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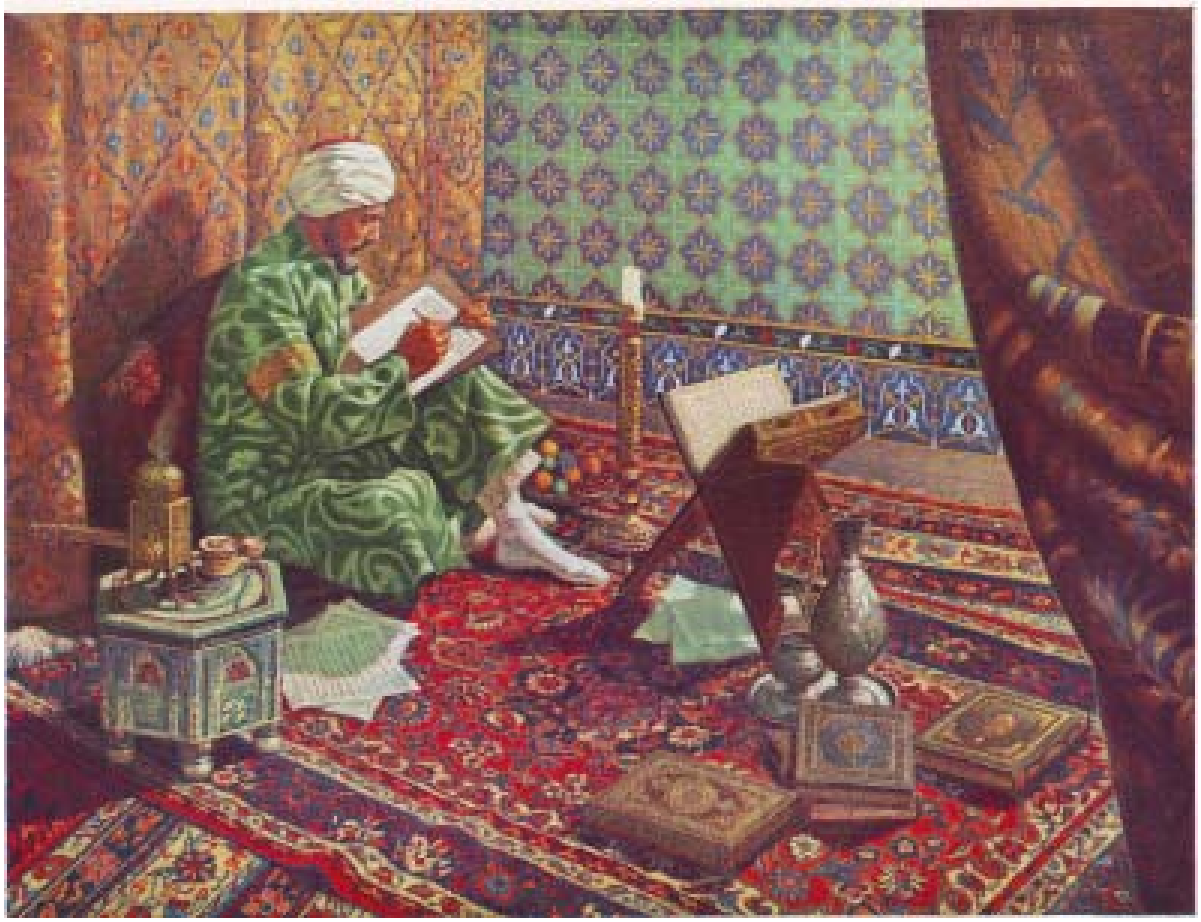

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Cover picture

AVICENNA – THE "PERSIAN GALEN"
(980-1037 A.D.)

Master of philosophy, poetry, and diplomacy as well as pharmacy, medicine, and natural science, the Persian, Avicenna, while in hiding in an apothecary's home, wrote pharmaceutical texts that were dominant throughout the world for many centuries.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Investigating kidney stone disease

Introduction

Urinary stone disease is extremely common world-wide albeit with extensive geographical variations among regions and countries, and often within each country. Generally, the lifetime risk of a kidney stone has been estimated as 10% – 15% in industrialised western countries, and 20% – 25% in the middle east [1]. Kidney stones are notoriously recurrent, at rates of about 40 percent within 5 years of the initial stone, and 75 percent within 10, rising to almost 90 percent by 25 years [2,3]. Nephrolithiasis is much commoner among adult men than among women in a ratio of about 2:1 although the incidence appears to rise in women and fall in men from the sixth decade of life, at least in the USA [4].

Reliable national data are unavailable in Sri Lanka for lifetime risk of a kidney stone, and several other aspects of nephrolithiasis such as qualitative and quantitative composition of stones, metabolic bases of stone disease, and its complications. But the numbers of patients undergoing extracorporeal shock wave lithotripsy (ESWL) annually at the National Hospital of Sri Lanka and the anecdotal experiences of local clinicians, for example, provide indirect testimony indicating a high incidence [5,6] of nephrolithiasis. Given the high incidence, its well known propensity for recurrence, and complications such as obstruction, sepsis, and potential for attenuation of renal function, cursory investigation and casual management of individual clinical episodes, without any attempt at identifying aetiology or instituting a preventative plan is unlikely to be regarded as ideal management from clinical, economic and social perspectives.

