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Poisoning Caused by a Mixture of Plant-Nutrient Substrates

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Abstract. A fatal case of a poisoning caused by a commercial mixture of plant-nutrient substrates is described. The preparation contained numerous inorganic compounds, such as heavy metal salts, ammonium compounds and nitrates. The patient developed severe renal, hepatic and respiratory failure. He was treated with five haemodialyses and finally his ventilation was controlled mechanically via a tracheostomy. In spite of ventilation with 100 % oxygen he remained hypoxaemic during the last two days and after intensive therapy for seven days he developed a fatal cardiac asystole.

The results of toxicological experiments performed on rabbits show that the toxicity of the preparation may be due to the combined action of NH^+ with Cu^{++}, Ni^{++} and Co^{++}.

The histopathological findings made in the patient and the animals are compared.

Key words: Poisoning — Ammonium Compounds — Cobalt — Copper — Nickel.

Zusammenfassung. Es wird ein tödlicher Vergiftungsfall durch eine kommerzielle Mischung von Substraten der Pflanzenwuchsmittel berichtet. Das Präparat enthielt viele anorganische Verbindungen, wie Salze der Schwermetalle, Amoniumverbindungen und Nitrate. Das Vergiftungsbild bestand aus schweren Nierenversagen, Leberinsuffizienz und Ateminsuffizienz. Der Patient wurde mit Hämodialysen und künstlicher Beatmung behandelt. Trotz Beatmung mit 100%igem Sauerstoff blieb er hypoxämisch während der 2 letzten Tage und nach Intensivbehandlung von 7 Tagen starb er durch Asystolie.

Die Resultate der toxikologischen Experimente mit Kaninchen zeigten, daß die Toxicität des Präparates auf der kombinierten Wirkung von NH^+, Cu^{++}, Ni^{++} und Co^{++} beruhen kann.

Schlüsselwörter: Vergiftung — Ammonium-Verbindungen — Kobalt — Kupfer — Nickel.

Poisonings caused by commercial mixtures of plant-nutrient substrates are probably quite rare. The present paper describes a fatal case of such poisoning. The liquid preparation taken by the patient contained numer-

ous inorganic compounds, such as heavy metal salts, ammonium compounds and nitrates[1]. Most heavy metals are hepatotoxic and/or nephrotoxic agents (Moeschlin, 1967) but in our case the lungs also were seriously affected. In order to obtain more information about the toxic effects and the lethal components of the mixture, some toxicological experiments were performed on rabbits.

Case Report

A 29-year-old man was brought to the emergency ward on August 3, 1967. Three days prior to admission he had taken 150 ml of *Kasvu*[1] with the intention of commiting suicide. On arrival he had a 1-day history of abdominal pain, vomiting and blood-stained sputum. On examination he was in severe pain and clinically jaundiced, with a blood pressure of 145/90 mmHg. Although fatigued he was quite orientated. His abdomen was tender and the liver extended 3 cm below the right costal margin. Serum creatinine was 13 mg/100 ml. Because the patient seemed to have severe renal and hepatic failure, he was transferred immediately to the intensive therapy unit.

The patient was anuric and only a poor diuresis could be provoked with fluid and mannitol infusions. Haemodialysis was started on the second hospital day, and after a few days diuresis began to be restored. Melaena, which occurred on the first hospital day, disappeared during the treatment. However, uraemia persisted until the death of the patient (Table 1).

The liver function tests revealed a combined picture of cholestasis and hepatocellular damage (Table 1). Bleeding time and coagulation time as well as P + P value and platelet count were within the normal ranges during the whole time of the treatment.

The chest X-ray taken immediately after admission revealed a normal cardiopulmonary status (Fig. 1a) and the Astrup analysis from capillary blood showed normal values. However, the patient was dyspnoeic and he was given 35% oxygen and his ventilation was intermittently assisted with the aid of a Bennett ventilator via a mouthpiece. The blood gas analysis made on August 5 revealed hypoxaemia (Table 2) although the chest radiogram was still quite normal. On the following day there was radiological evidence of pulmonary congestion. Tracheostomy was performed and after that his ventilation was continuously assisted or controlled mechanically. During the following days the pulmonary status declined (Fig. 1b) and on August 10 he remained slightly hypoxaemic in spite of mechanical ventilation with 100% oxygen (Table 2). The PCO_2 was not elevated at any time but occasionally there was slight metabolic acidosis which was corrected with sodium bicarbonate infusions.

