OXALOSIS IN RENAL TRANSPLANTS FOLLOWING METHOXYFLURANE
ANAESTHESIA


SUMMARY

Eight patients underwent allogeneic renal transplantation under methoxyflurane anaesthesia. All exhibited further impairment of renal function. Histological examination of the renal cortex of seven of these patients revealed precipitation of calcium oxalate crystals, these being the probable cause of the subsequent decrease in renal function. A transient polyuric phase was seen in one case in which autologous renal transplantation was carried out. When halothane, ether or cyclopropane was used for anaesthesia in renal transplantation, crystal formation was not seen. In ninety-four patients who underwent various types of general surgery no harmful renal effect which could be attributed to methoxyflurane was detected. Methoxyflurane is not a recommended anaesthetic agent for renal transplantation.

Methoxyflurane (2,2-dichloro-1,1-difluoroethylmethyl ether; Penthrane)* is a relatively new inhalation anaesthetic agent, which provides good muscle relaxation, has minimal depressant effect on the circulatory system, gives good postoperative analgesia and is non-explosive. Favourable experiences have been reported by several authors. Paddock, Parker and Guadagni, however, in 1964 reported that methoxyflurane can cause renal damage. Calcium oxalate crystals were found in biopsy material from such affected kidneys and similar reports have subsequently been published. In particular, the renal tubules seem to be primarily affected by methoxyflurane (Crandell, Pappas and MacDonald, 1966; Austin and Villandry, 1967; Elkington, FofHnet and Conn, 1968; Gant, Whalley and Baxter, 1969; Lebowitz, 1969).

Frascino, Vamene and Rosen (1970) reported 11 cases of renal damage possibly caused by methoxyflurane. In their series, 3 patients died from uraemia, while 2 suffered persistent irreversible reduction of renal function. The frequency of renal damage, however, seems to vary considerably. Crandell, Pappas and MacDonald (1966) found 16 cases among 94 patients, while Lapointe and Bele-Binda (1970) observed renal damage in 5 patients in a series of 17,335 who were anaesthetized with methoxyflurane (0.03%). Kuzucu (1970) found that tetracycline in association with methoxyflurane anaesthesia seems to induce formation of calcium oxalate crystals. There is substantial evidence to indicate that high output renal failure associated with methoxyflurane is dose-related (Kivalo and Saarikoski, 1971; Mazze, Trudell and Cousins, 1971).

Pitressin resistant polyuria and azotaemia in connection with calcium oxalate crystals in the renal tissues have been the characteristic findings in cases of renal damage after methoxyflurane anaesthesia (Paddock, Parker and Guadagni, 1964). McIntyre and Russell (1971) have offered a possible mechanism for the above-discussed changes. In the dog methoxyflurane inhibits renal adenosine triphosphatase activity, and even minute quantities of the agent can cause reduction in both PAH and inulin clearance.

Renal ischaemia occurring in connection with methoxyflurane anaesthesia most likely increases the risk for renal damage.

Holaday, Rudofsky and Treuhaft (1970) have shown that methoxyflurane can be demonstrated in human tissues as long as 9–12 days after anaesthesia. The agent is metabolized to a considerable degree, the degradation products being methoxydifluoroacetic acid and dichloro-acetic acid. One of these metabolites supposedly can be converted into oxalic acid.

The observation of reduced renal transplant function following methoxyflurane anaesthesia prompted...
an investigation of the renal function of all our patients undergoing anaesthesia with this agent.

METHODS

Anaesthesia.
Thiopentone was used for induction and suxamethonium to facilitate endotracheal intubation. The patients were artificially ventilated with a mixture of oxygen 2 l/min and nitrous oxide 2 l/min delivered to a circle system including a carbon dioxide absorber. A moderate hyperventilation was maintained by an automatic ventilator.

During the induction phase 2–1.5–1% methoxyflurane was given for 15–20 min. Thereafter the concentration was reduced to 1–0.2%, in most of the cases it being around 0.5–0.6%. Methoxyflurane was delivered from a calibrated vaporizer (Pentec*).