The object of this article is to propose a schema for establishing the aetiology of nephrolithiasis in stone-formers that is reasonably thorough and cost-effective in regard to treatment and preventing recurrences.

Terrestrial life necessitates a tight regulation of the body's water economy founded essentially on conservation, that mandates the excretion of a small volume of concentrated urine. Concomitantly, the strong endoskeletal system of terrestrial vertebrates with a substantially calcium-based foundation that is subject to constant remodelling, must perforce be equipped with versatile homeostatic mechanisms to regulate both calcium turnover and urinary excretion. Hence the eternally daunting challenge for the terrestrial vertebrate nephron throughout the aeons of evolution has been the maintenance in solution form in relatively low volumes of urine its various solutes, including calcium salts. Appreciation of this canny physiological balancing act has a direct bearing on the genesis of kidney stones, and the over-arching strategies for minimising stone recurrence, for 75% – 85% of them are calcium containing stones, and increasing daily urinary volume to 2 litres or more is a key component of the medical management of all types of kidney stones irrespective of their aetiology and chemical composition.

Composition of kidney stones

Calcium stones

The composition of kidney stones shows marked geographical variation in published studies. Table 1 shows data culled from two major sources pertaining mainly to the western hemisphere [7, 8], but modified to incorporate some data from selected Asian sources, too. The most conspicuous feature of nephrolithiasis is that calcium stones form 75% – 85% of all stones, and over 50 percent of this category are derived from patients with so-called idiopathic hypercalciuria, who are normocalcaemic but whose daily urinary calcium excretion exceeds 300mg in men and 240mg in women. These statistics demonstrate dramatically what has been noted above; that in view of the evolutionary prerequisite of excreting a limited volume of high osmolality urine, the physical chemistry of supersaturation [9] will take its inexorable course to promote crystallisation of various urinary solutes. The principal culprits are calcium phosphate and calcium oxalate, and frequently these occur mixed in calcium stones in varying proportions. Calcium phosphate usually has the composition [$Ca_5(PO_4)_6.OH_2$], which is hydroxy-apatite. Brushite [$Ca\ HPO_4.^2H_2O$] is a less common form (see Table 3).

Idiopathic hypercalciuria

Idiopathic hypercalciuria is a diagnosis made mainly by default, when urinary calcium excretion is increased in the absence of hypercalcaemia, as established by a diligent and exhaustive search for all its causes (Table 2). Hyperparathyroidism and cancer account for about 90 percent of cases of hyper-calcaemia. Hypercalcaemia is often episodic and may be missed unless the search is persistent.

Table 1. Principal causes of kidney stones in patients who show a particular cause of stone disease

Type of stone	*Percent of all stones*	*Percent of specific sub-type*	*Aetiology*	*M:F* ratio	*Clinical*
1. Calcium stones	75 - 85			2:1	
• Idiopathic hyper – calciuria		50 - 55	(?) Hereditary	2:1	Unexplained hypercalciuria
• Hyperuricosuria		20	Purine rich diet	3.5:4.2	Urine uric acid>750 mg/d
• Primary hyper – parathyroidism		5	Adenoma (?other neoplasm)	3.5:9.0	Hypercalcaemia; PTH raised
• Hyperoxaluria		Rare	Hereditary; Diet; Bowel pathology	1.5:1.0	Urine oxalate raised
• Distal RTA		Rare	Hereditary	1:1	Minimum urine pH>5.5; metabolic acidaemia
• Idiopathic stone disease		20	Unknown	1:1	None of the above present
2. Uric acid stones	5 - 9				
• Gout		40	Hereditary	3: 4	Clinical diagnosis of gout
• Idiopathic		60	(?) Hereditary	1 : 1	No gout: Uric acid stones
3. Struvite	10 - 14		Infection	2: 10	Struvite stones
4. Cystine	1		Hereditary	1 : 1	Cystine stones; Raised urinary cystine

Notes: Data from various sources providing qualitative and quantitative analyses of specific stones. Percentages and M : F ratios approximate. PTH = Parathormone; RTA = Renal tubular acidosis

Table 2. Main causes of hypercalcaemia

1. Primary hyperparathyroidism
   - Solitary adenoma
   - Multiple endocrine hyperplasia
2. Malignancy
   - Metastases from solid tumours
   - Humoral mechanisms from solid tumours
   - Haematologic malignancies (eg multiple myeloma, lymphoma)
3. Sarcoidosis and other granulomatous disease
4. Severe secondary and tertiary hyperparathyroidism
5. Milk-alkali syndrome

Other causes of increased bone turnover such as hyperthyroidism, Cushing syndrome, thiazide therapy and immobilisation should be excluded in the diagnosis of idiopathic hypercalciuria. High levels of NaCl excretion, usually the result of increased consumption or long term diuretics, may cause hypercalciuria as the excretion of divalent cations is linked to that of Na^+ ions.

Hyperuricosuria

The second commonest cause of calcium kidney stones (about 20%) is hyperuricosuria. The aetiology is a protein-rich diet, which is often accompanied by a high intake of NaCl. Consumption of meat, fish and poultry increases the intake of purine, and uric acid is the end product of purine breakdown.