The amount of fluid given daily was adjusted according to the fluid losses. Small doses of diazepam (5—10 mg i.v.) were given when needed for sedation during mechanical ventilation. Antibiotic treatment consisted at first of procaine penicillin (900000 IU daily i.m.) and cephalotine (2.0 g twice daily i.v.) and later of chloramphenicol sodium succinate (1.0 g twice daily in i.v. infusion). During the last three days hydrocortisone was given (100 mg three times daily i.v.).

Bacterial culture from blood was made twice, on August 5 and 8, and was negative. On August 7 the bacterial culture from tracheal secretion was negative

1 The content of *Kasvu*: $(NH_4)_2HPO_4$ 20.0, NH_4NO_3 12.5, KNO_3 11.0, K_2HPO_4 2.0, Na_3PO_4 0.75, K_2SO_4 0.5, $Na_2S_2O_3$ 0.1, $Na_2B_4O_7 \times 10\ H_2O$ 0.1, $FeSO_4$ 0.1, $MnSO_4$ 0.1, $MgSO_4$ 0.1, $NiSO_4$ 0.1, $CuSO_4$ 0.1, $CoSO_4$ 0.1, $ZnSO_4$ 0.1, aqua ad 100 ml.

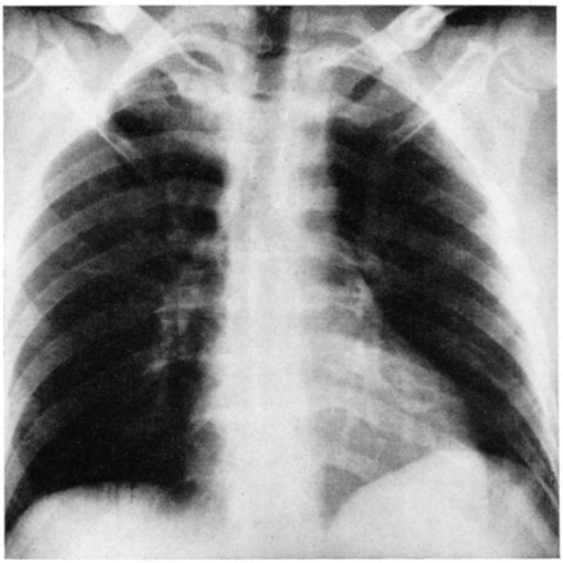


Fig. 1a and b. Chest X-ray pictures of the patient. a Immediately after admission, normal cardiopulmonary status

but from the specimen taken on August 9 there grew Klebsiella. Laboratory analyses revealed neither haemolysis of red cells nor methaemoglobinaemia. The copper content of serum was normal.

The electrocardiogram was monitored continuously on an oscilloscope. The ECG revealed an incomplete right bundle branch block and left axis deviation suggesting strain of both ventricles. During the last hours before death the patient developed supraventricular tachycardia which was followed by cardiac asystole.

Autopsy was performed on the seventh postmortem day.

The lungs were partially indurated. Congestion and oedema were noted on cut surfaces. The normal architecture of the lungs was disturbed and the general picture was honeycomb-like. In microscopic examination, haemorrhagic exudation, leucocytes, round cells, macrophages and fibrin were found to have accumulated in the alveolar spaces. Concentrically arranged hyaline membranes were also seen. The thickened alveolar septae showed round cell infiltrations, fibroblastic proliferation and hypertrophy of the muscle fibers (Fig. 2a). In the periphery of the lung one could see incipient obliterative bronchiolitis. There were also diffuse pleural haemorrhage and oedema.

The kidneys were enlarged (each weighing 300 g) and cloudy and the corticomedullary line was smudged. Microscopic examination revealed that the glomeruli were more bushy than usual and the capillary endothelial cells were slightly swollen. The basal membrane was unevenly thickened and partly reduplicated. The mesangium was oedematous and dilated. The tubules were dilated and their epithelium was flattened. The epithelium of the proximal tubules was finely