There were no significant complications during the anaesthesia. Haemorrhage was moderate and easily compensated.

Studies on renal tissue.
Specimens for histological examination were obtained in 7 cases either by an open biopsy or at autopsy (see table I).

*Cyprane Ltd, Keighley, England.

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**Light microscopic examination.** The material was immediately fixed in a 3% solution of glutaraldehyde for 20 hours, then rinsed in phosphate buffer, dehydrated in graded alcohol solutions and embedded in paraffin. Sections with a thickness of 3 microns were stained with Hematoxylin, P.A.S. according to McManus or with van Giessons stain. The sections were studied under a light microscope fitted with polarization equipment.

**Microradiographic examination.** Contact micro-radiograms were made from 0.75 mm thick slices of renal tissue fixed in 10% neutral formalin. The slices, which comprised whole sections of the kidney from the cortical surface to the apex of the papillae, were placed on Kodak Spectroscopic Plates 649-0 and exposed with Ni-filtered Cu-rays from an X-ray tube energized at 26 kV and 20 mA. In order to avoid direct contact between the wet specimen and the emulsion, thin plastic foils were placed between them. The plates were developed in Kodak D19b at 19°C for 4 minutes.

**X-ray crystallographic examination.** Small rod-shaped pieces of renal tissue measuring 0.4 x 0.4 x 2.5 mm were cut with a razor blade from the formalin fixed material after drying in air at room temperature for 12 hours. The diffraction pattern was

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**TABLE I. Clinical data in patients where methoxyflurane was used during renal transplantation.**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (days)</th>
<th>Renal disease</th>
<th>HLA-antigens</th>
<th>Ischaemia time (h)</th>
<th>Immunosuppression</th>
<th>Serum calcium (m.equiv/l.)</th>
<th>Serum phosphate (mg/100 ml)</th>
<th>Renal biopsy after</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>F</td>
<td>37</td>
<td>Chr.gl.nephr.</td>
<td>3, R*, -</td>
<td>1h 16m</td>
<td>Azathioprine</td>
<td>3.5-4.9</td>
<td>6.1-16.5</td>
<td>11 days crystals</td>
</tr>
<tr>
<td>II</td>
<td>F</td>
<td>30</td>
<td>Chr.gl.nephr.</td>
<td>2, 3, 5, -</td>
<td>20m</td>
<td>Steroids</td>
<td>4.2-4.9</td>
<td>7.7-13.0</td>
<td>crystals</td>
</tr>
<tr>
<td>III</td>
<td>M</td>
<td>46</td>
<td>Chr.gl.nephr.</td>
<td>2, 3, 7, -</td>
<td>10m</td>
<td>ALG</td>
<td>3.7-4.5</td>
<td>1.0-6.7</td>
<td>rejection</td>
</tr>
<tr>
<td>IV</td>
<td>F</td>
<td>33</td>
<td>Chr.gl.nephr.</td>
<td>1, 3, 7, LND</td>
<td>30m</td>
<td>X-ray therapy</td>
<td>4.2-4.9</td>
<td>3.0-4.2</td>
<td>rejection</td>
</tr>
<tr>
<td>V</td>
<td>M</td>
<td>28</td>
<td>Chr.gl.nephr.</td>
<td>2, 9, 12, -</td>
<td>40m</td>
<td>Lymph drainage</td>
<td>3.7-4.5</td>
<td>4.8-9.8</td>
<td>rejection</td>
</tr>
<tr>
<td>VI</td>
<td>F</td>
<td>44</td>
<td>Polyctes kidneys</td>
<td>1, 3, 8, LND</td>
<td>60m</td>
<td>-</td>
<td>4.1-4.5</td>
<td>3.0-7.7</td>
<td>rejection</td>
</tr>
<tr>
<td>VII</td>
<td>M</td>
<td>50</td>
<td>Chr.gl.nephr.</td>
<td>1, 3, 8, LND</td>
<td>45m</td>
<td>-</td>
<td>3.9-4.8</td>
<td>2.1-10.1</td>
<td>rejection</td>
</tr>
<tr>
<td>VIII</td>
<td>M</td>
<td>25</td>
<td>Chr.Pyelo-nephr.</td>
<td>Ba, 1, 7, -</td>
<td>33m</td>
<td>-</td>
<td>4.3-4.9</td>
<td>1.3-4.2</td>
<td>rejection</td>
</tr>
</tbody>
</table>
registered in a cylindrical Debye-Scherrer camera with a diameter of 114.6 mm using Ni-filtered Cu-rays at 40 kV and 20 mA. In some cases small concretions were dissected out of the fixated tissue under a Greennough microscope with the guidance of previous microradiograms. The concretions were ground and the material transferred to thin-walled glass capillaries which were fitted into the camera. Identification of the crystalline material was made through comparison with diffractograms registered from control material of known composition.