Urinary uric acid excretion exceeding 750 mg/day predisposes to calcium oxalate stone formation probably because sodium hydrogen urate or uric acid crystals that tend to form in the terminal portion of collecting ducts provide a suitable platform for calcium oxalate deposition.

Uric acid stones

Between 5% and 9% of all kidney stones are composed of uric acid, about 40 percent of such stone-formers have gout, and the balance are idiopathic (? hereditary) uric acid stone-formers. A habitually acid urine (pH<5.3) of low volume and high osmolality, and hyperuricosuria are the principal predisposing factors for uric acid stone formation. When urine pH is low supersaturation of uric acid can occur even with a normal level of daily excretion. With increasing prevalence generally of obesity and metabolic syndrome in the community the incidence of uric acid lithiasis is likely to increase, for insulin resistance diminishes renal tubular ammonia generation, with the result that urinary titratable acid excretion is increased and urinary pH lowered.

Distal renal tubular acidosis (Type 1)

This rare condition is characterised by a hyperchloraemic metabolic acidosis without an increased unmeasured anion gap, hypokalaemia, inappropriately alkaline urine (pH>5.5), hypocitraturia, hypercalciuria, and nephrocalcinosis or calcium phosphate stones. Most untreated children and adults will develop osteomalacia. Distal renal tubular acidosis (Type 1) is usually inherited as an autosomal dominant, although sporadic spontaneous mutations may occur. Relatives of patients should be screened, as it is a preventable cause of renal damage.

Table 3. Composition of the commoner kidney stones*

	Stones percent (approx)	*Remarks*
• Calcium oxalate	53	Radio-opaque and clearly demarcated
• Calcium phosphate (apatite)	25	
• Calcium phosphate (brushite)	3	
• Uric acid	7 – 10	Radiolucent, unless calcium mixed
• Magnesium ammonium phosphate (struvite)	5 – 8	Can be staghorn
• Cystine	1 – 2	Radiolucent or lightly opaque; can be staghorn

*Apatite $Ca_5 (PO_4)_6 [OH]_2$; Brushite $CaHPO_4 . 2H_2O$; Struvite $MgNH_4 . PO_4 . 6H_2O$. Calcium oxalate may be the monohydrate or dihydrate.

Treatment consists of sodium bicarbonate tablets, with dose adjustment to eliminate acidosis and hypercalciuria, and Shohl's solution, which contains sodium and potassium citrate.

Cystinuria

Cystinuria is one of the commonest inborn errors, and the most common inborn error of amino acid transport. It is inherited as an autosomal recessive trait that manifests in homozygotes as a defect in the transport of the dibasic amino acids cystine, ornithine, arginine and lysine in the apical brush border of proximal renal tubular cells and the jejunal mucosa. Cystine is the least soluble of all naturally occurring amino acids, so the inherited aminoaciduria in homozygotes predisposes to the formation of renal, ureteral and bladder stones. The clinical features of the disorder result solely from urinary cystine stone formation. Several types of homozygous cystinuria have been described. Heterozygotes also have varying patterns of aminoaciduria but do not form cystine stones.

The detection of a cystine stone is diagnostic of cystinuria. So is the detection of the characteristic flat, hexagonal and plate-like crystals of cystine in the sediment from first morning urine. The nitroprusside test for cystine is sensitive, hence often positive also in asymptomatic heterozygotes. The cherry red colour signifying a positive result is produced by homocystinuria and by acetonuria. Confirmation by paper chromatography, and in doubtful cases, by quantitative estimation using column chromatography may be required.

About 50 percent of stones passed by patients having cystinuria are "mixed stones", and about 10 percent of these may not contain detectable amounts of cystine, so the nitroprusside test is mandatory in **all** stone-formers to ensure that the diagnosis is not missed.

Treatment includes a daily water intake of at least 4 to 5 litres, optimally between 5 to 7 litres, and alkalinising urine with sodium bicarbonate and potassium citrate by mouth.

Hyperoxaluria

The daily urinary oxalate excretion is usually less than 30 mg except in people whose intake of oxalate rich food such as nuts, chocolate and spinach is excessive. The upper limit of normal urinary oxalate excretion is 40 mg per day, and excess consumption of oxalate-rich food may cause a mild hyperoxaluria (<70 mg per day). Oxalate is also an end product of normal human metabolism, contributing about 10 - 20 mg of the daily urinary excretion.

Enteric hyperoxaluria from increased gut absorption of oxalate is often a consequence of bariatric surgery for obesity such as bypassing intestinal segments or bile and pancreatic diversion, extensive Crohn disease of ileum, or small bowel inflammatory disease causing fat malabsorption.

Primary hyperoxaluria is an autosomal recessive disease. Type 1 primary hyperoxaluria is due to a deficiency of the peroxisomal enzyme alanine: glyoxalate aminotransferase, and Type 2 to a deficiency of D-glyceric dehydrogenase. Urinary oxalate excretion is very high, usually exceeding 100 mg per day, and recurrent calcium oxalate kidney stone disease often starts in childhood.

Dietary hyperoxaluria is amenable to dietary advice, increased fluid intake, and dietary supplements of calcium and magnesium to reduce intestinal absorption of oxalate. Enteric hyperoxaluria requires specialist management. Primary hyperoxaluria requires expert aggressive therapy with high fluid intake, neutral phosphate and oral pyridoxine. Even so, irreversible renal failure is common. Liver transplant with or without renal transplant has been successful in treatment.

