CASE REPORT

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Death Following Colchicine Poisoning

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ABSTRACT: A 45-year-old male was admitted to hospital after 2 to 3 days of vomiting, nausea, and diarrhea following an apparent overdose of colchicine tablets. During hospitalization his white blood cell count fell dramatically. At death, 33 h following initial hospitalization, pleural effusion with bilateral bronchopneumonia was evident, together with numerous bacterial colonies and marked hypocellularity of bone marrow and reduced megakaryocytes, erythroid, and myeloid cells. The most striking histological findings were numerous metaphasic mitotic figures in gastric and small bowel epithelia. Colchicine was detected, confirmed by high pressure liquid chromatography with photodiode array detection, and quantitated in antemortem plasma collected 3.3 h following hospitalization and in postmortem blood and bile. Colchicine was not detected in liver, vitreous humor, or stomach contents.

KEYWORDS: pathology and biology, poisoning, colchicine

Colchicine is a naturally occurring alkaloid found in flowers of the meadow saffron (*Colchicum autumnale*). Colchicine has been the drug of choice for acute gouty arthritis and as a prophylactic agent against such attacks. It has also been used for the treatment of amyloidosis in familial Mediterranean fever [*1*], condyloma acuminata [*2*] and, as it is a potent inhibitor of cellular mitosis, colchicine and its derivatives have been used recently in the treatment of some cancers [*3*].

Ingestion of as little as 7 mg colchicine has been reported to be fatal [*4*], while subjects have survived 30 to 50 mg of the drug [*2*]. Concentrations of colchicine have been detected in postmortem blood, ranging from 0.090 to 0.160 mg/L [*5*], although many reports have been unable to detect postmortem blood concentration [*6*]. The absence of drug at postmortem has been attributed to a short pharmacokinetic half-life of 20 min together with the fact that death can occur at any stage following the ingestion of a large dose, often more than 40 h after ingestion [*1*].

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In this paper we describe the clinical and postmortem observations of a colchicine overdose, and the use of HPLC with photodiode array for the detection, confirmation and quantification of tissues for colchicine.

Case Details

A 45-year-old white male was admitted to hospital with 2 to 3 days history of profuse vomiting, nausea and diarrhea associated with epigastric and back pain. He had a past history of bleeding peptic ulcer and some episodes of unexplained chest pain a few years earlier. He was a heavy smoker and had a history of alcohol abuse.

Three weeks prior to admission he presented to his family doctor with severe pain in the left great toe, which was diagnosed as acute gout, and Colgout tablets were prescribed. On admission to hospital he was oliguric, dehydrated with mild tenderness of the epigastrium. His blood pressure was 96/60, heart rate 200 beats per minute and temperature 38°C. His liver was palpable and a few "spiders" were noted on the skin of his back. There was no jaundice. Rectal examination showed no signs of bleeding. Full blood examination revealed moderate thrombocytopenia 73 $\times$ 10^9/L, white blood cell count was 8.6 $\times$ 10^9/L with shift to the left and leukocytes showing toxic granulation and vacuolation. He became hypotensive, required intubation, ventilation and shortly after admission was transferred to the Intensive Care Unit. On the second day of hospitalization his mother reported finding at home an empty bottle of colchicine (100 tablets, 500 microgram) that had been obtained three weeks previously. The full blood examination was repeated 6.5, 20.5 and 25.5 h after admission and revealed white blood cell count of 7.3 $\times$ 10^9/L, 3.5 $\times$ 10^9/L and 0.9 $\times$ 10^9/L, respectively. Platelets dropped to 58 $\times$ 10^9/L, 40 $\times$ 10^9/L, and 26 $\times$ 10^9/L at that same times. Prothrombin times was 25.4 s, 22.3 s and 21.0 s, respectively. The patient's condition continued to deteriorate, he remained hypoxic, hypotensive and became anuric. After 33 h from admission he developed sudden cardiac asystole. All subsequent resuscitation attempts were unsuccessful.