MATERIAL AND RESULTS

Methoxyflurane was used as the major anaesthetic agent in 102 patients anaesthetized at the Serafimer Hospital 1969–71. In 8 patients, who had renal insufficiency and uraemia, allogeneic renal transplantation was undertaken. These patients are referred to by their roman numerals (I–VIII). In the remaining 94 cases, all of which had a normal preoperative renal function, general surgical procedures of various kinds were performed.

Patients with preoperative renal insufficiency.

This group consisted of 8 patients who underwent allogeneic renal transplantation. In all of these cases a postoperative impairment of function of the transplant was seen. In 5 of the patients crystal precipitations were seen in the transplant. In 1 of them (III) precipitations were also seen in the patient’s own kidneys at the time of autopsy 45 days after surgery (fig. 4). In 2 patients (V, VI) the impaired function of the transplant subsequently prompted graft removal. In neither of these two cases could crystal precipitations be demonstrated in the biopsy specimens from the extirpated transplants. One patient (VIII), with a transient impairment of the transplant function, was not studied microscopically. This patient still, 23 months after the transplantation, displays good transplant function.

In table I is collected the main data concerning the patients with preoperative renal insufficiency and their transplants. From this table it is apparent that the donor-recipient antigen combination showed one (6 cases) and two (2 cases) mismatches, respectively (cf. Kissmeyer-Nielsen and Thorsby, 1970). The time of warm ischaemia was 10–76 min, and that of cold ischaemia 4–15 hours. The transplants were perfused with one of two kinds of cold electrolyte solution (Brunius, Fritjofsson and Gelin 1967; Collins, Bravo-Shugarman and Terasaki, 1969), in 7 cases dextran was added to the perfusate * (Manax et al., 1965). The immuno-suppressive therapy was based on azathioprine and steroids. In 5 cases antilymphocytic globulin, in 6 cases X-ray treatment of the transplant, in 3 cases thymectomy, and in 1 case lymph drainage was also used. The serum contents of calcium and phosphorus are also shown in this table. It is to be noted that most of the patients showed high phosphate values at some time. Diuresis from the transplant was seen in 2 cases during the surgery (I, V). After surgery transplant diuresis could not be exactly evaluated as all the patients had some diuresis from their own kidneys. Three patients (IV, VII, VIII) had sufficient renal function after 1–2 weeks, making further dialysis unnecessary. In the remaining cases sufficient function was not achieved, the transplants were either extirpated (I, V, VI) or the patients died (II, III).

Microscopic examination.

Biopsies and studies on kidneys at autopsy were carried out in 7 cases. The result of the histological examinations are seen in table I. In 5 cases optically bifringent crystals were seen. The present information suggests that the extent of precipitation was not stationary but actually decreased over a longer period of time in patients with urinary production: from the transplant (III, IV, V). This might explain the fact that crystals could not be seen when the first biopsy was taken 30 days after transplantation (VIII).

