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Paracetamol in therapeutics – not free of hepatic risk

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TITLE Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen (paracetamol) daily: a randomised controlled trial.

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LIST OF ABBREVIATIONS Upper limit of normal (ULN), body mass index (BMI), alanine aminotransferase (ALT)

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SUMMARY

This clinical trial of a new analgesic combination involved five treatment groups. The treatment groups were placebo (n=40), paracetamol 1g four times daily (n=27), 30 mg morphine and 1g paracetamol four times daily (n=26), 4mg of hydromorphone and 1g paracetamol four times daily (n=27) and 2 tablets of a combination of oxycodone 7.5mg and paracetamol 500mg four times daily (n=27). The regimens were administered to healthy volunteers in two clinical research facilities for up to 14 days. Meals were standardised. Liver enzymes were measured daily for the first eight days and then on alternate days unless they were above ULN.

The subjects were American volunteers aged between 18 and 45 years with an average BMI between 25 and 26.

In the placebo group, one volunteer had an ALT rise to 2–3 x ULN. In the treatment groups, over 50% of volunteers had an ALT rise of at least 2 x ULN with 25% having a peak ALT >5 x ULN. This effect was attributed to Paracetamol as it was used on its own and was common to all other test groups. When the peak ALT was expressed as multiples of the participant baseline ALTs, 49% of participants had at least a five-fold increase compared with only one taking placebo. The percentage of participants with an eight-fold increase was 27%. There was a relative risk of 6·2 (2·4–15·8) of a greater than threefold baseline ALT elevation when comparing all active treatments with placebo. Elevations of ALT > threefold were not seen prior to day three of treatment.

All enzymes returned to normal within two weeks of stopping treatment. There was no correlation with BMI, and often the level of paracetamol in the blood was below the limit of detection at the time of highest ALT elevation.

OPINION

Paracetamol is an extremely common medication taken by millions of individuals each year, either by itself or in combination with another analgesic. This article is interesting as it describes an unexpected finding in a clinical trial of a new analgesic. The proportion of healthy participants with a rise in ALT is remarkably high suggesting that paracetamol causes hepatocyte necrosis at a much lower dose than thought previously. The reason for this is not clear. The study revealed a slight increase in risk in Hispanic Americans compared with white Americans but no association with BMI or paracetamol level.

Anecdotally, we at the Scottish Liver Transplant Unit have seen significant liver impairment and, indeed, liver failure in individuals who have had the maximum normal dose of paracetamol (1g four times daily) in the context of poor nutrition and peri-operative fasting. The livers of these individuals may have reduced glutathione stores making them at least theoretically more susceptible to paracetamol hepatotoxicity. We have also been surprised at the level of hepatotoxicity encountered in individuals with either alcoholic or non-alcoholic fatty liver. However, there appears to have been no such 'priming' factors in the livers of these healthy participants.

The trial medication was stopped if the ALT reached 120, and, consequently it is unknown if, with continued medication, the liver injury would have increased further causing symptomatic liver impairment. The lessons for clinicians are that minor asymptomatic rises in ALT in

patients on paracetamol-based analgesia should prompt us to stop this medication and only investigate further if the ALT does not settle rapidly. Secondly, we should be wary of seemingly 'minor' overdoses of paracetamol, particularly if they are staggered, as there appears to be significant variation in the susceptibility of healthy individuals' livers to hepatotoxicity.

It is difficult to form strong opinions about the safety of paracetamol in patients with established liver disease from this study but I will be more wary from now on of suggesting prolonged periods of maximal doses for my patients. I will, however, continue to suggest that a day or two on the maximum dose or reduced doses for longer periods is safe in patients with compensated cirrhosis.

PAST PRESIDENTS

Sir Robert Christison (1797-1882)

This distinguished physician, after whom the eponymous Edinburgh Chair of Therapeutics was named, was born in that city, the son of a professor of Latin. After schooling at The Royal High School of Edinburgh, he studied in the Faculty of Arts for four years before entering the medical school and studying under Monro *Tertius,* graduating MD in 1819. He then worked for a short time in St Bartholomew's Hospital London before studying toxicology in Paris.

Biographies speak of him returning to Edinburgh to find that, at the age of twenty-four, he had been appointed Professor of Medical Jurisprudence. Presumably he had applied, or known that his name had been put forward! Medical Jurisprudence was an optional course, but he made a great success of it as judged by the number of students who attended his classes. In a short time, he was much in demand by the legal profession as an expert witness, especially when he demonstrated what had until then not been recognised, namely, the differences between injuries inflicted pre- and post-mortem. The most famous case in which his evidence was crucial was that of Burke, of the notorious duo Burke and Hare, who provided the corpses of their murdered victims to Edinburgh anatomists for dissection.

Curious as it may seem to us today, the incumbent of the Chair of Toxicology did not as a matter of course have the right to work as a physician in the Edinburgh Royal Infirmary but had to apply for such a post. Thus it was that in 1827 Christison became one of its physicians. In 1829 he published his *Treatise on Poisons* partly based on experiments he had conducted on himself, in particular the effects of oxalic acid, lead, arsenic, opium and hemlock. In the same year, he was appointed Adviser to the Crown in Scotland.

In 1832, he resigned his chair to become Professor of *Materia Medica* and Therapeutics at Edinburgh University and remained in that post to the end of his 55 years of work and service to medicine.

In a remarkable career, he was Professor, an outstanding researcher and teacher, Dean of the Faculty of Medicine, University Assessor and President of the Senatus. That was, however, but a small part of the totality of his achievments.

He chaired a committee of the General Medical Council responsible for the compilation of the first *Pharmacopoeia of Great Britain and Ireland,* and, in 1842, he published his *Dispensatory*, a commentary on the *Pharmacopoeia.* In succeeding years, countless papers on botanical specimens, drugs and their action on patients, made him a world authority on therapeutics.

More honours were to follow. In 1839, he was elected President of the Royal College of Physicians of Edinburgh, a post he again held in 1848, the same year in which he became Physician-in-Ordinary to the Queen in Scotland. Between 1868–73, he was President of the Royal Society of Edinburgh, and during that tenure he was created a Baronet by Queen Victoria on the recommendation of Gladstone the Prime Minister. When the British Medical Association held its first meeting in Edinburgh in 1858, Christison lectured on therapeutics and at its next meeting there in 1875 he was its President. He was awarded the Honorary degree of Doctor of Laws (LLD) by Edinburgh University in 1872, ten years before his death.

Christison will be remembered as a brilliant clinician, teacher, researcher and writer, and as a loyal servant of the University of Edinburgh. Some will perhaps recall, with sadness, that he was a staunch opponent to the admission of women to the Faculty of Medicine, especially when they also recall how many women have since gone on to brilliant careers after working with his successors in the Christison Chair of Therapeutics.

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