studies in humans, and a study in patients is ongoing. The data support observations of improved efficacy and reduced cardiotoxicity using this method of drug delivery, and suggest that in clinical use in metastatic breast cancer patients the liposomal formulation will provide an enhanced therapeutic index compared with conventional doxorubicin.

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Detection and characterisation of novel biliary metabolites of the anticancer agent ifosfamide using in-vivo and analytical ^{31}P MRS and mass spectrometry

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Introduction: Many drugs undergo biliary excretion, potentially affecting pharmacokinetics and toxicology. Conventional methods to study this are highly invasive. Here biliary excretion of metabolites of the alkylating agent Ifosfamide (IF) is demonstrated using *in vivo* ^{31}P Magnetic Resonance Spectroscopy (MRS). High resolution ^{31}P-MRS and analytical mass spectrometry enabled provisional assignment of the major biliary metabolite to the glutathione conjugate of IF. The conjugate represents a previously unreported metabolite of IF.

In vivo studies: Ten male Dunkin-Hartley guinea pigs (900 ± 20 g) were cannulated, anaesthetised and placed prone over a 5cm ^{1}H/^{31}P coil system[1] in a 1.5T Siemens Vision MR scanner. A peak at the IF frequency appears within 20 minutes of administration of 500mg/kg IF (Fig 1). Localised data (Fig 2) show that IF signal arises from the liver and gall bladder.

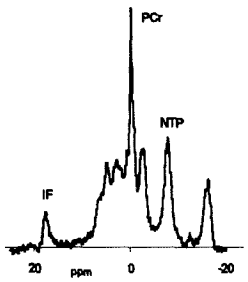

Fig. 1. Unlocalised ^{31}P MRS in vivo after 500 mg/kg IF

High Field ^{31}P MRS Studies of Bile: Spectra of extracted bile were acquired at 11.74 T (Fig 3). Spiking identified Peak 5 as IF. Published data from measurements in urine[2] suggest Peak 2 is carboxy IF, while Peak 3 is 2-dechloroethyl IF or 2,3-dechloroethyl IF. Peak 4 has not previously been reported. If gall bladder volume is 4 cm^3 then approximately 1.9% of injected IF is present as IF and its metabolites in the bile.

Identification of the 16.02 ppm peak using Liquid Chromatography Mass Spectrometry (LCMS): LC analytes were ionised and their masses measured using an ion trap mass spectrometer. The most intense peak detected not present in control bile had a molecular weight of 531, consistent with formation of a conjugate of IF where one Cl atom has been replaced with GSH. Comparative MSMS fragmentation of GSH, IF and the putative GS-IF conjugate showed patterns consistent with this.

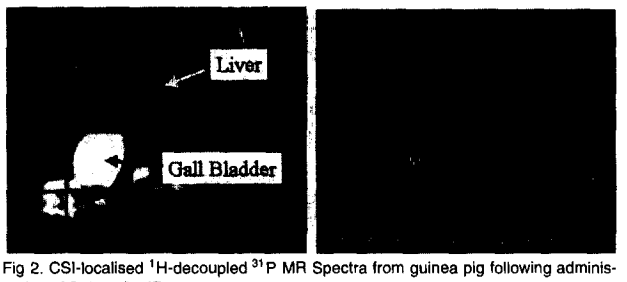

Fig 2. CSI-localised ^{1}H-decoupled ^{31}P MR Spectra from guinea pig following administration of 500 mg/kg IF

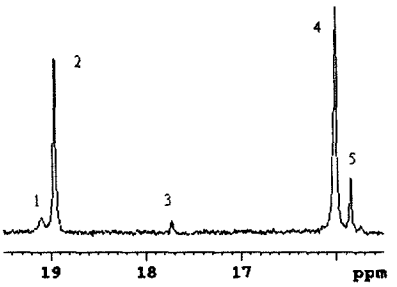

Fig 3. ^{31}P MR Spectrum from Bile at 11.74 T

Table 1. Metabolite concentrations in bile (N=10; mean ± s.d.)

Peak	ppm	Conc (mM)
1	19.09	0.49 ± 0.25
2	18.96	2.04 ± 1.04
3	17.74	0.16 ± 0.07
4	16.02	4.05 ± 2.38
5	15.86	1.19 ± 1.47

Conclusions: ^{31}P MRS signals *in vivo* of IF and its metabolites arise predominantly from liver and gall bladder. Biliary excretion of IF or its metabolites has not previously been reported. High-resolution ^{31}P MRS and mass spectrometry show the main metabolite present to be GSH conjugate of IF. These or other biliary metabolites may be implicated in previously described oxazophosphorine related cholecystitis[3-5].

Acknowledgements: This work was funded by Cancer Research UK (C1060/A808/G7643)

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Paediatric oncology

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Risk adapted treatment for childhood hepatoblastoma (HB): final report of the second study of the International Society of Paediatric Oncology' SIOPEL 2

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Background: SIOPEL2 was a co-operative, international pilot study aiming to test effectiveness - in terms of response, resection rate (RR, RsR), progression-free (PFS), overall survival (OS) - and toxicity of two chemotherapy regimens, incorporated into a therapeutic strategy based on