

# Hepatic and Renal Failure Associated with Amiodarone Infusion in a Patient with Hereditary Fructose Intolerance

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## ABSTRACT

*Hereditary fructose intolerance is a rare inherited metabolic disorder. Although fructose intolerance usually presents in the paediatric age group, individuals can survive into adulthood by self-manipulation of diet. Hospitalisation can become a high-risk environment for these individuals because of loss of control of their strict dietary constraints and the added danger of administration of medications containing fructose, sucrose and sorbitol. We report a case of hereditary fructose intolerance in an adult presenting with hepatic and renal failure associated with an amiodarone infusion and explore the possibility of polysorbate 80 as a cause of this patient's hepatic and renal failure. (Critical Care and Resuscitation 2002; 4: 112-115)*

**Key words:** Hereditary fructose intolerance, hepatic failure, renal failure, polysorbate 80

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Hereditary fructose intolerance (HFI) is a rare autosomal recessively transmitted disorder resulting from the catalytic deficiency of fructose 1-phosphate aldolase (aldolase B) in the liver, intestine and kidney. It has an estimated frequency of 1 in 18,000 and usually presents in the paediatric population,<sup>1</sup> although sporadic adult cases continue to be reported.<sup>2</sup> The individuals are usually symptom free unless they receive fructose, sucrose or sorbitol. Many are diagnosed during weaning. The newborn is symptom free as the carbohydrate source at this stage is lactose (the disaccharide of glucose and galactose). As sweetened milk formula and fructose containing solids are introduced, typical symptoms of fructose intolerance occur with poor feeding, vomiting, hypoglycaemia and metabolic acidosis. Prolonged fructose intake eventually leads to hepatomegaly, jaundice, haemorrhage, proximal renal tubular syndrome, and finally hepatic failure and death.

Those individuals who survive weaning usually do so by developing an aversion to foods that cause distressing symptoms. Voluntary dietary exclusion becomes refined over a lifetime by trial and error. Obviously once a diagnosis has been established a strict exclusion diet should be introduced.<sup>3,4</sup>

A further threat to patients with HFI is the presence of fructose, sucrose and sorbitol in medication. Cautious prescribing is important as sucrose and sorbitol are additives in many tablets and syrups. Numerous fatal or near fatal cases have been reported with the use of fructose in parenteral nutrition solutions and consequentially in most countries their availability has been restricted.<sup>5</sup>

We describe a case of HFI in an adult presenting with hepatic and renal failure associated with an amiodarone infusion and examine the possibility of polysorbate 80 as a cause of this patient's acute disorder.

## CASE REPORT

A man aged 65 years was referred to our intensive care unit (ICU) with a reduced level of consciousness, hypoglycaemia, hepatic dysfunction and renal impairment. His past medical history included type II diabetes mellitus, gout, peripheral vascular disease, stroke and ischaemic heart disease. He had undergone coronary artery bypass surgery 10 years previously and had a femoro-popliteal bypass and chemical sympathectomy performed one year ago for digital ulcers. However, as the latter had failed to heal with conservative therapy a forefoot amputation was performed under spinal anaes-

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thetia. During the postoperative period the patient developed atrial flutter. Digoxin and sotalol were commenced and an elective cardioversion was performed. Sinus rhythm was re-established and the patient was commenced on an amiodarone infusion to maintain sinus rhythm. Seven hours after commencing the amiodarone infusion he became drowsy, diaphoretic with poor peripheral perfusion and hypoglycaemic (plasma glucose 2.7 mmol/L) and was admitted to the ICU for further management.