Postmortem examination was performed 39 h after the death. The significant macro and microscopic findings showed pleural effusion with bilateral bronchopneumonia. Histologically numerous bacterial colonies with a weak inflammatory response were seen. *Staphylococcus aureus* and *Escherichia coli* were isolated from the lung tissue. Marked hypocellularity of bone marrow with reduced number of megakaryocytes, erythroid and myeloid cells were seen together with predominantly micronodular cirrhosis of liver with mild steatosis. The most striking histological findings were numerous metaphasic mitotic figures in gastric and small bowel epithelium. No epithelial atypia was seen (Fig. 1).

The gall bladder and extrahepatic bile ducts were normal. No gout tophi were present. Hospital plasma samples were obtained and postmortem specimens including blood, bile, liver, vitreous, and stomach contents were collected for toxicological analysis.

Full toxicological examinations of plasma obtained during hospitalization were performed. This involved an enzyme-multiplied immunoassay (EMIT) screen for methadone, opiates, amphetamines, cannabinoids, cocaine metabolites, benzodiazepines, and barbiturates. Plasma extracts were also analyzed on a capillary column gas chromatographic screen using nitrogen-phosphorous detection for basic and neutral drugs. An additional screen was conducted by gradient elution high performance liquid chromatography (HPLC) using photodiode array detection. This system was capable of detecting acidic and neutral compounds. Further tests for alcohol and the chloral hydrate metabolite, trichloroethanol were separately conducted. These routine analyses showed no evidence of common drugs or poisons including alcohol.

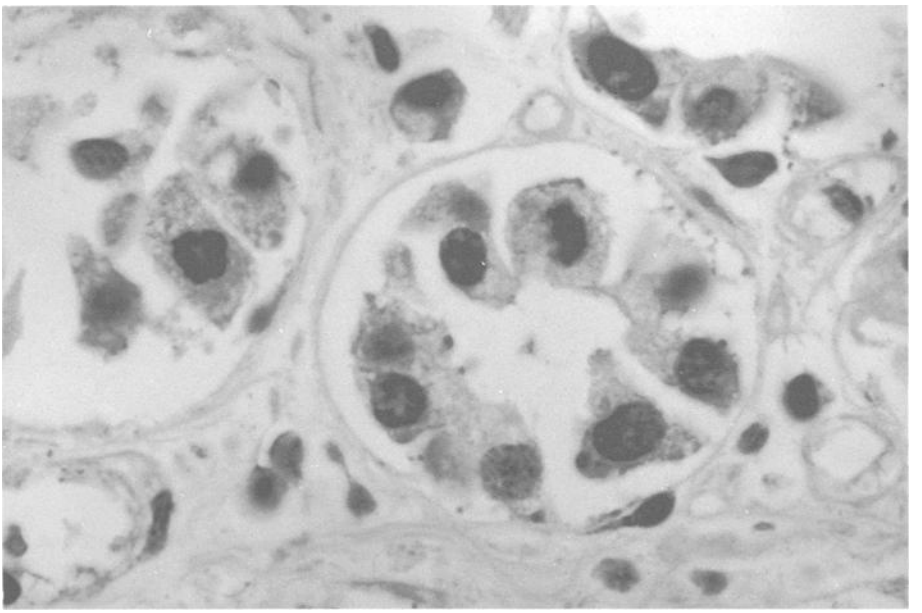

FIG. 1—*Numerous metaphasic mitotic figures in the gastric epithelium.*

Analytical Details

Materials

Acetonitrile and methanol were of HPLC grade (Mallinkrodt, Australia). All other chemicals were of Analytical Reagent grade (Ajax, Australia). Colchicine was provided by the Curator of Standards at the Australian Government Analytical Laboratories. Working standards were prepared fresh from a stock solution of 1 mg/mL. A calibration curve was prepared over the appropriate concentration range in the same medium as the postmortem and antemortem specimens.

Chromatographic Conditions

The HPLC system consisted of two LC-6AD constant flow pumps, SIL-6B autoinjector, system controller (SCL-6B), SPD-M6A photodiode array detector (Shimadzu Instruments, Oceania), and a PC-AD computer (Samsung 5550). A back-up tape drive, and additional SPD-6AV ultraviolet detector operating at 245 nm and a C-R4A integrator/plotter (Shimadzu) was connected in series after the photodiode array detector. The photodiode array detector was operated in a 1 nm band-pass mode monitoring light from 195 to 650 nm. Display was at 245 nm.

