systematic review the puzzle's intricacies may be disentangled.

The vast amount of available information underscores the value of systematic reviews. As T S Eliot asked in his poem "The Rock," "Where is the knowledge we have lost in information?" Moreover, decision makers of various types are inundated with unmanageable amounts of information. They have great need for systematic reviews that separate the known from the unknown and that save them from the position of knowing less than has been proved.¹⁶

Advantages of the systematic review are many. Whether scientific findings are consistent and can be generalised across populations, settings, and treatment variations or whether findings vary significantly by particular subsets can be gleaned. Unique advantages of quantitative systematic reviews or meta-analyses are increased power and precision in estimating effects and risks. Hopefully, both qualitative and quantitative systematic reviews, with their explicit methods, will limit bias and improve the reliability and accuracy of recommendations.

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Lesson of the Week

Cystitis and ureteric obstruction in patients taking tiaprofenic acid

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Take a full drug history, asking particularly about recent treatment with tiaprofenic acid, in any patient presenting with unexplained chronic cystitis

Three cases of cystitis associated with tiaprofenic acid, a non-steroidal anti-inflammatory drug, have been reported.¹ These patients recovered once the drug had been stopped, and none came to any permanent harm. We have encountered eight additional cases. Several of these patients had severe disease, which in one case was life threatening.

Case reports

CASE 1

A 69 year old woman presented with intolerably painful frequency and sterile haematuria. She had a long history of arthritis and had taken tiaprofenic acid for about two years. Intravenous urography showed normal upper tracts but she had a small contracted bladder with reddened friable mucosa on cystoscopy. Two months later she developed renal failure (blood urea 39 mmol/l, creatinine 236 μ mol/l). An ultrasound

examination showed bilateral ureteric obstruction and severe hydronephrosis. At surgery both ureters were thickened over their entire length and she had a cystectomy and ureteric diversion into an ileal conduit. The resected bladder was contracted and had a thickened wall. Much of the epithelial surface was ulcerated and replaced by granulation tissue.

Histological examination showed a dense chronic inflammatory infiltrate in the lamina propria with prominent eosinophils. This extended into the epithelium with associated spongiosis and into the muscle of the bladder wall with associated fibrosis. Similar changes were seen in the ureteric off cuts, causing marked luminal stenosis (figure).

After the operation she stopped taking tiaprofenic acid and her renal function rapidly returned to normal. Several months later she developed haematuria and her renal function deteriorated. She had started taking tiaprofenic acid again. She stopped the drug and her impaired renal function and haematuria resolved.

CASE 2

A 65 year old woman presented with frequency and nocturia which had become increasingly severe over a year. She had been taking tiaprofenic acid for more than two years for arthritis. Intravenous urography showed dilated upper tracts. Cystoscopy showed a small bladder with a friable "cobblestone" mucosa. A bladder biopsy showed prominent mucosal oedema and a moderate chronic inflammatory infiltrate in the lamina propria with frequent eosinophils. The epithelium showed glandular metaplasia. Her symptoms continued despite stopping the tiaprofenic acid, and a month later a cystectomy and a ureteric diversion into an ileal conduit were performed. Virtually all of the epithelium showed glandular metaplasia, and eosinophils were abundant. There was also extension of the inflammation and fibrosis into the muscle of the bladder wall and into both ureters causing severe luminal stenosis.

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Left: off cut of ureter from case 1 showing chronic inflammation reducing the lumen (arrowed) to a slit (haematoxylin and eosin stain). Right: bladder mucosa from case 1 showing chronic inflammation, epithelial spongiosis, and (arrowed) intraepithelial eosinophils recognised by their bilobar nuclei (haematoxylin and eosin stain).

CASE 3

A 75 year old man who had been followed up for seven years by cystoscopy after having non-invasive transitional cell carcinoma was found to have haemorrhagic friable bladder mucosa suggestive of in situ carcinoma. Over the next three months he developed severe urinary symptoms and haematuria. He had been taking tiaprofenic acid for three years. The bladder biopsy specimens from two cystoscopies showed a dense chronic inflammatory infiltrate in the lamina propria with frequent eosinophils. As in case 1 there were chronic inflammatory cells including eosinophils in the epithelium and spongiosis. He stopped the drug and his symptoms resolved.

CASE 4

A 60 year old woman with arthritis presented with a three month history of frequency and haematuria. She had been taking tiaprofenic acid for several months for arthritis, and although she had noticed some previous urinary symptoms they had become much worse after starting the drug. Intravenous urography showed a small irregular bladder, and this was confirmed on cystoscopy. The bladder mucosal biopsy showed very similar changes to those in case 3. She stopped taking tiaprofenic acid and her symptoms resolved.