On examination his blood pressure was 100/60 mmHg, pulse 85 beats per minute and his respiratory rate was 14 breaths per minute. The arterial blood gas revealed a metabolic acidosis, with a pH of 7.32, pCO<sub>2</sub> 36 mmHg, PO<sub>2</sub> 77 mmHg, bicarbonate 17.9 mmol/L and a base excess - 7.3 mmol/L, breathing air. The serum biochemistry revealed a sodium of 137 mmol/L, potassium 5.6 mmol/L, creatinine 0.17 mmol/L, chloride 99 mmol/L, lactate 7.9 mmol/L, anion gap 26 mEq/L, bilirubin 35 mmol/L, alkaline phosphatase 228 U/L, gamma glutamyl transferase 228 U/L and alanine amino transferase (ALT) 2100 U/L. The INR was 3.1 and the APPT was 51 seconds. An electrocardiogram showed no recent changes and the plasma troponin I was 0.4 (normal < 1.0 ug/mL).

The amiodarone infusion was discontinued and the hypoglycaemia was treated with an intravenous bolus of 20 mL of 50% dextrose.

Several hours later the patient's general condition appeared to improve. He was able to communicate, although appeared agitated and concerned by the fact that he had been given the wrong foods, stating that he had an intolerance of certain foods. Shortly after this he had a brief asystolic arrest which was treated with atropine and adrenaline and he was intubated, sedated and mechanically ventilated. A noradrenaline infusion was commenced. Plasma biochemistry at this stage revealed an ALT of 4700 U/L and an INR of 4.1. An abdominal ultrasound was performed which revealed no hepatic or renal abnormalities. In particular, the portal vein was patent with normal flow, the hepatic artery showed no evidence of arterial occlusion, the hepatic veins were patent and there was no ureteric obstruction. As the patient remained anuric with the serum creatinine increased to 0.4 mmol/L, continuous veno-venous haemodialysis was commenced. As it was unclear as to the cause of the sudden hypoglycaemia and hepatic and renal failure, it was decided that the possibility of bowel or liver ischaemia needed to be excluded. After correction of the coagulopathy a laparotomy was performed which revealed no abnormal bowel or hepatic perfusion.

Over the next 19 days in the ICU the patient gradually improved. His renal function recovered sufficiently for dialysis to be discontinued and the

hepatic dysfunction spontaneously improved. However, he developed respiratory failure secondary to nosocomial pneumonia which progressed to ARDS from which he was finally discharged some 40 days later. During this time the patient had another episode of unexplained metabolic acidosis, increased serum lactate, poor peripheral perfusion and bradycardic arrest.

The possibility of HFI was raised by the patient from reading an article in Readers Digest entitled "The man who hated sweets"<sup>6</sup> and from information obtained from the Internet. Both the patient and his sister, aged 73, had a life long intolerance of sweet food. This had been noted by their mother at the time of weaning who engineered a diet for both by trial and error. Both siblings had carried this dietary restriction with them into adulthood. Our patient had more lately become aware that in addition to food, there were various medications to which he was intolerant. Examination showed his teeth were in excellent condition for his age with only a few fillings. To confirm the diagnosis of HFI, a blood specimen was sent for DNA testing which revealed that the patient was homozygous for the A149P mutation, validating the diagnosis of HFI.

## DISCUSSION

Our case confirms that the disorder of HFI is compatible with normal life expectancy and that individuals can remain undiagnosed for many years. Some adult patients are diagnosed during a family investigation after the discovery of an affected infant relative. Others have presented following information discovered in the public domain.<sup>7</sup> Because affected individuals are usually free of dental caries, diagnoses have also been made by dentists.<sup>8</sup>

Fructose metabolism is via a pathway composed of three enzymes: fructokinase, aldolase B and triokinase. These enzymes convert fructose into intermediates of the glycolytic-gluconeogenic pathway. Aldolase B catalyses the splitting of fructose 1-phosphate into dihydroxyacetone phosphate and D-glyceraldehyde as well as the splitting of fructose 1,6-biphosphate into dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate.