Hypocitraturia

The association between hypocitraturia and urinary stone formation is well established. Either in combination with other metabolic disorders or as the sole contributory disorder hypocitraturia can be found in 20% - 40% of stone formers. In the latter case it is referred to as idiopathic hypocitraturia. Renal tubular acidosis, hypokalaemia and chronic diarrhoeal conditions are recognised causes of hypocitraturia.

Citrate is the most abundant urinary inhibitor of stone formation. The mechanism of its inhibitory action is twofold. It facilitates urinary base excretion without unduly raising urine pH, so that precipitation of calcium phosphate is minimised, and it forms insoluble complexes with calcium, reducing available calcium ions for crystallisation as calcium oxalate and phosphate.

Treatment of hypocitraturia is with oral potassium citrate. Its effectiveness in reducing recurrences in

calcium oxalate stone formers has been shown in two randomised placebo-controlled trials.

Struvite stones

Struvite stones form as a consequence of chronic infection commonly associated with stasis due to partial or nearly complete obstruction to urinary drainage, and instrumentation or surgery of the urinary tract. Bacteria armed with urease, particularly *Proteus*, invade the tract under such circumstances, especially when repeated antibiotic therapy has facilitated their emergence as the dominant species. Urease splits urea [$(NH_4)_2$:CO] to NH_3 and CO_2, with NH_3 immediately converting to NH_4^+, thus alkalinising urine to a pH usually over 8. The resulting precipitation Mg^{2+} and PO_4^{3-} favours formation of struvite ($MgNH_4PO_4$). $6H_2O$.

The management of struvite stones is removal of the stone by percutaneous nephrolithomy with or without ESWL followed by post-surgical sterilisation of the urinary tract with antibiotics based on urine cultures and culture of stone fragments.

Investigation of kidney stone disease

Kidney stone disease (ie. nephrolithiasis) is not a diagnosis but only a call for detailed investigation and appropriate management, with emphasis on preventing recurrence. The clinical features of stone disease include loin pain, ureteric colic, haematuria, and urinary tract obstruction and infection. The initial investigations are directed towards confirming whether a stone is present, its location, and possible complications (such as intra-renal or extra-renal obstruction and infection) and establishing certain baseline clinical parameters.

A plain abdominal xray of kidney, ureters and bladders (KUB) and ultrasound examination are generally available and commonly performed but radiolucent stones (eg cystine, uric acid) may be missed by the former and ureteric stones by the latter investigation. Helical CT-KUB without enhancement is the ideal imaging procedure, and a negative study excludes renal stone as the cause of suggestive symptoms and signs.

Baseline measures at first presentation include serum creatinine, serum calcium (with at least 2 repeat tests if the first and second are within normal reference range), serum electrolytes (Na^+, Cl^- and HCO_3^-) and serum urate. Initial urine tests would include a fresh midstream sample adequate for four aliquots: immediate pH, culture, routine physical, chemical and microscopic urine analysis, and a sodium nitroprusside test.

The above tests ought to be sufficient for management of the presenting clinical situation, as well as for providing a platform for evaluating the need for further investigation. A pH>5.5 in **fresh** urine in the presence of normal, low normal or low serum bicarbonate would exclude inherited or acquired renal tubular acidosis, a persistently normal corrected serum calcium should exclude all causes of hypercalaemia, a negative midstream fresh urine culture makes infection unlikely, and a negative sodium nitroprusside test renders a diagnosis of homozygous cystinuria highly unlikely, although purists might insist on repeating the last two tests at least once. And serum urate is often, but not always, raised in uric acid stone-formers.

Further investigation is specifically directed towards detecting hypercalciuria sans hypercalcaemia, hyperuricosuria sans gout or hyperuricaemia, and hyperoxaluria. For this purpose it is necessary to have two separate carefully supervised 24-hour urine collections examined. After taking measured aliquots for estimating uric acid, the remainder is acidified to prevent crystallisation of calcium phosphates and oxalates on the collection vessel walls. Polycystic kidney disease and medullary sponge kidney must be excluded by CT-KUB to complete the picture when indicated.

All the tests mentioned above could be done at intial presentation by including the pathology, clinical chemistry (or biochemistry), and radiology and imaging departments as partners of a well-knit research team. A few tests may need to be done conveniently later, on an outpatient basis. A motivated clinician who wishes to do a pioneering research study has a ready-made one in the metabolic bases of nephrolithiasis in Sri Lanka. Once a tertiary referral centre is established, clinicians in less well equipped hospitals will surely refer patients, perhaps even too many, for the research study!

Summary

The vast majority of patients with kidney stone disease have a remediable metabolic perturbation, simply waiting to be discovered, but systematic and thorough investigation and recording are clearly deficient in Sri

Lanka. All recurrent adult stone-formers and children with even one stone must be investigated. Meanwhile, lazybones may be glad to hear that simply increasing long term water intake to 2.5 litres or more daily in an adult stone-former will reduce recurrences by as much as 50 per cent regardless of aetiology, as demonstrated by a recent prospective controlled study.

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I have no conflicts of interest regarding this article.

