

*Case Report*

## Amoxicillin-induced acute renal failure

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### Introduction

Because of its favourable pharmacokinetics and antimicrobial efficacy, amoxicillin is widely used for perioperative antibiotic prophylaxis. We report here three cases of acute renal failure following the administration of amoxicillin during epilepsy surgery.

### Case 1

A 50-year-old Caucasian woman suffering from temporal lobe epilepsy refractory to antiepileptic drugs (AED) from the age of 2 years was admitted for partial left temporal lobe resection after extensive evaluation and non-invasive monitoring for determination of her epileptogenic focus. She was in good health without previous or concomitant diseases. Her medication consisted of carbamazepine 600 mg b.d. Laboratory work including creatinine (0.7 mg/dl) and urea (28 mg/dl) revealed no pathological findings. For perioperative antibiotic cover she received 4.4 g amoxicillin/clavulanic acid intravenously. Because there was no urine output even after 2 h after the start of surgery, an ultrasound of the abdomen was performed which showed an empty bladder with a Fowley-catheter in place and normal kidneys without signs of obstruction or dilation of the ureters. At the end of surgery, which lasted 275 min, the patient had received 3000 ml of crystalloids and frusemide 40 mg i.v. There were no hypotensive episodes, central venous pressures ranged from 7 to 10 mmHg.

Estimated blood loss was 300 ml. The urinary sediment showed numerous needle-shaped crystals and erythrocytes. Another 60 mg frusemide and i.v. fluids were administered which after 2 h resulted in brisk diuresis of 200–300 ml/h. Her serum-creatinine rose to 4.8 mg/dl on the second postoperative day, and urea 111 mg/dl, respectively, followed by decline to normal values over the next 5 days.

### Case 2

A 25-year-old Caucasian woman suffering from focal seizures since the age of 12 years, which were not sufficiently controlled by AED, was scheduled for implantation of subdural grid electrodes for invasive evaluation of her epileptic focus prior to ablative surgical therapy. Besides her epilepsy, she was fit and healthy. She was taking carbamazepine 800 mg b.d., and serum-carbamazepine levels were in the therapeutic range (10.4 mg/l). Preoperative laboratory values were normal, creatinine was 0.8 mg/dl and urea 30 mg/dl, suggesting normal renal function. For perioperative antibiotic cover she received 4.4 g amoxicillin/clavulanic acid. During the procedure, which lasted 220 min, she received 2000 ml of crystalloids and 1000 ml of hydroxyethyl-starch 6%. There was no blood loss. Central venous pressures ranged from 12 to 16 mmHg, and there were no hypotensive episodes. Three hours after induction of anaesthesia, the patient had passed only 15 ml of blood-stained urine and 20 mg of frusemide was given without effect. At the end of the uneventful surgery ultrasound of the abdomen was performed which showed normal kidneys and an empty urinary bladder with a urinary catheter in place. Over the next hour, diuresis increased spontaneously with an hourly urine output of 100–250 ml. There was a marked increase in creatinine and urea with a maximum of 4.7 and 97 mg/dl, respectively, on day 4 postoperation.

Sixteen days later, the same patient underwent a temporo-occipital cortical resection on the left under general anaesthesia to remove the seizure-focus.

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Preoperatively, creatinine was 1.1 mg/dl and urea 40 mg/dl, respectively. For perioperative antibiotic prophylaxis, she received 2 g cefotiam. The procedure lasted 11 h, and she had an hourly urine output of 80 ml. On the first postoperative day, creatinine was 1.0 mg/dl and urea 23 mg/dl.

### Case 3

An 18-year-old Caucasian woman who had undergone a partial resection of an left-temporal astrocytoma 3 years before, and who had been suffering from symptomatic temporal lobe epilepsy since then, presented for implantation of subdural strip and grid electrodes prior to resection of the remaining tumour which was thought to be her epileptogenic focus. She was on carbamazepine 600 mg b.d., the carbamazepine-serum level was 12.5 mg/dl. Creatinine and urea were in the normal range (0.9 and 21 mg/dl, respectively). After induction of anaesthesia amoxicillin/clavulanic acid 4.4 g was administered intravenously. During the operation, which lasted 260 min, the patient received 4100 ml crystalloids and 500 ml hydroxyethyl-starch 6% for fluid-replacement. The estimated blood loss was 400 ml. Total urine output was 400 ml, the collected urine was blood-stained which was thought to be due to traumatic insertion of the Fowley-catheter. The sediment showed abundant needle-shaped crystals and haematuria. Over the next 36 h, she passed 9.4 l urine. Creatinine and urea peaked on the second postoperative day at 5.0 and 84 mg/dl, respectively. Nineteen days later, in the same patient a partial resection of the left temporal lobe and an amygdalo-hippocampectomy was carried out. In the meantime, renal function had normalized (creatinine 0.7 mg/dl and urea 23 mg/dl). This time, imipenem was given for antibiotic cover. The patient went through the perioperative period without any problems.