Chromatography

The analytical column was a 5 μm particle size Novapak C18 (150 mm long × 4.6 μm ID) protected by a Novapak C18 guard column (Waters Associates). The mobile phase was 0.1 M KH_2PO_4, 5 μM pentane sulfonic acid (pH 6.0)/methanol/acetonitrile: 60/26.6/13.4. The total flow was 0.8 mL/min. Colchicine eluted at 6.6 min.

TABLE 1—*Colchicine concentrations following a fatal poisoning.*

Specimen	Colchicine concentration (mg/L)
Antemortem Plasma[a]	
1. +(3.3 h)	0.06
2. +(6.5 h)	N.D.
3. +(20.5 h)	N.D.
4. +(25.5 h)	N.D.
5. +(31.5 h)	N.D.
Postmortem specimens	
Blood	0.03
Bile	4.2
Liver	N.D.
Vitreous humor	N.D.
Stomach contents	N.D.

[a]( ) Numbers in parentheses refer to the time of sampling after hospital admission. N.D.—Not detected, detection limit 0.005 mg/L

Extraction

One millilitre of specimen was added to 10 mL silanized glass extraction tubes. Following the addition of 1 mL 1 M $NaHCO_3$, 7 mL of dichloromethane were added. The tubes were gently agitated for 30 min and then centrifuged at 3500 rpm for 10 min. The aqueous phase was aspirated off and the solvent transferred to fresh silanized glass tubes. The solvent was then evaporated using a Speed Vac concentrator (Savant Industries). Tubes were reconstituted with 200 μL 0.2% H_3PO_4 and vortexed. An aliquot of 50 μL was injected onto the HPLC.

Liver homogenates were prepared by homogenizing 10 g of freshly minced liver in 10 mL of water. The pH was adjusted to 10 using 1 M NaOH. Subtilisin (10 mg, Sigma) was added and the homogenate incubated for 60 min at 55°C. The pH was finally adjusted to 7.0 ± 0.5 with dilute mineral acid.

Results and Discussion

Administration of colchicine in therapeutic doses may be associated with well known side effects, the most common being abdominal pain, nausea, vomiting, diarrhea and steatorrhea [*7,8*]. Also, symptoms attributed to hypocalcemia in acute colchicine poisoning have been reported [*9*]. The use of colchicine has been reported with serious toxicity and fatalities occurring even after administration of therapeutic doses [*2,8*].

The clinical course described in this case is consistent with that reported in the literature describing colchicine poisonings. These include inhibition of colchicine binding with tubulin preventing its polymerization into microtubules which manifests morphologically in arrested metaphasic mitoses. Tissues with a high rate of cell divisions i.e., bone marrow, hair follicles and gastrointestinal epithelium are most severely affected [*6,10*]. Bone marrow aplasia with peripheral blood abnormalities belong to known toxic effects of colchicine [*11,12*]. Suppression of the bone marrow seen in this case, is demonstrated clinically by marked thrombocytopenia and leukopenia and demonstrated at autopsy by bone marrow aplasia. Colchicine induced epithelial atypia in gastrointestinal and respiratory epithelium has also been reported, [*10*], however it was not present in this case. Colchicine related deaths occur due to overwhelming infections [*9*], respiratory,