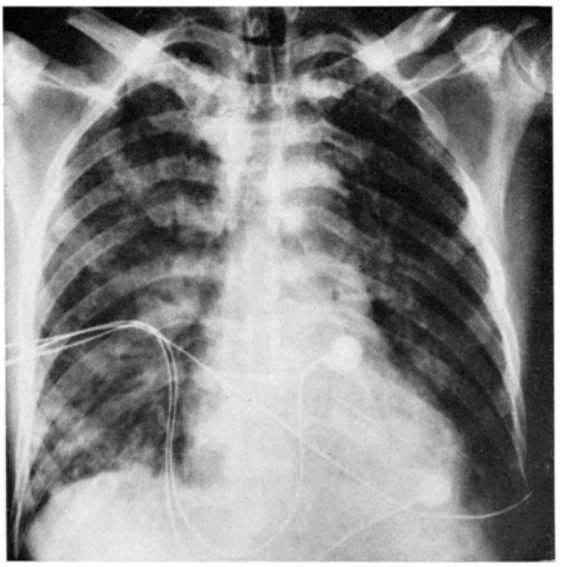


Fig. 1b. Six days after admission, marked changes

vacuolated (characteristic of the "Zucker-Speicher-Niere", Doerr and Uehlinger, 1966). In the epithelium of the distal tubules necrobiotic and necrotic changes were noted. Some hyaline and proteinaceous tubular casts were detected. In the interstitium of the medullary region there were small round cell infiltrations.

Examination of the liver revealed slight hepatocellular hypersensitive cholestatic injury.

Animal Experiments

On the basis of the information given by the manufacturer of *Kasvu*, an analogous liquid was prepared. The toxic action of the original and the analogous preparations was studied on white adult rabbits of both sexes. Various amounts of the liquids were given orally through a gastric tubing.

The toxic action of both preparations appeared slowly: 10—24 hours after their administration the rabbits exhibited respiratory difficulties, loss of consciousness and death. As shown in Table 3, the toxicity of both preparations was similar.

Investigations made with various combinations of the components of the preparation seemed to show that the toxicity was dependent on the combination of NH_4^+ with Cu^{++}, Ni^{++} and Co^{++} (Table 3).

Histopathological examinations were made on two rabbits which died after treatment with *Kasvu* and on one control animal. In the rabbits, too, the changes were localized mainly in the kidneys and the lungs. The hepatic changes encountered in the patient were not seen in the animals.

The lung specimens revealed severe congestion and oedema. The alveolar septae were thickened and round cell infiltration and slight fibrosis were present. Focal haemorrhages were seen, but hyaline membranes were not found (Fig. 2b).

Table 1. *Case report. Laboratory investigations*

Day	Laboratory data												
	pH of capillary blood	K^+ (mEq/l)	Na^+ (mEq/l)	Cl^- (mEq/l)	Haematocrit (%)	Serum creatinine (mg/100 ml)	Serum bilirubin (mg/100 ml)	GOT (IU)	GPT (IU)	LDH (IU)	Alkaline phosphatase (IU)	Urine (ml)	Haemodialysis (N:0)
August 3	7.39	4.8	134	84	44	13.0	7.0	165	280	410	—	75	—
August 4	7.33	4.0	132	88	47	12.4	—	71	160	340	118	75	I
August 5	7.34	5.0	132	—	37	13.0	—	—	—	—	—	75	II
	7.44	4.2	131	—	39	9.6	—	—	—	—	—	—	—
August 6	7.40	4.9	—	—	37	12.3	—	—	—	—	—	142	—
August 7	7.42	5.2	137	87	—	16.0	14.1	39	—	—	—	225	III
	7.45	4.6	142	94	35	12.4	(8.98 direct)	—	—	—	—	—	
August 8	7.43	5.9	131	84	35	17.0	—	—	—	—	—	300	
August 9	7.38	6.6	136	84	34	20.0	—	16	43	500	195	430	IV
	7.36	5.5	138	90	33	11.4	—	—	—	—	—	—	
August 10	7.35	5.2	—	89	34	15.0	30.0	—	—	—	—	—	V
	7.27	4.2	137	—	—	10.2	—	—	—	—	—	—	