In patients with HFI the capacity of aldolase B to split fructose 1-phosphate is severely impaired. The defect not only causes an impairment of the conversion of fructose into glucose but also causes a marked accumulation of fructose 1-phosphate in the fructose metabolising tissues. This accumulation is accompanied by a depletion of ATP and inorganic phosphate. The reduced inorganic phosphate activates adenosine deaminase and the xanthine oxidase pathways, with degradation of purine nucleotides to uric acid. Reduced intracellular concentrations of ATP accounts for the release of Mg<sup>2+</sup> by dissolution of the Mg-ATP complex,

causing the hypermagnesaemia observed following a fructose challenge. Fructosaemia, fructosuria, hypoglycaemia, and a metabolic lactic acidosis are also associated sequelae.<sup>9</sup>

The gene for human aldolase B has been mapped to chromosomal location 9q13-q32. The most prominent allele causing HFI in patients of European descent, is designated A149P and accounts for 65% of European HFI alleles so far studied.<sup>10</sup> It has a wide distribution among European populations, and has previously been found in New Zealand. Molecular analysis of human aldolase B genes using the polymerase chain reaction and DNA sequencing has to date identified 22 genetic lesions in patients with HFI. Currently direct DNA analysis utilising polymerase chain reaction to identify the aldolase B gene sequences (obtained from the somatic cells of patients), allows for a rapid non-invasive method of diagnosis. Prior to PCR technology, diagnosis had required either direct assay of fructoaldolase activity in tissue biopsy specimens or fructose challenge by intravenous infusion.

James *et al*,<sup>1</sup> reported the results of a study designed to obtain an estimate of the population frequency of the mutant aldolase B allele A149P by systematic analysis of DNA obtained from Guthrie card spots taken at birth. They identified 27 A149P heterozygotes from 2050 subjects born within a nine-month period (frequency approximately 1.3%). These data allow for a frequency of 1 in 23,000 homozygotes to be predicted for this allele (giving a disease frequency of 1 in 18,000 assuming that the A149P variant accounts for approximately 80% of mutant alleles).

The lack of appreciation by hospital staff of HFI, leads to a high risk environment for patients with undiagnosed HFI. On numerous occasions our patient complained about the type of food that was being delivered to his room. Retrospectively, it is reasonable to presume that due to loss of control of dietary constraints our patient could have been receiving a dangerous fructose load, eventually leading to a metabolic crisis with lactic acidosis and hepatorenal failure. The fact that our patient collapsed while receiving an amiodarone infusion is of interest. The vehicle for intravenous amiodarone (Cordarone X®) is polysorbate 80 (polyethylene sorbitan monooleate) which is used for solubilising, emulsifying and wetting medicinal products. The intravenous preparation of amiodarone contains 150 mg amiodarone and 300 mg polysorbate 80. Our patient received a bolus dose followed by infusion receiving a bolus dose of 600 mg of polysorbate followed by an infusion of 200 mg/hr.

Polysorbate 80 has previously been suggested as responsible for the acute hepatotoxicity of amiodarone as Rhodes *et al*,<sup>11</sup> describe a case with features very

similar to that which we describe. Polysorbate 80 has also been implicated in the E-ferol syndrome (characterised by hepatomegaly, splenomegaly, cholestatic jaundice, renal failure, and thrombocytopenia) which is associated with the use of an intravenous preparation of vitamin E containing polysorbate 80 and polysorbate 20.<sup>12</sup>

As polysorbates are made by reacting sorbitan esters (i.e. derivatives of sorbitol) with ethylene oxide, we wondered whether polysorbate 80 could be implicated in the acute deterioration seen in our case. Polysorbate 80 consists of a mixture of partial oleic esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. Little data exists on the metabolism of polysorbate 80, although van Tellingen *et al*,<sup>13</sup> describe rapid esterase-sensitive breakdown of polysorbate 80, and perhaps sorbitol could be released by this process. Nevertheless, we confirmed that the patient had fructose intolerance and that he developed hepatic and renal failure following the amiodarone infusion.

We believe that in the rare instance of a critically ill patient with HFI, the administration of intravenous (but not oral) amiodarone may be hazardous.

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