Safe and effective use of lithium

Summary

Lithium has proven efficacy in the treatment of bipolar disorder, both for acute mania and long-term mood stabilisation and prophylaxis

It is also useful in combating treatment-resistant depression.

Compared to other mood stabilisers, lithium has a favourable efficacy-tolerability balance.

Lithium is underused due to active marketing of alternatives and concerns regarding adverse effects, tolerability, and the perception that regular monitoring is difficult.

Key words: bipolar disorder, mood stabiliser, tolerability

(Aust Prescr 2013;36:18-21)

Introduction

Lithium has been available for over sixty years for bipolar disorder. A large empirical evidence base has ensured it remains a viable treatment option, even in the absence of sponsorship and promotion.[1-3]

Lithium has unique properties both as an antisuicidal and neuroprotective drug and, if used wisely, is relatively well tolerated and not complex to administer.

Despite this, its role as a mood stabiliser in practice has been limited because of concerns regarding tolerability and long-term risks, and the perception that regular and reliable monitoring of plasma concentrations is difficult.

Efficacy in bipolar disorder

Lithium is particularly effective in patients with recurrent bipolar I disorder in which episodes of depression and mania are punctuated by periods of remission (euthymia). Complex forms of bipolar disorder such as bipolar II disorder, mixed states, and rapid cycling are common, but respond less well to lithium (Table 1).

In recent years the reported response to lithium in bipolar disorder has diminished. This is partly because studies investigating new treatments, in which lithium has often served as a comparator, have increasingly used heterogeneous bipolar populations.[4] The patients usually have mixtures of bipolar disorder 'subtypes' from bipolar I disorder to major depression. Studies in first world countries often enrol individuals who have been refractory to pharmacotherapy, so not surprisingly the efficacy of lithium appears lower than expected.

A recent real-world study comparing lithium and valproate alone and in combination reaffirmed lithium as an effective first-line drug for maintenance therapy and perhaps the best drug for prophylaxis.[5] Recent guidelines state that in addition to its clear prophylactic properties, lithium is also efficacious in the acute phases of bipolar disorder (Table 1).[6]

Table 1. Lithium in mood disorders

Bipolar disorder	
Acute mania	Lithium monotherapy is a first-line option Antimanic action can take 6-10 days
	In practice lithium is often used in combination with neuroleptics and/or benzodiazepines to achieve a more rapid effect
Acute depression	Lithium monotherapy is less effective in treating acute depression than it is in treating mania
	Effect of antidepressant action can take 6-8 weeks
	Often used to augment mood stabiliser or antidepressant therapy
Maintenance/prophylaxis	Lithium is superior to placebo and most anticonvulsants and neuroleptics used in the treatment of bipolar disorder
	Outcome is better if therapy is initiated early
Rapid cycling/mixed states	Lithium is shown to decrease symptom severity and reduce morbidity, but is less likely to achieve remission of symptoms and recovery
Major depression	
Acute	Lithium monotherapy is superior to placebo but it is rarely used, particularly in acute settings
	Greater efficacy for patients with a family history of bipolar disorder
Chronic	Often used as an augmentation strategy
	Effective in combination with all antidepressants and can be prescribed adjunctively with all treatment modalities

Mania

Robust randomised controlled data from trials indicate that lithium is effective in treating acute mania. However, its relatively slow onset of action (6-10 days) means it is used in combination with short-term antipsychotics and benzodiazepines.[1]

Depression

The evidence for lithium monotherapy in the treatment of bipolar depression is not as impressive as that for mania, partly because it can take 6-8 weeks to take effect. Recent clinical trials suggest that lithium is more effective than placebo and therefore it remains an important option for treating bipolar depression.[7]

Maintenance and prophylaxis

The efficacy of lithium in prophylaxis has been robustly demonstrated by the BALANCE study.[5] With adequate adherence, long-term lithium successfully reduces suicidal ideation.[1] Consistency of treatment is therefore important and commencing maintenance therapy early provides the best possibility of improved long-term outcomes.[3] Furthermore, long-term therapy may confer neuroprotection by enhancing the viability of cells as well as preventing apoptosis.

Rapid cycling bipolar disorder and mixed states

Clinically, rapid cycling bipolar disorder and mixed states can often be difficult to differentiate[1] and in practice lithium is relatively less effective in achieving remission in both of these subtypes compared to bipolar I disorder. However, it does reduce symptom severity and can therefore be used combined with other psychotropic medications, especially when wanting to reduce the risk of suicide and achieve prophylaxis.

Starting lithium therapy

Lithium is available in a variety of formulations. The sustained slow-release formulation will have a lower peak plasma concentration which may be better tolerated by some patients. After oral administration lithium is absorbed in the gut and excreted wholly via the kidneys. It has very few interactions relating to hepatic metabolism. Steady-state lithium concentrations can usually be achieved after 4-5 days of daily administration. Lithium has a relatively narrow therapeutic index so it is important to maintain lithium plasma concentrations within a specific range for each individual to achieve a balance between efficacy and adverse effects.

