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Exploratory single blind study on polarising and light microscopic appearance of crystals of commonly prescribed drugs

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Abstract
Background: It is not unusual for the pathologist to encounter various drug crystals in urine sediment which are morphologically different from the ones in his cognitive domain. Paucity of literature on crystals of all the drugs, makes it difficult to identify them. This study aims at exploring the microscopic appearance of crystals of common drugs.
Material and Methods: Forty common drugs administered orally were included for the study. These drugs were mixed with distilled water on a slide, coverslipped and observed by two pathologists who were blinded. Of which one was a telepathologist who reported on images sent.
Results: Crystals varied in their appearance and birefringence, few resembled architecture of known structures in urine sediment. Acetaminophen with hexagonal architecture resembled cysteine, broad colourless rectangular ceftriaxone crystals mimicked waxy cast. No definite answer was available for few, These data along with the light and polarising microscopic features are discussed in detail.
Conclusion: Crystals of unusual appearance should alarm the pathologist to think of a drug and alert the physician in case of drugs causing renal damage.

Keywords: Crystalluria, drug crystals. urine sediment, microscopic crystals

Introduction
It is not unusual for the pathologist to encounter various drug crystals in urine sediment which are morphologically different from the ones in his cognitive domain. Paucity of literature on crystals of all the drugs, makes it difficult to identify them. crystalluria due to many drugs, their resemblance to other crystals or sediment may lead to misinterpretation [1, 2, 3].

This study aims at exploring the microscopic appearance of crystals of common drugs and document so that the knowledge aquired helps to avoid confusion, and misinterpretation. A thorough knowledge and careful history is needed for identification of these crystals.

Material and Methods
Commonly prescribed oral medicines irrespective of their form, ie either tablets, syrup, suspension or capsule commonly dispensed from hospital pharmacy were included for the study and were collected from the pharmacy. Injectable forms of drugs, Oily preparations, and other parenteral drugs were excluded.

One drop of suspension or syrup, or a, tiny quantity of powder from opened capsule or broken tablet was placed on a slide and gently mixed with a drop of distilled water to make a uniform suspension. Further dilution was done with distilled water whenever necessary to reduce the density of the crystals. coverslip was applied on this and the slides were observed under low power, high power and polarising microscope and morphology of crystals and polarising property were noted. Images of the same was captured in digital camera. then the wet preparation slides were given to two pathologist who were blinded. One was an inhouse pathologist working in clinical pathology laboratory. other was a telepathologist to whom the captured images of crystals were sent through whatsapp. The results or observations of all of them were noted and analysed. No history was provided to both pathologists. they were asked to report on the urine sediment. Responses were analysed and appearances of crystals were described.

Results and Discussion

Transient crystalluria may occur following administration of many drugs in association with or without renal/ urinary abnormalities. factors favouring the precipitation of crystals within le tubular lumina are exccesive or overdosage of the drug, dehydration, or hypoalbuminaemia, which increases the unbound drug which is ultrafiltrated by the glomerulus. [4, 5]

A brief account of crystals of few of the commonly used drugs which were mistaken are discussed.

Paracetamol appeared as Hexagonal / Benzene crystals mistaken for cysteine. (fig 1) cystinuria is a rare inherited autosomal recessive disorder. The sodium cyanide - nitroprusside test is a Rapid, simple, qualitative test which gives purple colour for cystinuria. These crystals had three dimensional architecture.