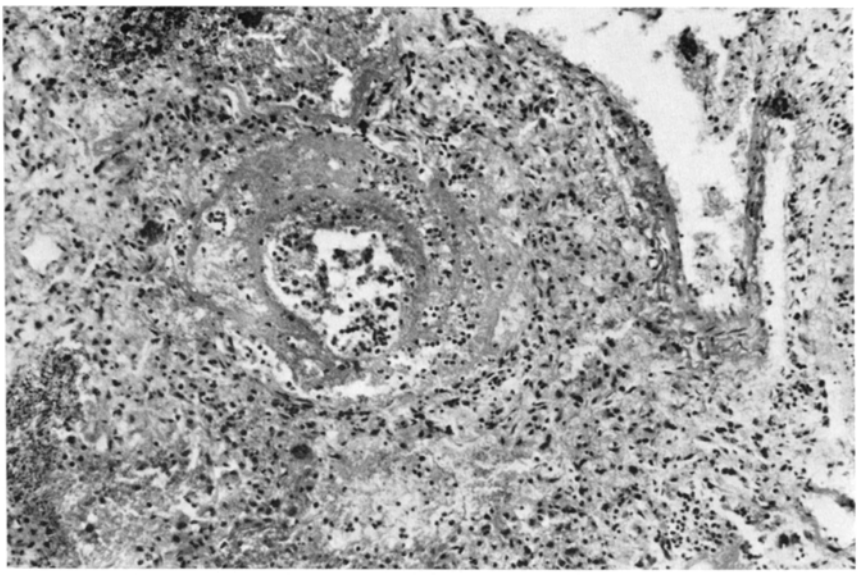
Table 2. *Case report. Arterial blood gas analyses and haemoglobin content of blood*

Day	PO_2 (mm Hg)	PCO_2 (mm Hg)	pH	Hb (g/100 ml)	Ventilation and oxygen content of inspired gas
August 5	46.0	32.5	7.39	15.1	Spontaneous, 21%
August 8	59.0	36.5	7.42	12.7	Bennett, 40%
August 10	50.0	42.0	7.31	11.7	Bennett, 100%

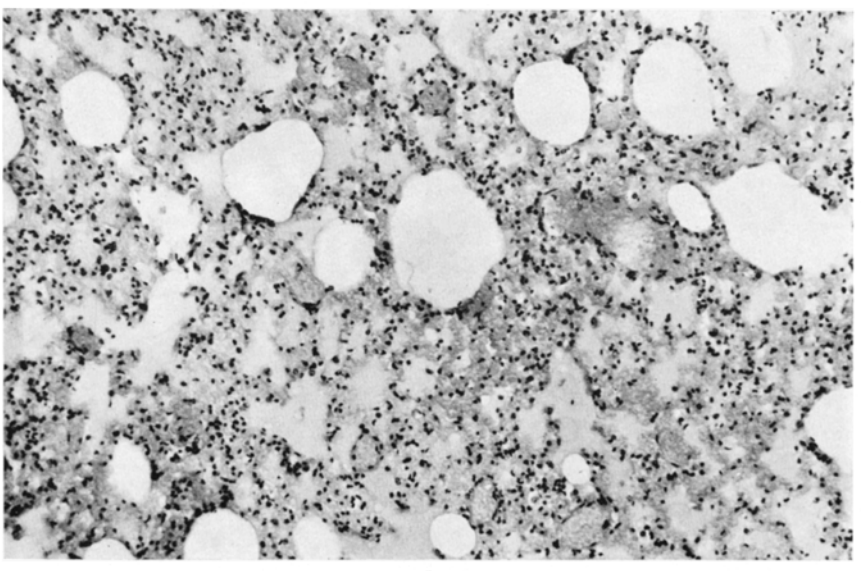
Table 3. *The lethal effects of* Kasvu *and of various combinations of its components on rabbits*

Preparation	Dose (ml/kg)	Number of rabbits	Survival (%)
Kasvu, original preparation	2.5	4	100
	6.0	4	0
	10.0	2	0
Own preparation analogous to *Kasvu*	3.0	2	100
	6.0	4	0
	10.0	2	0
Own preparation without NH_4NO_3 and KNO_3	6.0	2	0
	10.0	2	0
Own preparation without K_2SO_4, $Na_2S_2O_3$, $Na_2B_4O_7$, $FeSO_4$ and $MnSO_4$	6.0	2	100
	10.0	4	50
Own preparation without $MgSO_4$, $NiSO_4$, $CuSO_4$, $ZnSO_4$ and $CoSO_4$	6.0	2	100
	10.0	2	100
Own preparation without nitrates and phosphates	6.0	2	100
	10.0	2	100
$NH_4NO_3 + KNO_3$	6.0	2	100
	10.0	2	100
$(NH_4)_2HPO_4 + K_2HPO_4 + Na_3PO_4$	6.0	2	100
	10.0	1	100
$(NH_4)_2HPO_4 + NH_4NO_3 + CuSO_4 + NiSO_4 + CoSO_4$	6.0	2	100
	10.0	4	0