The bifringent crystals in the cortex of the kidneys were situated in the tubular lumina, in the epithelial cells of the proximal convuluted tubules and in the interstitial tissues (figs. 1, 2). The proximal tubules were seen to be somewhat dilated with a thin epithelium and a moderate amount of protein cylinders. The microscopic appearance was found to be qualitatively the same in all the specimens studied. The quantitative differences, on the other hand, were apparent.

In 1 case (VI) a hyperacute reaction was diagnosed on clinical symptoms and histological examination. In 4 patients (III, IV, V, VII) a slight rejection was diagnosed histologically at 1–2 occasions.

Microradiogram showed deposition of strongly radiopaque particles in the renal cortex (figs. 3, 4). Also in the papillary area the same particles were

*Perfadex, Pharmacia, Uppsala, Sweden.
Fig. 1. Patient I. Renal cortex with dilated tubules and atrophic epithelium. A large number of optically birefringent crystals are present in the tubular lumen, tubular epithelium and the interstitial connective tissue. Polarized light ×500.

Fig. 2. Patient I. Birefringent crystals in the tubular epithelium. Polarized light ×1500.

Fig. 3. Patient II. Contact microradiogram of kidney. The smooth renal surface is seen in the upper part of the picture and in the underlying cortex a diffuse precipitation of radiopaque particles is present. The particles measure 50-100 microns in diameter. ×27.

Fig. 4. Patient III. Contact microradiogram of the renal cortex (upper) and parts of the medulla (lower) from the patient's own kidney. The radiopaque material shows a more irregular distribution at the cortical-medullary border with large aggregates of different size. The maximum diameter is circa 0.5 mm. ×27.
found but far less extensively than in the cortex. The size of the particles varied between 25–500 microns.

X-ray diffraction pattern obtained from renal cortex tissues revealed calcium oxalate monohydrate and smaller amounts of calcium oxalate dihydrate (fig. 5).

Patients with preoperative normal renal function.

This group comprised 94 patients with normal serum creatinine levels preoperatively. In 4 of these cases an increase in serum creatinine was found postoperatively. Three of them underwent major abdominal surgery and were found to have malignant disease with metastases. The impaired kidney function in these cases can most likely be explained by a poor general condition and the extent of surgery performed. The fourth case was a 41-year-old woman who was operated upon because of a unilateral papilloma of the ureter. A resection of the distal part of the ureter and an auto-transplantation was performed (the renal artery was anastomosed to the internal iliac artery). The patient had a normal kidney on the other side. During anaesthesia and surgery, the patient experienced an excessive diuresis with dehydration and subsequent fall in blood pressure. In a few weeks' time the renal function was normalized. Histological examination of the kidney was not carried out.

In conclusion, there were no permanent signs of renal impairment which could be attributed to methoxyflurane in these patients.

DISCUSSION

Patients with normal preoperative renal function did not show signs of permanent renal damage after methoxyflurane anaesthesia. However, those patients with renal insufficiency, all of whom underwent renal transplantation, exhibited further impairment of renal function, precipitation of crystals in 5 of the transplants examined and in addition in 1 case (III) in the patient's own kidneys. The demonstrated precipitations of calcium oxalate most likely induced the impairment of renal function. In 2 transplant cases no crystals were found as pointed out above. This, however, could be explained by the fact that the renal biopsies were taken late in patients' postoperative course. The discussed cases differ from the rest of our renal transplant cases, mainly by the fact that these patients were anaesthetized with methoxyflurane. In the remaining cases in which crystal precipitations have not been shown, other agents were used (halothane, ether or cyclopropane; cf. Löfström, 1967). It seems likely that methoxyflurane anaesthesia has contributed to the precipitation of the crystals as has been discussed in the literature reviewed in the introduction of this paper. In the case where the patient's own kidneys at autopsy were found to contain large amounts of precipitates of crystals, it seems likely that the patient's disease (chronic glomerulonephritis) might also be of aetiological importance for the precipitation of the crystals in the patient's own kidneys (Macaluso and Berg, 1959; Bennett and Rosenblum, 1961).