CASE 5

A 62 year old woman presented with a four month history of severe frequency and haematuria. She had been taking tiaprofenic acid for over two years. Intravenous urography showed a small irregular bladder, and this was confirmed at cystoscopy. The biopsy of the bladder mucosa showed similar changes to those in cases 3 and 4. Although most of the epithelium was denuded, that which remained showed intraepithelial chronic inflammatory cells, including eosinophils associated with spongiosis. She stopped taking tiaprofenic acid and her symptoms resolved.

CASE 6

A 72 year old woman with arthritis was being followed up after treatment for non-invasive papillary carcinoma of the bladder four years earlier. Over the last year her bladder mucosa had become oedematous and haemorrhagic, and for three months she had reported painful frequency and haematuria. A bladder biopsy showed no evidence of residual tumour, but there were severe chronic inflammatory changes similar to those seen in cases 3-5. She had been taking tiaprofenic acid for four years. This was stopped and her symptoms resolved.

CASE 7

A 47 year old woman had had urinary symptoms since developing a cauda equina lesion after a laminectomy. Cystoscopy at this time had shown a flaccid bladder. Five years later she presented with a four month history of sterile haematuria and severe painful frequency. She had been taking tiaprofenic acid for four years. Her treatment was changed to flurbiprofen but her symptoms had not improved after four months. Another cystoscopy showed a small contracted bladder (300 ml) with a friable haemorrhagic mucosa. The biopsy showed mucosal changes similar to those seen in cases 3-6. Her symptoms subsequently started to improve.

CASE 8

A 72 year old woman with arthritis had been taking tiaprofenic acid for several years. She had been regularly reviewed by cystoscopy for four years after treatment of non-invasive papillary transitional cell carcinoma of the bladder. She presented with frequency and sterile haematuria. Cystoscopy showed a

small contracted bladder with haemorrhagic mucosa. The biopsy specimen showed similar changes to those seen in cases 3-7. She was advised to stop taking tiaprofenic acid and her symptoms improved.

Discussion

Tiaprofenic acid is not widely used yet in a medium sized district general hospital we encountered eight cases in which this drug was associated with an unusual form of chronic cystitis. Such an association is unlikely to be due to chance alone. The fact that in several patients the symptoms resolved when the drug was stopped further strengthens the case for the drug being the cause of the disease. In case 1 the patient's symptoms resolved when the drug was stopped, returned when she started taking the drug again, and then resolved when it was stopped for the second time.

The previous report suggested that stopping the drug leads to resolution of symptoms,¹ but this did not occur in case 2 or 7. This is perhaps not surprising as once fibrosis has developed in the bladder wall it is unlikely that the bladder will ever return to normal. The ureteric obstruction in cases 1 and 2 is particularly worrying and could be fatal.

There are many causes of a shrunken inflamed bladder, but in Britain the commonest is interstitial cystitis. It is important to distinguish between interstitial cystitis and cystitis associated with tiaprofenic acid when considering treatment. The first is an unrelenting disease of unknown aetiology,^{2,3} which often has to be treated surgically, while the second may resolve if the drug is stopped. Some histological features that seem to suggest cystitis related to tiaprofenic acid rather than interstitial cystitis are the presence of numerous eosinophils, prominent intraepithelial chronic inflammatory cells, and extension of these inflammatory changes into the mucosa of the ureters. Eosinophils are a well established feature of drug related inflammation at other sites such as the liver and the skin and may be a marker of an analogous process in the bladder. The poorly defined idiopathic entity "eosinophilic cystitis" also shows abundant eosinophils, and this would have to be considered in the differential diagnosis.^{4,5} Tiaprofenic acid associated cystitis could be one form of eosinophilic cystitis.

The type of inflammation seen in the bladder wall suggests that the disease is essentially a hypersensitive immune response to tiaprofenic acid or its metabolites. The intraepithelial chronic inflammatory cells along with the spongiosis and ulceration suggest that the epithelium is the main target of inflammation.

In the cases presented here the history of taking tiaprofenic acid was not always obtained at presentation. This highlights the need to ask about its use in patients with unexplained cystitis, especially those with arthritis. In conclusion, our study suggests that tiaprofenic acid associated cystitis can be a serious disease. This type of drug reaction should be considered clinically in all cases of unexplained chronic cystitis. Early diagnosis is particularly important because irreversible damage to the bladder wall may occur if the disease is allowed to progress, and in the worst cases ureteric obstruction and renal failure may threaten the patient's life.

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