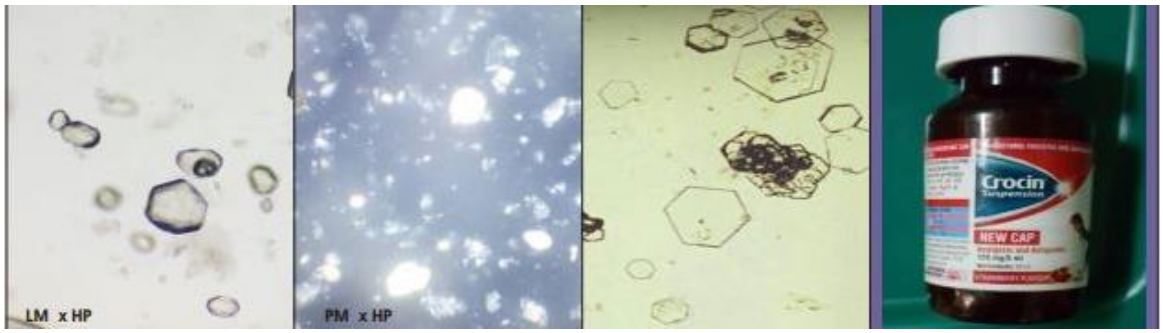

Fig 1: Paracetamol Hexagonal / Benzene crystals mistaken for cysteine.

Amoxycillin was Mistaken for Hippuric acid crystals. (fig 2) Hippuric acid crystals are yellow-brown or colorless elongated prisms or plates and maybe so thin to resemble needles and they often cluster together in acidic and neutral pH urine and are soluble in Ether.

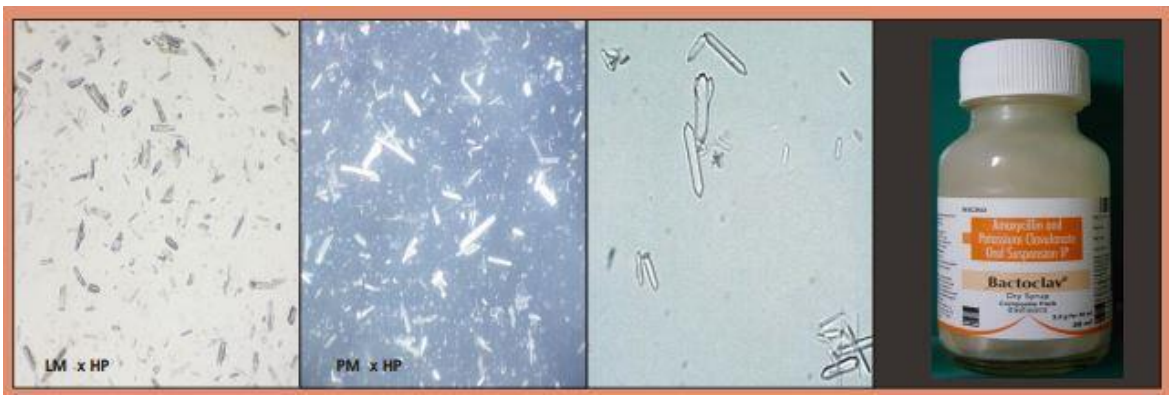

Fig 2: Amoxycillin Mistaken for Hippuric acid.

Cephalosporins, Atenelol, Telmisartan were mistaken as waxycasts. (fig 3) There is a caution here as waxy and broad casts indicate severe Renal disease/renal failure and waxy cast (>5-10 per HPF) is significant.

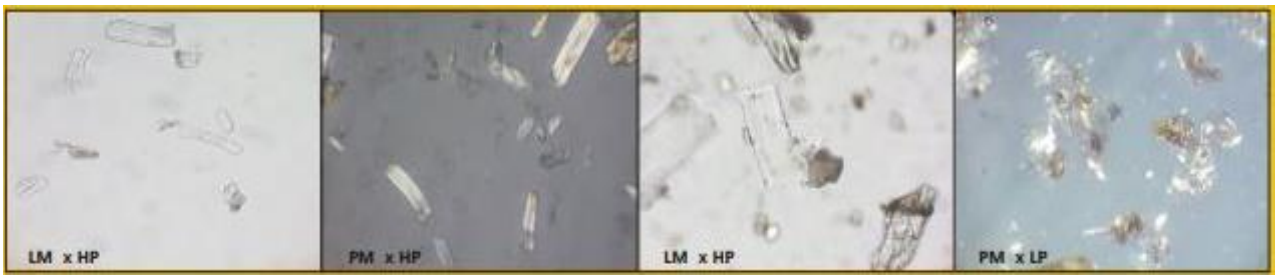

Fig 3: Atenelol, Telmisartan mistaken for Waxy and broad casts

Thyroxine Crystals appeared Polygonal, flat with slight birefringence and interpreted as drug crystals with no identity or Calcium carbonate. Frusemide crystals were were like Maltese cross. (fig 4)