In the kidneys the glomerular tufts were bushy. There was slight oedema and proliferation in the endothelial and epithelial cells of the capillaries. The basal membrane was unevenly thickened. The mesangium was distended and oedematous. There was PAS-positive material situated in the mesangium and the tubular epithelium.



a



b

Fig. 2a and b. Micrographs of the lungs. a Human lung: interstitial pneumonia with concentric alveolar hyaline membranes; heavy congestion, oedema and small haemorrhages. b Rabbit lung: incipient interstitial pneumonia, heavy congestion, oedema and small haemorrhages. × 165 v.G. (a and b: for reproduction reduced to $^2/_3$)

Discussion

The high content of nitrates in *Kasvu* might have been the cause of the lethal action of this preparation (Wirth *et al.*, 1967) but this is not supported by the results of our animal experiments or by the fact there was no methaemoglobinaemia in the patient. The amounts of the other compounds in *Kasvu* are relatively small (Moeschlin, 1967) and therefore it is likely that the toxicity of the preparation was due either to the synergistic action of various compounds or to the production of some toxic complexes. These two possibilities are closely bound together.

Most heavy metals are capable of forming complexes with organic molecules (Passow *et al.*, 1961). Bjerrum (1941) has shown that cobalt, copper and nickel readily form complex compounds with ammonia, too. Our animal experiments showed that the toxicity of *Kasvu* may arise from the combination of some heavy-metal salts (copper, cobalt, nickel) with ammonium compounds. The potential toxicity of this kind of combination was revealed also in some in vitro perfusion experiments in which fluid transport through the isolated intestinal wall was inhibited by the simultaneous action of cobalt and ammonium salts but not by either salt alone (Takki, Heinonen and Mattila, 1970, unpublished observation). As far as we know, there is no previous information on the toxic effects of combinations of heavy metal and ammonium compounds.

Obviously the death of our patient was due to severe renal, hepatic and respiratory failure. The histopathological findings in the kidneys of the patient and of the animals resemble the lesions encountered in heavy metal poisonings (Doerr and Uehlinger, 1966). However, the patient's kidneys also revealed changes which probably were ascribable to the therapy: the fine vacuolar degeneration of the epithelium of the proximal tubuli, which was not detected in experimental animals, was interpreted as accumulation of cardohydrates (mannitol). It is also possible that the pulmonary changes found in the patient were partially due to uraemia (Heard, 1958) and/or oxygen therapy (Regele, 1967). The hyaline membranes seen on the inner surfaces of the alveoli may be encountered in uraemic as well as in so called "respirator" lungs. However, because the experimental animals also had respiratory difficulties and their lungs exhibited marked histopathological changes, it is obvious that the toxicity of the *Kasvu* preparation is due in part to its effect on the lungs.

References

Bjerrum, J.: Metal amine formation in aqueous solution. In: Treatise on analytical chemistry. Vol. I (I. M. Kolthoff and P. J. Elving, *eds.*). New York: The Interscience Encyclopedia, Inc. 1959.

Doerr, W., Uehlinger, E.: Spezielle pathologische Anatomie, Niere und ableitende Harnwege, Bd. III, S. 179. (H. U. Zollinger, Hrsg.). Berlin-Heidelberg-New York: Springer 1966.

Heard, K. M., Posey, E. L., Long, J. W.: Fulminating uremic pneumonitis associated with acute ischemic nephropathy (lower nephron nephrosis). Amer. J. Med. **24**, 157 (1958).

Moeschlin, S.: Klinik und Therapie der Vergiftungen, 4. Aufl. Stuttgart: Georg Thieme 1965.

Passow, H., Rothstein, A., Clarkson, T. W.: The general pharmacology of the heavy metals. Pharmacol. Rev. **13**, 185 (1961).

Regele, H.: Veränderungen der menschlichen Lungen unter maschineller Beatmung. Beitr. path. Anat. **136**, 165 (1967).

Wirth, W., Hecht, G., Gloxhuber, C.: Toxikologie-Fibel. S. 72. Stuttgart: Georg Thieme 1967.

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