver Surgery

Researchers
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Aim
1. To determine the mechanism through which heme oxygenase-1 protects liver cells from injury
2. To assess whether heme oxygenase-1 could be induced with heme arginate in patients undergoing liver surgery

Project Outline/Methodology
This project contained both a mechanistic laboratory study and a clinical trial in patients undergoing liver surgery. Liver cells (hepatocytes and Kupffer cells) were isolated from liver removed from patients undergoing liver surgery. These cells were tested in laboraory models of ischaemia reperfusion injury, which replicated the acidic environment that occurs during liver surgery. Kupffer cell (resident liver inflammatory cells) behaviour was tested before and after heme oxygenase-1 induction (HO-1). A phase I/II clinical trial was performed in patients undergoing liver surgery. In this randomised, double blind trial, patients were randomised to receive either heme arginate or placebo. Their baseline HO-1 epxression was measured in serum and circulating white blood cells, and compared with that following treatment. Liver tissue was obtained during surgery to assess HO-1 expression in the liver. The patients were followed up for the duration of their hospital stay to identify and adverse events of complications.

Key Results
The drug heme arginate was found to strongly induce heme oxygenase-1 in human liver cells and in Kupffer cells. Kupffer cells treated with heme arginate to induce HO-1 produced high levels of IL10, a molecule with 'anti-inflammatory' properties which may be beneficial in injured tissues. White blood cells treated with heme arginate were able to protect culted slices of liver tissue from damage, confirming a biological effect of this change in behaviour.

In the clinical trial, heme arginate was found to strongly induce HO-1 expression in circulating white blood cells and in liver tissue. There were no deaths in either group, no adverse effects were noted following heme arginate administration, and it was safe to use in patients having liver surgery.

Conclusions
This study demonstrated that heme arginate can be used to induce heme oxygenase-1 both in the laboratory and in patients. It further shows that this drug can be safely used in patients undergoing major surgery.

What does this study add to the field?
This study demonstrates for the first time that HO-1 can be pharmacologically induced in human liver and criculating cells as required. There is a wealth of experimental evidence that HO-1 has therapeutic potential, but to date that has been hampered by the lack of a suitable HO-1 inducing agent suitable for clinical use. This study allows heme arginate to be used for studies with a definiteive clinically relevant endpoint.

Implications for Practice or Policy
Further work is required before this can be applied to routine clinical use. However, if subsequent trials confirm the effects seen in laboratory experiments, HO-1 induction could be used in solid organ transplantation and major vascular and heart surgery.

Where to next?
This trial estabilshes that heme arginate can be used to induce HO-1 in human organs. The next stage is to perform further trials with a clinical endpoint to see if this can be used to improve outcomes for patients in a variety of settings. One study is already underway in patients having a kidney transplant and a further study is gathering preliminary evidence for a possible role in patients having heart attacks. Trials in liver surgery and liver transplantation are under development.

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