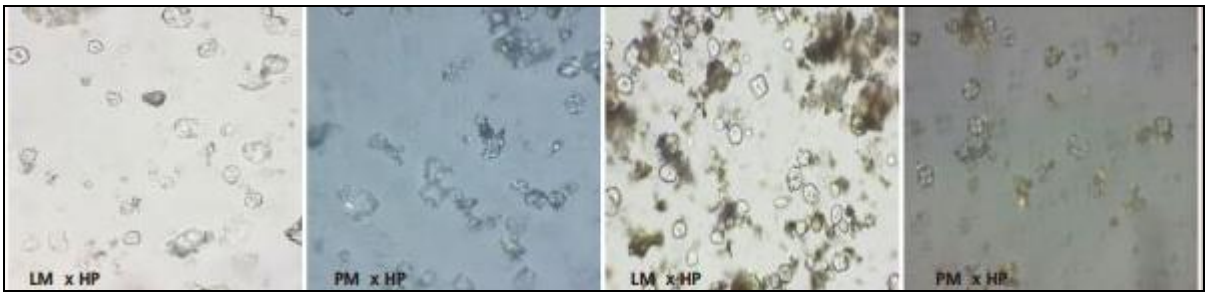

Fig 4: Frusemide - crystals were like Maltese cross.

Ciprofloxacin crystals appeared as Round to rectangular conglomeration of needle shaped crystals with birefringence at places. Ibuprofen and ciprofloxacin was identified as Drug crystals (fig 5).

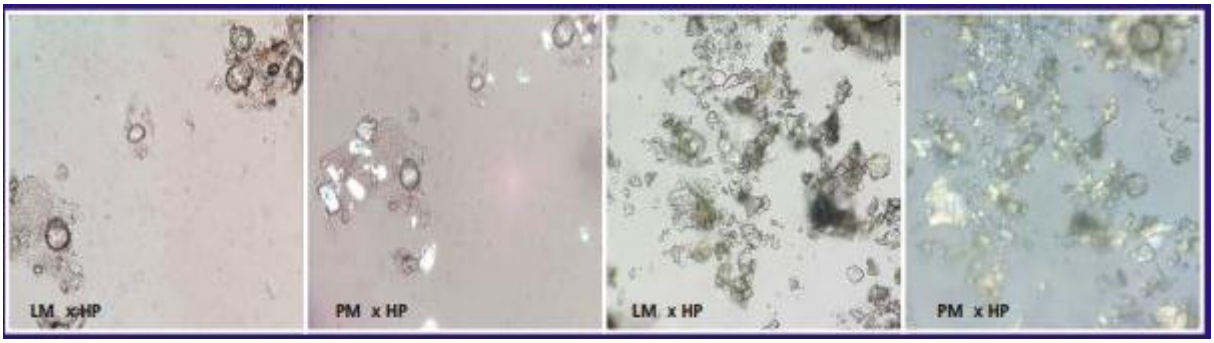

Fig 5: Ciprofloxacin and Ibuprofen identified as Drug crystals, birefringent

Many drugs appeared as aggregates of finely granular material without any defining shape at the light microscopic level. (fig 6) They have to be observed better at high magnification (unless there are large amounts of them) as they mimic bacteria. Though these were reported as amorphous crystals they can be mistaken for urates, phosphates or xanthine.