To minimise adverse effects when starting lithium de novo it should be administered in small divided doses then titrated gradually to achieve plasma concentrations of 0.6-0.8 mmol/L, while monitoring for these effects. Concentrations of up to 0.8-1.0 mmol/L may be needed for lithium-naïve patients and for treating acute recurrence of mania. Recent long-term studies suggest that even relatively low concentrations (0.6-0.8 mmol/L) confer reasonable prophylaxis, and are better tolerated.

Maintenance and prophylaxis therapy

The primary aim of prophylaxis is to prevent the recurrence of symptoms while minimising adverse effects and maintaining compliance. Lithium can be given as a once-daily dose for maintenance therapy. Most importantly, plasma lithium concentrations should be optimised to the symptom profile of the individual. Patients more prone to developing depressive episodes may benefit from concentrations of 0.4-0.8 mmol/L, whereas those more likely to become manic may require concentrations of 0.6-1.0 mmol/L long term.

Short-term adverse effects

Tremor, general fatigue, diarrhoea, thirst, polyuria, nausea, headache and vomiting are common initially, but are usually transient (1-2 days) and dose dependent. Most of these adverse effects are associated with rapid changes in plasma lithium concentrations and therefore should be anticipated whenever the dose of lithium is altered, and especially when it is increased.[8] If adverse effects persist for weeks or are particularly troublesome, lithium should be decreased or stopped. In practice this is rarely necessary and lithium can usually be reintroduced while titrating the dose carefully.

Long-term adverse effects

There are several adverse effects associated with long-term use of lithium and regular patient monitoring is required (Table 2).

Kidneys

Lithium affects the concentrating ability of the kidney, leading to polyuria and secondary thirst, but it is controversial whether lithium causes irreversible kidney damage. Approximately 10% of patients on lithium are prone to developing diabetes insipidus.[9] It is this renal insufficiency which is often thought to contribute to end-stage renal failure. Patients with renal impairment may remain on lithium treatments with appropriate dosage adjustments.

Table 2. Recommendations for monitoring patients on lithium

Parameter	*Investigation*	*When to monitor*
Lithium	Plasma lithium concentrations*	Monitor closely for first few days and aim to achieve concentrations within the therapeutic range Monitor every 3-6 months for long-term lithium use
Renal function	Urea and creatinine Electrolytes	Baseline then at 6 months Baseline then annually
Thyroid function	Thyroid stimulating hormone concentrations	Baseline then at 6 months Annually for long-term lithium use
Parathyroid function	Calcium concentrations	Baseline then annually
Weight	Waist circumference, body mass index	Baseline then annually

Adapted from guidelines from the International Society for Bipolar Disorders.[11] More frequent investigation may be required if clinically indicated or a change in mood state is observed.

* In the event of acute toxicity (>2 mmol/L), lithium should be ceased immediately and haemodialysis can be used to reduce lithium in the blood

Thyroid

Lithium also affects thyroid function reducing the availability of thyroxine. The incidence of hypothyroidism is six-fold higher in patients on lithium as compared to the general population. Hypothyroidism in turn increases the likelihood of developing clinical depression.[8] Patients on lithium should therefore be routinely assessed for hypothyroidism and treated with thyroxine replacement if indicated.[8] It needs to be stressed however that hypothyroidism is not a contraindication for therapy.

Parathyroid

Parathyroid function can also be compromised by lithium. Patients on lithium are therefore prone to develop hypercalcaemia secondary to elevated parathyroid concentrations. Hyperparathyroidism that produces significant hypercalcaemia is a possible contraindication for continuing lithium so there is a need to monitor plasma calcium concentrations.[10]

Weight gain

Modest weight gain of 1-2 kg is common (5%) in patients on long-term lithium therapy. The trajectory of weight gain is steep at the beginning but soon plateaus. Diet, exercise and lifestyle advice are essential when patients start treatment.

Teratogenic effects

It appears that the risk of teratogenic effects from lithium has been exaggerated in the past.[10] However, there is a small risk and lithium is best avoided during pregnancy. Management during pregnancy should be collaborative and requires careful informed consideration of the risks.

Toxicity and its management

In acute lithium intoxication, the increase in plasma concentrations (>2 mmol/L) can be potentially lethal. Once renal excretion reaches its maximum, lithium accumulates rapidly and symptoms worsen. However, high plasma concentrations may cause relatively mild symptoms, and in these instances individuals often recover without permanent neurological damage. This occurs because lithium can take up to 24 hours to cross the blood-brain barrier, and brain concentrations usually peak eight hours after oral administration.

With lifelong treatment, lithium can gradually accumulate within the brain and lead to chronic neural toxicity because it has a longer half-life in the brain than in plasma. Symptoms such as lethargy, drowsiness, muscle weakness and hand tremor are indicative of neural toxicity and can manifest even at therapeutic concentrations of lithium. Toxicity from chronic lithium use is also subject to increases in dose and individual factors such as diminished renal function and ageing which may result in increased plasma concentrations.

It is therefore essential to monitor patients for symptoms of toxicity and assess plasma lithium concentrations every 3-6 months. If toxicity occurs, treatment should be stopped and prompt action taken to prevent serious damage.

Monitoring lithium

While it is generally recommended that plasma lithium concentrations may be monitored every 3-6 months,[11] current evidence suggests that unless otherwise indicated, annual monitoring may be sufficient (Table2).