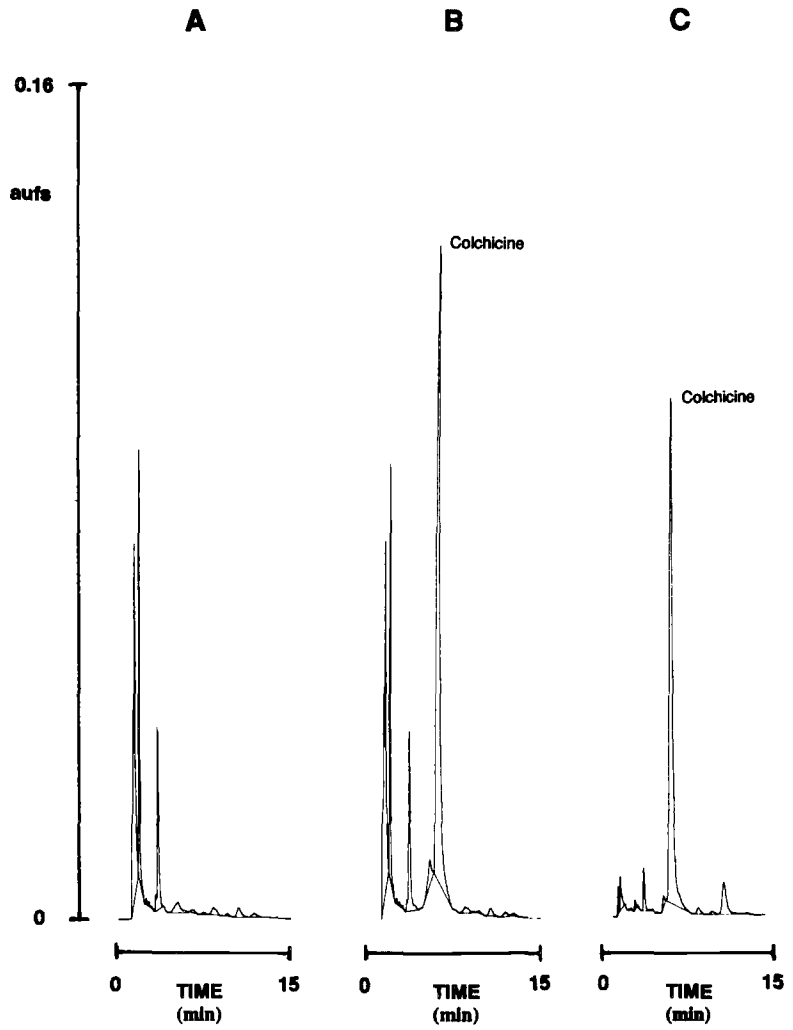

FIG. 2—*Chromatograms of colchicine determination in bile.* (A) *blank bile*; (B) *bile standard at 5.0 mg/L*; (C) *case bile calculated at 4.2 mg/L.*

or multi organ failure [*13*]. Sepsis occurring in such cases is often the result of severe intestinal wall damage [*14*]. Adhesiveness, hemotaxis and degranulation, all the main functions of granulocytes may also be affected by colchicine.

The concentrations of colchicine detected in the deceased are shown in Table 1. A plasma concentration of 0.06 mg/L, approximately 3 h after admission to hospital is similar to other reports of colchicine poisonings [*15*], although not as high as one report in blood of 0.25 mg/L at 2 h after ingestion [*16*]. For comparison, plasma concentrations of 0.003 to 0.01 mg/L have been reported following therapeutic administration [*2*]. A lack of colchicine in subsequent plasma samples is consistent with a short pharmacokinetic half-life of 20 min.

Colchicine is rapidly taken up into cells and bound to intracellular microtubular proteins [*17*]. Following colchicine administration, the peak concentration in white blood

cells is at least sixteen-fold higher than the peak concentration in plasma [*18*]. Therefore the concentration of the drug in whole blood may be higher than its concentration in the comparable plasma fraction. This may explain the high blood level reported by Caplan and colleagues [*16*], and the detection of a postmortem blood concentration of 0.03 mg/L in the present case where death was approximately 33 h after initial admission to hospital.

In light of the report by Allender [*19*], it was of interest to note that there was no detectable evidence of colchicine in liver, particularly considering the relatively large amount present in bile (Fig. 2). Wallace and co-workers [*20*] demonstrated that a significant route of excretion of colchicine is via the bile. Up to 40% of colchicine may be excreted into bile, urine, and feces [*17*]. In this case biliary concentrations were significant and much higher than blood. Urine was not available for analysis in the present case. Colchicine was not detected in vitreous humor and stomach contents.

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