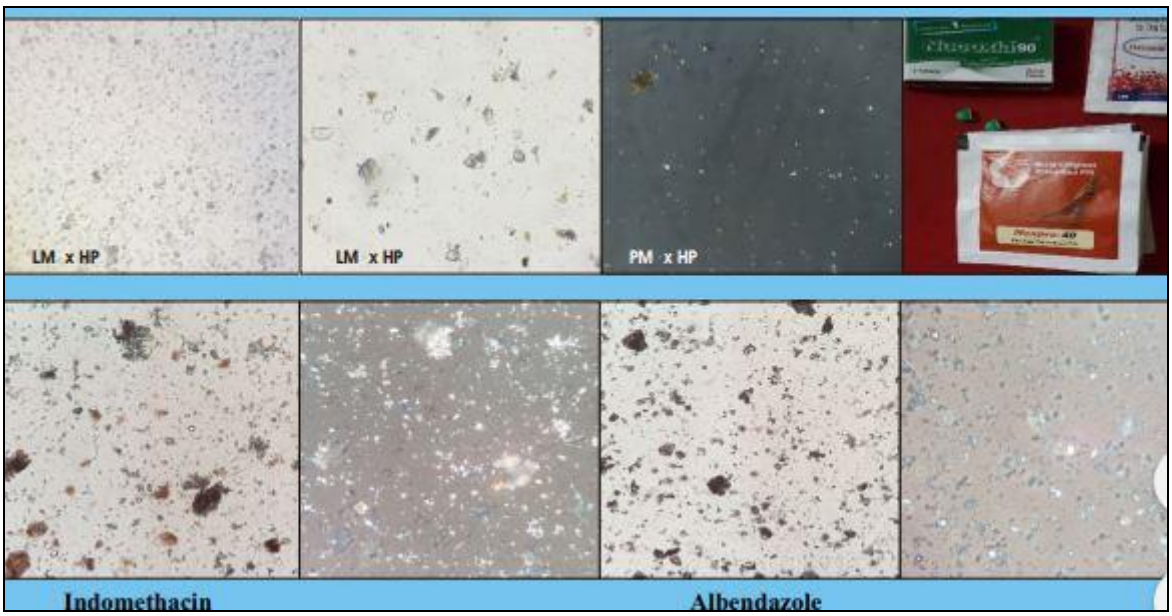

Fig 6: Amorphous crystals.

The following drugs were reported as amorphous crystals with no definite identity. Calcimax (Calcium, Phosphorus, Magnesium, Zinc, Vitamin D3), Shelcal (calcium with vitamin D3, B12),
Diclofenac potassium, Nucoxia90 (Etoricoxib), Nexpro-40(Esomeprazole Magnesium) Limcee (Vitamin C - Chewable tablets), Albedazole, Indomethacin.
Pathologists should have the capability to identify not only the important particles in the urinary sediment but also most common artifacts in the form of drug induced crystals. The use of polarized light is of key importance for the identification of selected particles. urinary sediment findings should be interpreted on the background of the clinical context. Correct methods to be followed at pre analytical phase for urine collection and sample handling. Every clinical pathology laboratory has to be equipped with Phase

contrast microscopy with polarizing filters. Crystals of unusual appearance should alarm the pathologist to think of a drug. In case of drugs causing renal damage (eg. Ciprofloxacin) pathologist has to alert the physician. Crystals can be seen in urolithiasis or acute crystal nephropathy. Visualizing crystals under the microscope does not guarantee that the crystals were present in the urinary system. Crystals can continue to form after micturition due to changes in temperature, as can occur if the urine is stored at room temperature or in a refrigerator, or changes in urinary pH, in the presence of infection due to urea-splitting organisms [1-3].

Conclusion

Crystals of unusual appearance should alarm the pathologist to think of a drug and alert the physician in case of drugs causing renal damage.

This study contributed new knowledge and helped to prepare an image chart for reference in clinical pathology laboratory and for Postgraduate teaching. Further studies using more drugs and varying pH buffers and phase contrast microscopy with polarising filters is recommended.

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