### Discussion

We present three cases of acute renal failure in epilepsy patients undergoing neurosurgical interventions under general anaesthesia for treatment of their AED-refractory seizures. All three patients received a standard general anaesthesia with propofol for induction and maintenance of anaesthesia, atracurium for facilitation of endotracheal intubation and muscle relaxation and remifentanyl for analgesia. Haemodynamic changes such as hypotension or blood loss as possible causes of acute renal failure could be ruled out since the onset of acute renal failure was immediately after induction of anaesthesia and haemodynamics of all three patients were invasively and continuously monitored. In all three cases, acute renal failure followed induction of anaesthesia and administration of amoxicillin. In

our institution amoxicillin has been used widely during major neurosurgical operations in hundreds of patients for >6 years without obvious side effects. We therefore initially concentrated on a possible interaction of AEDs including carbamazepine and drugs used for anaesthesia as the reason for renal failure.

There are case reports of carbamazepine-induced impairment of renal function and even acute renal failure [1,2]. Carbamazepine may cause slight impairment of tubular function since children chronically treated with carbamazepine demonstrate a significant increase of  $\alpha_1$ -microglobulin excretion compared with an untreated control population [3] but this effect is insignificant from a clinical standpoint. Another well-described side effect of carbamazepine is the development of the syndrome of inappropriate secretion of anti-diuretic hormone, SIADH. This effect was even clinically used to treat diabetes insipidus but plasma levels of anti-diuretic hormone are not affected by carbamazepine. The mechanism is probably a sensitization of the collecting duct to the actions of anti-diuretic hormone by carbamazepine [4]. Thus, the administration of carbamazepine leads to a decrease in diuresis and an increase in urine osmolality [5].

The infrared-spectrometry performed on the crystals strongly suggested that amoxicillin was involved in the pathogenesis of renal failure in these patients. There are numerous case reports about impairment of renal function and acute renal failure following amoxicillin administration [6]. Crystalluria in subjects treated with high doses of amoxicillin is a well-known phenomenon and is described in most cases of amoxicillin related renal failure. In a pharmacokinetic study on intravenously infused amoxicillin in six healthy volunteers, Sjövall *et al.* [7] observed a massive macroscopic crystalluria in one of the subjects with low urine-pH and low diuresis which led to the withdrawal of this subject from the study. The same study concluded that in contrast to other  $\beta$ -lactam antibiotics, the renal clearance of amoxicillin appears to be independent of plasma concentration, i.e. plasma-concentrations after administration of amoxicillin in the usual dosage range are well below those required for saturation of tubular secretion. The solubility of amoxicillin under physiological conditions in human urine is pH-dependent, and macroscopic crystalluria is probably due to the urinary concentration of amoxicillin exceeding the urinary solubility of the drug, which by itself is dependent of urine-pH [7]. Our patients had received a dose of ~60 mg/kg/day. In the literature, an amount of 90 mg/kg/day (divided in two to three doses) is usually considered a high-dose. There are reports of doses up to 300 mg/kg/day. Insofar, amount of amoxicillin we used was a moderate to high dose.

We suggest that the concomitant use of carbamazepine in our patients lead to high urine osmolality and therefore high tubular concentrations of amoxicillin facilitating the urinary crystallization of

amoxicillin. Preoperative fasting and subclinical dehydration altering urine-pH may have further aggravated these effects and set the basis for crystallization of amoxicillin. When using amoxicillin in patients on AED, especially carbamazepine, special attention should be paid to the hydration status of the patients.

Two of our three patients underwent a second neurosurgical intervention a few weeks after their episode with perioperative renal failure. On this occasion, they received antibiotics different from amoxicillin (cefotiam, imipenem) without any events. In the meantime, more than 60 patients on chronic AED-medication underwent epilepsy surgery at our institution. Since the omission of amoxicillin and the institution of a third-generation cephalosporine into our perioperative antibiotic protocol no adverse reactions were observed.

*Conflict of interest statement.* None declared.

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