Adherence

Adverse effects are the most commonly cited reason for poor adherence. Of these, weight gain is the most distressing.[8] Not surprisingly, individuals who report multiple adverse effects are less likely to be adherent, and additional factors such as stigma and acceptance of the illness are important to bear in mind.[12]

The need to take medication when symptom-free is a key concern. This viewpoint often reflects a degree of denial by the patient because they are feeling better. This is more evident in younger individuals, those who have been recently diagnosed, and those taking lithium long-term. Patients who are not in a strong doctor-patient relationship and those who are less informed about the disorder and its treatment are generally less adherent.

Enhancing adherence requires a multifaceted approach involving education and monitoring of the patient. Close monitoring of patients improves adherence in two ways. First, it allows tailoring of the therapeutic dose to suit the individual, so that therapeutic benefit is optimised and the likelihood of adverse effects is minimised. Second, regular monitoring increases contact and therefore patients are likely to receive more frequent supervision and better education concerning their illness and its management.

Other strategies include educating family and friends to recognise the early signs of relapse and using a suitable means to manage stressors. Caregiver support increases adherence.[13] Encouraging patients to make a firm commitment to treatment before it starts, and coupling pharmacotherapy with psychotherapy, have also been shown to improve patient outcomes.[8]

Conclusion

Lithium can be used as monotherapy or in combination with other medications for the treatment of bipolar disorder. It is most efficacious in maintenance and prophylaxis and is widely used as a mood stabiliser, and has efficacy in both poles of the disorder. It is important to monitor both response and adverse effects and to regularly measure the plasma concentrations of lithium. This ensures adequacy of treatment and enhances compliance. If used wisely, lithium is relatively well tolerated and not complex to administer. It remains one of a handful of potentially life-changing treatments in psychiatry.

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Mumps

Introduction

Mumps is an acute viral infection, occurring mainly in children although no age is exempt. It was first described as early as 5th century BC by Hippocrates.

Aetiology

Mumps is caused by an RNA virus belonging to the genus Rubulavirus of Paramyxoviridae family. It is an enveloped virus rapidly inactivated by heat and ultraviolet light. Only one antigenic type has been described and humans are the only known natural hosts. Transmission occurs by direct spread from droplets by sneezing and coughing infected people and by direct contact. Virus enters the host through the respiratory tract and multiplies in the upper respiratory tract epithelium and regional lymph nodes. This is followed by viraemia and spread of virus to other organs such as salivary glands, testes, pancreas, ovaries and central nervous system.

Epidemiology

Mumps occurs world-wide. In unvaccinated populations annual incidence is estimated to be 100 to 1000 cases per 100000 population. Highest incidence is reported in the 5 - 9 year age group. With the introduction of an effective vaccine epidemiological patterns are changing and the disease is becoming more common in adults.

Clinical features

Mumps virus infection is asympomatic in up to 20% of infected people. Symptomatic infection presents after an incubation period of 16 - 18 days with non-specific symptoms such as low grade fever, malaise, anorexia, myalgia and headache. In the classic presentation this prodrome is followed by parotid gland involvement within 1 - 2 days of illness. The patient might present with an earache during the initial stage of the illness. Physical examination will show tender swelling of the parotid area. Parotid gland involvement is usually bilateral, but can be unilateral in up to 25%. Mumps virus can infect many tissues. Parotitis is the commonest clinical manifestation and it is seen in up to 80% of infected people. Apart from the parotid gland any other salivary gland can be affected. Obstruction of the lymphatic drainage by enlarged sublingual and submandibular glands can produce swelling of the tongue and presternal pitting oedema.

Complications

CNS involvement is common, and CSF pleocytosis is present in more than half the patients. But clinical meningitis occurs only in about 10% - 15% of patients, and is usually a self-limiting benign condition. Encephalitis is seen rarely (0.1%), but is a serious complication as it can lead to permanent neurological damage. Orchitis affects 20 - 30% of post-pubertal males. It is rare before puberty and usually unilateral, but can be bilateral in up to 30% of boys. Mumps orchitis may result in testicular atrophy in up to 50% of patients, but resulting sterility is rare even with bilateral involvement. Other rare complications include oophoritis, sensorineural hearing loss, pancreatitis, arthritis, myocarditis and nephritis.

Diagnosis

Mumps is diagnosed clinically. Laboratory diagnosis is not usually required. But if necessary the disease can be confirmed by virus isolation, polymerase chain reaction (PCR) or serological studies. Commonly used serological tests include detection of IgM antibodies which usually become positive within a few days of the illness, or by a fourfold rise in IgG titre between acute and convalescent sera. Serological tests are not reliable in patients who have received mumps vaccine.

Treatment

Mumps is a self-limiting illness. Management is symptomatic and antiviral drugs are not indicated. Pain caused by parotid and other salivary gland inflammation can be relieved by appropriate use of analgesics such as paracetamol or ibuprofen. Cold or warm compresses may be helpful to relieve discomfort caused by parotitis.

Orchitis is managed symptomatically with bed rest, gentle support of the scrotum, cold compresses, and analgesics. Subcutaneous interferon alfa 2b may promote rapid recovery and prevent subsequent testicular atrophy and subfertility. Steroids or incision of the tunics albiginea is effective in prevention of testicular atrophy.