In chronic renal insufficiency there is a marked tendency toward secondary hyperparathyroidism (McIntosh, Peterson and McPhaul, 1966). This seems to be caused by decreased excretion of phosphates via the kidneys. As seen in table I, in most of the cases a high phosphate content in the serum was seen with a probable increased risk of calcium precipitation in the kidneys. None of the patients was treated with tetracycline.

One of our patients (IV) received a second transplant because of poor transplant function. She exhibited crystal precipitations in the new transplant but not in the old one. This seems to indicate that trauma is of some importance for the precipitation of crystals, since during transplantation the transplant is ischaemic for varying periods of time (which if long lasting may lead to impairment of the renal function secondary to tubular necrosis). Ischaemia and/or tubular necrosis might predispose towards precipitation of calcium oxalate after methoxyflurane anaesthesia.
The crystal precipitation described was reversible, as demonstrated by cases III, IV and V. In these patients crystals were seen early in the post-transplant course (at 36, 10 and 19 days, respectively). The crystals had partly or completely disappeared at a later examination (at 45, 101 and 33 days).

Our findings as well as those of the literature stress that methoxyflurane is not a suitable anaesthetic agent for renal transplantation.

REFERENCE


**OXALOSE DANS LES TRANSPLANTS RENAISS APRES ANESTHESIE AU METHOXYFLURANE**

ZUSAMMENFASSUNG

Huit patients ont subi une transplantation rénale allogène sous anesthésie au méthoxyflurane. Tous ont manifesté une détérioration additionnelle de la fonction rénale. L'examen histologique du cortex rénal chez sept de ces patients révélait une précipitation de cristaux d'oxalate calcique, qui sont probablement la cause de la réduction consécutive de la fonction rénale. Une phase passagère de polyurie a été observée dans un cas de transplantation rénale autologue. La formation de cristaux ne se développa pas lorsqu'on utilisait halothane, ether ou cyclopropane pour l'anesthésie de la transplantation rénale. On ne détecta aucun effet nocif rénal, qui pourrait être attribué au méthoxyflurane, chez nonantequatre patients qui subirent diverses interventions chirurgicales générales. Methoxyflurane n'est donc pas un anesthésique recommandé pour la transplantation rénale.

**ABLAGERUNG VON OXALATEN (OXALOSE) IN NIERENTRANSPLANTATEN NACH METHOXYFLURANE-NARKOSE**

Ocho pacientes fueron sometidos a transplantaclón renal alógeno bajo anestesia con metoxiflurano. Todos mostraron una mayor disminución de la función renal. El examen histológico de la corteza renal de siete de estos pacientes reveló precipitación de cristaux de oxalato cálcico, siendo ésta probablemente la causa de la disminución subsiguiente de la función renal. Fue observada una fase poliúrica transitoria en un caso en que se efectuó una transplantaclón renal autóloga. No se observó formación de cristaux cuando se empleó halotano, éter o ciclopropano para la anestesia en la transplantaclón renal. En noventa y cuatro pacientes sometidos a diversos tipos de cirugía general no fue detectado ningún efecto renal nocivo que pudiera ser atribuido al metoxiflurano. No se recomienda el metoxiflurano como agente anestésico para la transplantaclón renal.

**RESUMEN**

Ocho pacientes fueron sometidos a transplantaclón renal alógena bajo anestesia con metoxiflurano. Todos mostraron una mayor disminución de la función renal. El examen histológico de la corteza renal de siete de estos pacientes reveló precipitación de cristaux de oxalato cálcico, siendo ésta probablemente la causa de la disminución subsiguiente de la función renal. Fue observada una fase poliúrica transitoria en un caso en que se efectuó una transplantaclón renal autóloga. No se observó formación de cristaux cuando se empleó halotano, éter o ciclopropano para la anestesia en la transplantaclón renal. En noventa y cuatro pacientes sometidos a diversos tipos de cirugía general no fue detectado ningún efecto renal nocivo que pudiera ser atribuido al metoxiflurano. No se recomienda el metoxiflurano como agente anestésico para la transplantaclón renal.