Mumps prevention

The infectious period of mumps is generally considered to be 3 days before and 5 days after the onset of illness. Rarely patients may be infectious up to 7 days before and 9 days after. Current recommendation is to isolate patients for at least 5 days after onset of parotitis.

Mumps vaccine

Introduction of the mumps vaccine has led to a significant drop in incidence of mumps in developed countries. Currently used vaccine is a live attenuated vaccine. It was first available in the market in the 1960s and since then many countries have introduced it in their national immunization programs.

Composition

Vaccine commonly contains either Jeryl Lynn or Urabe strain of attenuated mumps virus. It is produced in a chick embryo cell culture and contains neomycin, sorbitol and gelatin. It is available as a freeze dried vaccine which has to be reconstituted using the diluents provided. In Sri Lanka mumps vaccine is available in combination with measles and rubella vaccines as a trivalent vaccine. A quadrivalent vaccine containing varicella zoster vaccine is available in some parts of the world.

Vaccine efficacy

Initial clinical trial data suggested more than 95% efficacy of mumps vaccine following a single dose. But a more recent Cochrane review concluded an effectiveness of 64% to 66% for a single dose and 83% to 88% for two doses against laboratory confirmed mumps. Vaccination is considered to provide protection against infection for at least 20 years. Current recommendation is to vaccinate with 2 doses given at least 4 weeks apart.

Indications

In Sri Lanka the mumps vaccine is a part of national immunization program. It is offered as trivalent MMR vaccine at the ages of 1 and 3 years. Doses given before 1 year of age are not substitutes for routine vaccination. Vaccination is also indicated to immunise susceptible adults.

Contraindications

Severely immune compromised persons because of immunodeficiency or immunosuppressive therapy, and people with a history of severe allergic reaction to mumps vaccine or its components such as gelatin and neomycin should not be offered mumps vaccination. Pregnant women should not be given the vaccine and pregnancy should be avoided for 4 weeks following vaccination. Breastfeeding women can be vaccinated. Vaccine may be given to egg allergic children and the HIV infected, but not to severely immune compromised people.

Adverse effects

In general mumps vaccine is a safe vaccine. Adverse events are rare or mild in nature. These include parotitis, fever and hypersensitivity reactions, and very rarely aseptic meningitis, encephalitis, orchitis and deafness.

Immunization after exposure is safe. Even though it may not prevent the disease it will provide protection against future exposures. Post-exposure prophylaxis with mumps immunoglobulin has not been shown to be effective. Mumps is a notifiable disease in Sri Lanka. Suspected patients should be notified to the relevant medical officer of health for further investigation.

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Conflicts of interest. None declared.

Self-assessment questions

(Select the ***best*** response in each question)

1. Distal renal tubular acidosis Type 1 is characterized by
   (a) autosomal recessive inheritance
   (b) hypochloraemic metabolic acidosis
   (c) an increased unmeasured anion gap
   (d) a fresh urine pH of < 5.4
   (e) hypocitraturia

2. Regarding uric acid stones:
   (a) About 15% of all kidney stones are uric acid stones
   (b) Over 50% of uric acid stone-formers have gout
   (c) A low volume of high osmalality acidic urine below pH 5.3 predisposes to uric acid stone formation
   (d) Allopurinol is useful to dissolve uric acid stones
   (e) Hyperuricosuria constitutes about 50-55 percent of calcium stone-formers

3. In long term lithium therapy for bipolar disorder and resistant depression
   (a) plasma concentration should be monitored at least once a month
   (b) plasma concentration should be maintained within the range 1.0 to 1.5 mmol/l
   (c) the drug undergoes extensive hepatic metabolism
   (d) renal function and thyroid function should be assessed at least annually
   (e) brain concentration of lithium reaches a peak within 2 hours of oral administration

4. Mumps
   (a) during pregnancy is known to cause congenital malformations in the newborn
   (b) causes asymptomatic aseptic meningitis (CSF pleocytosis) in 50% - 60% of patients
   (c) immunoglobulin is affective for post-exposure prophylaxis
   (d) vaccine given as two doses has an efficacy > 95%
   (e) may be safely used in patients on immunosuppressive therapy

Answers to self-assessment questions

Question 1. True: **(a)**. The acidosis in RTA Type 1 is hyperchloraemic, and the "unmeasured" anion (eg sulphate, phosphate, acetoacetate, lactate) gap is in the normal range. A fresh urine pH < 5.4 excludes RTA Type 1, and hypercitrauria is feature of that condition. (See first article, this issue).

Question 2. True: **(c)**. Less than 10% of uric acid stone-formers have gout; hyperuricosuria constitutes about 20% of calcium stone-formers; and allopurinol is a xanthine-oxidase inhibitor, an enzyme crucial for purine breakdown, and not a stone solvent. (See first article, this issue).

Question 3. True: **(d)**. Plasma concentration of lithium should be measured only once in 3-6 months depending on individual factors, except during first dose-adjustment period, and its concentration should be between 0.6 - 0.8 mmol/l. (See second article, this issue).

Question 4. True: **(b)**. Immunoglobulin is not effective in post-exposure prophylaxis in mumps. The vaccine is safe in pregnancy (see SLMA Guidelines and Information on Vaccines, 2011), but should not be used during immune suppressive therapy. (See third article, this issue).

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